Evaluation of Factors Damaging the Bronchial Wall in Lung Transplantation

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Background: Lung transplantation has become important in treating end-stage lung disease; however, bronchial complications are common. Lack of bronchial arterial circulation, ischemic time, and acute rejection episodes may damage the bronchial wall. In this study, we analyzed factors that may hamper bronchial airway healing, requiring intervention after lung transplantation.

Methods: We collected data from a consecutive series of 81 transplantations performed between 1993 and 2002 and evaluated recipients for bronchial complications. In 30 single and 51 sequential bilateral lung transplantations, a total of 132 anastomoses were performed. Four patients (3 bilateral and 1 single lung transplant recipients who died within the first 14 post-operative days were excluded from the analysis. Finally, 125 lung grafts remained for statistical analysis of factors influencing bronchial complications.

Results: Peri-operative mortality was 8.9%. Eleven patients (14.7%) experienced severe bronchial complications in 16 of 125 evaluated bronchial anastomoses (12.8%) and required surgical treatment or bronchoscopic interventional therapy. In a multivariate logistic regression model, severe reperfusion edema (adjusted odds ratio, 8.3; $p = 0.002$) and rejection episode within the 1st post-operative month (adjusted odds ratio, 4.1; $p = 0.036$) were associated with bronchial complications. Using the univariate model, we found that factors such as interleukin-2–antibody induction therapy, immunosuppression, or bronchial anastomotic technique had significant influence on bronchial healing, whereas we could not confirm this when using multivariate anasysis.

Conclusions: Preventing reperfusion edema with optimized lung preservation and with early and aggressive medical treatment or mechanical hemodynamical support (e.g., veno-arterial extra corporal membrane oxygenation are necessary to avoid prolonged ventilation dependence, which may result in bronchial complications. Furthermore, avoiding early rejection episodes promotes uncomplicated bronchial healing. J Heart Lung Transplant 2005;24:275–81. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

In contrast to all other organs, the lung is left without nutrient bronchial circulation after transplantation. Blood supply to lungs and bronchial mucosa is provided only from the pulmonary artery, because the bronchial arteries are discontinued during organ harvesting and usually are not re-anastomosed in the recipient. Re-establishing bronchial arterial blood flow has been attempted in experimental and in clinical lung transplantation,[1–7] especially during the early 1990s. However, widespread clinical application of bronchial revascularization has not become standard, and large series are lacking. Further, impairmed bronchial circulation caused by ischemia–reperfusion injury additionally may promote bronchial wall ischemia and enhance the development of bronchial complications.[8,9] Prolonged ventilation using high airway pressure also may be harmful by increasing physiologic desquamation of bronchial mucosa after lung transplantation.

In the immediate post-operative period, impaired circulation is marked by desquamation and necrosis of the bronchial mucosa at the anastomotic site as well as distally in the main stem and lobar bronchi. At regular intervals, flexible bronchoscopy is necessary to diagnose potential progression of these alterations and to enable intervention in the case of progression toward bronchial complications.

For these reasons, impaired bronchial healing is a common event after lung transplantation, frequently

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requiring repeated interventional or surgical therapy and consecutively limiting quality of life and post-transplant survival. According to international literature, complications that affect the bronchial anastomosis occur at a rate of between 7% and 14%.[10]

Within the past decade, improvements in lung preservation and in surgical techniques and the use of better immunosuppressive agents have decreased peri-operative mortality and bronchial complications after lung transplantation.

Predisposing factors for bronchial-healing complications have never been investigated in a risk-factor model. Thus, we performed a logistic regression analysis to identify factors associated with these complications in a series of 81 consecutive transplantations.

For this purpose, we investigated potential pre-, intra- and post-operative risk factors assumed to influence bronchial healing.

METHODS

Patients

From November 1993 to September 2002, 81 consecutive lung transplantation (30 single and 51 bilateral), including 6 retransplantations, were performed in 75 patients. Five patients required invasive ventilation before transplantation. Previous lung surgery was documented in 31 cases (38.3%), i.e., primarily lung-volume reduction surgery (14 patients, 17.3%). Chronic obstructive pulmonary disease was the most common indication for lung transplantation (52.0%), followed by α_1-antitrypsin–deficiency emphysema (16.0%). The usual criteria, as described by Morrison et al[11] and Winton[12] were applied for donor and recipient selection. Table 1 lists patient and transplant characteristics. Transplant recipients were observed for a median follow-up time of 15.5 months and were evaluated for severe bronchial complications according to the following criteria:

Any bronchial complications that required surgical treatment or bronchoscopic interventional therapy served as the primary end-points of this study. We defined bronchial complications as 1) anastomotic dehiscence; 2) bronchial stenosis; 3) granulation tissue; or 4) bronchomalacia that required dilation, laser recanalization, stent implantation, bronchoplastic surgery, or retransplantation.

Only mucosal necrosis was documented but was not defined as a bronchial complication if conservative therapy was sufficient.

Exclusion Criteria

Two men and 2 women died within 2 weeks after transplantation of causes unrelated to airway-specific problems and were excluded because of short bronchoscopic follow-up. Two (1 man and 1 woman) died of acute myocardial infarction. One woman with cystic fibrosis died of cerebrovascular thrombosis, and 1 male recipient died of unrestrained viral pneumonia.

Table 1. Pre- and Intra-operative Characteristics of Recipients (all 81 transplants in 75 Patients)

Recipients	
Age (years)	51.8 ± 12.2
Sex	
Female	38/75 (50.7%)
Male	37/75 (49.3%)
Median waiting time	4.0 months (0–40.7)
Previous lung surgery	31/81 (38.3%)
Body mass index	21.3 ± 4.7 kg/m^2
Pre-transplant diagnosis (initial)	
Retransplantations (all)	6/81 (7.4%)
Chonic obstructive pulmonary disease	39/75 (52.0%)
Alpha$_1$-antitrypsin emphysema	12/75 (16.0%)
Cystic fibrosis	8/75 (10.7%)
Fibrosis	8/75 (10.7%)
Eisenmenger's syndrome	3/75 (4.0%)
Chronic thromboembolic pulmonary hypertension	2/75 (2.6%)
Other	3/75 (4.0%)
Intra-operative characteristics	
Bilateral lung transplantation	51/81 (62.9%)
Clamshell incision (if bilateral)	20/51 (39.2%)
Cardiopulmonary bypass support	29/81 (35.8%)
Ischemic time	
First lung implanted or unilateral	260.6 ± 64.4 min
Second lung implanted (if bilateral)	354.8 ± 64.9 min
Initial immunosuppression	
Cyclosporine	63/81 (77.8%)
Tacrolimus	18/81 (22.2%)
Anti-thymocyte globulin induction therapy	27/81 (33.3%)
Interleukin-2 antibody induction therapy	49/81 (60.5%)
Organ preservation solution	
Euro-Collins	39/81 (48.1%)
Perfadex	42/81 (51.9%)
Surgical technique (bronchus)	
Anterior wall interrupted-suture	45/81 (55.6%)
Total running-suture	36/81 (44.4%)

Anastomoses at Risk Analysis

As previously described by Date et al[13] and Alvarez et al[14], we performed a bronchus-based evaluation. After applying exclusion criteria, we evaluated all lung grafts of the remaining patients (2 lung grafts in the case of bilateral and 1 in the case of single lung transplantation) for bronchial complications that required surgical treatment or inventional therapy and divided recipients into an event group (bronchial complication with intervention) and an event-free group (lung grafts free from bronchial complications). Subsequently, we analyzed parameters associated with bronchial complications using appropriate statistical testing.

Consequently, a total of 125 anastomoses at risk in 71 patients (77 transplantations, 6 retransplantations included) remained for investigation.

Surgical Technique and Immunosuppression

The same cardiothoracic surgeon performed all transplantations. The standard surgical technique described by Cremer et al[15] was used for implanting the lung grafts. Cardiopulmonary bypass support was required in 29 of 81 transplantations (35.8%) because of pulmonary hypertension, increased pulmonary artery pressure during manual pre-clamping, or respiratory or hemodynamic instability during 1-lung ventilation. In 36 transplantations (44.4%), bronchial end-to-end anastomosis was performed using 4-0 polydioxanone sulfate running-sutures for the complete anastomosis, whereas interrupted sutures of the cartilaginous portion of the bronchus (telescope anastomosis by horizontal mattress suture, figure-of-eight, or single stitch) were performed in the other 45 transplantations (55.6%).

Initial post-operative maintenance immunosuppression consisted of standard triple therapy including prednisolone (Aprednisolon®, Nycomed GmbH, Austria), cyclosporine (Sandimmun, Novartis, Switzerland) or tacrolimus (Prograf, Fujisaawa, Japan) and azathioprine (Imurek, Glaxo Wellcome Operations, England) or mycophenolate mofetil (Cellcept, Roche, Switzerland) following an internationally recommended dose regimen. Anti-thymocyte globulin (Fresenius Kabi, Graz, Austria) was administered in 32 transplantation cases (39.5%), starting at the 1st post-transplant day. Induction therapy using an interleukin-2–receptor antibody (IL-2) (daclizumab, Zenapax, Roche, Switzerland in 44 cases; basiliximab, Novartis, Switzerland in 5 cases) was carried out in 49 transplantations (60.5%). Interleukin-2–receptor antibody therapy was started intra-operatively after induction of anesthesia.

Reperfusion Edema

At the end of the surgery, fiberoptic bronchoscopy was performed to monitor the anastomosis and to clear the bronchial system from blood and secretions. Furthermore, reperfusion edema was evaluated. To avoid interobserver variability, bronchoscopies were performed by the same surgeon, and findings were documented in a bronchoscopic report. Reperfusion edema was diagnosed exclusively by bronchoscopy and classified into 3 grades according to the observed edematous fluid: Grade I, no intrabronchial edema fluid detected; Grade II, moderate reperfusion edema; traces of frothy, intrabronchial, edematous fluid; bronchoscopic clearance possible; and Grade III, severe reperfusion edema, profuse intrabronchial aqueous fluid, bronchoscopic aspiration without effect.

Bronchoscopy was repeated several times during the post-operative hospital stay: at least 24 to 48 hours after transplantion, at the time of extubation, at discharge from the intensive care unit, and at least every 2 to 3 days within the 1st post-transplant month, or whenever indicated by clinical suspicion of rejection or infection. Additionally, transbronchial biopsies for surveillance were performed according to a scheduled regimen before hospital discharge and when clinically indicated.

Diagnosis of Acute Rejection

Acute rejection was diagnosed by transbronchial biopsy specimen and graded according to the International Society for Heart and Lung Transplantation classification[16] or by clinical suspicion with successful treatment with 3 days of intravenous corticosteroids.

Statistical Analysis

We assessed possible associations between bronchial complications and potentially predictive clinical features using univariate and multivariate analysis. To test for univariate differences in categoric variables, we used Pearson's chi-square test or Fisher's exact test (when appropriate). For continuous variables, we used the Student's *t*-test or the Mann-Whitney U test (if assumption of a Gaussian distribution was not fulfilled). We performed multivariate logistic regression analysis to determine the odds ratios (OR) and the 95% confidence intervals (CI) for potential predictors of bronchial complications. Thereby, we based the selection of variables on univariate comparisons (entry criteria, $p < 0.05$) and on clinical relevance. We considered $p < 0.05$ to indicate statistical significance.

RESULTS

Bronchial Complications

We reviewed 125 bronchial anastomoses at risk in 71 patients (77 transplantations). Bronchial complications, mostly occurring within the 1st few months, developed in 11 patients (12 transplantations), resulting in surgical treatment or interventional therapy in 16 anastomoses. For an overview of bronchial complications, see Figure 1. Anastomoses showing bronchial stenosis caused by granulation tissue (10 anastomoses) could be treated by bronchoscopic laser debridement. Interventional therapy with consecutive surgical treatment was necessary in 2 anastomoses in 2 recipients. Bronchoplastic surgery had to be performed in 3 patients. Anastomotic dehiscence that required retransplantation occurred in 1 male patient who had received single lung transplant. He underwent successful retransplantation after he had been rescheduled at the 9th post-operative day. After bilateral retransplantation had been performed, he experienced a unilateral bronchial stenosis, requiring Polyflex-stent implantation 7 months after retransplan-

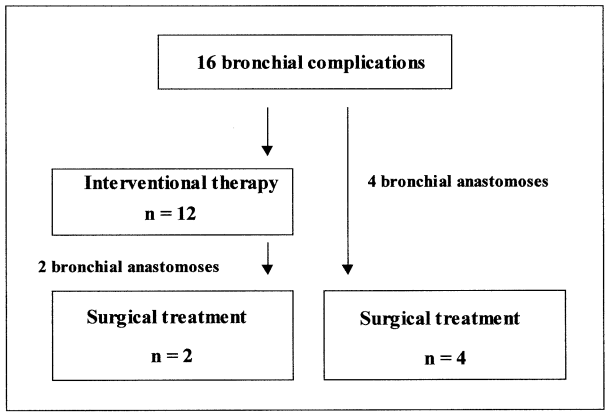

Figure 1. Overview of bronchial complications and interventions performed.

tation. He died 4 months later of acute bronchial artery bleeding in the stented area.

Risk Factor Analysis

Sixteen anastomoses that required surgical treatment or interventional therapy (event group) were compared with 109 anastomoses free from severe bronchial complications (event-free group).

Pre- and Intra-operative Factors Influencing Bronchial Complications, Univariate Analysis

Table 2 shows demographic factors, their distribution within the groups, and their associations with bronchial complications. Demographic factors such as age, sex, body mass index, chronic obstructive pulmonary disease, or previous pulmonary surgery were not associated significantly with bronchial complications. Moreover, no donor demographic factor contributed significantly to the bronchial complication rate.

Bilateral lung transplantation did not show a greater bronchial complication rate compared with single lung transplantation. Furthermore, the need for cardiopulmonary bypass assistance was not a risk factor for developing bronchial complications. Regarding ischemic time, no influence could be identified. However, we encountered severe bronchoscopically detected reperfusion edema, at a much greater incidence in the event group than in the event-free group ($p < 0.001$). Patients with severe reperfusion edema had a significantly longer ventilation time (66.2 vs 36.3 hours, $p < 0.001$) and needed greater positive end-expiratory pressures (PEEP, 14.8 cm H_2O vs 11.6 cm H_2O, $p < 0.001$) than did recipients without reperfusion edema. Induction therapy with an IL-2–receptor antibody was significantly associated with fewer bronchial healing problems ($p = 0.041$). Patients treated with cyclosporine demonstrated significantly better bronchial healing compared with patients initially treated with tacrolimus ($p = 0.003$). Mycophenolate mofetil therapy was not superior to azathioprine therapy ($p = 0.194$). Total running-suture technique, however, was associated significantly with fewer bronchial complications than were interrupted-suture techniques ($p = 0.006$). We found that the use of Perfadex® (Vitrolife, Goeteborg, Sweden) instead of Euro-Collins® (Fresenius Kabi, Graz, Austria) may provide better protection for the bronchial wall, even though this effect did not reach statistical significance ($p = 0.065$).

A rejection episode within the 1st post-operative month that required corticosteroid bolus therapy for 3 days increased the risk of later bronchial healing distur-

Table 2. Comparison of Recipient- and Donor-relevant Factors in Association With Bronchial Complications Requiring Surgical Treatment or Interventional Therapy (Univariate Anastomoses-based Evaluation)

	No bronchial complications $n = 109$ (100%)	Severe bronchial complications $n = 16$ (100%)	p Value
Recipient			
Age (years)	49.8 ± 13.0	54.0 ± 13.4	0.246
Male sex (%)	51 (46.8%)	10 (62.5%)	0.240
Body mass index (kg/m^2)	20.7 ± 4.6	22.7 ± 4.8	0.099
Pulmonary disease			
COPD (%)	55 (49.5%)	6 (37.5%)	0.368
Previous lung surgery (%)	43 (39.4%)	3 (18.8%)	0.165
Donor			
Age (years)	37.4 ± 11.9	36.0 ± 15.4	0.734
Male sex (%)	55 (50.5%)	10 (62.5%)	0.407
Body mass index (kg/m^2)	20.5 ± 4.7	22.9 ± 4.5	0.066
Ventilation time (hours)	69.0 ± 49.7	65.2 ± 56.5	0.809
ICU stay >4 days (%)	29 (26.7%)	4 (25.0%)	0.922
Hypotensive period (%)	26 (23.9%)	5 (31.3%)	0.492
Chest trauma (%)	9 (8.3%)	1 (6.3%)	0.961

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

bancies ($p = 0.026$), whereas peri-operative infections did not influence the development of bronchial complications (33.9% vs 31.3%, $p = 0.981$).

Mean post-operative ventilation time was approximately 3 times longer in patients with bronchial complications (97.7 vs 38.6 hours, $p < 0.001$). Additionally, invasiveness of ventilation (maximum PEEP, 13.9 vs 12.2 cm H_2O; $p = 0.012$) and duration of ventilation at the maximum pressure (37.1 vs 19 hours, $p < 0.001$) was significantly longer, especially in the early post-operative period. Ventilation time in a biphasic positive-airway-pressure mode was increased 2-fold in the event group (50.4 vs 24.9 hours, $p = 0.001$). Only 1 patient who had been ventilated with a maximum PEEP of <12 cm H_2O required a laser necrosectomy for impaired bronchial healing. All other patients with later bronchial complications had been ventilated with a maximum PEEP of up to 18 cm H_2O (Table 3).

Multivariate Risk Factor Analysis

We included factors determined by univariate analysis to be significant as covariates in a multivariate logistic regression model. Severe edema formation increased the risk for later bronchial complications 8.3-fold (CI, 2.1–33.1; $p = 0.002$). Induction therapy with an IL-2–receptor antibody was associated with fewer bronchial complications in the univariate analysis; however, we could not confirm this effect using the multivariate model (OR = 0.94, p = 0.951). A rejection episode within the 1st post-transplant month that required intravenous corticosteroid treatment was associated with a 4.1-fold increased risk of bronchial complications (CI, 1.1–15.67; $p = 0.036$). Total running-suture technique showed a smaller complication rate compared with interrupted-suture techniques in the multivariate analysis; however, suture technique was no predictor of later bronchial complications (OR = 0.58, $p = 0.640$). We did not include ventilation-associated parameters in the multivariate analysis because long ventilation time ($p < 0.001$) and increased airway pressures ($p < 0.001$) correlated significantly with severe reperfusion edema, a factor already included in the multivariate model. Table 4 shows results of the multivariate analysis in detail.

DISCUSSION

To our knowledge, this is the 1st study that identifies severe reperfusion edema and early rejection episodes as independent predictors of bronchial complications. Severe reperfusion edema increased the incidence of bronchial complications >8-fold. Additionally, an early rejection episode that required corticosteroid administration increased the risk for surgical treatment or interventional therapy for bronchial complications.

Several studies have attempted to identify predisposing parameters for bronchial complications after lung transplantation. Date et al[13] indicated that better rejection surveillance decreases the prevalence of bronchial complications. Alvarez and Santos[14] demonstrated that early post-operative extubation may play a role in decreasing the incidence of bronchial complications.

Table 3. Comparison of Intra- and Post-operative Factors in Association With Bronchial Complications Requiring Surgical Treatment or Interventional Therapy (Univariate Anastomoses-based Evaluation)

	No bronchial complication $n = 109$ (100%)	Severe bronchial complications $n = 16$ (100%)	p Value
Intra-operative			
Bilateral lung transplantation (%)	85 (78.0%)	11 (68.8%)	0.525
Cardiopulmonary bypass (%)	42 (38.5%)	5 (31.3%)	0.574
Muscle-sparing incision (%)	56 (51.4%)	4 (25.0%)	0.062
Ischemic time (minutes)	296.4 ± 78.1	309.9 ± 88.8	0.585
Severe reperfusion edema (%)	27 (24.8%)	11 (68.8%)	<0.001
Anti-thymocyte globulin use (%)	39 (35.8%)	10 (62.5%)	
Interleukin-2–receptor antibody use (%)	70 (64.2%)	6 (37.5%)	0.041
Immunosuppression			
Cyclosporine (%)	90 (82.6%)	8 (50.0%)	0.003
Azathioprine (%)	33 (30.3%)	7 (43.8%)	0.194
Surgical technique			
Anterior wall interrupted-suture (%)	54 (49.5%)	14 (87.5%)	
Total running-suture (%)	55 (50.5%)	2 (12.5%)	0.006
Organ preservation solution			
Perfadex (%)	61 (56.0%)	6 (37.5%)	
Euro-Collins (%)	48 (44.0%)	10 (62.5%)	0.065
Post-operative			
Rejection within 1st month (%)	19 (17.4%)	7 (43.8%)	0.026
Peri-operative infection (%)	37 (33.9%)	5 (31.3%)	0.981

Table 4. Multivariate Logistic Regression Analysis to Evaluate Independent Risk Factors for Severe Bronchial Complications

	Odds ratio	95% Confidence intervals	*p* Value
Rejection within 1st postop. month	4.1	1.1–15.67	0.036
Interleukin-2–receptor antibody induction therapy	0.94	0.14–6.4	0.951
Tacrolimus vs cyclosporine	4.38	0.84–22.9	0.08
Severe reperfusion edema	8.3	2.1–33.1	0.002
Bronchial suture technique	0.58	0.058–5.7	0.640

We demonstrated that severe reperfusion edema is the main predictor of later bronchial complications, and we additionally state that edema formation is the only factor that was associated with prolonged post-operative ventilation. Khan et al[17] described a total edema rate of 57%, diagnosed radiographically with chest X-rays and graded into 5 severity classes. In our series, reperfusion edema was diagnosed endoscopically, using a simpler 3-scale definition. The advantage of endoscopic edema-grading may be immediate diagnosis at completion of the surgery and direct visualization of edema fluid. We are convinced that the endoscopic method is superior to evaluating chest X-rays because it is less observer dependent. Moreover, the same surgeon performed all bronchoscopies in our series, eliminating intersubjective bias.

In contrast to the results of Khan et al,[17] the need for cardiopulmonary support influenced neither edema formation nor later bronchial complications. Planned application of extracorporal membrane oxygenation (ECMO) is an established method in avoiding reperfusion edema with controlled reperfusion. In single and in bilateral lung transplantation, veno-arterial ECMO support may protect the transplanted lung from initial hyperperfusion.[18,19] However, coagulation disturbances and vascular complications caused by ECMO (e.g., aortic dissection, lymph fistula, femoral artery aneurysm) must be considered in ECMO application for indications other than hemodynamic support.

Preventing and sufficiently treating edema seem to be the prime factors in avoiding bronchial complications. The role of immunosuppressive induction therapy with IL-2–receptor antibodies in decreasing reperfusion edema remains under discussion. Experimentally, Klausner et al[20] showed that immunosupportive therapy with IL-2 leads to respiratory dysfunction caused by increased vascular permeability mediated by oxygen free-radicals.

Nevertheless, Marom et al[21] did not find a beneficial effect of IL-2–receptor antibody therapy on reperfusion edema in clinical lung transplantation. According to our study, an early rejection episode within the 1st post-operative month that requires corticosteroid therapy predisposes the patient to bronchial complications. However, it has been demonstrated that pre-transplant corticosteroid use does not adversely affect outcome after lung transplantation.[22] Further, Wilson et al[23] showed that post-operatively administered steroids had no influence on later airway complications.

In line with the St. Louis[13] and the Cordoba[14] lung transplant groups, we could demonstrate that post-operative ventilation time is prolonged significantly in patients with later bronchial complications. Experimentally, Herold et al[24] showed that a post-operative decrease in peribronchial oxygen tension can be influenced neither by improvement of pulmonary artery flow nor by the addition of nitric oxide. In contrast, Yokomise et al[25] reported the beneficial effects of increased PEEP on retrograde collateral blood flow from the pulmonary artery. In this regard, we could identify only reperfusion edema as a significant parameter associated with prolonged and invasive ventilation, yet we agree with the St. Louis group[13] that mechanical ventilation alone does not predispose a patient to bronchial complications.

Concerning initial immunosuppressive therapy, cyclosporine (but not tacrolimus), is known to have an anti-apoptotic effect because of its cyclophyllin-D–binding effect and therefore may be beneficial for bronchial viability, especially in the post-ischemic period.[26]

According to our results, we think that severe edema formation, consecutively prolonged post-operative ventilation, and early rejection enhance the risk of bronchial complications.

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