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A review of the role of GERD-induced aspiration after lung transplantation

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Abstract

The increased prevalence of gastroesophageal reflux disease (GERD) in lung transplantation patients has been established; however, many questions persist regarding the relationship of GERD to aspiration and its potential to induce pulmonary allograft failure. Moreover, the biological implications of aspiration in lung transplantation have yet to be fully elucidated. The goal of this review was to assess the relationship between GERD and aspiration, focusing on the role of these events in the development of allograft injury after lung transplantation.

Keywords

Gastroesophageal reflux disease (GERD); Aspiration; Lung transplantation; Ambulatory pH-monitoring; Esophageal multichannel pH impedance; Laparoscopic antireflux surgery (LARS)

Lung transplantation is a well-accepted therapeutic option for selected patients with end-stage lung disease. However, the median survival of patients after lung transplantation is only 5 years, whereby allograft failure is most often the consequence of distal airway fibrosis, resulting in obliterative bronchiolitis (OB) [1, 2]. In addition, bronchiolitis obliterans syndrome (BOS), the physiological hallmark of OB, develops in almost half of lung transplant recipients within 5 years and is a source of considerable morbidity because of its detrimental effect on lung function and quality of life [1].

The pathophysiology of OB is poorly understood. However, evidence suggests that OB might represent a nonimmunologic aberrant response to a chronic stimulus injury [3–6]. Gastroesophageal reflux disease (GERD) can be responsible for this chronic injury. Several studies have shown that the presence of GERD in lung transplant recipients is a risk factor for the development and progression of BOS because of the high prevalence of GERD demonstrated after lung transplantation and because surgical control of GERD may control

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the decline in lung function characteristic of BOS [4–6]. Other studies have shown that the mechanism by which lung injury occurs in patients with GERD after lung transplantation might be due to the aspiration of gastroduodenal refluxate. In an animal model of aspiration after lung transplantation, Hartwig et al. [3] and Li et al. [7] found that exposure of the lung to gastric contents promoted accelerated allograft failure and BOS.

The current literature, however, supports only a strong association between GERD and BOS, but not causality. Evidence of aspiration involves the direct detection of substances from the lungs that are produced exclusively in the gastrointestinal tract, such as bile acids and pepsin. Invasive pH-monitoring, which is the most common test for the diagnosis of GERD today, functions only as a surrogate marker of risk for aspiration though it cannot diagnose aspiration itself. In essence, the presence of GERD does not automatically imply aspiration or predict lung damage. Studies have shown that dual pH-monitoring can identify patients with distal and proximal reflux, but it falls short of being able to identify which of these patients aspirate. Sweet et al. [8] have shown that although GERD may be related to aspiration, the value of proximal pH-monitoring is unreliable for its diagnosis. They showed that proximal esophageal pH testing, as described by D'Ovidio et al., had a sensitivity of 75%, specificity of 81%, and a likelihood ratio of 4 for detecting molecular markers of aspiration in the bronchoalveolar lavage (BAL) [8]. Another drawback of esophageal pH-monitoring is that it is able to detect acid reflux only in the esophagus. However, esophageal multichannel intraluminal impedance can detect and quantify the gastroesophageal reflux while the patient suppresses acid secretion by taking proton pump inhibitors (PPIs) (i.e., nonacid reflux) [9]. A study that characterized acid and nonacid reflux by esophageal impedance and the degree of aspiration (measured by both pepsin and bile acids in the BAL) showed that 71% of lung transplant recipients on PPIs had increased nonacid reflux and that treatment with PPIs was not associated with reduced total number of reflux events, number of nonacid reflux events, and volume exposure or proximal extent of reflux [10]. Moreover, pepsin and bile acids in the BAL were not reduced by PPIs. This is an important finding, as it suggests that only surgical correction of reflux could control the aspiration of gastroduodenal contents. Nevertheless, this study did not propose a definite cause–effect relationship between GERD and lung injury after lung transplantation.

Establishing such a causal role implies that one must be sure that the cause precedes the effect and that the effect has not been caused by other factors. When such logic cannot be definitively proven, then proof of causality requires the fulfillment of other criteria such as strength and consistency of associations, a temporal and dose-dependent relationship, and biological plausibility [11]. Some studies have attempted to prove these conditions by studying the presence of markers of aspiration in the BAL of lung allografts. A study by Ward et al. [12] found pepsin in the BAL of all 13 patients after lung transplantation and no pepsin in the BAL of controls. Stovold et al. [13], in their cross-sectional study of 36 lung transplant patients, have shown that elevated levels of pepsin were consistently detected in the BAL of lung allografts (stable recipients, subjects with acute rejection, and subjects with BOS), with the highest levels found in the patients with acute rejection. D'Ovidio et al. [14] found that 20 of 120 lung transplant patients had high concentrations of bile acids, with the highest concentrations found in 70% of patients with early onset (<1 year post transplant) and high severity of BOS, suggesting a temporal and a dose-related association. The authors also reported a putative mechanism of biological plausibility by illustrating that elevated bile acids in the BAL were associated with alveolar neutrophilia and high concentrations of interleukin-8 (IL-8), two factors that may be involved in an inflammatory process and early development of BOS. Interestingly, similar increases in IL-8 levels and neutrophilia have recently been demonstrated in a porcine model of aspiration-induced acute lung injury, highlighting this as a potential response to aspiration-induced inflammation in humans [15]. In another study, a temporal and dose-dependent relationship was observed between the

presence of bile acids in the BAL at 3 months after lung transplant and development of BOS [16]. In this study, the incidence of BOS at 30 months among patients with high levels of bile acids in the BAL was four times higher than that of patients with undetectable bile acids. The authors also found that the presence of bile acids in the BAL was associated with decreased surfactant proteins and surfactant phospholipids. These findings suggested that aspiration of bile acids might have caused lung injury by impairing the innate immunity of the allograft [16]. Finally, in another cross-sectional study, Blondeau et al. [10] detected pepsin in the BAL of all patients with reflux after lung transplant, and bile in the BAL of only half of the patients. The median concentration of pepsin detected in the BAL of lung transplant patients was higher than in nontransplant patients. In contrast to the results of Stovold et al., Blondeau et al. [10] failed to detect elevated pepsin in the BAL or increased esophageal reflux on pH-monitoring in patients with BOS. However, 70% of the patients with BOS had bile acids in the BAL compared with 31% of patients without BOS. These results suggested that pepsin might be a very sensitive marker of aspiration, whereas bile acids are a more specific marker of BOS [10]. This is interesting because although GERD might cause aspiration, this event may not automatically be connected to chronic rejection after lung transplantation.

If aspiration is a link between GERD and BOS, one would also expect that increased concentrations of markers of aspiration would be associated with a more rapid decline in lung allograft function and a higher incidence of BOS, and that surgical treatment of aspiration, as suggested by Blondeau et al., would preserve, or improve, pulmonary allograft function. Our group aimed to prove this hypothesis in a prospective study on 64 lung transplant patients in whom we collected BAL over time, which was then tested for pepsin [17]. We then compared pepsin concentrations in the BAL of 11 healthy controls and those lung transplant patients with and without GERD on pH-monitoring, and after treatment of GERD by laparoscopic antireflux surgery (LARS). We also compared the time to the development of BOS between groups based on GERD status or the presence of pepsin in the BAL. We found that pepsin concentrations were absent in controls, elevated in the BAL of lung transplant patients regardless of their reflux status, and lower in patients after surgical correction of reflux compared to patients with GERD who did not undergo LARS [17]. Moreover, we showed that those with evidence of aspiration as determined by detectable pepsin concentrations in their BAL had a quicker progression to BOS than those without detectable pepsin levels [17]. While previous studies supported only a strong therapeutic potential of LARS in treating GERD and BOS, our study, which focused mainly on the direct detection of aspiration over time, may have confirmed the role of LARS in the management of these patients by supporting a pathogenic role of pepsin in aspiration-induced lung failure. However, as with most other studies focused on GERD, aspiration, and BOS in lung transplantation, our study investigated neither the definitive pathogenic mechanism by which the aspiration event can cause lung allograft injury at the cellular and molecular level nor how LARS may be protective from such injury. In perhaps the only study to date that assessed the immunological impact of LARS in lung transplant patients; Neujahr et al. [18] demonstrated a significant reduction in potentially damaging effector CD8 cells in the BAL fluid after surgical correction of GERD. Although it was a small series of only eight patients, the authors were able to document a plausible means to explain the pattern of allograft protection that LARS appears to afford lung transplant patients with GERD. They correctly concluded that randomization of patients may be required to establish LARS as the standard of care in these patients. Finally, it is also apparent that a greater understanding of aspiration at the cellular and molecular levels is needed to solidify the role of LARS for GERD in lung transplantation.

In the absence of a concrete biological mechanism by which aspiration may cause lung injury, the target of therapy has focused on LARS as a treatment of GERD and a means of

stopping GERD-induced aspiration after lung transplantation. Consequently, our group has reported an acceptable safety profile of LARS in these patients, which we do as a total 360° Nissen fundoplication as early after lung transplantation as possible, dependent on the tolerability of general anesthesia [19, 20]. Patients are deemed candidates for LARS on the basis of positive esophageal pH-monitoring, the presence of pepsin in the BAL fluid, and/or evidence of aspiration on transbronchial biopsy (defined by the presence of exogenous material with foreign-body giant-cell reaction, large lipid droplets, and/or macrophages with large vacuoles). The rationale behind the surgical treatment of reflux is that GERD-induced aspiration is a mechanical process that can be treated by restoring a physiologic antireflux barrier. This is in contrast to the mechanism of PPIs, which only alter the pH of the refluxate with no protective affect against nonacid reflux. This latter point is important since Mertens et al. [21] have shown that patients treated with PPIs nonetheless may still demonstrate evidence of an inflammatory reaction in bronchial epithelial cells. Therefore, though PPIs may reduce the acidity of gastroesophageal refluxate, they seem to have a limited (if any) role in preventing aspiration in these patients. Conversely, prokinetic agents (such as macrolide antibiotics and metoclopramide) might play an important therapeutic role. However, Mertens et al. [22] have shown that aspiration of bile acids reduces survival in lung transplant recipients with BOS despite azithromycin; thus, it appears that the efficacy and mechanism of prokinetics for preventing BOS requires further investigation. Hopefully a randomized clinical trial currently underway at Duke University will clarify the role and indication for LARS and medical therapy for GERD and aspiration in these patients.

Conclusions

Altogether, evidence seems to strongly support the causal role of GERD-induced aspiration in the development of lung transplant failure. However, no study is conclusive. Upcoming research should aim at identifying the underlying pathogenic mechanism of allograft injury. Moreover, as many of the published studies are cross-sectional, future longitudinal studies should prospectively evaluate larger cohorts of patients with longer follow-up. These studies should also include standardized comparisons of clinical, laboratory, and pathology findings which would identify correlations to lung function, infection status, and number and severity of rejection episodes. Finally, the role of LARS is increasingly recognized as a valid therapeutic option for GERD-induced aspiration after lung transplantation. LARS corrects the mechanical risk factors for GERD, and by restoring the antireflux barrier it can effectively prevent aspiration, may restore or stabilize lung function, and potentially impact lung transplant recipient survival.

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