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The Current Status of Lung Transplantation

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Key words: Lung transplantation – pulmonary diseases – donor shortage – bronchiolitis obliterans – chronic rejection.

Schlüsselwörter: Lungentransplantation – Lungenkrankheiten – Organspendermangel – Bronchiolitis obliterans – chronische Organabstoßung.

Summary: Background: (Heart-)Lung transplantation has become an accepted surgical therapy for selected patients suffering from a variety of (cardio-)pulmonary diseases.
Methods: The objective of this paper is to give an overview on the international knowledge, trends and results of lung transplantation, including the experience with 72 lung and heart-lung transplantations at the University Hospital of Leuven, Belgium is described.
Results: According to the International Registry for Heart and Lung Transplantation, the number of lung and heart-lung transplantations has plateaued over the last few years. Donor age in both types of transplants is still increasing with less suitable donor organs available. Therefore, alternative treatment modalities such as lung volume reduction surgery for patients suffering from emphysema and pulmonary tromboendarterectomy for patients with pulmonary hypertension secondary to chronic pulmonary emboli, are now receiving renewed interest. Overall 5-year survival following pulmonary transplantation is close to 40 %. Morbidity of chronic immunosuppression and late graft failure from chronic rejection presenting as bronchiolitis obliterans syndrome remain the major drawbacks of this surgical treatment.
Conclusions: A greater donor supply is necessary until xenotransplantation becomes a practical reality. Future efforts to improve the results of lung transplantation should be directed towards both a better control of immune response of the allograft and an effective treatment for bronchiolitis obliterans.

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Aktueller Stand der Lungentransplantation

Zusammenfassung: Grundlagen: Die (Herz-)Lungentransplantation ist heute eine allgemein anerkannte Form der chirurgischen Behandlung vieler kardiopulmonaler Erkrankungen.
Methodik: Anhand einer Übersicht mit Einbeziehen der Erfahrung des Universitätskrankenhauses Leuven (Belgien) mit 72 Lungen- und Herz-Lungentransplantationen werden der aktuelle Stand der internationalen Kenntnisse, die Trends und Resultate der Lungentransplantation dargestellt.
Ergebnisse: Laut Bericht des „International Registry for Heart and Lung Transplantation" hat die Zahl der Lungen- und Herz-Lungen-Transplantationen in den letzten Jahren ein Plateau erreicht. Das Alter der Spender in beiden Transplantationstypen steigt, die Zahl der brauchbaren Organe sinkt. Alternative Behandlungsverfahren gewinnen an Bedeutung: Patienten mit Emphysem werden einer Lungenvolumenreduktionschirurgie, Patienten mit pulmonalem Bluthochdruck nach Lungenembolie einer pulmonalen Thrombendarterektomie zugeführt. Die 5-Jahres-Überlebensrate nach Lungentransplantation erreicht knapp 40%. Die Morbidität der chronischen Immunsuppression und der späte Organverlust wegen chronischer Organabstoßung, die sich als Bronchiolitis-obliterans-Syndrom präsentiert, bleiben das Hauptproblem dieser chirurgischen Behandlung.
Schlußfolgerungen: Ein größeres Spenderaufkommen ist so lange notwendig, bis die Xenotransplantation zu einer praktischen Realität wird. Zukünftige Bemühungen zur Verbesserung der Resultate der Lungentransplantation sollten sich der besseren Kontrolle der Immunenreaktion auf das Allotransplantat sowie der effektiven Behandlung der Bronchiolitis obliterans widmen.

Introduction

Since the 1st long-term clinical successes in heart-lung transplantation for pulmonary vascular disease in 1981 at Stanford (63), in single lung transplantation for pulmonary fibrosis in 1983 (74), and in double lung transplantation for chronic obstructive lung disease in 1986 (17) both at Toronto, replacement of the lung has now become an accepted treatment modality for carefully selected patients suffering from a variety of end-stage lung diseases. In the 1990, lung transplantation has come of age. Activity has expanded rapidly all over the western world and results have been good (38). However, the limitations have become apparent too.

This article will review the current status of lung transplantation with an emphasis on the obstacles, the indications, the international and own center experience, and the drawbacks of lung transplantation.

Current activities

According to the International Registry for Heart and Lung Transplantation, the number of heart-lung transplantations performed each year has peaked in 1989 and has plateaued since then. Isolated lung transplantation has enjoyed continued growth until 1995 and also seems to be plateauing now (38). More than 2400 heart-lungs and nearly 8000 single and double lungs have been transplanted worldwide at the end of 1997. Donor age in all types of transplants is still increasing with less suitable donor organs available.

Indications and recipient selection

Lung and heart-lung transplantations have rapidly evolved to offer hope of a longer and better quality of life to patients suffering from end-stage diseases of the lungs, or lungs and heart, for whom no other medical or surgical therapies were formerly available. This treatment in its various forms represents a therapy of last resort. Patients should have a life expectancy of less than 12 to18 months when placed on the waiting list.

Table 1. Recipient selection – general guidelines.

Clinically and physiologically severe disease
Medical therapy ineffective or unavailable
Limited life expectancy, usually less than 12 to 18 months when listed
Ambulatory with rehabilitation potential
Acceptable nutritional status, 80 to 120 % of body weight
Satisfactory psychosocial profile and support system

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Table 2. Recipient selection – contraindications.

Acutely ill or unstable clinical status
Uncontrolled or untreatable pulmonary or extrapulmonary infection
Previous malignancy (skin tumors excepted)
Significant dysfunction of other vital organs, especially liver, kidney, and central nervous system
Significant coronary disease or left ventricular dysfunction (heart-lung excepted)
Active cigarette smoking
Drug or alcohol dependency
Unresolvable psychosocial problems or noncompliance with medical management

Most lung transplant programs screen referrals and select candidates according to a strict protocol. General guidelines for recipient selection and contraindications for transplantation were recently reviewed by an International Coordinating Committee (54) and are summarized in Tables 1 and 2, respectively. Other factors such as ventilator dependence (29), previous cardiothoracic surgery (25, 26), and preexisting medical conditions like hypertension, diabetes mellitus, and osteoporosis (1) that will be aggravated by the post-transplantation medical regimen, must be integrated individually.

Typical age restrictions have been less than 45 to 50 years for heart-lung transplantation, less than 50 to 55 years for bilateral lung transplantation, and less than 60 to 65 years for single lung transplantation.

The indications for lung and heart-lung transplantation have spanned the spectrum of lung diseases, but the most common diagnoses have been chronic obstructive pulmonary disease (COPD), α_1-antitrypsin deficiency emphysema, idiopathic pulmonary fibrosis, cystic fibrosis, primary pulmonary hypertension, and Eisenmenger's syndrome (Table 3). Less common indications have included bronchiectasis, sarcoidosis, lymphangioleiomyomatosis, histiocytosis X, and (post-transplant) bronchiolitis obliterans of the lung.

Because of donor shortage and long waiting times for individuals listed for transplantation, alternative surgical treatment modalities such as lung volume reduction surgery for patients suffering from emphysema (18, 64, 90) and pulmonary thromboendarterectomy for patients with pulmonary hypertension secondary to chronic pulmonary emboli (42), have recently gained renewed interest.

Table 3. Indications for lung and heart-lung transplantation.*

	Transplant Procedure		
Diagnosis	**Heart-Lung (%)**	**Double Lung** (%)**	**Single Lung (%)**
Chronic obstructive pulmonary disease	3.8	18.2	44.1
α_1-Antitrypsin deficiency emphysema	2.3	10.5	11.1
Idiopathic pulmonary fibrosis	2.7	7.5	20.9
Cystic fibrosis	15.6	33.6	2.0
Primary pulmonary hypertension	25.9	10.2	5.2
Congenital heart disease	27.7		
Retransplantation	2.8	2.2	3.0
Other	19.2	17.7	13.7

* Data from the Registry of The International Society of Heart and Lung Transplantation, 15th Annual Report, July 1998 (38).

** Includes both en bloc double lung and bilateral sequential lung transplants.

Timing and choice of the procedure

Transplantation is appropriate when other therapeutic options have failed and when the patient's prognosis is expected to be improved by the procedure. Quality of life is the prime motivation for transplantation for many patients, but prognosis should be the main determinant of timing. Disease-specific guidelines for timing of referral are summarized in Table 4 (54).

Heart-lung and lung transplantation have been performed for most end-stage lung diseases. Heart-lung transplantation should be reserved for patients who cannot be treated by lung transplantation alone. The compulsory indications are Eisenmenger's syndrome with a surgically uncorrectable anomaly or end-stage lung disease with concurrent severe cardiac disease. Severe right ventricular failure, as is the case in patients with primary or secondary pulmonary hypertension, has been reversible after isolated lung transplantation, and, theoretically, Cor pulmonale is not a contraindication to this approach. Therefore, single lung transplantation, sometimes in combination with a repair of the congenital cardiac defect, has been advocated in patients with pulmonary hypertension, mainly in North America because of the lack of suitable heart-lung blocks as a result of many heart transplantation programs in the country (3, 58). In Europe, however, many transplantation centers still prefer heart-lung or double lung transplantation in patients with Eisenmenger's syndrome or primary pulmonary hypertension because early postoperative management after single transplantation in these patients can be very difficult and any complication in the transplanted lung can be accompanied by severe gas exchange disturbances because of ventilation-perfusion mismatching between the native and transplanted lung (7, 50).

Bilateral lung replacement is mandatory in patients with generalized bronchiectasis or other forms of chronic pulmonary infection such as cystic fibrosis or Kartagener's syndrome. Although heart-lung transplantation has been performed initially,

Table 4. Guidelines for timing referral.

Emphysema	Postbronchodilator FEV_1 < 25 % predicted Hypoxia at rest: PaO_2 < 55 to 60 mm Hg Hypercapnia Secondary pulmonary hypertension Clinical course: rapid rate of decline of FEV1 or life-threatening exacerbations
Cystic fibrosis	Postbronchodilator FEV_1 < 30 % predicted Hypoxia at rest: PaO_2 < 55 mm Hg Hypercapnia Clinical course: increasing frequency and severity of exacerbations
Idiopathic pulmonary fibrosis	VC, TLC < 60 to 65 % predicted Hypoxia at rest: PaO_2 < 55 mm Hg Secondary pulmonary hypertension Clinical, radiographic, or physiologic progression on medical therapy
Primary pulmonary hypertension	New York Heart Association functional class III or IV Mean right atrial pressure > 10 mm Hg Mean pulmonary arterial pressure > 50 mm Hg Cardiac index < 2.5/min/m^2

bilateral lung transplantation has become the procedure of choice in most centers. Bilateral lobar transplantation from cadaveric (67) or living-related (68) donors has recently been advocated in small recipients because there is little chance of obtaining size-matched cadaveric donor organs.

Bilateral or single lung transplantation can be performed for most other lung diseases. In patients with emphysema, pulmonary function test results have, not surprisingly, been better after bilateral lung transplantation, but the difference in exercise capacity has been less dramatic (30, 73). Bilateral lung recipients have had a slightly superior actuarial survival as these patients have more functional lung reserve once bronchiolitis obliterans syndrome will develop (71). Bilateral transplantation also allows greater latitude for donor-recipient matching than unilateral transplantation (87). Single lung transplantation in these patients, however, is a simpler and shorter operation with a lower perioperative complication rate than bilateral lung transplantation (53). The emphysematous native lung, however, has a propensity to become hyperinflated if the lung compliance decreases in the allograft as a result of the development of bronchiolitis obliterans (49, 66). Infectious complications in the native lung, especially tuberculous and fungal, are not infrequent and may be very difficult to treat in patients with chronic immunosuppression (23, 66). Most centers, therefore, will offer bilateral lung transplantation to younger patients (< 50 years), especially those with α_1-antitrypsin deficiency emphysema, while single lung transplantation is reserved for older patients, mostly smoking-induced emphysema.

Single lung transplantation has been the standard procedure in patients with idiopathic pulmonary fibrosis (74). The low lung compliance and high vascular resistance of the remaining native lung preferentially direct both ventilation and perfusion to the transplanted lung.

The organ donor

The shortage of donor organs has been one of the major deterrents to solid organ transplantation. Brain death may rapidly result in injury to the lungs from aspiration, infection, neurogenic edema, or contusion following trauma. In our experience, only 10 % of all potential organ donors still have lungs suitable for transplantation compared to 97 % for kidneys, 64 % for liver, and 60 % for heart (78).

In order to alleviate this critical organ shortage, there is a growing interest in increasing the potential donor pool by turning to marginal donors (72) or alternative sources such as the use of lobar (67) or split (19) transplants, living-related donors (68), or occasionally, the use of lungs from a circulation-arrested cadaver (52).

General exclusionary criteria for cadaveric organ donation include untreated septicemia, viral hepatitis, HIV infection, intravenous drug abuse, and malignancy (except primary brain tumor). Typical lung donor criteria are summarized in Table 5. Direct inspection of both organs at the operating table remains the final step in assessing the suitability of the donor lungs (70). In our experience, 21% of donor organs accepted by telephone were still turned down at the time of organ retrieval (80).

Donor-recipient matching is primarily based on ABO blood group compatibility and size as estimated from predicted lung volumes. A CMV-negative organ should be transplanted preferentially into a CMV negative recipient, although CMV mismatching is not a contraindication to transplantation in most centers. A prospective crossmatch between donor and recipient blood is mandatory in patients with known HLA antibodies.

Table 5. Guidelines for donor selection.

Age ≤ 60 years
No history of significant lung disease
Limited cumulative cigarette smoking history
Clear lung field on chest radiograph
Adequate oxygenation (PaO_2 > 300 mm Hg at FiO_2 = 1.0 and PEEP = 5 cm H_2O)
No gross abnormalities on bronchoscopic inspection
Satisfactory appearance on external examination

Lung preservation

In the transition from the donor to the recipient, the donor lung is subjected to 2 major insults, ischemia and reperfusion. The goal of preservation is to retain the morphologic and physiologic integrity of the lung. Numerous factors such as the composition of the preservation solution, temperature, lung volume, oxygen concentration, and many pharmacologic additives have been tested experimentally (46), but few have been investigated clinically. Several approaches to lung preservation have been used clinically, but single flush perfusion of the lungs either with a cold crystalloid solution (Euro-Collins [15], University of Wisconsin [37] or Low Potassium Dextran [69]) or with modified blood (83) has become the standard preservation technique with good results. Current methods are satisfactory for ischemic times up to 6 to 8 hours, but primary graft failure even after a short ischemic period might still be a significant problem (12).

After dissection and systemic anticoagulation with heparine, a bolus of a prostanoid is administered for pulmonary vasodilation followed by cold flush of heart and lungs via a catheter in the ascending aorta and pulmonary trunk, respectively. Both thoracic organs are then further cooled with iced saline slush. In case of isolated lung transplantation, the heart is excised first leaving a cuff of left atrium attached to both lungs. The double lung block is then extracted with the trachea stapled following inflation of both lungs. It is then separated into left and right lung by midline division of the posterior pericardium, the left atrial cuff and the pulmonary trunk at its bifurcation. Finally, the left main bronchus is doubly stapled and transected keeping both lungs well inflated during the ischemic interval (Fig. 1). Each lung is submerged in the preservation solution, packed in sterile bags, and transported in an ice box (70).

The operation

Heart-lung transplantation is performed through a median sternotomy. After institution of cardiopulmonary bypass, the heart is extracted first followed by excision of both lungs. A bilateral pericardial tunnel is created posteriorly to the phrenic nerve. The heart-lung block is sewn in by anastomosing the donor's and recipient's trachea, right atrium, and ascending aorta (41).

A standard posterolateral thoracotomy incision is made for single lung transplantation (16, 32). With ventilation to the contralateral lung, the pulmonary artery of the lung to be excised is clamped to assess the possibility of cardiopulmonary bypass, which is always on standby (24, 36). Bypass has rarely been needed in recipients with obstructive lung disease, but is more

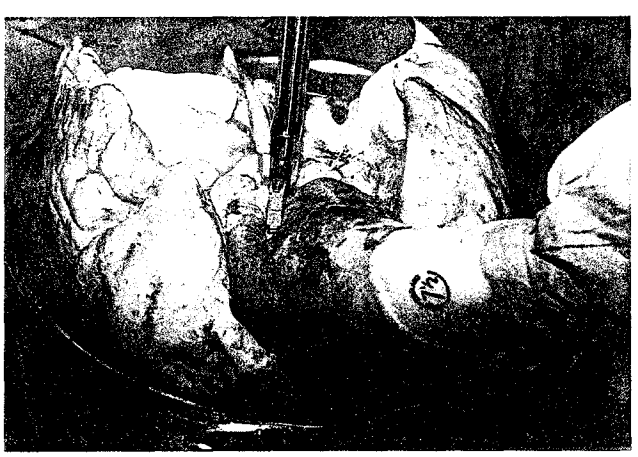

Fig. 1. The double lung block is divided by stapling the left main bronchus keeping both lungs well inflated during preservation.

Fig. 2. Peroperative view after double lung transplantation performed through a bilateral anterior thoracotomy.

frequently required in patients with restrictive lung disease, especially in the presence of pulmonary hypertension. The native lung is extracted and the donor lung is implanted by three consecutive anastomoses: bronchus, pulmonary artery, and left atrial cuff at the confluens of both pulmonary veins.

Replacement of both lungs was originally performed en bloc through a median sternotomy by anastomosing the trachea, left atrium, and pulmonary trunk (59). Because of the high incidence of, sometimes severe airway complications (17), this technique has now been abandoned by most transplant teams in favor of the separate and sequential implantation of left and right lung as in single lung transplantation (6, 27, 57). This operation is performed through a bilateral anterior thoracotomy with transverse division of the sternum and, theoretically, can be performed without the use of cardiopulmonary bypass (Fig. 2).

The bronchial anastomosis is the most delicate because of the relative ischemia of the donor bronchus. Most teams will, therefore, cover the airway anastomosis with viable tissue (e.g. peribronchial fat, pericardial flap, intercostal muscle bundle, or even omentum [16]). Some teams prefer to revascularize the airways by anastomosing the bronchial artery/-ies to the recipients mammary artery or a venous graft, both in single lung (20, 88) and in en bloc double lung (60) transplantation with excellent results. This technique, however, may prolong operative time and therefore graft ischemia and is certainly technically more demanding. The hope of avoiding long-term problems such as chronic rejection or bronchiolitis obliterans by revascularizing the airways has not yet been demonstrated (60).

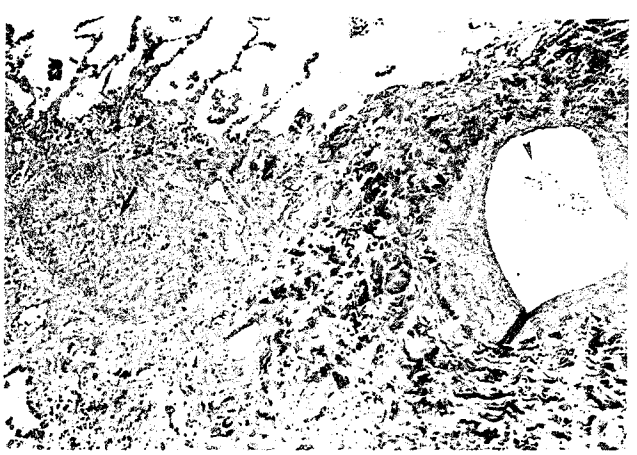

Fig. 3. Histologic appearance of bronchiolitis obliterans. The bronchiolus (arrow) is completely obstructed with fibrous tissue, the arteriolus (arrowheads), however, remains patent.

Outcome

Survival

Actuarial survival is well known from the International Registry for Heart and Lung Transplantation (ISHLT) (38). Survival results after lung transplantation are still lieing behind those of heart transplantation. The overall 5-year survival is reported to be about 40 %. Overall, there has been no significant difference in survival between single and bilateral lung transplantation, but en bloc double lung transplantation and heart-lung transplantation have had lower survival rates than single or bilateral transplantations. For COPD and pulmonary hypertension the best operation is still a matter of debate, but no statistically significant advantage has been perceived for single versus bilateral transplantation for either of these diagnoses. The difference in survival amongst the diagnoses during the first 3 months reflects the higher perioperative mortality that accompanies the operation and the postoperative complications in the more complex diseases like primary pulmonary hypertension, idiopathic pulmonary fibrosis, and cystic fibrosis. According to the ISHLT registry, the following factors were associated with a significantly increased odds ratio for death in the first year after lung transplantation: recipient ventilator or ICU dependent, recipient diagnoses other than COPD, recipient age greater than 40 years or retransplantation (38).

Infection and early graft failure have been the main causes of early death, whereas chronic allograft rejection and infection resulting from augmented immunosuppression have been the principal reasons for late death (10, 38).

A recent analysis reported data to support a survival benefit of lung transplantation for patients with cystic fibrosis and interstitial pulmonary fibrosis but not for patients with emphysema (39). This study suggested that lung transplantation for patients with emphysema is difficult to justify on the grounds of survival considerations alone. It has been suggested, therefore, that allocation of pulmonary allografts in terms of total waiting time should consider redressing the balance in favor of those with the most life-threatening pulmonary conditions (21). Lung volume reduction surgery has recently altered the management and referral patterns of emphysema patients with significant lung dysfunction (18, 64). Although the degree of improvement is not as great as with transplantation (30), the operative mortality of this procedure is probably lower avoiding the side effects of chronic immunosuppression. The relative roles of volume reduction surgery and transplantation in emphysema patients remain to be properly defined. There might still be a selected subgroup of emphysema patients (e.g with hypercapnia or pulmonary hypertension) for whom the prognosis is improved by transplantation (21).

Complications

Anastomotic airway dehiscence resulting from bronchial ischemia was the surgical Achilles' heel of lung transplantation in the initial experience (16). The prevalence of airway complications – dehiscence, stenosis, and bronchomalacia – nowadays, has been reported to be 10 to 20 %, but the associated mortality has been very low (22, 86). Anastomotic technique, perioperative corticosteroid treatment, lung preservation technique and ischemic time, rejection and infection have been considered potentially important influences. Vascular anastomotic complications following lung transplantation are rare but carry a high mortality (13, 33).

Rejection is the single most important limitation to better medium and long-term survival. Despite current triple drug immunosuppressive regimens (cyclosporine or tacrolimus [44], azathioprine, and steroids), the incidence of acute rejection is high (45, 76), and, while acute rejection is infrequently fatal, it has been repeatedly identified as the principal risk factor for chronic rejection (4, 31, 48). The prevalence of chronic rejection

presenting as bronchiolitis obliterans syndrome (BOS) (40) is reported to be around 50 % to 60 % in major series (62, 71). Chronic allograft dysfunction is a clinicopathologic syndrome that is characterized histologically (Fig. 3) by obliteration of the smaller airways with fibrous tissue (89) as diagnosed on transbronchial biopsies (75) and physiologically by worsening airflow limitation (40). Prevention of BOS is the goal, but current strategies have not shown much promise (76). Recently, our group has reported on the measurement of exhaled NO, a marker of airway inflammation, as a tool for monitoring chronic rejection in lung transplant recipients (81). BOS has been treated by augmenting or modifying the immunosuppressive regimen (8, 65), by total lymphoid irradiation (77), or, occasionally by retransplantation (84). Results following retransplantation have been poor compared to those of primary transplantation with a 3-year survival in a collected series of 230 patients of only 33 % (56). In view of the scarcity of lung donors and the poor results, patient selection for retransplantation should remain restricted to good candidates.

Infection has been a leading cause of early and late morbidity and mortality after transplantation. The allograft has been the most common location for infection, but the native lung has also been a site of infection after single lung transplantation (66). The spectrum of pathogens has included bacteria, viruses, fungi, and protozoa, but bacterial pneumonia, especially with Pseudomonas and Staphylococcus species, CMV pneumonitis, and invasive aspergillosis have been the most problematic (23).

The prevalence of lymphoproliferative disorders following lung transplantation has been approximately 6 % and has been closely related to Epstein-Barr virus infection (2). Regression of this disease may follow a reduction in immunosuppression with an increased risk of acute rejection.

Recurrence of the primary disease in the allograft has been reported mainly in patients transplanted for sarcoidosis (43), lymphangioleiomyomatosis (55), and desquamative interstitial pneumonitis (82).

As other solid organ recipients, lung transplant patients have a panoply of other medical and surgical problems (85) that are side effects of chronic immunosuppression or general medical problems that are aggravated by the post-transplantation regimen, including systemic hypertension, deep venous thrombosis and pulmonary embolism (47), osteoporosis (1), obesity, mild to moderate renal insufficiency, diabetes mellitus, anemia, gastroparesis (5), hypercholesterolemia, cholecystitis, and diverticulitis. This adds substantially to the morbidity associated with lung transplantation in some recipients.

Functional improvement

Cardiopulmonary function is dependent on the underlying disease and the type of transplant. In patients with idiopathic pulmonary fibrosis following single lung transplantation, the preponderance of lung function (ventilation and perfusion) is contributed by the allograft resulting in a significant improvement in vital capacity from ± 40 to ± 70 % of predicted value and diffusing capacity from ± 30 to ± 60 % of predicted value at 1 year after the transplantation (35).

In patients with cystic fibrosis following bilateral lung or heart-lung transplantation, the mean FEV1 around 20 % of the predicted normal value before transplantation will increase to approximately 70 % by 3 months after transplantation (28).

In patients with COPD and α_1-antitrypsin deficiency emphysema, the mean FEV1 has typically been ± 20 % predicted and will reach 45 to 60 % of the predicted value following single lung transplantation (53, 73). The pulmonary allograft provides most of the function, usually receiving 70 to 80 % of the perfusion and 60 to 80 % of the ventilation. After bilateral lung or heart-lung transplantation, the FEV_1 has been in the (nearly) normal range. Exercise capacity, as measured by the 6-min walking distance has been modestly, though not always statistically, better after bilateral lung and heart-lung transplantation than after single lung transplantation (53, 73).

In patients with pulmonary hypertension, the hemodynamic profile will return to normal after heart-lung or bilateral lung transplantation and will improve dramatically after single lung transplantation with good recovery of right ventricular dysfunction (58). This last type of transplant creates a relative ventilation-perfusion imbalance with the ventilation evenly divided between the native lung and the allograft because of similar compliance but with the preponderance of perfusion (> 80 %) directed to the allograft because of the high vascular resistance in the native lung (3, 58). This may result in severe oxygenation difficulties in case of diminished ventilation of the allograft due to e.g. bronchiolitis obliterans.

Exercise capacity improves after all forms of lung transplantation to only 40 to 60% of the predicted normal value. These limitations are not cardiac or ventilatory but rather peripheral as a re-

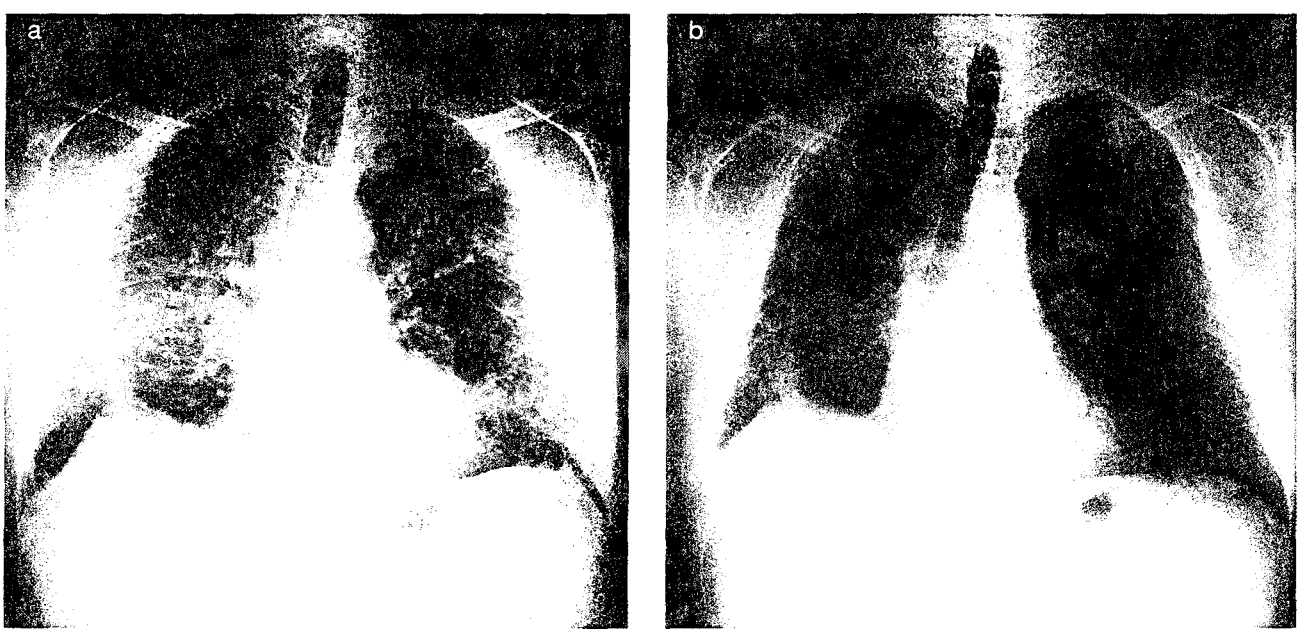

Fig. 4. Chest X-ray in a 50-year old male patient with idiopathic pulmonary fibrosis before (a) and 1 month after (b) left single lung transplantation. The fibrotic native lung is smaller when compared to the transplanted lung.

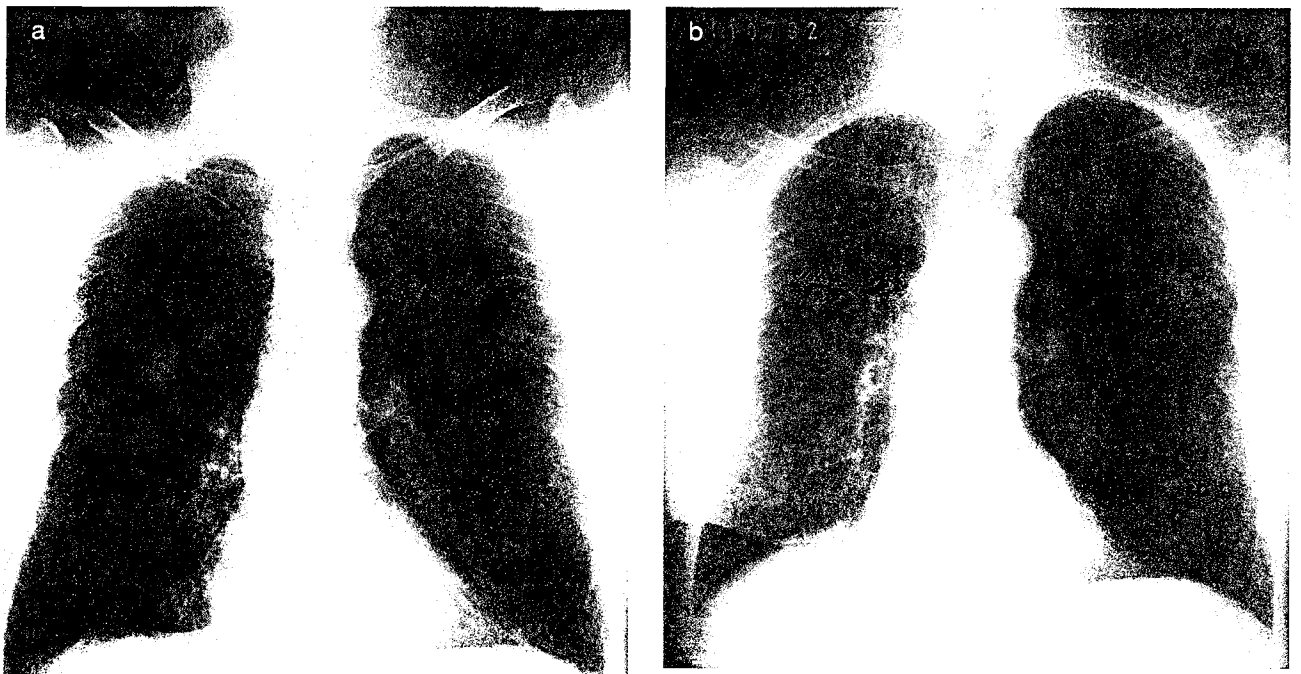

Fig. 5. Chest X-ray in a 45-year old male patient with α_1-antitrypsine deficiency emphysema before (a) and 6 months after (b) right single lung transplantation. The hyperinflated native lung is larger when compared to the transplanted lung.

sult of skeletal muscle deconditioning, atrophy or steroid myopathy (51).

Quality of life

Several studies have documented a significant improvement in both overall and health related quality of life starting the first few months after lung transplantation, including perceptions of physical and social function, role activity, and general and mental health (9, 11, 14, 34, 61). This improvement may again deteriorate when complications such as chronic rejection occur.

Decisions on whether to offer lung transplantation or volume reduction surgery to patients with emphysema are complex and must take into account not only the duration of expected survival, but also quality of life (39).

Experience at the University Hospitals Leuven

The transplant program at the University Hospitals Leuven, Belgium was initiated at the beginning of 1991. Our initial experience with isolated lung transplantation has been published previously (79). Between July 1991 and October 1997, 81 patients were listed for transplantation. 9 patients (11 %) have died before a suitable organ became available: pre-transplant diagnosis was idiopathic pulmonary fibrosis (n = 4), primary pulmonary hypertension (n = 3), cystic fibrosis (n = 1), and Eisenmenger's syndrome (n = 1). In the same period, 72 patients, 38 males and 34 females, have been transplanted. The mean (± SEM) age at the time of transplant was 45 ± 1 years. The arterial oxygen tension at rest breathing room air (n = 54) was 55 ± 2 mm Hg. The 6-minutes walking distance (n = 58) was 232 ± 13 meters. The indication for transplantation is listed in Table 6. 38 patients were transplanted with a single lung (Fig. 4 to 6), 15 with a bilateral lung (Fig. 7) and 19 with a heart-lung.

Table 6. Diagnosis and type of transplantation in 72 recipients at the University Hospitals Leuven.

Diagnosis	Single Lung	Double Lung	Heart-Lung	Total
Emphysema	23	6	1	30
Bronchiectasis (idiopathic)		1		1
Idiopathic pulmonary fibrosis	9			9
Sarcoidosis	3	1		4
Histiocytosis X	1			1
Pulmonary hemosiderosis	1			1
Cystic fibrosis		6		6
Primary pulmonary hypertension	1	1	6	8
Chronic pulmonary emboli			2	2
Eisenmenger's syndrome			10	10
Total	38	15	19	72

Table 7. Cause of death in 72 lung transplant recipients at the University Hospitals Leuven.

Diagnosis	n
Chronic rejection	12
Systemic infection (i.e. Aspergillus)	12
Primary organ failure	3
Colonic perforation	3
Neurologic complication	2
Bronchial anastomotic dehiscence	2
Perioperative bleeding	2
Pulmonary embolus	1
Sudden death	1
Total	38

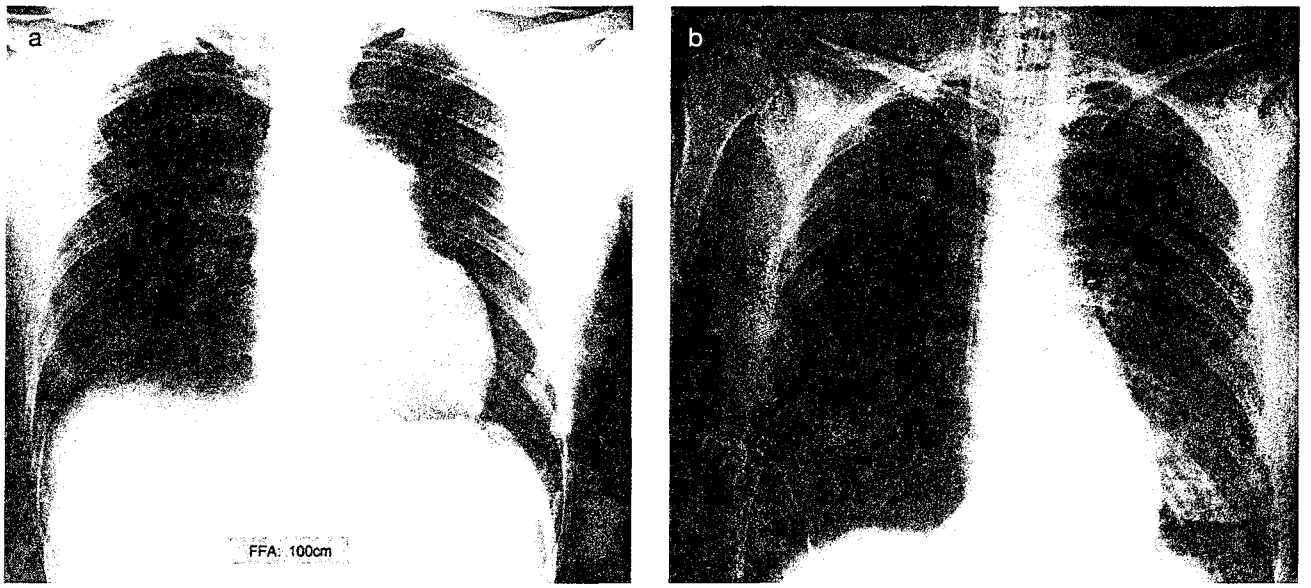

Fig. 6. Chest X-ray in a 29-year old female patient with primary pulmonary hypertension before (a) and 2 weeks after (b) left single lung transplantation. The dilated right heart has regained normal radiographic appearance.

Lungs were retrieved from 72 donors, 39 males and 33 females with a mean age of 33 ± 1 years. Arterial oxygen tension on a FiO_2 of 1.0 and PEEP + 5 cm H_2O was 511 ± 9 mm Hg. Cause of death in the donors was cranio-cerebral trauma (n = 44), spontaneous intracranial bleeding (n = 26), intracerebral tumor (n = 1), and asphyxia (n = 1). Donors were located in Belgium (n = 37), Germany (n = 30), Austria (n = 3), the Netherlands (n = 1) and outside Eurotransplant (n = 1).

The mean time on the waiting list for a suitable organ to become available was 152 ± 22 days for a single lung, 265 ± 60 days for a bilateral lung, and 283 ± 47 days for a heart-lung; $p < 0.05$ single lung versus heart-lung (Fig. 8 A). Waiting time was 196 ± 28 days for patients with blood group 0 (n = 31), 202 ± 35 days for blood group A (n = 30), 492 ± 97 days for blood group B (n = 5), and 85 ± 37 days for blood group AB (n = 6); $p < 0.05$ blood group B versus other blood groups (Fig. 8 B).

The overall mean ischemic time was 265 ± 9 min. It was 252 ± 9 min for single lung transplant, 332 ± 26 min and 418 ± 16 min for the 1st and 2nd lung, respectively, in bilateral lung transplant and 240 ± 16 min in heart-lung transplant ($p < 0.05$ for single lung and heart-lung versus double lung). Cardiopulmonary bypass was used in 10/38 single lung transplants and in 10/15 bilateral lung transplants.

The overall incidence of bronchiolitis obliterans syndrome in patients surviving longer than 6 months following the transplant was 45%. The freedom from BOS in our experience was 83 % at 1 year, 68 % at 2 years, and 39 % at 3, 4, 5, and 6 years following the transplant (Fig. 9).

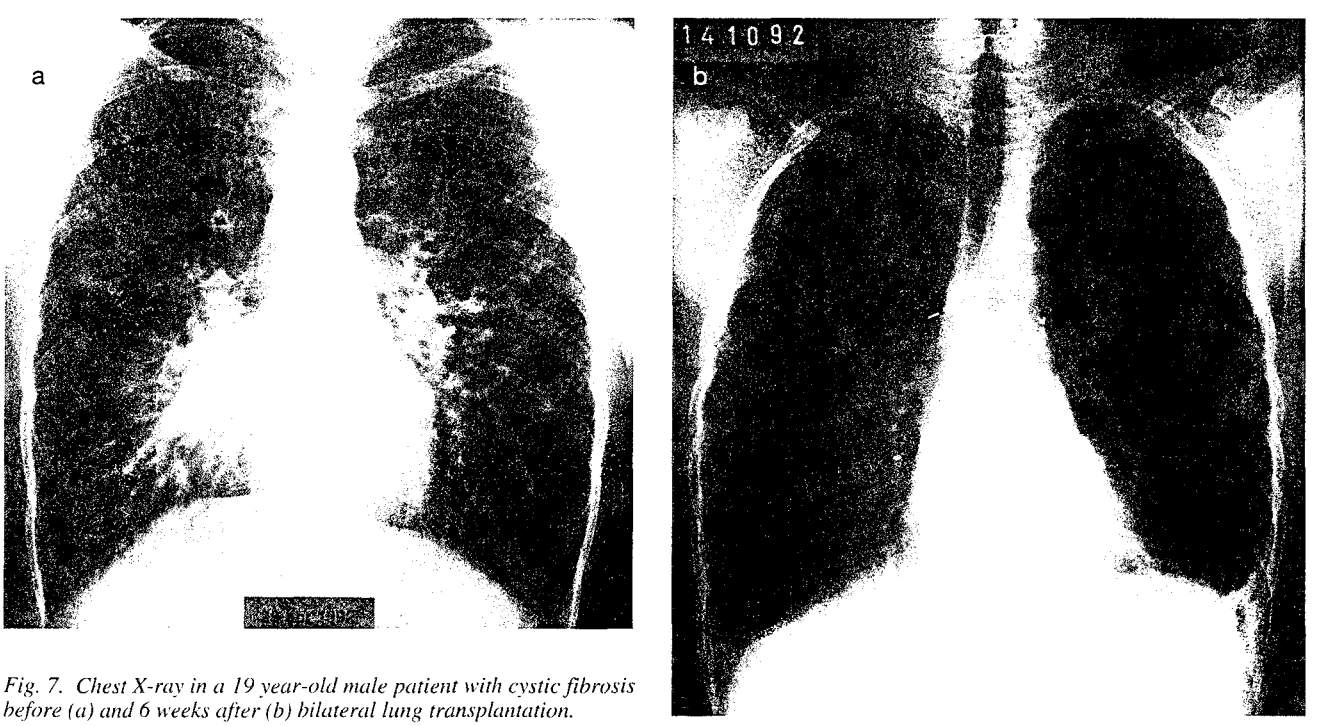

Fig. 7. Chest X-ray in a 19 year-old male patient with cystic fibrosis before (a) and 6 weeks after (b) bilateral lung transplantation.

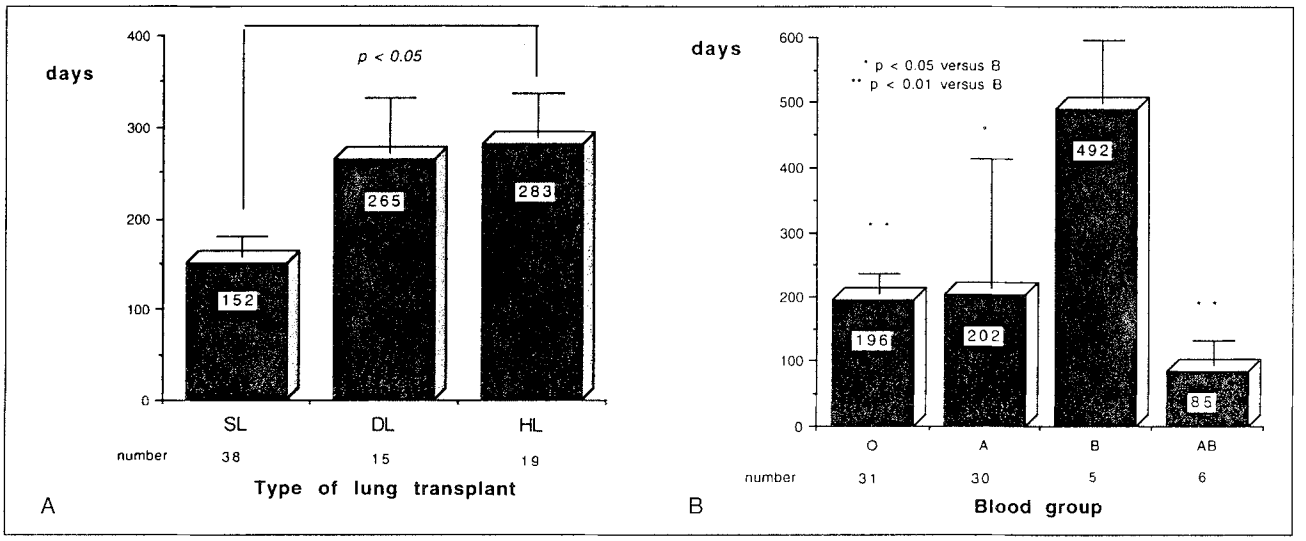

Fig. 8. Mean time on the waiting list in 72 recipients according to type of transplant (A) and blood group (B). SL: single lung; DL: double lung; HL: heart-lung.

Overall 3- and 5-year survival was 43 % and 39 %, respectively (Fig. 10). The early and late causes of death in our patients are listed in Table 7. Survival at three years was 42 % for single lung recipients (n = 10), 29 % for double lung (n = 1), and 61 % for heart-lung (n = 6) (Fig. 11). This difference in survival can be partially explained by a high incidence of systemic infections, especially with Aspergillus, in our isolated lung transplant patients during our initial experience. This problem has been significantly reduced since we now routinely administer nebulized amphotericine in all recipients during the first postoperative weeks. As a result, overall 3-year survival has improved with longer experience (36 % in patients no 1 to no 36 versus 52 % in patients no 37 to no 72; $p < 0.05$) (Fig. 12).

Conclusions

In recent years enormous progress has been made in lung transplantation for patients with end-stage pulmonary disease. Nonetheless major problems persist and will require a solution if lung transplantation is to advance beyond the stage of technical achievement. A greater donor supply is necessary until xenotransplantation becomes a practical reality. Chronic rejection remains the most frequent direct or indirect cause of late mortality. A better understanding of the pathogenesis of bronchiolitis obliterans will help define strategies for prevention and possibly treatment.

Addendum

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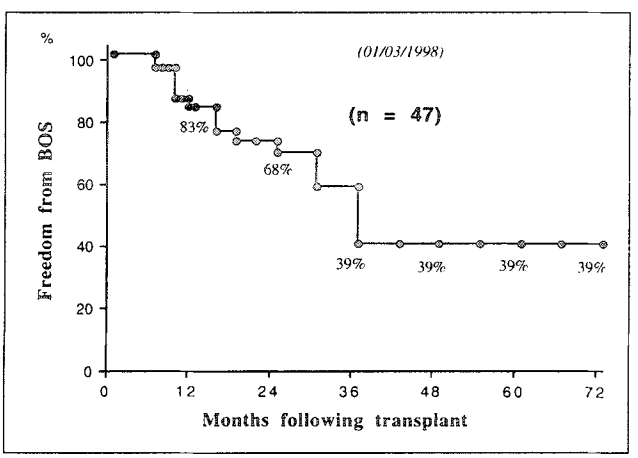

Fig. 9. Freedom from bronchiolitis obliterans syndrome (BOS) in patients surviving longer than 6 months following transplantation.

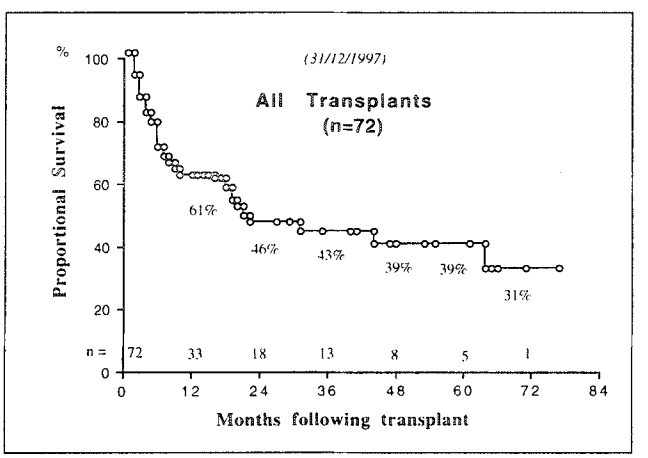

Fig. 10. Overall survival in 72 lung transplant recipients.

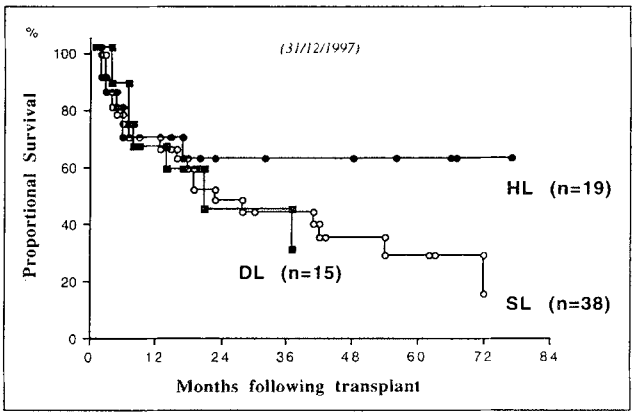

Fig. 11. Survival in 72 recipients according to type of lung transplantation. The end-point of the curve represents 1 patient in heart-lung (HL), single lung (SL), and double lung (DL) transplantation each.

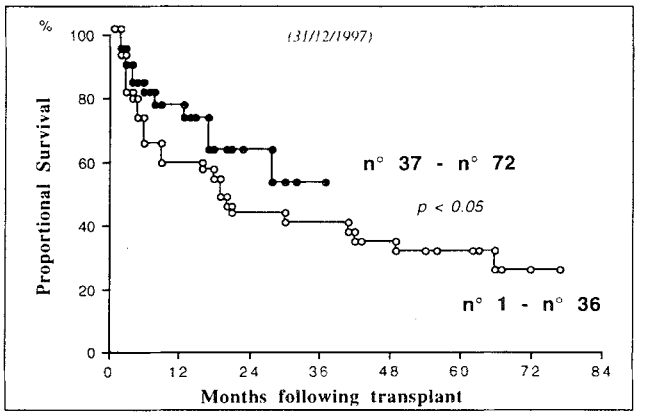

Fig. 12. Survival in 72 recipients comparing the first half (1991 to 1994) and the 2nd half (1995 to 1997) of transplanted patients.

leden); Psychiatry *(P. Igodt, C. Put);* Radiology *(J. Bogaert, W. De Wever, G. Marchal, J. Verschakelen);* Tissue Typing *(M. P. Emonds);* Thoracic Surgery *(W. Coosemans, P. De Leyn, G. Deneffe, T. Lerut, D. Van Raemdonck);* Transplant Coordinators *(J. Pirenne, L. Roels, F. Van Gelder);* Transplant Laboratory *(M. Waer);* Social Work *(D. Delva, A. Cloeck).*

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