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Bronchial complications after lung transplantation are associated with primary lung graft dysfunction and surgical technique

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BACKGROUND: After lung transplantation, bronchial complications are one of the major concerns for surgeons and physicians. In the era of evolving immunosuppressive regimens and surgical approaches, we have reassessed risk factors for bronchial complications after lung transplantation.

METHODS: We undertook a retrospective study of all consecutive lung transplantations performed at a single center from 2004 to 2014. We monitored the incidence of symptomatic bronchial complications. Demographic data of donors and recipients were also studied. Our objective was to evaluate the impact of 3 subsequent immunosuppressive regimens (including the use of induction therapy), and of a technical modification of bronchial anastomosis on the incidence of airway complications.

RESULTS: We performed 270 consecutive lung transplantations during the study period. On multivariate analysis, bronchial complications were not directly associated with the different immunosuppressive regimens. In subgroup analysis, when comparing different immunosuppressive regimens, primary graft dysfunction within 72 hours (odds ratio [OR] = 2.55; $p = 0.08$), lung infection within the first month (OR = 2.96; $p = 0.039$), diabetes before transplantation (OR = 2.66; $p = 0.11$) and chronic obstructive pulmonary disease (OR = 2.20; $p = 0.04$) appeared as major risk factors (c-index = 0.77 on multivariate analysis). The use of a modified bronchial suture technique was associated with fewer bronchial complications (OR = 0.47; $p = 0.059$) (c-index = 0.71 on multivariate analysis).

CONCLUSIONS: The mode of immunosuppression had no influence on airway complications. We were able to reproduce the beneficial effect of a modified suture technique.

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Lung transplantation is the only life-sparing treatment for patients reaching end-stage respiratory disease. Impaired healing of the bronchial anastomosis was the first complication ever reported in its history.[1] Bronchial complications

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appear with considerable incidence, ranging from 4.9% to 18%, and dependent mortality ranges from 2% to 4%.[2] Bronchial complications are one of the major concerns of transplant surgeons and physicians. First attempts at classification were made by Couraud et al in 1992 and by Shennib and Massard in 1994, based on bronchoscopy findings, without considering clinical relevance.[3,4] Another grading system based on symptomatic events was presented by Date et al.[5] Pejorative-looking necrosis may have no consequences for the patient, whereas a small fistula may cause prolonged air leak with the need for prolonged chest tube drainage or surgical repair. Stenosis or malacia lead to loss of respiratory function with sputum retention and require repeated bronchoscopy for dilation or stenting. Complete dehiscence may have dramatic consequences, with massive hemoptysis and rupture into the pulmonary artery.[5]

Several studies have aimed at identifying risk factors for airway complications. Modulation of the common final pathway, represented by bronchial ischemia, is influenced by various factors, including duration of cold ischemia during organ preservation, mechanical ventilation in the donor, mechanical ventilation in the recipient, post-operative complications, steroids and immunosuppressive regimens and surgical technique.[2–8]

Recent insights identified at least 3 areas where innovative approaches can interfere: immunosuppressive therapies; surgical technique; and primary graft dysfunction (PGD).

Immunosuppressive drugs have revealed anti-proliferative properties. For example, inhibitors of mammalian target-of-rapamycin (mTOR) were prohibited after the report by Groetzner et al on bronchial dehiscence and massive hemoptysis.[8] Use of steroids in this setting has been controversial: they have been considered to have anti-proliferative characteristics and to cause complications, yet their anti-inflammatory effects may also support better healing.[9,10] Most transplant teams start steroids intra-operatively and maintain use from the initial post-operative period.[11,12] In the majority of published series on bronchial complications, immunosuppression consisted of combination cyclosporine and azathioprine. A single study compared cyclosporine with tacrolimus, and azathioprine with mycophenolate mofetil (MMF).[13] The authors obviated a higher complication rate when tacrolimus was given; the difference was close to significance on multivariate analysis (odds ratio [OR] = 4.38; $p = 0.08$).[13]

As use of immunosuppressive drugs is mandatory, improving the surgical technique is a critical issue. For Date et al, use of a mattress suture caused bronchial complications when compared with a simple suture or figure-of-eight suture.[5] The respective effect of end-to-end versus telescoping anastomosis remains controversial. Early experimental work in the 1970s demonstrated that the shorter the donor bronchus is trimmed, the less the severe the ischemia.[14,15] Based on the clinical observation that necrosis most often occurs in the terminal main bronchus of the donor or in the truncus intermedius, Weder et al demonstrated that extended trimming of the donor bronchus down to the lobar carina significantly lowered the prevalence of bronchial complications. The investigators reported no dehiscence[16]; the rate of airway complications was 4.9% at 1 month and 2.4% at 6 months.[16] Quite similarly, van Berkel et al reported the same beneficial effect.[17]

Finally, reperfusion injury may be detrimental to bronchial healing, because interstitial pulmonary edema opposes to the collateral blood flow from the pulmonary to the bronchial arteries.[2,18] In this study we aimed to assess the influence of newer immunosuppressive drugs and the Weder-type bronchial trimming technique on healing of the bronchial anastomosis. The impact of PGD was studied as well.

Methods

Study design

We conducted a retrospective study that included all patients who underwent lung transplantation at our institution between January 1, 2004 and December 31, 2014. The study was approved by the ethics committee for clinical research of the French Society for Thoracic Surgery. The record of each lung transplant recipient was screened for donor and recipient demographic characteristics, details of the surgical procedure, immunosuppressive regimen, immediate post-operative outcome (especially occurrence of PGD according to the International Society for Heart and Lung Transplantation [ISHLT] grading system[19]) and the mid-term outcome events up to 6 months after the transplantation (Tables 1 and 2).

Objectives

The main objective of our study was to ascertain the impact of 3 different immunosuppressive regimens and a modified surgical technique on the incidence of airway complications. We assessed the different immunosuppressive regimens, the surgical technique

Table 1 Recipient and Donor Characteristics of Study Patients

Recipient
Demographic and medical history
Age at the time of LTx (years)
BMI (kg/m^2)
Denutrition (defined as BMI $<$18 kg/m^2)
Diabetes before LTx
Immunosuppressive therapy at the time of LTx
Oral steroids before LTx
Lung disease indication for LTx
COPD
Fibrosis
CF
Other, including re-transplantation and pulmonary hypertension
Donor
Age at the time of organ donation
Cause of death
PaO_2: arterial partial pressure of oxygen at the time of lung acceptance when ventilated with 100% inspired fraction of oxygen and 5 cm
H_2O positive end-expiratory pressure

BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; LTx, lung transplantation.