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Full Reports

The Intersection of GERD, Aspiration, and Lung Transplantation

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Abstract

Lung transplantation is a radical but life-saving treatment option for patients with end-stage lung diseases, such as idiopathic pulmonary fibrosis (IPF) and scleroderma. In light of the proposed association and controversy linking gastroesophageal reflux disease (GERD) to IPF and lung transplant outcome, the American Gastroenterological Association convened during the DDW in Washington in May 2015 a multidisciplinary group of experts in the field of GERD and lung transplantation to make considerations about the care of these patients based on available data and subsequent expert panel discussion at this symposium. The following topics were discussed: (1) pathophysiology of GERD-induced pulmonary symptoms, (2) GERD evaluation before and after lung transplantation, (3) outcome of lung transplantation for IPF and scleroderma, and (4) role of laparoscopic fundoplication before or after lung transplantation.

Introduction

Lung transplantation is a radical but life-saving treatment option for patients with end-stage lung diseases (ESLDs), such as idiopathic pulmonary fibrosis (IPF) and scleroderma.

Based on the most recent data from the U.S. Department of Health and Human Services, nearly 30,000 primary lung transplants have been performed since 1988.[1] Even though the overall graft survival has increased over the years, as of 2015, the median 1-, 3-, and 5-year graft survival was 83.1%, 62.1%, and 46.2%,[1] respectively, still lower than that of the kidneys and livers.

The most common cause of chronic allograft dysfunction is known as *obliterative bronchiolitis*, a process of fibrosis that starts in the small bronchioles of the transplanted lung. The clinical correlate is the bronchiolitis obliterans syndrome (BOS), characterized by a progressive deterioration of lung function as measured by the forced 1-second expiratory volume (FEV_1). Although the pathophysiology of BOS is unknown, theories of BOS and rejection after transplantation have centered on the combined interaction of immunologic and nonimmune factors. Nonimmune factors, such as gastroesophageal reflux disease (GERD), have been postulated to induce rejection by triggering a nonallogenic injury to the transplanted lungs by aspiration of gastroesophageal contents.[2] Similarly, before transplantation, the presence of GERD-induced aspiration has been linked to pulmonary failure, particularly in patients with IPF.[3] Therefore, GERD is thought to play a significant role in the decline in lung function before transplantation and the rejection after lung transplantation, likely by causing aspiration-mediated lung injury.

In light of the proposed association and controversy linking GERD to IPF and lung transplant outcome, the American Gastroenterological Association convened during the DDW in Washington in May 2015 a multidisciplinary group of experts in the field of GERD and lung transplantation to make considerations for the care of these patients based on available data and subsequent expert panel discussion at this symposium. The following topics were discussed: (1) pathophysiology of GERD-induced pulmonary symptoms, (2) GERD evaluation before and after lung transplantation, (3)

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outcome of lung transplantation for IPF and scleroderma, and (4) role of laparoscopic fundoplication before or after lung transplantation.

Pathophysiology of GERD and Its Importance in Patients with ESLD and Lung Transplant Patients

Traditionally, the presence and severity of GERD were related to the incompetence of the lower esophageal sphincter, the abnormal esophageal peristalsis, and the presence and size of hiatal hernia.[4] Today, emphasis is also placed on the role of mixed gastroesophageal reflux[5] and on the transdiaphragmatic pressure gradient[6] as both have important therapeutic implications.

The importance of the mixed gastroesophageal reflux is evident when one compares the number of reflux episodes on and off proton pump inhibitors (PPI) therapy using multichannel intraluminal impedance and pH monitoring, a finding that has significant implications on the choice of treatment for patients with GERD and aspiration. For instance, Tamhankar et al. showed that PPIs just change the pH of the gastric refluxate from acidic to weakly acidic or alkaline but do not change the occurrence and the number of reflux episodes.[5] The authors concluded, ''PPI treatment, while altering the pH of the gastric juice, does not correct the defects in the gastroesophageal barrier and consequently does not eliminate the presence and frequency of refluxed gastric contents.'' Hence, if one considers aspiration the central focus of lung deterioration before and after lung transplant, it is clear that treatment with PPI is not as effective as a fundoplication, which is able to stop any type of reflux events regardless of their pH. In addition, emphasis has been placed on the role of the transdiaphragmatic pressure gradient in causing GERD. A study from the University of California San Francisco showed that for a 5-point increase in the body mass index, there was a 3-point rise in the DeMeester score.[5] This is particularly relevant in obese patients in whom there is an increased gradient because of a higher abdominal pressure and a more negative intrathoracic pressure.[7]

Evaluation of Patients with ESLD Before and After Lung Transplant

Testing for esophageal motility and GERD is very important in the management of patients with ESLD and after lung transplantation.

The assessment of esophageal motility relied on conventional manometry for many years. Nowadays, a more common approach is to use high-resolution manometry (HRM), which incorporates a large number of closely spaced pressure sensors and provides spatiotemporal plots of esophageal pressure changes, leading to higher diagnostic accuracy. Esophageal motor disorders are common in patients with advanced lung disease. A study that assessed 30 lung transplant candidates with HRM found intermittent or frequent failed peristalsis in 20 (66%) of them.[8] More recently, in 73 patients being evaluated for lung transplant, HRM revealed a hypotensive lower esophageal sphincter (LES) in 23% and hypomotility of the esophageal body in 36%.[1] While esophageal manometry does not provide a diagnosis of GERD, it is mandatory for the following reasons: (1) proper positioning of the pH probe, (2) before antireflux surgery to rule out achalasia masquerading as GERD, and (3) to detect severe impairment or absent peristalsis, particularly in patients with scleroderma.[9] GERD is often suspected when patients complain of typical symptoms, such as heartburn and regurgitation. However, these symptoms have variable sensitivity and specificity for diagnosing GERD. In addition, patients with GERD and ESLD are often asymptomatic.[10] In a study of patients awaiting lung transplant, 33% of those who tested positive for GERD by pH monitoring had no heartburn or regurgitation.[11] Endoscopy can provide a diagnosis of GERD when erosive esophagitis is detected; however, this finding is present in only one third of untreated patients,[12] and it is even less common in those treated with a PPI. Thus, at the present time, the most reliable method for establishing the presence of pathological gastroesophageal reflux is through ambulatory pH monitoring or by pH monitoring combined with impedance.

The prevalence of GERD is very high in patients with advanced pulmonary disease undergoing transplant evaluation. In a study of 62 patients awaiting lung transplant, 24-hour pH monitoring was positive for GERD in 58%.[1] A positive pH test before transplant is associated with worse outcomes after transplant. This was demonstrated in a study of 114 patients in whom pretransplant GERD was diagnosed by pH monitoring. During follow-up after transplant, allograft function was decreased in patients with pretransplant GERD compared to those without GERD, such that by 18 months, FEV_1 was 70% of predicted in patients with GERD versus 83% among non-GERD patients.[5] Furthermore, survival early after transplant was significantly lower in the GERD patients. Testing for GERD with pH monitoring is also useful after transplant. In 60 lung transplant recipients who underwent pH monitoring 3 months after transplant or at the time of their first acute rejection, a multivariate model showed that GERD was associated with a significantly increased rate of acute rejection and with earlier as well as multiple episodes and rejection.[12]

There are limited data regarding the utility of pH–impedance monitoring in lung transplant patients. The main advantage of pH–impedance monitoring is the ability to detect reflux with a pH above 4, which is highly relevant in lung transplant patients on treatment with a PPI because nonacidic reflux may be harmful as suggested by lower allograft function in GERD patients treated with PPI compared to those who undergo early fundoplication.[13] This may be explained by reflux of bile and pepsin even when pH is above 4.0, as shown by a study of 24 lung transplant recipients evaluated by impedance–pH monitoring and bronchoalveolar lavage fluid (BALF) analysis 1 year after transplant, revealing an association between increased nocturnal weakly acidic reflux and the presence of bile in BALF.[14]

A more accurate way to document reflux and aspiration of gastric contents in patients with pulmonary disease is by measurement of pepsin or bile acids in BALF obtained during bronchoscopy. In a study of 105 lung transplant recipients, the BALF concentrations of pepsin were significantly higher in the 29 patients who developed BOS compared to those without BOS.[15] Similarly, bile acid measurement in BALF in 120 transplant recipients showed that freedom from BOS was significantly shortened in patients with elevated BALF bile acids.[16]

Evidence that GERD Plays a Role in Causing or Worsening Lung Diseases, such as IPF

GERD is highly prevalent and often silent in patients with IPF.[2] Raghu et al. reported a prevalence of abnormal reflux

by 24-hour pH monitoring of 87% in 65 patients with IPF, with a prevalence of proximal reflux of 63%.[3] Similarly, Sweet et al. evaluated 109 ESLD patients awaiting lung transplantation and found that distal reflux was present in 68% of patients and proximal reflux was present in 37% of patients.[10] Moreover, Allaix et al., in a study of 22 GERD and IPF patients who were compared to 80 controls with GERD only, showed that in patients with GERD and IPF the proximal esophageal acid exposure was higher and that the supine acid clearance was slower compared with those with GERD only.[17] The high prevalence of GERD and proximal reflux suggests that these patients are more susceptible to aspiration, the postulated ultimate mechanism of chronic lung injury. In addition, because in lung transplant candidates reflux is often silent, a screening protocol for GERD should always include manometry and pH monitoring. The presence of pepsin or bile acids should be systematically sought in the BALF as a proof of aspiration of gastric contents. Similarly, these tests should also be routinely performed in any patient after lung transplantation even if abnormal reflux was not present at the time of the pretransplant evaluation. D'Ovidio et al. showed that in patients after lung transplantation, bile was commonly detected in the BALF.[18] In addition, they showed that freedom from BOS was reduced in patients with abnormal esophageal reflux or when bile acids were present in their BALF. They concluded that reflux-mediated aspiration was a risk factor for the development of BOS after transplant and that aspiration of bile acids was associated with impaired allograft innate immunity.[8]

Evidence that Antireflux Surgery in Patients with IPF Can Block the Progression of the Disease

If GERD is highly prevalent and often silent in patients with ESLD before transplantation, and if pretransplant GERD is associated with worse early allograft function and survival,[19] then one may argue that GERD should be controlled before the deterioration, leading to lung transplantation. Linden et al. compared the outcome of 14 patients with GERD and IPF on the lung transplant list who underwent laparoscopic antireflux surgery (LARS) with that of a control group of 31 patients with GERD and IPF on the transplant list who did not undergo LARS. They found that in patients with IPF who underwent LARS, there was stabilization of oxygen requirements, whereas controls had a significant deterioration in oxygen requirements.[20] Hoppo et al. evaluated 19 patients with GERD and ESLD before lung transplant and found that 1 year after LARS the FEV_1 improved in 85% of them and that episodes of pneumonia and acute rejection stabilized.[21] Longer survival in patients with IPF taking PPI or after Nissen fundoplication was also documented by Lee et al.[22] To further clarify the effect of reflux control in patients with GERD and IPF, the National Institutes of Health is sponsoring a phase II multicenter study of laparoscopic fundoplication for the treatment of GERD in IPF patients (University of California San Francisco; University of Washington, Seattle; University of Michigan; University of Wisconsin, Madison; and University of Chicago). This study aims to determine if by blocking reflux the natural history of the disease can be changed, and specifically, it aims to determine the impact of LARS on the decline of forced vital capacity (FVC) to determine the safety of LARS in patients with IPF.

Evidence that Early Antireflux Surgery in Patients with GERD After Lung Transplant Can Prevent BOS or At Least Block Its Progression

Even though BOS is multifactorial, GERD probably plays a major role, and surgical treatment of GERD with LARS has been shown to reduce the incidence of BOS and associated with a delay in the onset or progression of BOS or even with improvement in lung function. Fisichella et al. showed that LARS could stop aspiration by providing a mechanical barrier to reflux. They categorized those who had aspiration as those who had any pepsin in their BALF (pepsin was undetectable in the BALF of controls) and found that lung transplant patients with LARS had minimal pepsin levels in their BALF.[23] Davis et al. studied 128 patients who had esophageal function tests after lung transplantation.[24] Among these, 43 patients underwent LARS, while the other patients served as controls. At the time of LARS, 26 patients had BOS, whereas after the fundoplication, BOS resolved in 13 patients. In addition, Davis et al. found that 6 months after LARS the FEV_1 improved by 24% compared to preoperative values and that the overall actuarial survival was better when a patient had no objective evidence of reflux on pH monitoring. Davis et al. were the first to speculate that an early fundoplication (within 6 months) may improve lung function and affect the resolution of BOS.

Cantu et al. built on these findings and investigated if early fundoplication would prevent BOS and improve survival. They found that patients who underwent early LARS had 100% freedom from BOS at 1 and 3 years compared with those with reflux who did not undergo LARS (96% and 60% at 1 and 3 years, respectively).[25] In patients after LARS, the actuarial survival was 100% at 1 and 3 years compared with those with reflux and no intervention (92% and 76% at 1 and 3 years, respectively).

Hartwig et al. subsequently showed that early LARS might indeed preserve lung allograft function by finding that lung transplant patients with abnormal reflux who did not undergo LARS had worse predicted peak and 1-year FEV_1 results compared to those who had LARS.[13] Finally, Lo et al. evaluated the impact of the timing of LARS (before and after transplantation) on early allograft injury and found that late LARS (>6 months after lung transplant) resulted in increased risk of early allograft injury compared to pretransplant and early LARS (<6 months).[26] These findings support the use of LARS early after transplantation or even before transplantation to minimize the impact of reflux-induced aspiration on allograft injury.

Early fundoplication after lung transplantation, before worsening lung function, has been shown to be safe. Gasper et al. showed that 35 operations (15 performed before and 20 after transplantation) were all completed laparoscopically, and 33 (94%) patients recovered uneventfully (one was readmitted for urinary tract infection and one died for causes nonrelated to the transplant).[27] The median hospital length of stay was 2 days. Similarly, Fisichella et al. analyzed the perioperative morbidity and mortality of 29 consecutive lung transplant patients and 23 consecutive patients without ESLD (control group). They showed that the morbidity and mortality of LARS in lung transplant patients and the control group were equivalent.[28]

Scleroderma and Esophageal Dysmotility in Lung Transplantation: Clinical Implications and Outcome

Scleroderma is an autoimmune collagen vascular disease characterized by fibrosis of small arteries and arterioles, which presents with cutaneous and/or visceral manifestations. In addition to the skin, the gastrointestinal tract, lung, kidney, and heart are the most commonly involved organs. Today, pulmonary disease is the main organ-specific cause of death in the scleroderma patient population, with 3-year mortality exceeding 50%.[29] The main manifestations of lung disease are interstitial fibrosis (50% of patients) and pulmonary arterial hypertension (5%–12%).[30] Because medical therapy has limited efficacy in scleroderma lung disease, lung transplantation is the only definitive treatment option for patients with scleroderma lung disease. However, given the concern regarding the impact of concomitant extrapulmonary manifestations of scleroderma—particularly esophageal dysmotility with gastroesophageal reflux and aspiration—lung transplantation remains controversial in these patients.

This view, however, has slowly changed over time. A review of the United Network for Organ Sharing (UNOS) database in 2005 identified 47 patients who underwent lung transplant for scleroderma with survival at 1 and 3 years of 68% and 46%, respectively.[31] These survival figures were not significantly different from those seen with contemporary interstitial lung disease (ILD) patients (76% and 59%; $P = .25$), indicating that sustained acceptable outcomes were indeed possible in this patient population. Given the specific concerns regarding transplantation in the setting of GERD, Sottile et al. examined the outcome of lung transplants in patients with documented reflux as defined by a DeMeester score >14.7.[29] In comparison to a matched cohort of IPF patients, there were no differences in survival at 1 year (83% versus 91%) and 5 years (76% versus 64%; $P = .47$). Esophageal dysfunction was not associated with a difference in BOS or an increased mortality following transplantation.

The ongoing management of gastroesophageal reflux and aspiration in patients with scleroderma is a critical component. Patient should be assessed with esophageal manometry and pH monitoring. If abnormal reflux is present, antireflux surgery has been shown to offer benefit in both survival and reduced rejection following lung transplantation.[25] However, in the setting of the significant esophageal dysfunction in scleroderma, fundoplication can aggravate dysphagia, even if a partial fundoplication is performed.[32] Kent et al. proposed that Roux-en-Y esophagojejunostomy might be a better option in these patients, offering improved reflux control and less dysphagia compared to fundoplication.[33]

In the most recent update of the guidelines for the selection of transplant candidates, The International Society for Heart & Lung Transplantation stated, ''carefully selected candidates with (scleroderma) can undergo successful lung transplantation.''[34] Ultimately, the decision regarding transplant candidacy must be made on a case-by-case basis, taking into consideration the severity of lung disease and the concomitant comorbidities.

Conclusions

The mechanism by which GERD contributes to the development of IPF and BOS and rejection after transplant has not been well elucidated. Evidence is conflicting because studies are limited in their size and mostly uncontrolled. Nevertheless, the evidence available seems to suggest that GERD should be recognized and treated early in patients with IPF: the phase II NIH prospective and randomized trial currently in course might shed definitive light on the role of GERD in the pathogenesis of this disease. Awareness of the medical community, from family practitioners to pulmonologists, that GERD may play a role in the pathogenesis of lung diseases and in the rejection process after lung transplant is of paramount importance.

With the caveat that most of the studies are retrospective and based on small number of patients, the reader should realize that guidelines are difficult to be proposed. However, based on the review of the available literature and the personal experience of the participants to this symposium, the following considerations were made:

- Every patient with IPF and scleroderma and ESLD should be screened for GERD by manometry, pH monitoring, and possibly by bronchoscopy with analysis of the BALF for pepsin or bile acids, irrespective of the presence of symptoms.
- If the presence of GERD and aspiration is established and the patient is considered a candidate for an operation under general anesthesia, LARS should be considered.
- Every patient early after lung transplant should be screened for GERD by manometry, pH monitoring, and possibly by bronchoscopy with analysis of the BALF for pepsin or bile acids, irrespective of the presence of symptoms.
- If GERD is detected, a fundoplication should be performed as soon as the diagnosis is established and before the development of BOS.

Disclosure Statement

No competing financial interests exist.

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