Airway complications after lung transplantation: a review of 151 anastomoses

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Abstract

Objective: To analyze the incidence, treatment and follow up of airway complications after lung transplantation. Methods: From October 1993 to April 2000, 104 lung transplants were performed in 101 patients. One hundred and fifty one bronchial anastomoses at risk were included in the study (29 single lung and 61 sequential double lung). Donor lungs were flushed both antegradely and retrogradely with Eurocollins. In the recipients, either a single or a sequential bilateral lung transplantation was performed when indicated. The bronchial anastomosis was telescoped and covered with peribronchial tissue in all cases. Postoperative fiberoptic bronchoscopic examinations were dictated by clinical grounds. Recipient variables were recorded and analyzed to assess possible differences between both complicated and non-complicated groups. Results: Eight bronchial anastomotic complications (5.3%) occurred in six patients (6.8%). All complicated cases developed in sequential bilateral lung recipients ($P < 0.08$): stenosis ($n = 5$), granulation tissue ($n = 2$), and bronchial dehiscence ($n = 1$). Treatment consisted of lobectomy and subsequent completion pneumonectomy in one patient, rigid bronchoscopy dilation in two, balloon bronchodilation in two, laser debridement and stenting in one, and conservative therapy in two cases. One patient with severe sepsis and bronchial dehiscence died on day +30. The rest of the patients remain well so far. Airway complications were related to longer intubation periods ($P < 0.01$). Other perioperative donor and recipient factors including the incidence of infections and acute rejection episodes, and actuarial survival, did not differ between groups. Conclusion: In our experience, the incidence of airway complications after lung transplantation is 5.3%. The careful surgical technique and organ preservation, the close surveillance of rejection and infection, and early postoperative extubation might play a role in reducing this incidence. Either surgical therapy or bronchoscopic dilation and stenting methods may contribute to resolve these complications. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Lung transplantation; Airway complications; Bronchial healing; Preservation

1. Introduction

Airway complications have been a major factor limiting the development of lung transplantation. In the first 15 years after the first human lung transplantation by Hardy in 1963 [1], approximately 40 lung transplants were performed with no long-term survivors, and the majority died as a result of bronchial dehiscence [2].

Lung transplantation is the only solid organ transplant in which the systemic arterial blood supply is not routinely anastomosed at the time of transplantation, and bronchial complications have been attributed to ischemia of the donor bronchus [3]. However, other factors such as rejection [4], immunosuppression [5], infections [6] or inadequate organ preservation [3] may compromise airway healing as well. The more recent improvements in patient selection, preservation, surgical technique and immunosuppressive therapy have led to a decrease in the incidence of airway complications after lung transplantation. Thus, whereas airway complications comprised up to 80% of the bronchial anastomoses performed before 1983 [7], more recently, the risk of any kind of airway complication after transplantation ranges from 10 to 15% per anastomosis, with a related mortality rate of 2 to 3% [3].

Despite these improvements, some controversy still remains regarding the ideal method for management of the bronchial anastomosis at the time of transplantation and thereafter, when a bronchial complication arises. In
the present series, we describe our experience in lung transplantation reviewing the incidence, treatment and follow-up of airway complications and determining factors related to the development of such complications.

2. Methods

2.1. Patients

From October 1993 to April 2000, 104 lung transplants were performed in 101 patients at our Hospital. Ninety patients met the study criteria, surviving at least 2 weeks after transplantation, including 29 single lung (SLT) and 61 sequential bilateral lung transplants (SBLT) (151 bronchial anastomoses at risk). Fourteen patients who did not survive more than 2 weeks died of causes unrelated to their airway anastomoses and were excluded from the study due to insufficient follow-up. The preoperative diagnosis for SLT patients was emphysema (n = 10), idiopathic pulmonary fibrosis (n = 18), and lymphangiomatomatosis (n = 1). The diagnosis for SBLT recipients was cystic fibrosis (n = 30), emphysema (n = 17), bronchiectasis (n = 7), idiopathic pulmonary fibrosis (n = 3), and other indication in four patients. Fifty-two percent of the anastomoses (15 of 29) in the SLT patients were done on the left side.

2.2. Donor lung procurement

The donor lung procurement was performed following the standard technique of combined cardiopulmonary extraction [8]. At the time of median sternotomy, the donor was given 10 mg/kg methylprednisolone (Soludomerin, Pharmacia & Upjohn, Barcelona, Spain). After the heart and lungs were dissected free, the donor was systemically anticoagulated with 300 U/kg heparin. The aorta and pulmonary artery (PA) were each cannulated in turn, and 1 mg of prostaglandin E1 was administered directly into the donor main PA before cross-clamping the aorta. The lungs were flushed antegrade via the main PA with modified Eurocollins solution (60 ml/kg, 4°C, 30 cm H₂O), venting the perfusate through the left atrial appendage. Throughout the period of perfusion and removal, the lungs were ventilated at tidal volume (F₁O₂ <1) and topically cooled. On completion of the perfusate, the heart was removed first, the trachea was double-stapled and transected, and the lungs were removed at end-tidal inflation. Immediately after lung harvesting, our practice from the start of our lung transplant program includes an additional retrograde second flushing of modified Eurocollins solution to optimize the lung preservation by perfusing the bronchial circulation [9]. The lungs were stored in 4°C modified Eurocollins solution for transportation. At bronchial dissection, the donor bronchus was shortened to two rings proximal to the upper lobe takeoff and care was taken to preserve peribronchial tissue.

2.3. Operative technique

In the recipients, either a SLT or a SBLT was performed when indicated, following the standard technique [10]. With the native lung removed, the donor implantation started with the bronchial anastomosis. In all cases the bronchial anastomoses were telescoped, either the donor bronchus into the recipient or inversely, depending on the size discrepancy between both donor and recipient bronchi. A running membranous suture with 4-0 polydioxanone (PDS) (Ethicon Inc.; Sommerville, NJ) followed by a telescoping suture with 4-0 PDS as described by Griffith et al. [11] was performed in all recipients. The bronchial anastomosis was covered with peribronchial tissue. Direct bronchial artery revascularization was not used.

After the bronchial anastomosis was completed, the pulmonary artery and the left atrium were anastomosed in a standard fashion. Cardiopulmonary bypass was instituted in case of inability to maintain the recipient on one lung during pneumonectomy or implantation, or in case of graft dysfunction after the first lung was implanted. After completion of the transplant, a fiberoptic bronchoscopy was undertaken to assess the viability of the bronchial anastomoses and to aspirate secretions in the airways.

2.4. Postoperative management

Patients were ventilated until they were able to maintain adequate gas exchange and tidal volumes. The objective was to achieve the weaning from mechanical ventilation within 48–72 h postoperatively.

Immunosuppression was based on a triple therapy: cyclosporine or tracolimus, azathioprine or mycophenolate mofetil, and steroids. Methylprednisolone administration was begun intravenously in the operating room (10 mg/kg before reperfusion). Immediately after completion of the lung transplantation, cyclosporine (Sandimmun; Novartis, Basle, Switzerland) was started at doses enough to achieve blood levels of 350–400 ng/ml, and methylprednisolone was maintained at diminishing doses until the 4th postoperative day, to be switched to deflazacort (Dezacor; Hoechst Marion Roussel, Barcelona, Spain) (1.5 mg/kg per day). Azathioprine (Imurel; Medeva Pharma, Madrid, Spain) (2 mg/kg per day) was started 48–72 h postoperatively (when the initial results of donor and recipient cultures were obtained). However, mycophenolate mofetil (Cellcept; Roche Lab. Inc. Nutley, NJ) (2–3 g/day) instead of azathioprine was given in some patients included in other trials. Patients presenting recurrent acute rejection episodes or development of bronchiolitis obliterans syndrome (BOS) were switched from cyclosporine to tracolimus (Prograf; Fujisawa, Killorglin, Co. Kerry, Ireland) at doses enough to achieve blood levels of 10–20 ng/ml. BOS was diagnosed with transbronchial lung biopsy and/or when no other explanation for persistent declines in the forced expiratory volume in 1 s (FEV₁) could be found, and scored according
to a previously proposed system [12]. No cytolitic therapy was used systematically. Episodes of acute rejection were diagnosed by clinical criteria and transbronchial lung biopsy in the absence of a positive bronchoalveolar lavage culture, and were treated with bolus doses of methylprednisolone (10 mg/kg per day) for 3 consecutive days.

Antimicrobial therapy was administered based on anti-biotic sensitivities from preoperative sputum cultures of the recipient and from the donor bronchoaspirate. Post-operative bronchoscopies were performed 24–48 h post-transplant, at the time of extubation and discharge, and thereafter whenever a clinical suspicion of infection or rejection appeared. Late postoperative routine surveillance bronchoscopies were not performed.

For purposes of this review, an airway complication was defined as a finding of dehiscence, stenosis or malacia of the airway either necessitating a therapeutic intervention (surgery, dilation, debridement, laser therapy or stent placement) or only conservative measures.

2.5. Data collection: statistics

All data were collected retrospectively. General demographic data, surgical and other postoperative variables were recorded. Pearson’s chi-square test and Fisher exact test were used to assess differences between categoric variables. Unpaired Student’s t-test was used to compare means between two quantitative variables. Actuarial survival was calculated using the Kaplan–Meier method and Log–Rank test. Data are presented as mean ± standard error. Differences were considered significant for P-values less than 0.05. The statistical analysis was performed with SPSS 5.0 for Windows software system.

3. Results

One hundred and fifty one bronchial anastomoses at risk were reviewed in 90 patients (29 SLT and 61 SBLT). Eight bronchial anastomotic complications (5.3%) occurred in six patients (6.8%). There were four men and two women with mean age of 30 ± 6 years (range 13–57 years). All complicated cases developed in SBLT recipients (P = 0.08): stenosis in five airways, granulation tissue in two and bronchial dehiscence in one case. Bronchomalacia was not seen in any patient.

Patient demographics, airway anastomotic complication type, and interval to the treatment of complications is described in Table 1. One patient with severe sepsis and bronchial dehiscence died 1 month post-transplantation. The rest of the patients remain well after the treatment or conservative measures.

Donor factors such as age, positive cultures in bronchoaspirate, intubation time, oxygenation and ischemic time, were not significantly different between patients with and without airway complications (Table 2). Recipient preoperative factors such as age, diagnosis, preoperative steroid use, and need of preoperative mechanical ventilation, were not different between both groups (Table 2). On the contrary, complicated patients presented longer periods of postoperative mechanical ventilation, and ICU and hospital stays. Number of both acute rejection episodes and pneumonia episodes were not significantly different between both groups (Table 3).

When postoperative oxygenation changes were compared between complicated and non-complicated patients, no significant differences were observed when an airway complication appeared (Fig. 1A), however, the FEV1 declined significantly in complicated patients beyond the 3rd month post-transplant when compared to those without airway complications (Fig. 1B). Despite the small number of complicated patients, actuarial survival between both groups was assessed (Fig. 2). No significant differences in survival were observed.

3.1. Management of stenosis

The majority of complicated cases presented bronchial stenosis (5 of 151 anastomoses at risk; 3.3%). They were three patients with unilateral bronchial stenosis (right in one
and left in two cases) and another with bilateral bronchial stenosis.

Patient 1 (see Table 1) developed a right bronchial stenosis distal to the anastomosis 3 months post-transplant. After several failed balloon dilatation procedures and repeated episodes of collapse and pneumonia of the middle and lower lobes, the patient underwent a lower and middle lobe bilobectomy 130 days post-transplant. A subsequent bronchial stump fistula appeared and a completion pneumonectomy was performed 1 month later. After the procedure, the patient remained well.

Patient 2 presented a bilateral bronchial anastomotic stenosis in the early postoperative period, likely related to the small lumen of the donor bronchi. The stenoses progressed until 5 and 4 mm of bronchial lumen on both sides without need of stent placement.

Patient 4 developed a left bronchial stenosis 3 months post-transplant producing repeated episodes of atelectasis and pneumonia secondary to a persistent collapse distal to the stenosis. After repeated balloon dilatation procedures and laser debridement, an 11 mm Dumon silicone stent (Bryan Corp., Woburn, MA) was placed under rigid bronchoscopy without complications. At present, the stent remains in place with good clinical results.

Patient 6 was retransplanted for obliterative bronchiolitis.

Table 2
Comparison of donor and recipient preoperative factors between both complicated and non-complicated patients (percentage of cases within each group in parenthesis)\(^a\)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Non-complicated (n = 84)</th>
<th>Complicated (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>24</td>
<td>20</td>
<td>0.21</td>
</tr>
<tr>
<td>Positive cultures in BAS (yes)</td>
<td>29 (34)</td>
<td>2 (33)</td>
<td>0.67</td>
</tr>
<tr>
<td>Gram negative</td>
<td>5 (6)</td>
<td>0</td>
<td>0.81</td>
</tr>
<tr>
<td>Gram positive</td>
<td>24 (28)</td>
<td>1 (17)</td>
<td>0.73</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>6 (6)</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>Candida</td>
<td>2 (2)</td>
<td>0</td>
<td>0.92</td>
</tr>
<tr>
<td>Multi-resistant</td>
<td>12 (14)</td>
<td>1 (17)</td>
<td>0.44</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>43</td>
<td>67</td>
<td>0.30</td>
</tr>
<tr>
<td>PaO(_2)/FiO(_2) (mmHg)</td>
<td>451</td>
<td>520</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischemic time (2nd lung) (min)</td>
<td>489</td>
<td>496</td>
<td>0.68</td>
</tr>
<tr>
<td>Recipient</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37</td>
<td>30</td>
<td>0.36</td>
</tr>
<tr>
<td>Diagnosis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>24 (28)</td>
<td>3 (50)</td>
<td>0.07</td>
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<tr>
<td>Cystic fibrosis</td>
<td>28 (33)</td>
<td>2 (33)</td>
<td></td>
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<tr>
<td>Obliterative bronchiolitis</td>
<td>0</td>
<td>1 (17)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>21 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Preop. steroid use (yes)</td>
<td>51 (61)</td>
<td>2 (33)</td>
<td>0.91</td>
</tr>
<tr>
<td>Preop. mechanical ventilation (yes)</td>
<td>10 (12)</td>
<td>1 (17)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

\(^a\) BAS, donor bronchoaspirate; COPD, chronic obstructive pulmonary disease.

Table 3
Comparison of recipient postoperative factors between both complicated and non-complicated patients (percentage of patients within each group in parenthesis)\(^a\)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Non-complicated (n = 84)</th>
<th>Complicated (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLT</td>
<td>29 (34)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>SBLT</td>
<td>55 (65)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>CPB (yes)</td>
<td>6 (7)</td>
<td>0</td>
<td>0.79</td>
</tr>
<tr>
<td>Mechanical ventilation (h)</td>
<td>28</td>
<td>142</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>4</td>
<td>16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>23</td>
<td>36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Acute rejection episodes (n)</td>
<td>1.7</td>
<td>2</td>
<td>0.85</td>
</tr>
<tr>
<td>Pneumonia episodes (n)</td>
<td>3.5</td>
<td>4</td>
<td>0.53</td>
</tr>
</tbody>
</table>

\(^a\) SLT, single lung transplant; SBLT, sequential bilateral lung transplant; CPB, cardiopulmonary bypass; ICU, intensive care unit.
and developed a left bronchial stricture soon after transplantation. To date, the patient has been successfully managed with several dilatation procedures under rigid bronchoscopy. The proximity of the left upper lobe takeoff has obstructed the stent placement and, probably, the progression of the stenosis will need a pulmonary resection in the future.

3.2. Management of exophytic granulation tissue

Only patient 5 presented a bilateral stenosis secondary to a granulation tissue ingrowth. This patient has had the airway colonized by Pseudomonas sp. and Candida, therefore, a conservative therapy has been followed. Nevertheless, with the airway infection controlled, laser ablation will be the therapy of choice.

3.3. Management of dehiscence

We have not observed partial bronchial dehiscence in this series. Patient 3 presented a severe left bronchial dehiscence few days after the lung transplant. He underwent a previous bilateral lung volume reduction surgery for emphysema and after a difficult dissection and double lung implantation, with long ischemic times and intraoperative hemodynamic instability, the patient developed an early graft dysfunction and cardiac failure. The left bronchial dehiscence progressed with no attempt to resuturing the bronchus due to the severity of the patient. He died on 30 postoperative day due to sepsis and multiorgan failure.

4. Discussion

Airway complications have been one of the main limiting factors of lung transplantation [7], and continue to occur despite advances in operative technique and organ preservation. The early experience with en-bloc double-lung transplantation revealed a high incidence of lethal tracheal anastomotic dehiscences. The sequential bilateral lung transplantation was then developed with the expectation that airway complications would be similar to those observed after single lung transplantation. Among 28 SBLT performed by the St. Louis Group [13], there was only one lethal airway necrosis and another eight patients (29%) experienced various airway complications. In SLT, the experience has been more favourable with a risk of airway complications ranging from 10 to 15% and a related mortality of 2 to 3% [3]. Improvements in lung preservation and bronchial anastomotic technique have significantly diminished the incidence of severe bronchial anastomotic complications. In our series, the incidence of bronchial complications (5.3%) was below the reported incidence in larger series.

Several factors play a role in the etiology of airway complications. Bronchial ischemia is thought to be a significant contributor to the development of complications. The bronchial arterial circulation is lost during the harvest of the donor lungs. Consequently, the viability of the donor bronchus is initially dependent upon retrograde low-pressure collaterals derived from the pulmonary artery [4]. Thus, several techniques have been developed to protect the bronchial anastomosis such as keeping the donor bronchus as short as possible and wrapping the anastomosis...
with vascularized pedicles [3]. Also, direct revascularization of donor bronchial arteries has been attempted [14], however, there is currently no evidence to support its use as superior to modern airway anastomotic techniques without bronchial revascularization [15]. In addition, we recently reported the possible beneficial effect of double antegrade and retrograde flush perfusion in the donor lungs at the time of harvest, by preserving the bronchial circulation and favoring the bronchial healing [9]. Possibly, this technique might play a role in the low incidence of bronchial complications reported herein.

Other risk factors are thought to play a role in the pathogenesis of airway complications. Initially, it was believed that perioperative steroid therapy might have a deleterious effect on airway healing [5]. With further experience, it has been demonstrated that low doses (<15 mg/day) may not be dangerous or even beneficial due to its effect preventing rejection and ameliorating the reperfusion injury [16]. In our experience, low to moderate doses of steroids pre and postoperatively did not affect bronchial healing (Table 2). The acute rejection has been correlated with anastomotic stenosis by the increase in pulmonary vascular resistance and decreased pulmonary collateral bronchial blood supply [17]. However, in our series, as in others reported previously [18], no significant differences were found between complicated and non-complicated patients in terms of acute rejection episodes. Although infrequent, acute rejection episodes within the 1st week post-transplant usually respond to steroid therapy, and beyond 7–10 days a new blood supply to the bronchial anastomosis has been established, thus, rejection did not prove to be a risk factor for bronchial complications in our series. Similarly, although infections may impair the bronchial healing [3], and a higher rate of airway complications have been reported in patients with septic lung disease (cystic fibrosis) [6], we have not observed more incidence of pneumonia episodes in complicated patients. On the contrary, those patients with prolonged mechanical ventilation developed more frequently airway complications (Table 3), but it has been reported that mechanical ventilation itself does not predispose to increased incidence of airway complications since positive end-expiratory pressure augments retrograde collateral bronchial mucosal flow [19]. Therefore, other factors such as the presence of early graft dysfunction among others, may explain this observation.

The anastomotic technique is also a critical factor in minimizing airway complications. Not only the shortening of the donor bronchus, but also the telescoping anastomosis has proved to be useful in preventing bronchial anastomotic complications [3]. More recently, some investigations have demonstrated no additional advantage of the telescoping technique over the end-to-end anastomosis [15], however, due to the low rate of airway complications, we have been using the telescoping technique from the start of our lung transplant program. Therefore, possible differences among surgical techniques were not assessed.

Despite the significant number of lung transplants performed in this series, the few cases of airway complications observed did not allow a consistent statistical analysis of the various perioperative variables discussed above. Tables 2 and 3 show several donor and recipient perioperative factors that might be implicated in the development of airway complications, however, due to the few number of complicated cases, no significant differences were observed. Only a longer postoperative intubation time, and subsequent longer ICU and hospital stays were observed in patients with bronchial complications. Probably, those causes leading to a prolonged mechanical ventilation rather than the prolonged intubation time itself might play a role in the pathogenesis of bronchial complications.

Bronchial stenosis has been the most frequent complication after transplantation and several therapeutic options have been reported. Anastomotic obstruction caused by exophytic granulation tissue can usually be managed by rigid bronchoscopy with or without laser debridement [6]. Also, a silicone stent placement may be an option after laser debulking. The patient 5 in this series presented a bilateral stenosis secondary to granulation tissue, but his airway was colonized by *Pseudomonas* sp. and *Candida*, and no attempt to laser ablation has been made yet. Scar or ischemic stenoses (not granulomatous) at the anastomotic level or distal to the anastomosis are usually treated successfully with repeated dilatations under rigid bronchoscopy [20] or balloon dilatations under flexible bronchoscopy [21], with laser debridement and either silicone or expandable metal stents [22], and also surgically with lung resections or retransplantation [23], although these latter procedures have been made occasionally. In our limited experience, the patient who underwent a silicone stent placement after laser debulking did well without dislodgement, mucus plugging or granulation tissue growing around the end of the stent, as it has been reported previously [3,15]. The experience of surgical resection for these patients is limited. The Hannover Group [23] performed sleeve resections of stenotic bronchial segments with good results. When the stenosis extends down into the upper and lower lobe bronchi, lobectomy, pneumonectomy or retransplant may be the only solution. In our experience, the possibility of a surgical resection for those patients with distal airway stenoses complicating the lung parenchyma is an option to be considered. Thus, patient 1 of our series, presenting a long stenosis of the intermediate bronchus without improvement after several dilatation procedures, underwent a surgical resection (bilobectomy and subsequent completion pneumonectomy) with excellent clinical and functional postoperative status.

Bronchial dehiscence remains a disastrous complication in the post-transplant period. Most cases occur early after transplantation, are difficult to treat, and are associated with high mortality. Partial dehiscences can be treated expectantly, and usually heal satisfactorily when an adequate pleural drainage maintains the lung parenchyma expanded.
[3,15]. Conversely, complete dehiscence is generally catastrophic and an attempt at repair is appropriate as an initial step [24], but it has a high failure rate and may result in transplant pneumonectomy. Our experience with dehiscence has been disappointing. The severe postoperative status of the patient 3 obstructed the reintervention and died 1 month post-transplant due to severe sepsis and multi-organic failure. To date, we have not observed malacic airways in our series. In summary, in our experience the incidence or airway complications after lung transplantation is 5.3%. The careful surgical technique and organ preservation, the close surveillance of rejection and infection, and early postoperative extubation might play a role in reducing this incidence. Either surgical therapy or bronchoscopic dilatation and stenting methods may contribute to resolve these complications.

References