Lung transplantation – 10-year experience

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Abstract

Objective: The experience at our institution with various forms of lung transplantation (heart-lung, double lung and single lung) from December 1987 to September 1998 is reviewed and discussed. Methods: During this decade, 282 procedures (46 heart-lungs (HLTx), 142 double lungs (DLTx) and 94 single lungs (SLTx)) have been performed in 258 patients (140 male, 118 female; age: 38 ± 13 years). Major indications included pulmonary fibrosis (n = 73), obstructive lung disease (n = 55), cystic fibrosis (n = 48), primary pulmonary hypertension (n = 36), secondary pulmonary hypertension (majority Eisenmenger’s syndrome) (n = 30), and retransplantation (n = 24). Results: Early postoperative mortality (<90 days) was 13.9% (n = 36). The 1-, 3-, and 5-year survival rates in all recipients was 77, 70 and 63\% respectively. There was no significant difference in 1-year survival rates between the different procedures (HLTx: 78\%, DLTx: 77\%, SLTx: 77\%). Significantly better 1-year survival was achieved in patients with cystic fibrosis (89\%), pulmonary fibrosis (81\%), obstructive lung disease (74\%), and Eisenmenger’s syndrome (83\%) when compared to patients with primary pulmonary hypertension (55\%). Survival rates remained unchanged during this period despite expanding indications during the last years. Causes of death in 90 recipients (HLTx: n = 19, DLTx: n = 37, SLTx: n = 34) included sepsis (n = 42), obliterative bronchiolitis (n = 28), cardiac failure (n = 5), and early allograft dysfunction (n = 2). Freedom from bronchiolitis obliterans syndrome (BOS) (>stage I ISHLT) was 80\% at 1 year and 45\% at 5 years. Conclusions: Lung transplantation offers a true therapeutic option with good early and mid-term results. Yet, chronic graft dysfunction represents a major obstacle for long-term benefit of this procedure. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Lung; Transplantation; Survival; Bronchiolitis obliterans syndrome

1. Introduction

Starting in December 1987, heart-lung transplantation was added to the thoracic program at Hannover Medical School. Shortly thereafter, single (1988) and bilateral sequential (1990) lung transplantation was introduced. Since then, paralleling a decrease in heart transplantation, lung transplantation increased markedly reaching approximately 40 procedures in 1998 in our institution (Fig. 1). This mirrors the continuous expansion of various forms of pulmonary transplantation worldwide where a plateau in performed procedures was reached during the last three years [1]. Despite a continuous increase in donor age, the gap between patients needs and availability of the procedure widened considerably in the US and less pronounced in the Eurotransplant area [2,3]. Scarcity of donor organs, improved surgical techniques, as well as increased experience and broadened knowledge implemented many changes in pulmonary transplantation. Aim of this report is to review our experience with lung transplantation over the last decade and to present our current standards. For the purpose of illustration, we compare the early 5-year experience (December 1987–December 1992; 90 patients) to the more recent years (January 1993–September 1998; 168 patients) with respect to indication and outcome.

2. Patients and methods

Between December 1987 and September 1998, 258 patients (140 male/118 female; mean age: 38 ± 13 years; range: 3–65 years) underwent 282 procedures (24 redo transplantation, including two re-redo operations). Major indications included pulmonary fibrosis (n = 73), obstructive lung disease (n = 55), cystic fibrosis (n = 48), primary pulmonary hypertension (n = 36), secondary pulmonary...
hypertension (primarily Eisenmenger’s syndrome) (n = 30), and retransplantation (n = 24). Double lung transplantation (n = 142; 50%) was the most commonly performed procedure followed by single lung (n = 94; 33%) and heart-lung (n = 46; 16%). Ten of our patients were under 18 years of age with one patient undergoing retransplantation at the age of 14. Four heart-lungs, four double lungs, and three single lungs were performed in this patient group. The dominating pathology in the pediatric group was primary and secondary pulmonary hypertension (n = 5) as well as cystic fibrosis (n = 3).

Our early experience includes 90 patients undergoing 99 operations: 28 heart-lungs (28%), 40 single lungs (40%) and 31 double lungs (31%). The more recent group of transplanted patients (n = 168; 183 procedures) demonstrated a significant decrease in heart-lung replacements (n = 18, 10%; P < 0.0001), slight decrease in single lungs (n = 54, 30%; P = 0.09), and a consequential increase in double lungs (n = 111, 61%; P < 0.0001). The proportion of retransplantation remained stable throughout the study period. Nine patients (10%) required a redo-procedure in the early years and 15 patients (9%) in the last 5 years. The underlying indications for different procedures by transplantation period are reported in Fig. 2.

Initially, donor organs were selected restrictively from size-matched, ABO blood group identical, brain dead individuals. During the study period, 234 patients have received ABO identical and 23 patients ABO compatible donor organs as primary transplants. One patient was transplanted erroneously ABO incompatible (recipient O/ donor A). He is alive and well with normal pulmonary function 2 years after bilateral lung transplantation for emphysema. Over the years, donor criteria were liberalized constantly in accordance with international experience [4]. Size-matching was almost abandoned recently in patients requiring urgent transplantation, utilizing lobar transplantation (n = 5) or multiple atypical resections (n = 11) in oversized donor lungs [5,6]. Paralleling the change in donor criteria, recipient acceptance also broadened. Currently, higher age, multidrug antibiotic resistance, previous lung surgery, pleurodesis or pleurectomy as well as pretransplant ventilation or extracorporeal life support (ECMO) are not considered absolute contraindications in our patients [7,8]. Pretransplant donor/recipient CMV matching was not performed in our patients. Burkholderia cepacia is not considered a contraindication for transplantation, but could be identified only in one patient prior to transplantation.

### 2.1. Surgical technique and perioperative management

Heart-lung transplantation is usually performed via a median sternotomy, as has been reported elsewhere [9]. More recently, a bilateral anterior thoracotomy in the fourth intercostal space, similar to bilateral sequential lung transplantation, has been used for patients with extensive aortopulmonary collaterals for better exposure of the descending aorta. Initially, donor organs were selected restrictively from size-matched, ABO blood group identical, brain dead individuals. During the study period, 234 patients have received ABO identical and 23 patients ABO compatible donor organs as primary transplants. One patient was transplanted erroneously ABO incompatible (recipient O/ donor A). He is alive and well with normal pulmonary function 2 years after bilateral lung transplantation for emphysema. Over the years, donor criteria were liberalized constantly in accordance with international experience [4]. Size-matching was almost abandoned recently in patients requiring urgent transplantation, utilizing lobar transplantation (n = 5) or multiple atypical resections (n = 11) in oversized donor lungs [5,6]. Paralleling the change in donor criteria, recipient acceptance also broadened. Currently, higher age, multidrug antibiotic resistance, previous lung surgery, pleurodesis or pleurectomy as well as pretransplant ventilation or extracorporeal life support (ECMO) are not considered absolute contraindications in our patients [7,8]. Pretransplant donor/recipient CMV matching was not performed in our patients. Burkholderia cepacia is not considered a contraindication for transplantation, but could be identified only in one patient prior to transplantation.
thoracic aorta. Timing of the operation is crucial because explantation of recipient organs can be difficult and time consuming due to extensive adhesions if one or more cardiac operations were performed in the patient’s history.

Single and bilateral sequential lung transplantation is performed in a standard fashion [10]. A bilateral anterior thoracotomy in the fourth intercostal space without transection of the sternum has been used in a small number of patients without severe adhesions for double lung transplantation with good success. Utmost care is used to preserve the collateral blood supply to the donor bronchus from the pulmonary artery. Limited dissection of peribronchial tissue, shortening of the donor bronchus up to one cartilage proximal to the upper lobe and careful suture technique (interrupted PDS® sutures: membranous part 4/0, cartilaginous part 3/0) has proven valuable for bronchial healing in our experience. Additionally, an antibiotic/fibrin glue compound has been applied around the bronchial anastomoses in the majority of patients. No routine omental or pericardial wrapping of the bronchial anastomoses has been performed and bronchial arteries were not reimplanted. For improvement of bronchial microcirculation heparin (100 U/kg) was administered prior to crossclamping of the pulmonary artery, has been continued as an intravenous infusion (200 U/kg) for 4 days and was then replaced by subcutaneous injection (15 000 U/day) for 10 days.

In patients without the use of cardiopulmonary bypass, a special challenge for the right-sided graft occurs during the subsequent left-sided pneumonectomy. The transplanted lung is then overflown with the full cardiac output following hours of ischemia increasing the risk for reperfusion injury. We routinely implemented extracorporeal circulation when the mean pulmonary artery pressure rose > 35 mmHg following crossclamping of the left pulmonary artery, despite stable hemodynamics and adequate oxygenation.

Following the operation, the double lumen tube is replaced by a single lumen nasotracheal tube, the patient is bronchoscoped to remove secretions from the lungs and to examine the anastomoses.

Prophylactic administration of broad spectrum antibiotics (currently a combination of tobramycin, ceftazidim and flunoxacillin) was applied for a minimum of 7 days. Thereafter, the antibiotic therapy was adapted according to microbiological analysis of bronchoalveolar lavage. During the last years, all patients inhaled nebulized colistin postoperatively for 2 weeks. Long-term prophylaxis with colistin was continued in patients with evidence of Pseudomonas colonization of the transplanted lungs.

Postoperative CMV-prophylaxis consisted of 5–10 g/day hyperimmunoglobulin for 3 days as well as gancyclovir (10 mg/kg) for 2 weeks. On identification of CMV immediate early antigen (pp65) or suspected CMV infection, a 3-week course with gancyclovir was started.

Fungal prophylaxis included the administration of fluconazol or itraconazol as well as inhaled amphotericin B.

2.2. Immunosuppression and acute rejection

Standard immunosuppression has been based on cyclosporine A, azathioprine and prednisolone. Cytolytic induction therapy using anti-thymocyte-globulin (ATG, Biotest) was applied during the first 4 years routinely for a period of 3–5 days. Since then its use has been limited to the discretion of the surgeon, usually in selected patients with significant renal dysfunction. Intravenous cyclosporine A is usually administered within 6 hours postoperatively. The initial dose (1 mg/kg) is increased within the following 1–2 weeks up to 10 mg/kg depending on renal and hepatic function. Cyclosporine A serum level (monoclonal assay) is aimed at 220–300 ng/ml for the first year with reduction to 150–200 ng/ml for the following years. Patients also receive 1–2 mg/kg azathioprine with a target white blood cell count of 4000 cells/mm³ or greater. Prednisolone (1000 mg i.v.) is administered intraoperatively followed by three doses of 250 mg at 12 h intervals. Prednisolone maintenance therapy is started on the second postoperative day (initially 0.5 mg/kg and tapered to 0.07 mg/kg within 1 year). More recently, a clinical trial for evaluation of mycofenolic acid as substitute for azathioprine in de novo immunosuppression has been entered, with the results still pending.

Diagnosis of rejection episodes remains still challenging as clinical signs are unspecific and resemble those of infection and preservation injury. Initial treatment of pulmonary rejection episodes follows a regimen of pulsed steroids (3 × 1000 mg). Repetitive pulsed steroids in combination with monoclonal or polyclonal antibodies were used in case of ongoing or recurrent acute rejection episodes. Concomitantly, various modifications of basic immunosuppression have been performed in such patients over the years. Currently, cyclosporine and azathioprine are replaced by tacrolimus and mycofenolic acid in patients requiring three or more treatments for acute rejection within the first 6 months.

2.3. Statistical analysis

Continuous variables are expressed as mean plus or minus one standard deviation (SD). Survival after surgery and freedom from BOS were analyzed by Kaplan–Meier method. Evaluation of survival difference between groups, as well as for indications of procedures was conducted by log-rank test. Differences between surgical procedures and outcome in cystic fibrosis and pulmonary hypertension patients were evaluated with Mann–Whitney rank-sum test, χ² test or Kruskal–Wallis test, where appropriate. Statistical analysis was performed using SPSS for Windows 8.0 software system (SPSS Inc., Chicago, IL). A P-value of < 0.05 was considered significant.
3. Results

3.1. Survival

Early postoperative mortality (<90 days) was 14% (n = 36). Nine patients required retransplantation (30 ± 24 days; range: 9–68 days) during this time interval due to acute graft failure and necrosis at the bronchial anastomosis (n = 1). The 1-, 3-, and 5-year survival rates for all 258 recipients were 77, 70, and 63%, respectively. Graft survival for the same time interval was only 71, 63, and 56% (P = n.s.), reflecting the influence of our retransplantation policy on patient survival (Fig. 3a). Survival for patients undergoing primary retransplantation (n = 22) at 1, 3, and 5 years was 70, 60 and 53%, respectively. Survival rates for retransplantation in early (>POD 90; n = 9) and chronic graft failure (<POD 90; n = 13) were comparable (67 vs. 73% at 1 year, 53 vs. 52% at 5 years).

There was no significant difference in survival for the 90 early patients compared to the 168 recent ones. The difference between the groups at 1, 3 and 5 years was 81 vs. 75%, 76 vs. 67% and 68 vs. 61%, respectively (Fig. 3b). Additionally, 1-year-survival was comparable between primary procedures (HLTx: 78%; DLTx: 77%; SLTx 77%) and remained alike throughout the study period (Fig. 3c). Significantly better survival was achieved in patients with cystic fibrosis (1-year: 89%, 5-year: 68%; log rank test: P = 0.0002; Breslow: P = 0.0002; Tarone Ware: P = 0.0001), pulmonary fibrosis (1-year: 81%, 5-year: 60%; log rank test: P = 0.003; Breslow: P = 0.0009; Tarone Ware: P = 0.001), obstructive lung disease (1-year: 74%, 5-year: 68%; log rank test: P = 0.003; Breslow: P = 0.004; Tarone Ware: P = 0.004), and Eisenmenger’s syndrome (1-year: 83%, 5-year: 74%; log rank test: P = 0.002; Breslow: P = 0.005; Tarone Ware: P = 0.003) when compared to patients with primary pulmonary hypertension (1-year: 55%; 5-year: 39%) (Fig. 4). Of particular interest has been the excellent survival in the cystic fibrosis group despite underlying infectious lung disease. Comparing patients transplanted for pulmonary hypertension (n = 66) to the cystic fibrosis group (n = 41) not only survival but also use of available intensive care resources was significantly different (Table 1). Choice of procedure did not alter the early postoperative course in the hypertensive group (Table 2). However, there was a tendency towards superior 1- and 5-year survival in patients receiving heart lung transplantations, when compared to lung transplantations.

Table 1

<table>
<thead>
<tr>
<th>Survival</th>
<th>PHT</th>
<th>CF</th>
<th>P</th>
</tr>
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<tr>
<td>1 year</td>
<td>69%</td>
<td>90%</td>
<td>0.002</td>
</tr>
<tr>
<td>5 year</td>
<td>55%</td>
<td>78%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mortality (90 days)</td>
<td>21%</td>
<td>5%</td>
<td>0.03</td>
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<tr>
<td>Ventilation (days)</td>
<td>27 ± 33</td>
<td>3 ± 3</td>
<td>&lt; 0.0001</td>
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<tr>
<td>(range)</td>
<td>(1–43)</td>
<td>(1–12)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>62 ± 40</td>
<td>29 ± 12</td>
<td>&lt; 0.0001</td>
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<tr>
<td>(range)</td>
<td>(14–174)</td>
<td>(12–79)</td>
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Fig. 3. Survival after pulmonary transplantation at Hannover Medical School. Numbers in parenthesis report patients at risk and error bars represent 1 SD. (a) Overall survival after surgery (retransplantation not censored) (December 1987–September 1998; n = 258) and graft survival (retransplantation, censored). (b) Survival after surgery by time interval of pulmonary transplantation. (c) Survival after surgery by type of primary procedure.
tion alone (HLTx: 77 and 62%; DLTx: 40 and 40%; SLTx: 50 and 50%; log rank test: \( P \leq 0.02 \)).

There was no difference in survival for ABO identical vs. ABO compatible primary transplantation (1-year: 76% and 5-year: 57% for identical vs. 1-year: 71% and 5-year: 47% for compatible organs, respectively). Furthermore, pretransplant CMV status of the recipients had no influence on survival (1-year: 80% and 5-year: 65% for CMV + vs. 1-year: 76% and 5-year: 64% for CMV – patients, respectively).

Causes of death in the 90 non-survivors (HLTx: \( n = 19 \); DLTx: \( n = 37 \); SLTx: \( n = 34 \)) indicate that infection (\( n = 42 \)) and chronic rejection (\( n = 28 \)) were the major problems. Other causes of mortality are reported in Table 3. Early death (< POD 90; \( n = 36 \)) was caused by infection in 64% of patients followed by cardiac failure (11%) and other causes (14%). Late death (> POD 90; \( n = 54 \)) was due to chronic graft failure in the majority of patients (52%), followed by infection (35%), and other causes (6%). Further analysis did not reveal any significant differences between early and late transplant periods or type of procedure.

3.2. Bronchiolitis obliterans syndrome

Chronic allograft rejection is the major risk factor for patient survival after 90 days. Home spirometry is used routinely in all our patients to monitor pulmonary function in addition to regular follow-up visits in our department. Transbronchial biopsy is used only in selected cases for exclusion of infection or acute rejection. Freedom from bronchiolitis obliterans syndrome (BOS) (defined as > stage I of ISHLT classification) was 80% at 1 year and 45% at 5 years (Fig. 5) resulting in an attrition rate of 10–15%/year. Several protocols have been applied in our center during the 10-year period in an attempt to stop the further decline in lung function. As such, intensified immunosuppression with pulsed steroids, cytolytic therapy and increased dosages of maintenance steroids were administered. We also tried high-dose immunoglobulin therapy and rescue application of tacrolimus and methotrexate. None of these treatment protocols had a convincing and durable effect on the decline of lung function.

In a subgroup of 147 patients, influence of cytolytic induction therapy (ATG, Biotest) on late survival and freedom from BOS (> stage I ISHLT) was evaluated. Fifty patients with and 96 without initial ATG therapy, who survived for a minimum of 6 months, were studied. Clinical and intraoperative characteristics were comparable between groups. Late survival was not altered with completely identical curves for both groups at 1, 3 and 5 years (+ATG: 95, 80, 75%, -ATG: 80, 75, 70% respectively). Further analysis did not reveal any significant differences between early and late transplant periods or type of procedure.
88, 78%; − ATG: 95, 89, 79%, respectively). Freedom from BOS was slightly higher at 2 years for the + ATG group (79 vs. 69%) without reaching statistical significance. After 3 years of follow-up both curves were identical again.

4. Comments

Over the last decade lung transplantation has changed from an experimental approach to an accepted therapeutic option for patients with endstage pulmonary failure. Improvement of results derived from selection of appropriate candidates, operative choices, surgical techniques and postoperative surveillance and treatment of infection and rejection. Our experience with 258 patients clearly suggests that excellent short- and long-term results can be obtained by an individual lung transplant center. Overall 1-, 3-, and 5-year survival rates in the ISHLT registry, compiling data from 150 lung and 122 heart-lung transplantation programs, are around 71, 55, and 42% for lungs and 60, 48, and 40% for heart-lungs, respectively [1]. Our results (77, 70, and 63%) compare favorable with the international experience. When looking at outcome in our patients transplanted before and after January 1993, lack of improvement of survival is evident. This may result from a more liberal acceptance of critically ill patients as well as utilization of borderline donor organs. Similar experience has been reported for pulmonary transplantation performed after 1990 from the international community [1].

4.1. Patient selection and choice of procedure

Despite maximal utilization of available organs, which led to a decline in heart-lung replacements, single lung transplantation decreased also in favor of bilateral sequential lung transplantation in recent years. This reflects a change in our institutional policy for preferred procedures in patients with pulmonary hypertension and chronic obstructive lung disease during the last decade. Contrary to the international experience, where the majority of single lung transplantation (55%) are performed for chronic obstructive lung disease [1], we prefer bilateral sequential lung transplantation in the majority of our emphysema patients. It avoids problems with over inflation of the native lung early postoperatively as well as infectious complications during follow-up and minimizes the risk of death due to spontaneous pneumothorax, which has occurred twice in our patients. In emphysema patients a more sophisticated, disease based approach utilizing lung transplantation combined with lung volume reduction surgery might have a significant influence on future patient management [11].

In patients with pulmonary hypertension our initial approach was heart-lung replacement. Due to severe limitations of available donor organ blocks and following promising reports with single lung transplantation we changed to this procedure but abandoned it shortly thereafter because of the difficult peri- and postoperative course. In single lung transplantation for pulmonary hypertension 90% of cardiac output is directed towards the transplanted lung, because of its lower vascular resistance. Consequently, a ventilation/perfusion mismatch unequivocally will occur during episodes of transplant dysfunction (reperfusion edema, rejection, infection), which is poorly tolerated in our experience. Double lung transplantation achieves better functional recovery and a reduced graft related mortality when compared to single lung transplantation [12]. Yet, this issue is still discussed controversially and neither procedure has emerged as a clearly superior approach in the literature [13]. Our results suggest better survival after heart-lung transplantation for patients with pulmonary hypertension compared to lung transplantation alone. This might reflect a bias in patient selection, as the vast majority of heart-lung recipients were transplanted in the early years of our program. Additionally, severe shortage of donor organs currently prohibits a more liberal use of heart-lung transplantation, as the waiting time for this procedure increased during the decade to almost 3 years now at our center. Comparative waiting time for single or double lung transplantation today is 1 year.

In addition to procedural changes patient selection was influenced during this decade by improvements in medical therapy as well as organ preserving surgical alternatives [14–16]. This stresses the importance of tight interdisciplinary cooperation in the management of these patients. In all patients with pulmonary hypertension referred for transplantation, we currently assess their response to intermittent nebulized prostacyclin before or during enlistment for transplantation with promising results [17]. Furthermore, pulmonary thromboendarterectomy as well as lung volume reduction surgery have broadened surgical therapy and are evaluated as treatment strategies in patients referred for transplantation. Whereas pulmonary thromboendarterectomy is considered treatment of choice in patients with pulmonary hypertension due to thromboembolism, we believe that long-term results of lung volume reduction surgery and clear patient selection criteria are needed to judge the value of this procedure.

4.2. Postoperative management

Contrary to other centers, transbronchial lung biopsies are not performed on a routine basis early after transplantation or during any episode suspicious of lung rejection in our program. Standard bronchoscopy is done in regular intervals in the early postoperative period until endobronchial healing is completed. Thereafter pulmonary function parameters (determined by home spirometry) are used exclusively for further graft surveillance in asymptomatic outpatients. Additionally, in patients with deteriorating lung function in the early as well as late postoperative period bronchoalveolar lavage is performed to exclude infection. Unlike purulent bacterial infections, acutely rejecting lungs often present with small amounts of ubiquitous non-liquid whitish
secretions. The material obtained by bronchoalveolar lavage is analyzed for bacterial and viral organisms and fungi. In patients with poor clinical condition, in whom pulmonary infection is unlikely, methylprednisolone is initiated immediately after bronchoscopy. Otherwise, the therapy is withheld until the gram stain and CMV early antigen (pp65) test results are available to exclude an infectious episode as the cause of pulmonary deterioration. Lack of clinical improvement after the first course of steroids in patients with suspected acute rejection represents an indication for transbronchial lung biopsy in our program. For identification of optimal target areas a high resolution CT-scan is performed before biopsy.

Rejection monitoring by routine surveillance lung biopsies is still discussed controversially in the literature and has not proven helpful in the management of stable asymptomatic patients more than 2 years after transplantation [13,18,19]. Similar to others, in our hands routine transbronchial biopsy has achieved a low sensitivity and specificity of the histologic findings in the specimens and very little impact on patient treatment [20]. Whether aggressive treatment of asymptomatic, biopsy proven acute rejection will lead to a reduced prevalence of BOS remains yet to be demonstrated.

Infection represents the major cause of early as well as late death in our patients. This corresponds well with the experience of other centers. Pathogens include bacteria, viruses, fungi and protozoa, with bacterial pneumonia, CMV pneumonitis and invasive aspergillosis being the most problematic [13]. In all our recipients with cystic fibrosis colonization of the transplanted lungs with *Pseudomonas* strains occurred during 6 weeks postoperatively. In the majority of cases, the bacterial strains had been identified before transplantation [21].

Our causes of early death demonstrate only a small number of early graft dysfunction. This may reflect a liberal acceptance for retransplantation in patients with severe reperfusion injury as well as an intensified postoperative care including NO-inhalation, surfactant instillation and application of C-1 esterase inhibitor in selected recipients [22]. Additionally, in our last 33 patients modification of lung preservation has been undertaken, changing from modified Euro–Collins to low-potassium-dextran (LPD) solution. Studies from our laboratory as well as from others have suggested an improved postischemic lung function following preservation with LPD-solution [23,24]. Thus, a clinical trial has been started recently to further evaluate the potential benefit of this conservation protocol.

4.3. Bronchiolitis obliterans syndrome

The most important factor limiting long-term survival and quality of life after lung transplantation is chronic allograft rejection. Histologically, bronchiolitis obliterans (a diffuse, concentrical, luminal narrowing of the terminal bronchioli) is the characteristic finding in the lungs resulting clinically in a progressive loss of vital capacity and FEV1 with an obstructive airflow pattern. Transbronchial biopsies achieve low sensitivity and specificity so that spirometric parameters are used to define BOS after exclusion of acute rejection, infection and airway stenoses [25,26]. Our data indicate that 5 years following lung transplantation 55% of patients demonstrate clinical evidence of chronic rejection. Frequent acute rejection episodes could be identified as the most significant risk factor for development of BOS in several reports [13,27,28]. Additionally, CMV pneumonitis may be a predisposition for BOS but its significance is still discussed controversially. A possible mechanism of CMV infection for BOS development is the induced upregulation of MHC class II antigens in the transplanted lungs, making them more prone to acute rejection episodes [29]. Preventive measures other than aggressive treatment of acute rejection episodes and CMV pneumonitis and — probably — CMV prophylaxis are currently not evident [13]. Once BOS is diagnosed augmentation and modification of basis immunosuppression is empirically performed by most transplant centers including corticosteroids, polyclonal and monoclonal antibodies, methotrexate, tacrolimus, mycofenolic acid, aerosolized cyclosporine and total lymphoid irradiation with modest and often transient improvement of lung function similar to our experience [13]. Mean survival rates after diagnosis were 66% at 1 year and 37% at 5 years in a Stanford series, with the majority of patients dying of pneumonia [28]. With improved early results and a continuous increase in successful transplantation the question of retransplantation ultimately rises for these patients [30]. Due to its amplification of donor organ shortage and still inferior outcome when compared to first time transplants this issue is discussed highly controversial [31]. In our opinion, absence of other therapeutic options as well as acceptable survival rates makes lung retransplantation a therapeutic option in selected patients with end-stage BOS.

5. Conclusion

Lung and heart-lung transplantation has evolved during the last decade from a highly experimental procedure to a valuable therapeutic option for patients with terminal cardiac or pulmonary disease. Many early problems could be solved and long-term survival results are very promising. Yet, the high prevalence of chronic allograft rejection poses a major threat to the concept of lung transplantation. We are thus challenged to improve immunosuppressive strategies and lung preservation techniques as well as to evaluate new strategies of tolerance induction and gene therapy to cope with the future necessities in the field of lung transplantation.
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References

retransplanted. These patients do very badly even when they have been retransplanted if you look at the IHLST data. Have you been able to identify within that subpopulation any factors which would discriminate whether you actually retransplant them and get a better result or not?

**Dr. Harringer:** In the subanalysis of these 21 patients, 1-year survival in this group is just below our regular 1-year survival, ranging around 70%. I think one critical factor for retransplantation is that these patients are in a fairly well nutritional status and that they go ambulatory into retransplantation. If you wait too long these patients will deteriorate so dramatically that your results will not be acceptable. So far, our patient group is very small, and it does not correspond to the IHLST experience. It is very difficult to predict which of these patients will develop BOS again once they are retransplanted. We have seen patients who developed it very early and we have seen patients who did well for 5, 6 years and still are doing well after retransplantation.

**Dr. Varela (Madrid, Spain):** What is your current preservation protocol, and for patients with pulmonary hypertension, what kind of pulmonary transplant do you favor?

**Dr. Harringer:** Right now we have switched our preservation protocol from Euro-Collins to low-potassium dextran solution. We are currently evaluating the low-potassium dextran solution in a clinical study protocol. We think that the reperfusion edema and reperfusion injury has decreased dramatically compared to Euro-Collins solution. With regard to pulmonary hypertension, our experience with single lung transplantation and pulmonary hypertension is bad. So we do as a routine procedure bilateral sequential lung transplantation in these patients.

**Mr. Murday (London, England):** To examine survival you need to have some comparison, some group of patients with whom you can compare survival without transplantation. Of course that has always been a great difficulty. I think to date there isn’t anything in the published literature that really demonstrates an improved survival with lung transplantation, although it is something many of us would accept as being the case. Can you tell us how your survival data compares with any control group, for example, waiting list mortality?

**Dr. Harringer:** There was a very nice paper published in Lancet in January this year demonstrating that for the patient group of pulmonary fibrosis and for cystic fibrosis there is definitely a survival benefit with lung transplantation. In the same study there was no survival benefit for the patients with emphysema on the waiting list. Despite survival, you also have to keep in mind that you achieve an extreme improvement with regard to physical fitness and life quality in these patients. So I think the issue with the emphysema patients is not yet settled, but for cystic fibrosis and for pulmonary fibrosis patients, there is a significantly improved course with lung transplantation compared to the patients on the waiting list.