Reflux and Allograft Dysfunction: Is There a Connection?

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KEYWORDS

• Lung transplantation • Gastroesophageal reflux disease • Fundoplication • Antireflux surgery
• Gastroduodenal aspiration • Allograft dysfunction • Bronchiolitis obliterans syndrome
• Chronic lung allograft dysfunction

KEY POINTS

- Patients undergoing lung transplantation have a higher rate of reflux after transplantation than before, whether caused by the surgical procedure itself or treatment-related effects (eg, immunosuppressive medications).
- Reflux following lung transplantation is associated with an increase in gastroduodenal aspiration, and this is associated with decreased lung function.
- There are limited data on the association of reflux and survival.
- Antireflux surgery is safe and the preferred method for treating documented reflux in the lung transplant population.
- Although data have demonstrated that lung function stabilizes following antireflux surgery, there is limited information with regards to survival benefit.

INTRODUCTION

Lung transplantation has seen tremendous growth since 1963 when the first lung was transplanted into a 58-year-old man suffering from squamous cell carcinoma.[1] Although the patient only survived for 18 days, it provided a new option for the treatment of patients with end-stage lung disease.[1] As of 2011, 3640 single and bilateral orthotopic lung transplantations were being performed per year.[2] Survival has steadily increased and as of 2013, median survival following transplantation was 5.6 years, up from 5.3 years in 2010.[2,3] Despite improving success, certain complications associated with lung transplantation continue to limit optimal survival. Earliest among these is primary graft dysfunction, which is defined as hypoxia, pulmonary edema, and pulmonary infiltrates that occur immediately following transplantation.[4] Although often transient, it continues to be a significant source of early mortality.[5]

BRONCHIOLITIS OBLITERANS SYNDROME

Following the acute period, most morbidity and mortality in lung transplantation is associated with either infectious complications or the development of bronchiolitis obliterans.[6] Bronchiolitis

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obliterans is a histopathologic diagnosis consisting of fibrous scaring of the lung tissue leading to a progressive decrease in the forced expiratory volume in 1 second (FEV_1).[7] This tissue-based diagnosis is consistent with most chronic rejection. Given the difficulty of obtaining a tissue diagnosis, the term bronchiolitis obliterans syndrome (BOS) was devised to account for patients demonstrating a progressive reduction in airflow (decreasing FEV_1) following lung transplantation without another identifiable cause.[7,8] BOS is categorized by five distinct stages each defined by a percent reduction from baseline FEV_1 or forced expiratory flow between 25% and 75% of the forced vital capacity (FEV_{25-75}; **Table 1**).[7,9]

More recently, a new terminology has been developed to categorize patients with declining allograft function termed chronic lung allograft dysfunction, which includes BOS along with other less characteristic forms of persistently decreased lung function (**Fig. 1**).[10] Furthermore, restrictive allograft syndrome, a subset of chronic lung allograft dysfunction with a physiologically different presentation than BOS, has been demonstrated to have even worse survival than most patients with chronic lung allograft dysfunction.[11] These patients present with more restrictive findings on pulmonary function testing, often characterized as a decline in total lung capacity.[11]

Numerous factors have been associated with the development of BOS, including chronic rejection, repeat episodes of acute rejection, infection, and gastroesophageal reflux disease (GERD).[12–14] Hartwig and colleagues[14] demonstrated that patients with abnormal pH probe testing had increased rates of decline in their FEV_1 following lung transplantation, and that this decline was significantly worse if patients did not undergo fundoplication. Despite these data and evidence from other single institution studies, it has only been demonstrated that there is an association between reflux and allograft dysfunction, not a cause-effect relationship. This article reviews the current evidence regarding the role of reflux in allograft dysfunction (**Box 1**).

Table 1
Classification of bronchiolitis obliterans syndrome

BOS Classification	Diagnostic Criteria
BOS 0	FEV_1 >90% and FEF_{25-75} >75% of baseline
BOS 0-p	FEV_1 81%–90% and/or FEF_{25-75} ≤75% of baseline
BOS 1	FEV_1 66%–80% of baseline
BOS 2	FEV_1 51%–65% of baseline
BOS 3	FEV_1 ≤50% of baseline

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1, forced expiratory volume in 1 second.

Data from Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002;21:297–310; and Bando K, Paradis IL, Similo S, et al. Obliterative bronchiolitis after lung and heart-lung transplantation. An analysis of risk factors and management. J Thorac Cardiovasc Surg 1995;110:4–13 [discussion: 13–4].

REFLUX FOLLOWING LUNG TRANSPLANTATION

For the purposes of this article, "reflux" is referred to as contents that are of a gastroduodenal nature that regurgitate up the esophagus into the pharynx. The hypothetical role of reflux in the development of BOS is because of aspiration, or the inhalation of reflux contents into the lungs. For obvious reasons, aspiration of either gastric or duodenal contents into the allograft can lead to substantial harm. Unfortunately, significant evidence has demonstrated that lung transplantation itself may increase the rate of reflux. For instance, Young and colleagues[15] demonstrated significant increases in abnormal acid contact during 24-hour pH monitoring following lung transplantation compared with before. Furthermore, studies have demonstrated reflux is increased in patients undergoing bilateral lung transplantation compared with single lung transplantation, and increased reflux is also seen in patients undergoing retransplantation as compared with primary transplantation.[16,17] Lastly, Ward and colleagues[18] and Stovold and colleagues[19] demonstrated that, compared with nontransplant recipients, post–lung transplant patients have increased levels of pepsin, a protein produced in the stomach, in bronchoalveolar lavage (BAL) fluid, although whether this is caused by the transplant or the underlying diagnosis is unclear. Together, these studies suggest that some process of the surgical procedure may increase the rate of reflux. It has been hypothesized that, because of the anatomic proximity of the vagal nerve to the surgical site, this may be caused by vagal nerve manipulation, which is known to cause issues with gastroparesis and reflux following several upper abdominal surgeries.[20–22] Alternatively, it may be secondary to the side effects of immunosuppression required for transplantation.[21]

Nonacid Reflux

Although pH monitoring is traditionally associated with the diagnosis of reflux, there is also significant