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ORIGINAL ARTICLE

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Lung transplantation for emphysema. Lung hyperinflation: incidence and outcome

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Abstract Lung transplantation, single or bilateral sequential, is the final option for patients with emphysema. This study analyzed the outcome of lung transplants for emphysema (single or double), and evaluates the incidence, predictive factors and prognosis of lung hyperinflation (LHI) in unilateral transplants. We prospectively studied patients undergoing lung transplantation for emphysema. On admission to the Intensive Care Unit (ICU) and at 12, 24, 48 and 72 h we tested the patients' respiratory function, oxygen arterial pressure (P_aO_2) and mean pulmonary arterial pressure (MPAP) before transplantation. LHI incidence, duration of mechanical ventilation and hypoxemia, ICU stay and mortality was also analyzed. We studied 34 consecutive patients undergoing lung transplantation for emphysema, 14 single and 20 bilateral. Single-lung transplantation had a higher mortality (50%) than double-lung transplantation (11%), with an odds ratio of 9.0 (1.3–48.7). Of the 14 patients who received a single graft, 9 patients (64%) developed LHI. No predictive factors for LHI could be established. Duration of mechanical ventilation (22 vs 3 days) and ICU stay (36 vs 6 days) was much longer in patients with LHI; however, only ICU stay reached statistical significance ($P=0.011$). Mortality in patients with LHI was higher, 67% vs 20% (NS). We conclude that single-lung transplant in emphysema patients has a worse prognosis than bilateral transplant, with a 9-fold higher mortality rate. LHI is a common event in single-lung transplant for emphysema and is associated in our patients with a longer stay at the ICU.

Keywords Lung transplantation · Pulmonary emphysema · Lung hyperinflation · Respiratory insufficiency · Artificial respiration

Abbreviations FEV1 (%): Forced expiratory volume in 1 second (in percentage of theoretical value) · FVC (%): Forced vital capacity (in percentage of theoretical value) · ICU: Intensive care unit · LHI: Lung hyperinflation · MPAP: Mean pulmonary arterial pressure · P_aO_2: Oxygen arterial pressure · MOFS: Multiple organ failure syndrome · SIMV: Synchronized intermittent mandatory ventilation · A/CMV: Assist–control mechanical ventilation

Introduction

In single-lung transplantation, previous status of the native lungs may affect functioning of the lung graft, particularly in patients with pulmonary emphysema, in whom ventilation/perfusion alterations may occur [1]. Lung hyperinflation (LHI), which results from this imbalance, leads to difficult weaning from mechanical

ventilation and hemodynamic alterations. LHI has been associated with prolonged mechanical ventilation [2, 3] and even with higher early mortality [2].

However, owing to the difficulties of organ procurement and the greater complexity of double-lung transplants, both experimental and clinical studies advocated the practice of single-lung transplantation in patients with pulmonary emphysema. Some of these studies concluded that ventilation/perfusion alterations are not always produced, and only occur when reimplantation injury appears in the grafted lung [4].

The aim of this study was to analyze the development of both single and double lung transplants for emphysema and evaluate the incidence, predictive factors and prognosis of LHI in unilateral transplants.

Materials and methods

We studied prospectively 34 patients who underwent lung transplantation for emphysema between June 1996 and October 2000. The study was approved by our institutional review board which did not require informed consent. The decision to perform single or bilateral sequential transplantation was taken depending on the presence of associated factors; usually general double-lung transplant was done in younger people or in patients with associated bronchiectasies. The immunosuppressive regimen included triple therapy with cyclosporine, azathioprine and steroids. Postoperative antibiotic therapy included amoxicillin-clavulanate (2 g/8 h) plus aztreonam (1 g/8 h), but this treatment was modified according to the last cultures carried out in donors and recipients with septic disease. Intravenous ganciclovir and cotrimoxazol was used to prevent *cytomegalovirus* and *pneumocystis carinii* infection respectively. Our lung transplant program started 12 years ago and global results of this program are in accordance with the international registries [5].

Respiratory function test, oxygen arterial pressure (P_aO_2) and mean pulmonary arterial pressure (MPAP) prior to transplantation, type of transplant surgery and duration of ischemia were recorded. Arterial blood gases and MPAP were registered on admission to the Intensive Care Unit (ICU) and at 12, 24, 48 and 72 h. Initially and in unstable situations, we used a fraction of inspired oxygen levels of about 90 to 100%, but it should be decreased as soon as possible to provide arterial oxygen tension of 80 to 110 mmHg. Usually we started mechanical ventilation with A/CMV or SIMV ventilation, a tidal volume of 7 to 10 ml/kg, a respiratory rate of 12 to 15 and with PEEP between 5 to 8 cm H_2O, maintaining a plateau pressure under 35 cm H_2O.

We also analyzed re-implantation injury and LHI incidence in the immediate post-operative period, duration of mechanical ventilation and hypoxia (defined as the number of days that the patient needed more than 30% oxygen), the length of stay at the ICU and mortality.

Lung hyperinflation was defined as mediastinal shift towards the lung graft with flattening of the ipsilateral diaphragm associated with respiratory dysfunction, often weaning difficulty or hemodynamic instability [2]. Reimplantation injury was defined as severe hypoxemia with a P_aO_2/F_iO_2 ratio below 150 mmHg and diffuse radiologic infiltrates in the immediate postoperative period, when other causes of early respiratory failure such as heart failure, rejection or cytomegalovirus-induced pneumonitis had been ruled out [6].

Results are expressed as means ± standard deviation, but some markedly abnormally distributed variables (duration of mechanical ventilation, hypoxemia or ICU stay) were expressed as median (25^{th}–75^{th} percentiles). Fisher's exact test was used to compare qualitative variables, the Mann-Whitney U test for quantitative variables and Friedman ANOVA for analysis of parameter development. The odds ratio with its confidence interval was calculated when the relationship between two qualitative variables was significant. *P* values below 0.05 were considered significant.

Results

The study included 34 patients: 30 men and 4 women with a mean age of 50 ± 3 years. Single lung transplantation was performed in 14 patients, 8 right and 6 left lungs, and 20 bilateral sequential lung transplantations. APACHE II was 19 ± 7 on ICU admission. Nine patients (28%) died in the ICU.

Table 1 Transplant type, previous condition of patients and outcome

Parameter	Single-lung transplant $n=14$	Bipulmonary transplantation $n=20$
Age (years)	53 ± 6	48 ± 8
FVC (%)	36 ± 16	43 ± 12
FEV1 (%)	20 ± 10	22 ± 8
Walking test (m)	178 ± 76	241 ± 114
MPAP (mmHg)	34 ± 10	27 ± 8
Basal PaO2 (mmHg)	64 ± 20	87 ± 79
APACHE II	20 ± 4	19 ± 8
Mechanical ventilation (days)[a]	6 (2–26)	2 (1–33)
Hypoxemia (days)[a]	3 (3–18)	2 (1–3)
ICU stay (days)[a]	11 (6–47)	9 (6–37)
Mortality (%)*	7 (50%)	2 (11%)

*$P<0.017$
[a]Median (25th–75th percentiles)

Patients undergoing double-lung transplantation were younger than those with a single graft, but without statistical significance (Table 1). Preoperative respiratory function test, MPAP, walking-test and basal P_aO_2 were similar in both types of transplant surgeries.

Duration of ischemia was 269 ± 75 min in unilateral transplants and 248 ± 41 min and 403 ± 69 min in bilateral transplants for the first and second grafts, respectively. Duration of mechanical ventilation, hypoxemia and ICU stay were similar.

Mortality of patients who underwent single-lung transplant surgery was higher than in those undergoing double-lung transplantation, showing an odds ratio of 9.0 (1.3–48.7). Of the 14 patients with single-lung transplantation, 7 (50%) died in the ICU; whereas, of the 20 patients with a double graft, only 2 (10%) died, showing a clear difference in early mortality ($P < 0.017$). In the same period the mortality of patients who underwent single-lung transplant surgery in our hospital was 25%, excluding emphysema patients (21%).

Of the 14 patients with a single-lung transplant, 9 (64%) developed LHI. Inter-sex distribution and age were similar between patients with and without LHI (Table 2). Two patients with alpha-1-antitrypsin deficiency underwent single-lung transplantation and presented LHI.

The high proportion of LHI when the graft was left-sided, 5 of 6 (83%) compared with 4 of 8 (50%) on the right, is noteworthy. This difference did not reach statistical significance, owing to the small size of the sample. Ischemia duration (first graft) and APACHE II were similar in both groups.

The incidence of reimplantation injury was similar in both groups: 3 out of 9 (33%) patients with LHI and 2 out of 5 (40%) without LHI. We did not find differences in MPAP, P_aO_2/F_iO_2 and P_aCO_2 between both groups neither on admission to the ICU nor at 12, 24, 48 and 72 h.

Duration of mechanical ventilation and hypoxemia was longer in patients with LHI (Table 2), though without statistical significance. LHI was associated with a significantly longer stay at the ICU, 36 (21–68) days in patients with LHI versus 6 (3–10) days in patients without LHI ($P = 0.011$). Of the 9 patients with LHI, 6 (67%) died but only 1 (20%) of the other 5, although the difference did not reach statistical significance owing to the small size of the sample.

Double-lumen tube was used in six patients: in four patients after onset of LHI and in two patients as prophylaxis, although one patient presented LHI. When double-lumen tube was available, we used high PEEP in the pulmonary graft and, depending on the graft's situation, hypoventilation of the native lung.

The lateral decubitus position was a further technique used when LHI occurred. We used it when hyperinflation of the native lung caused hemodynamic instability by compression of the mediastinal anatomical structures, showing rapid clinical improvements, though with frequent recurrence when the patient was placed in the lateral decubitus position. One of the patients had undergone reduction in contralateral lung volume before undergoing lung transplantation, although LHI was not avoided. One patient required a lung re-transplant owing to poor function of the lung graft compressed by the native lung; the new implant presented the same development as the former with severe LHI, and he died 48 days after receiving the first transplant.

Death of patients with lung hyperinflation were basically caused by infections (Table 3), associated with a long stay at the ICU and difficulty in the weaning process. In all patients, the length of stay at the ICU coincided with the duration of mechanical ventilation.

Table 2 Previous condition and outcome of patients with or without lung hyperinflation

Parameter	Lung hyperinflation $n=9$	No lung hyperinflation $n=5$
Age (years)	55 ± 6	50 ± 6
FVC (%)	33 ± 15	41 ± 19
FEV1 (%)	19 ± 7	21 ± 14
Walking test (m)	167 ± 80	204 ± 85
MPAP (mmHg)	30 ± 6	39 ± 14
Basal PaO2 (mmHg)	70 ± 23	52 ± 4
APACHE II	20 ± 4	18 ± 5
Mechanical ventilation (days)[a]	22 (3–35)	3 (1–5)
Hypoxemia (days)[a]	8 (3–22)	4 (3–6)
ICU stay (days)*[a]	36 (21–68)	6 (3–10)
Mortality (%)	6 (67%)	1 (20%)

*$P = 0.011$
[a]Median (25th–75th percentiles)

Table 3 Causes of death and length of stay at the ICU in LHI patients

Patient number	Cause of death	ICU stay and duration of mechanical ventilation[a]
1	Cerebral death (peroperatory anoxia)	3
2	Sepsis and MOFS	27
3	MOFS with digestive bleeding	48
4	Septic shock	83
5	Pneumonia with MOFS	6
6	Respiratory failure by invasive aspergillosis	23
7	Sepsis with MOFS	20

[a]All these patients had needed mechanical ventilation until death

Discussion

In general, double-lung transplantation is only recommended in patients in whom a single-lung transplant fails to resolve the problem, as in cases of cystic fibrosis or bilateral bronchiectasis. On the other hand, single-lung transplantation is technically more simple and requires shorter surgery and duration of ischemia; thus the prognosis is usually better [7, 8].

Both single and double transplantations are currently indicated for patients with lung emphysema [4]. Initially, it was proposed that patients should receive a double-lung transplant owing to the risk of ventilation/perfusion alterations associated with single-lung transplants. The high vascular resistance and static compliance of the native emphysematous lung lead to a rapid increase in perfusion of the newly-implanted lung, up to 70% of the total, and a decrease in its ventilation, up to 30% of the total [9].

Subsequent studies showed that ventilation/perfusion alterations are not constant and are usually associated with characteristic alterations of the graft [10, 11] such as rejection, infection or reimplantation injury. Furthermore, hyperinflation of the native lung causes graft compression, but only when the function of the newly-implanted lung is impaired.

Results of these studies, added to the lack of donors and greater technical complexity, led to single-lung transplantation being reconsidered in these patients, particularly in older patients [12].

In general, single-lung transplantation offers better early prognosis than double-lung transplantation [13], because surgery is less complex and the duration of ischemia is shorter, but there are some potential complications such as hyperinflation of the native lung, infection and pneumothorax [14]. Pulmonary emphysema is a pathology that can condition development after lung transplantation the most. The mortality rate of our emphysema patients who underwent single-lung transplantation was higher than that of patients who received a double-lung transplant ($P < 0.017$). The risk of death in emphysema patients receiving a single-lung transplant was nine-fold higher than the ones undergoing double-lung transplantation.

The incidence of LHI in our patients was high (64%), similar to that of the Manchester series [2] (44% of patients); nevertheless, other series show lower incidence (31%, 26%) [3, 14]. In our series, patients who developed LHI had a previous slightly lower MPAP, but this parameter proved to be significantly higher in the LHI group in the Manchester study [2]. Patients with an evident obstructive component have a greater tendency towards LHI [2]. Curiously, left implants also predispose to the onset of LHI. When bullous lesions are symmetric, the transplant should be performed, if possible, in the right position since the mediastinal anatomical structures appear to hinder overdistension of the implant [13]. Other techniques described to prevent LHI include giant bulla resection and the use of implants larger than the native lung [15]. Currently, we cannot explain the high incidence of LHI in our patients, because the factors that condition the appearance of this complication are not known; therefore, we ignore if the high incidence could be explained by some uncontrolled parameter.

Some authors observed air trapping with mediastinal shift without clinical changes in their patients [14, 16]. Since in our series, LHI was defined when there were respiratory disfunctions or hemodynamic instability, our patients showed longer duration of mechanical ventilation and a significantly prolonged stay at the ICU. These results are similar to others' series [1, 3].

Conservative treatment basically consists of hypoxemia management. Lateral decubitus position and differential ventilation may also be useful [15, 17].

Lateral decubitus position (with the graft in a non-dependant position) allows reduction in hyperinflated lung ventilation, and has been successfully used by us as an emergency measure in hemodynamic unstable situations. However, it is not effective in the patient's weaning process, since LHI appears again when the patient is placed back into the lateral decubitus position. Despite this fact, we recommend maintaining this position as long as possible to improve the ventilation of the graft and to allow it to reach a good function in the early postoperative period, as well as to avoid hemodynamic alterations secondary to LHI.

Differential ventilation permits controlled decrease in ventilation of the hyperinflated lung [18], but it was never widely applied [14]. It also allows the use of elevated PEEP in the graft, usually restricted in this kind of patient (due to the risk of hyperinflation) and even, depending on the graft's function, hypoventilation of the native lung. One important inconvenience of this procedure is that the endotracheal tube used must have a double lumen. The distal end is usually placed in the native lung and the lateral lumen in the transplanted lung, for suture protection; however, it is even more difficult to maintain the adequate position for a prolonged period of time. Furthermore, as the lumen size of the endotracheal tube is smaller, it easily becomes obstructed by bronchial secretions. To maintain the tube in the correct position, deep sedation is mandatory and even on occasion muscle relaxation, both of which hinder the weaning process. Some authors also describe the use of tracheal cannulas which greatly improve tube management [19]. However, differential ventilation is an efficacious maintenance technique but not the solution to the problem, because when the patient breathes spontaneously, a differential ventilation is not possible.

The surgical treatment proposed in these cases is reduction of the native lung; however, the common problem is that the native lung is essential for survival. Consequently, manipulation of the hyperinflated lung may be even more detrimental for the patient. In exceptional cases bulla resection, lobectomy or even pneumectomy may aid management of the patient [15, 20]. Retransplantation of the implanted lung is an additional option and could be efficacious, although it did not change the development in our patient. Transplant of the contralateral lung constitutes the third option, although it may only be feasible late in the postoperative development of patients with chronic LHI [2].

The causes of mortality in our patients were fundamentally due to infection. LHI rarely causes death, but leads to prolonged mechanical ventilation, and longer stay at the ICU, with an increased incidence of infection-related complications, which finally leads to death. Patients 1 and 5 had short stays, and so LHI probably did not influence their result. Likewise, patient 6 showed an invasive aspergillosis, which could in itself account for its development.

Our study is limited by its small number of single transplant patients, but even with such a small sample, we have obtained significant differences in terms of the length of stay at the ICU and mortality. We believe that if the sample had been larger, we would have observed an even greater difference between both groups of patients, such as, for example, in the duration of mechanical ventilation. We therefore propose a new perspective when dealing with patients undergoing lung transplantation for emphysema.

In conclusion, in our patients with emphysema the single-lung transplant has a worse prognosis than the double-lung transplant, with a 9-fold higher mortality. Moreover, LHI is a common event in single-lung transplantation in emphysema patients. It is difficult to predict which patients will develop LHI, and when it occurs it leads to prolonged mechanical ventilation and, consequently, a longer stay at the ICU. From our results, we might conclude that double-lung transplantation should be performed in these patients whenever possible.

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