Review Article

Secrets for successful laparoscopic antireflux surgery: patients with pulmonary diseases

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Abstract: Gastroesophageal reflux disease (GERD) has been associated to a spectrum of respiratory disorders such as idiopathic pulmonary fibrosis (IPF), asthma, and chronic obstructive pulmonary disease (COPD). Several factors including increased trans-diaphragmatic pressure gradient, flattening of the diaphragm, and medication side effects affecting relaxation of the lower esophageal sphincter have linked GERD with pulmonary diseases. While medical therapy alters the pH of the gastric juice, it does not eliminate the occurrence of gastroesophageal reflux episodes, which cause regurgitation and respiratory symptoms. Selected group of patients with pulmonary disease and proven GERD may benefit from antireflux surgery.

Keywords: Gastroesophageal reflux disease (GERD); pulmonary diseases; anti-reflux surgery; lung transplant

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Introduction

Antireflux surgery has made great strides to address the growing prevalence of gastroesophageal reflux disease (GERD). In North America, it is estimated that 20% of people suffer from symptoms of GERD (1,2). GERD has been linked to a spectrum of respiratory disorders such as idiopathic pulmonary fibrosis (IPF), asthma, and chronic obstructive pulmonary disease (COPD) (2-6). Healthcare expenditures related to extra-esophageal symptoms have been projected to surpass 50 billion dollars, and 86% of this expense is related to pharmaceutical cost (7).

The physiologic processes to explain the relationship between GERD and lung diseases are multifactorial and not completely understood. Several factors including increased trans-diaphragmatic pressure gradient, flattening of the diaphragm, and medication side effects affecting relaxation of the lower esophageal sphincter play a role (8-10). Teasing out the causative effects of these processes will help develop clear treatment strategies to slow or reverse their impact on respiratory conditions.

This has been studied most aggressively in the lung transplant population as pre-transplant GERD has been linked to poor survival and worse acute graft function (11). Medications, including H2 blockers and proton pump inhibitors (PPI), are commonly prescribed in these patients. However, medications alone do not address silent non-acidic reflux, food granules, and inflammatory mediators that can contribute to worsening pulmonary disease. Recent studies associating negative long-term side effects such as osteoporosis and pneumonia to chronic PPI use contribute to the growing evidence supporting surgical intervention (12). Antireflux surgery remains the gold standard to ensure GERD does not lead to exacerbation of pulmonary disease.

The aims of this manuscript are to review current

literature associating pulmonary diseases to GERD, and detail the role of antireflux surgery in the treatment algorithm of these conditions.

Difficulties in diagnosing GERD in lung disease patients

Several symptoms used to diagnose GERD share common ground with respiratory conditions. These include chronic cough, hoarseness, and dyspnea. Although rare, some patients may present with only extra-esophageal complaints, which are attributed to their primary lung condition. On the other hand, some patients with GERD may be asymptomatic but are experiencing pulmonary sequela from their silent reflux. In fact, 30% of people in a cohort study of 822 patients with a clinical diagnosis of GERD had normal ambulatory pH monitoring (13).

Therefore, it is important to diagnose GERD carefully with objective data when patients present with known GERD-related symptoms or belong to at-risk patient populations. For instance, abnormal distal reflux by 24-hour pH monitoring was diagnosed in 87% of 65 patients with IPF and in 68% of 109 lung transplant candidates (14,15). Other components of GERD have been documented in end stage lung disease. Keshavjee *et al.* showed an incidence of hypotensive lower esophageal sphincter in almost 80% of patients awaiting lung transplant; additionally, 44% of this population had delayed gastric emptying (16). Abnormal or absent peristalsis such as in scleroderma may contribute to symptomatology. Abnormal esophageal motility has been linked to delayed acid clearance and more severe mucosal injury (17-19). Correction of reflux by fundoplication has been shown to also improve peristalsis (20).

Pathophysiology of GERD in relation to bronchoconstrictive diseases

GERD is a highly prevalent condition in patients with asthma, COPD, and cystic fibrosis (CF). Due to the widespread proposed mechanisms, it is difficult to tease out if GERD in these conditions is a primary or secondary phenomenon of the respiratory disease.

In patients with asthma, reflux can contribute to more frequent exacerbations and worsen respiratory symptoms. Mechanisms proposed for this association include activation of the esophago-bronchial reflex, increased bronchial reactivity, and microaspiration events (17). These processes can also be projected to patients with COPD. In addition, anatomical alterations in COPD create a perfect climate for the development of reflux including increased trans-diaphragmatic pressure gradient, flattening of the diaphragm and increased central drive (8-10). Of note though, COPD patients with GERD have not been shown to have a defective esophago-gastric junction or abnormal peristalsis (6). This difference in mechanism illustrates the unique physiology of GERD in COPD. Of particular importance is the role COPD plays in disrupting respiratory dynamics. Manometry data in a cohort of COPD patients showed higher trans-diaphragmatic pressure gradient and lower LES basal pressure in the subset of patients with objectively defined GERD (6). A higher trans-diaphragmatic gradient correlated to higher DeMeester scores (6).

Both asthma and COPD require medications which may cause LES relaxation. Beta agonist bronchodilators like albuterol sulfate increase the thoracic pressure by improving pulmonary function and decreasing the chest wall volume. Due to an increase in the abdominal compartment pressures with administration, the overall gradient has been shown to remain unchanged (21). In a study examining the manometric data before and after inhaled beta agonist bronchodilators, a normal LES pressure was present in 80% pretreatment; this decreased to 40% post-treatment (21). Patients may take these medications causing a drop in LES pressure several times a day, contributing to the number of GERD episodes.

The association between CF and GERD is not as well understood. Hallberg *et al.* demonstrated that increased gastric acid secretion accompanies the known reduction in pancreatic bicarbonate secretion in CF (22), although documented alkaline reflux episodes have been found in this population (23). Therefore, acid exposure alone does not fully explain the incidence of GERD in this population. Most of the data centers on the effects of aspiration on the respiratory tract. An analysis of saliva showed bile acids in 40% of adults with CF (24). This supports a hypothesis of aspiration as a contributing factor to GERD. In addition, more proximal GERD may be present which has been linked to a greater prevalence of respiratory symptoms (25).

Pathophysiology of GERD in relation to lung transplant patients

GERD has been shown to play a role in the development of pulmonary fibrosis and of the rejection after lung transplant. Despite advances in lung transplantation, long-term survival is threatened by development of bronchiolitis

obliterans syndrome (BOS), the most common cause of chronic allograft dysfunction. BOS is characterized by obliteration of the small airways with fibrosis in addition to recurrent pulmonary infections. After onset of BOS post-transplant, five-year survival is only 30–40% (26). Alloimmune causes of airway epithelial destruction were previously the hallmark of this syndrome; however, non-alloimmune injuries may instigate the development of BOS even in the early post-transplant phase. Animal studies have shown increased number of allograft CD8+ T cells, known mediators of acute rejection, after aspiration events (27). These aspiration events may not coincide with an acidic event, causing difficulty in monitoring this data point. Even with less acidic pH, reflux of bile and pepsin can occur as evidenced by a Blondeau *et al.* study showing increased nocturnal weakly acidic reflux in conjunction with bile in bronchoalveolar lavage fluid (BALF) (28). Presence of pepsin and bile acid in BALF samples has been identified as a risk factor to the onset and progression of BOS (29,30). Aspiration is not the only culprit to precipitate GERD post-transplant. Iatrogenic vagal injury during the operation and side effects of immunosuppressive medications both contribute to delayed gastric emptying (31).

Because of its frequent silent nature and high prevalence, GERD screening has become part of routine preoperative work-up in chronic lung disease. In a subset of lung transplant candidates undergoing high-resolution manometry, 23% were found to have a hypotensive LES and 36% had esophageal body hypomotility (32). A similar cohort study showed pH monitoring diagnostic of GERD in 58% of transplant candidates (32). Accurate diagnosis of GERD in pre and post transplant patient is essential to improving morbidity and mortality after such an invasive and costly procedure. It is not enough to diagnose GERD, but to quantify the degree of GERD, so that appropriate interventions including fundoplication may be performed to slow lung fibrosis.

Role of antireflux surgery in patients with chronic lung disease

Evidence supporting non-acidic episodes of reflux in patients with lung disorders demonstrates the inherent pitfalls in treating these patients with PPI medication. The principle mechanism of altering pH does little to change the frequency of gastric reflux episodes (33).

In asthma, few randomized controlled trials (RCTs) exist allocating asthmatics to treatment with medical or surgical treatment. One RCT with population of 62 asthma patients with GERD showed improved symptom severity scores at two-year follow-up with surgical treatment versus medical therapy (34). However, objective data including peak expiratory flow, pulmonary function tests, and asthma medication requirements between the two groups were not statistically significant (34). In a more recent RCT by Pointner *et al.*, 100 patients with extra-esophageal GERD symptoms were randomized to Toupet *vs.* Nissen fundoplication. In patients with asthma, symptoms improved with both Nissen and Toupet fundoplication, however the improvement in symptom score in Toupet fundoplication was not significant (35). Nissen fundoplication may be the indicated surgical procedure for treatment of asthma. Benefits of antireflux surgery on improving asthma are clearly established in the literature. Prospective data showed an improvement in 83% of asthma patients undergoing laparoscopic Nissen fundoplication (36). For asthma uncontrolled with pharmacotherapy alone, it is prudent to evaluate for GERD and discuss who would benefit from antireflux surgery.

Unfortunately, similar studies have not been performed in COPD patients. Due to unique pathophysiology of the interplay between each lung disease and GERD, extrapolation of data to other subsets of lung disease may not be accurate. Further studies are needed to determine appropriate work-up and indications for antireflux surgery in chronic respiratory disease.

The strongest data for antireflux surgery in chronic lung disease centers on the transplant population. Most of these patients suffer from progressive fibrosis, which is hastened by uncontrolled GERD. The question arises as to when is the best time to intervene surgically on these patients. An argument can be made that a survival benefit may arise if GERD is controlled prior to transplantation. Linden *et al.* compared a group of 14 lung transplant candidates undergoing laparoscopic antireflux surgery (LARS) to a control group of 31 candidates not undergoing LARS. This study showed that oxygen requirements stabilized in the LARS group, compared to increasing oxygen requirements in the control group as the disease progressed (37).

Decreasing aspiration events has a major role in protecting lung allograft function. In addition, clear benefit survival benefit has been established to intervening with LARS. Cantu *et al.* established early fundoplication as preventive to the development of BOS post-transplant. BOS was absent in 96% and 60% of patients undergoing LARS at 1- and 3-year follow-up respectively. Survival

at 3 years was 100% compared to 76% of the control group with no LARS intervention (38). Worsening fibrosis and decreased survival post-transplant illuminate the opportunity to intervene in early in this disease progression. One could argue that addressing GERD preoperatively my lead to improved survival post-transplant. Lo *et al.* established that early intervention (pre-transplant or <6 months from transplant) decreased early allograft injury in comparison to late LARS (>6 months from transplant) (39). Currently a NIH sponsored phase II multicenter study is ongoing to address how LARS impacts the decline of forced vital capacity in IPF patients.

As described earlier, the pathophysiology and severity of GERD may be altered in the post-transplant setting. LARS alters the anatomy of the gastroesophageal junction, providing a mechanical barrier to aspiration. Analysis of BALF samples commonly contains bile after transplant (40). Lower levels of pepsin in BALF samples have been found in transplant patients' post-LARS, suggesting decreased aspiration events in this group (41). Davis *et al.* supported the impact of LARS on BOS. In 128 patients post transplant, 43 underwent LARS with BOS resolving in 50% patients with BOS present at the time of the operation (42).

Intervening prior to development of fibrosis and BOS is of paramount importance. The key window of opportunity arises early after lung transplant to ensure delay in the onset or progression of BOS. Despite being on chronic immunosuppression, LARS has been shown to be safe in this post-transplant population. Gasper *et al.* studied the morbidity and safety of LARS. Of 35 operations, all remained laparoscopic without conversion to open and 94% of patients recovered without complication (43). Average postoperative length of stay was 2 days.

Conclusions

The physiologic processes to explain the relationship between GERD and lung diseases are multifactorial, and not completely understood. Because of its frequently silent nature and high prevalence, GERD screening should be performed in patients with chronic lung disease. While medical therapy alters the pH of the gastric juice, it does not eliminate the occurrence of gastroesophageal reflux episodes, which cause regurgitation and respiratory symptoms. Selected group of patients with pulmonary disease and proven GERD may benefit from antireflux surgery.

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