Published in final edited form as:
Surgery. 2010 October ; 148(4): 737–745. doi:10.1016/j.surg.2010.07.011.

Gastroesophageal reflux disease after lung transplantation: Pathophysiology and implications for treatment

Christopher S. Davis, MD[a], **Vidya Shankaran, MD**[a], **Elizabeth J. Kovacs, PhD**[a], **James Gagermeier, MD**[b], **Daniel Dilling, MD**[b], **Charles G. Alex, MD**[b], **Robert B. Love, MD**[c], **James Sinacore, PhD**[d], and **P. Marco Fisichella, MD**[a]

[a] Department of Surgery, Loyola University Medical Center, Stritch School of Medicine, Maywood, IL

[b] Department of Medicine—Division of Pulmonary and Critical Care Medicine, Loyola University Medical Center, Stritch School of Medicine, Maywood, IL

[c] Department of Thoracic and Cardiovascular Surgery, Loyola University Medical Center, Stritch School of Medicine, Maywood, IL

[d] Department of Preventive Medicine and Epidemiology, Loyola University Medical Center, Stritch School of Medicine, Maywood, IL

Abstract

Background—Gastroesophageal reflux disease (GERD) is thought to be a risk factor for the development or progression of chronic rejection after lung transplantation. However, the prevalence of GERD and its risk factors, including esophageal dysmotility, hiatal hernia and delayed gastric emptying after lung transplantation, are still unknown. In addition, the prevalence of Barrett's esophagus, a known complication of GERD, has not been determined in these patients. The purpose of this study was to determine the prevalence and extent of GERD, as well as the frequency of these risk factors and complications of GERD in lung transplant patients.

Methods—Thirty-five consecutive patients underwent a combination of esophageal function testing, upper endoscopy, barium swallow, and gastric emptying scan after lung transplantation.

Results—In this patient population, the prevalence of GERD was 51% and 22% in those who had been retransplanted. Of patients with GERD,36% had ineffective esophageal motility (IEM), compared with 6% of patients without GERD (P = .037). No patient demonstrated hiatal hernia on barium swallow. The prevalence of delayed gastric emptying was 36%. The prevalence of biopsy-confirmed Barrett's esophagus was 12%.

Conclusion—Our study shows that, after lung transplantation, more than half of patients had GERD, and that GERD was more common after retransplantation. IEM and delayed gastric emptying are frequent in patients with GERD. Hiatal hernia is rare. The prevalence of Barrett's esophagus is not negligible. We conclude that GERD is highly prevalent after lung transplantation, and that delayed gastric emptying and Barrett's esophagus should always be suspected after lung transplantation because they are common risks factors and complications of GERD.

Lung transplantation is currently performed on selected patients with end-stage lung disease. However, the median survival of patients after lung transplantation is inferior to that of any

Reprint requests: P. Marco Fisichella, MD, Swallowing Center, Department of Surgery, Stritch School of Medicine, Loyola University Medical Center, 2160 South First Avenue, Room 3226, Maywood, IL 60153. pfisichella@lumc.edu.

Presentation to the annual meeting of the Central Surgical Association, Chicago, Illinois, March 10–13, 2010.

other solid organ transplantation, only 5 years.[1] This low survival rate is primarily due to the development of obliterative bronchiolitis, which clinically manifests as bronchiolitis obliterans syndrome (BOS).[2] BOS 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 obliterative bronchiolitis is not fully understood. However, evidence suggests that obliterative bronchiolitis might represent a nonimmunologic aberrant response to a chronic stimulus injury.[3–6] Recently, gastroesophageal reflux disease (GERD) has been proposed as a potential factor responsible for chronic injury. Several studies have indirectly 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 operative control of GERD may control the decline in lung function characteristic of BOS.[4–7] Despite the evidence that supports the detrimental effect of GERD before and after lung transplantation, the prevalence of risk factors of GERD, including esophageal dysmotility, hiatal hernia, and delayed gastric emptying, are still unknown. In addition, the prevalence of Barrett's esophagus, a known complication of GERD, has not been determined in lung transplant patients. The purpose of this study was to determine the prevalence and extent of GERD, as well as the frequency of these risk factors and complications of GERD in lung transplant patients.

PATIENTS AND METHODS

Thirty-five consecutive patients underwent a symptomatic assessment, a combination of esophageal function testing (esophageal high-resolution impedance manometry and dual-sensor pH-monitoring), upper endoscopy, barium swallow, and gastric emptying scan after single lung transplantation, bilateral lung transplantation, or retransplantation.

Symptomatic assessment

All patients were interviewed by a single physician before undergoing esophageal function testing. During this visit, all patients underwent symptomatic assessment, including the type, dosage, and schedule of anti-secretory medications used (proton pump inhibitors [PPIs] or histamine H_2-receptor antagonists), transplant history, and metabolic evaluation, including the calculation of body mass index.

Esophageal high-resolution impedance manometry

After an overnight fast, the patients underwent esophageal high-resolution impedance manometry using a 32-channel solid state catheter (insight HRIM system with BioVIEW software; Sandhill Scientific Inc., Denver, CO) with 4 active impedance channels located at 5, 10, 15, and 20 cm above the high-pressure zone of the lower esophageal sphincter (LES). This system assessed the esophageal muscular activity in both the LES and the esophageal body with high-resolution manometry and the esophageal bolus transit dynamics with impedance. The system also assisted in locating the distance of the LES from the nostril and determined its pressure, length, and relaxation (normal LES pressure, 10–45 mm Hg; relaxation was determined by a drop of the resting pressure to a residual pressure of <8 mm Hg). The esophageal body function was assessed after the patients performed 10 serial swallows in the supine position with 5 mL of normal saline (liquid swallows) and 5 mL of viscous material (viscous swallows), each separated by 20 seconds. The amplitude, duration, and velocity of the peristaltic waves were simultaneously recorded. Peristaltic wave amplitude was then calculated for the distal esophagus (distal esophageal amplitude [DEA]) based on data recorded from pressure sensors located 5 and 10 cm above the LES. Esophageal motility was considered normal on manometry if normal peristaltic waves were present in >80% of the swallows with DEA <180 mm Hg. Ineffective esophageal motility

(IEM) was manometrically defined when DEA was <30 mm Hg or when >30% simultaneous waves were present in the distal esophagus.[8] The system also utilized impedance to analyze esophageal bolus transit dynamics. Transit abnormalities were defined as abnormal liquid transit if >30% of the 10 liquid swallows had incomplete transit and abnormal viscous transit if >40% of 10 viscous swallows had incomplete bolus transit.[9] Completeness of bolus transit was defined by successful bolus exit from all 3 distal impedance sensors (15, 10, and 5 cm above the LES). The bolus was identified (bolus entry) when the change of impedance value dropped 50% from the baseline and returned (bolus exit) to >50% of the baseline for >5 seconds.[9]

Ambulatory pH monitoring

PPIs were stopped for 14 days and histamine H_2-receptor antagonists were stopped for 3 days before pH monitoring in all patients. A dual-sensor pH catheter (Sleuth system with BioVIEW software; Sandhill Scientific, Inc.) was passed through the nose and the 2 pH sensors were positioned 5 and 20 cm, respectively, from the manometrically determined upper border of the LES. This allowed us to measure the pH in the distal (5 cm above the LES) and in the proximal esophagus (20 cm above the LES). The pH catheter was then connected to a recording device that was worn by the patient for approximately 24 hours. Patients were asked to perform their normal activities and maintain an unrestricted diet. They were instructed to record the occurrence of their symptoms, as well as time and duration of meals, and time and duration of supine and upright position. The DeMeester score was calculated by the software for the distal pH recordings by taking into account: the percentage of total time pH <4; the percentage of upright time with pH <4; the percentage of supine time with pH <4; the number of reflux episodes in 24 hours; the number of reflux episodes >5 minutes; and the duration of the longest reflux episode. A score >14.7 was considered abnormal.[10] Proximal reflux was defined as >1% total time that pH <4 recorded at the proximal sensor (located 20 cm above the LES).[11]

Upper endoscopy

An upper endoscopy with biopsies of the gastroesophageal junction was performed in patients with GERD. The definitive confirmation of Barrett's metaplasia was obtained by pathologic interpretation of the endoscopic biopsies. Dysplasia was classified as negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, or high-grade dysplasia.[12]

Barium swallow

The presence and size of a hiatal hernia was assessed by measuring the axial length of the hernia, relative to the diaphragm, in the upright position on a posteroanterior barium esophagram, using eFilm Lite software (Merge Healthcare; Milwaukee, WI). The hiatal hernia was classified as small if its axial length was <3 cm, moderate if its axial length was 3–5 cm, and large if its axial length was >5 cm.

Gastric emptying scan

Nuclear medicine gastric emptying studies were performed in patients with GERD by obtaining dynamic scintigraphic images through the abdomen for 90 minutes after oral administration of 0.4 mCi ^{99m}Tc–labeled sulfur colloid in ovalbumin. Gastric emptying was considered delayed if computer analysis demonstrated that <30% of the gastric contents were emptied into the small bowel by 90 minutes.

Statistical analysis

Tests of statistical significance were conducted with SPSS Statistical Software, version 16 (SPSS, Chicago, IL). Nonparametric statistical methods were utilized. The Chi-square test

for association was used for differences in groups on categorical variables (eg, reason for transplant) and the Mann-Whitney *U* test was used for scaled variables (eg, age). Results were reported as percentages for categorical variables and as median (with interquartile range) for scaled variables. A difference between observed variables was considered statistically significant when $P < .05$.

This study was approved by the Loyola University Medical Center Institutional Review Board (LU202258).

RESULTS

After lung transplantation, the prevalence of GERD was 51% (18/35 patients; 15 patients (48%) had GERD on pH monitoring, whereas 3 patients had typical symptoms of GERD and evidence of aspiration on bronchoscopy and refused pH monitoring; Table I). Patients with and without GERD had comparable clinical characteristics. Both groups were composed of patients with similar age, gender, race, body habitus, and prevalence of end-stage lung diseases (Table I).

The manometric profile of the LES was similar between patients with and without GERD (Table II). Patients in both groups had similar resting pressures, as well as total and abdominal LES lengths. In addition, the LES had a normal resting pressure in 87% of patients with GERD and 94% of patients without GERD ($P = .47$).

The manometric profile of the esophageal body was different between patients with and without GERD (Table II). The DEA was lower in patients with GERD (median DEA, 46 vs 90 mmHg in patients without GERD; $P = .029$; Table II). Similarly, IEM was more common among patients with GERD. Specifically, 36% of patients with GERD had IEM compared with 6% of patients without GERD ($P = .04$). Significantly delayed esophageal transit (both liquid and viscous) was also noted in patients with GERD (53% vs 18% in patients without GERD; $P = .037$), as were delays in liquid and solid transit when independently assessed (60% vs 18% in patients without GERD [$P = .015$] and 80% vs 29% in patients without GERD [$P = .004$], respectively). The analysis of the distal reflux profile of patients with GERD showed that these patients had more, and longer, episodes of reflux; more exposure to acid reflux in the supine and upright positions; and slower total acid clearance in both the supine and upright positions (Table II).

Analysis of the proximal reflux profile showed a significantly higher prevalence of proximal GERD (50% vs 13% of patients without GERD; $P = .032$), and that these patients experienced more severe proximal reflux in the supine position compared with patients without GERD ($P = .0034$). Proximal GERD occurred in 2 patients with normal distal esophageal acid exposure: 1 patient had chronic obstructive asthma and 1 had chronic obstructive pulmonary disease, for which they both underwent bilateral lung transplantation; 1 patient had a normal esophageal motility profile, whereas the patient with chronic obstructive asthma had an abnormal esophageal transit (both liquid and viscous) and a hypotensive LES.

The relationship between type of transplant and presence, or absence, of GERD after lung transplantation is illustrated in Table III. Patients who underwent single lung transplantation were less likely to have GERD. Specifically, 69% of patients without GERD had a single lung transplant compared with only 31% of patients with GERD and single lung transplant ($P = .047$). Conversely, patients who have been retransplanted were more likely to present with GERD. In fact, 22% of patients with GERD had been retransplanted, whereas none of the patients without GERD had been retransplanted. The distribution of the underlying end-

stage lung disease (obstructive or restrictive) was similar among the transplant groups (unilateral, bilateral, retransplant; $P = .7$).

None of the patients with GERD demonstrated hiatal hernia on barium swallow. Only 18% of patients without GERD underwent a barium swallow and none had hiatal hernia.

The prevalence of delayed gastric emptying in patients with GERD was 36% (2 patients with α_1-antitrypsin deficiency, 1 with idiopathic pulmonary fibrosis, and 2 with cystic fibrosis): 4 patients received bilateral lung transplants and 1 was re-transplanted; 3 patients had abnormally delayed esophageal transit (both liquid and viscous).

The prevalence of biopsy-confirmed Barrett's esophagus was 12% (1 patient with scleroderma and 1 with emphysema). One patient had a normal LES and esophageal motility profile, whereas the patient with scleroderma had a hypotensive LES and an abnormally delayed esophageal transit (both liquid and viscous). None of the patients had dysplasia.

When we analyzed the effect of the underlying lung pathology on the pathophysiologic risk factors for GERD and its complications, we found that the type of end-stage lung disease (obstructive or restrictive) had no influence on the manometric and pH-metric profile, the presence of delayed gastric emptying, or the prevalence of Barrett's esophagus.

DISCUSSION

Our results demonstrate that after lung transplantation: GERD is highly prevalent, especially after retransplantation; proximal reflux is common and more severe in the supine position; abnormal esophageal motility and transit are frequent in patients with GERD; hiatal hernia is rare; delayed gastric emptying is present in one third of patients with GERD; and the prevalence of Barrett's esophagus is not negligible.

Prevalence and extent of GERD after lung transplantation

In this study, the prevalence of GERD in lung transplant recipients is 51% (or 48% when measured by pH monitoring alone). Our data confirm the observations of others that GERD is highly prevalent after lung transplantation.[5,6,13] For instance, Young et al[13] and Hadjiliadis et al[5] showed a high prevalence (65% and 70%, respectively) of distal esophageal reflux after lung transplantation. The lower prevalence in our study may be due to referral bias, because not all lung transplant patients are referred for evaluation, given its impracticality. Nevertheless, the high prevalence of GERD after lung transplantation is an important finding because it may demonstrate, although indirectly, that reflux in lung transplant recipients could contribute to the development and progression of BOS.

Although we were not able to demonstrate a relationship between the underlying cause of pulmonary failure and the risk of reflux after lung transplantation, we have found that the type of lung transplant may play a role in the pathophysiology of GERD. In particular, we have found GERD in all of those who had been retransplanted, compared with only 31% of patients with single lung transplant. The reasons for this finding is unclear and prior reports failed to demonstrate such an association.[13] We speculate that an increased risk of esophageal or vagal nerve injury during retransplantation, the persistence of severe pulmonary disease that eventually leads to retransplantation, or an increased gastroesophageal pressure gradient may contribute to the development or exacerbation of GERD. Analysis of a larger cohort is required to further substantiate these results.

Our study also showed that half of lung transplant patients with GERD were subject to proximal reflux, which was more pronounced when supine. Similar findings were reported

by Burton et al.[7] Although they did not specify the overall percentage of patients who had proximal reflux, they reported a 71% prevalence of proximal reflux in the supine position in their cohort of lung transplant patients. The detrimental effect of proximal reflux, especially when supine, lies in its potential to predispose to microaspiration. D'Ovidio et al[14] demonstrated that proximal reflux in the supine position was common in patients who were found to have bile in their bronchoalveolar lavage. More recently, Blondeau et al[15] showed that even nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients. Therefore, our findings underscore the potential of proximal and supine reflux as a predisposing risk factor for microaspiration and allograft injury in lung transplant patients.

Risk factors of GERD after lung transplantation

It is commonly believed that the etiology of GERD is multifactorial and that abnormalities of the manometric profile of the LES (eg, low resting pressure or transient relaxations) or its location (as with the presence of hiatal hernia), as well as abnormalities of the motility of the esophagus (eg, ineffective peristalsis or slow transit) and the stomach (eg, delayed gastric emptying) all play a pathogenic role in patients without end-stage lung diseases. However, the mechanism and extent by which each of these factors contributes to the etiology of GERD after lung transplantation is unknown.

In this study, we found that abnormal LES pressures played a limited role in GERD after lung transplantation as 87% of those with GERD and 94% of those without GERD had a normal LES manometric profile. We believe that these normal LES resting pressures and normal total and abdominal LES lengths are determined by the fact that the LES was located intra-abdominally, and that no patient had a hiatal hernia. This is an important finding because, although it is known that hiatal hernia is a definite risk factor in the general population with GERD and that hiatal hernia size is a strong predictor of severe GERD, the real contribution of the hiatal hernia in the pathogenesis of GERD in the lung transplant population is still under scrutiny.[16,17] In fact, no report has directly measured the prevalence of hiatal hernia in the lung transplant population, and data available from the literature are scant. For instance, Cantu et al[6] indirectly showed a positive association of hiatal hernia with GERD after lung transplantation (19% of patients with GERD had a hiatal hernia as compared with only 2% without GERD), yet their study did not detail how the diagnosis of hiatal hernia was made. Nonetheless, both our work and that of Cantu et al[6] demonstrate a much lower frequency of hiatal hernia in the lung transplant patient as opposed to the general population with GERD. In fact, Patti et al[17] showed that in patients with GERD without end-stage lung diseases the prevalence of hiatal hernia on barium swallow was 54% (51 patients out of 95 patients with GERD on pH monitoring). Therefore, the lower prevalence of hiatal hernia among lung transplant recipients suggests that other risk factors for GERD may play a more definite role in this patient population.

Abnormalities of the motility of the esophagus (eg, ineffective peristalsis or slow transit) and the stomach (eg, delayed gastric emptying) may be more important risk factors for GERD in the lung transplant population. In this study, we found that a high number of patients with GERD had IEM and that all patients with GERD had decreased DEA, clearance, and prolonged esophageal transit time on impedance compared with patients without GERD. This confirms the findings of Gasper et al,[18] who showed abnormal esophageal motility in 80% of patients after transplantation. Our study also showed that delayed gastric emptying was present in 36% of lung transplant patients with GERD. Although the real prevalence of delayed gastric emptying after lung transplantation is unknown, some studies estimate that it ranges from 23% to 92%. For instance, Gasper et al[18] showed that 77% of their post-transplant patients with GERD had delayed gastric emptying of solids or liquids. Conversely, Young et al[13] showed that 33% of lung transplant patients with GERD had gastroparesis, compared with 57% of those without GERD. This

discrepancy may be the result of selection bias of subjects studied, diagnostic criteria, or may be a function of type of transplant received (single versus double lung, or combined heart–lung transplantation).[5,13,14,18,19–21] Regardless, the high prevalence of delayed gastric emptying that we demonstrated is an important finding, because in this patient population gastric stasis has been shown to be a source of considerable morbidity and mortality because of its potential to cause aspiration.[19,20,22,23]

Lung transplantation and Barrett's esophagus

In our cohort of lung transplant patients the prevalence of Barrett's esophagus was 12%. Similar results have been reported by Burton et al,[7] who showed a prevalence of 13%. Interestingly, the prevalence of Barrett's esophagus in the lung transplant population is similar to that of the general population with symptomatic GERD.[24] Lung transplant patients share many of the risk factors with the general population with GERD, including male gender, IEM, prolonged reflux episodes, and a long history of GERD symptoms.[25] The concern for the lung transplant patient is that the potential progression of Barrett's esophagus to adenocarcinoma may be worsened by immunosuppression.[26,27] More important, lung transplant patients with Barrett's esophagus developed metaplasia despite a daily PPI regimen, which is routinely initiated in all patients during pretransplant evaluation. This is relevant because this finding suggests that PPIs may play a limited role in the management of GERD in this patient population, because they cannot prevent GERD-induced aspiration and may not protect against Barrett's esophagus. Until evidence suggests otherwise, we recommend laparoscopic fundoplication with frequent endoscopic surveillance and endoscopic ablative therapy for Barrett's metaplasia.

We acknowledge specific limitations of our study. First, the overall sample size is relatively small, rendering a multivariate analysis difficult. Second, not all lung transplant patients without GERD were further assessed by upper endoscopy or gastric emptying studies, limiting the comparisons of delayed gastric emptying, hiatal hernia, and Barrett's esophagus between groups with and without GERD. However, we believe that these studies would have added little to the clinical management of patients without GERD.

We conclude that GERD is highly prevalent in the lung transplant population and that delayed gastric emptying and Barrett's esophagus should always be suspected after lung transplantation because they are common risk factors for and complications of GERD. Furthermore, in the evaluation of the patient with end-stage lung disease or after lung transplantation, we recommend the use of esophageal function testing, with the addition of upper endoscopy and gastric emptying studies in those testing positive for GERD. We believe that the diagnosis of GERD in lung transplant patients should be an aggressive endeavor as GERD may contribute to BOS and rejection. This effort should be directed at the early surgical correction of reflux (even before lung transplantation if possible), when the patient is fit to undergo elective surgery and has no contraindications (eg, oxygen requirements at rest and pulmonary hypertension). Therefore, in lung transplant patients with GERD, we support the role of laparoscopic antireflux surgery as a means to correct the risk factors for GERD and to prevent its complications, with the goal of preserving lung function.

References

1. Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel A, et al. Registry for the International Society for Heart and Lung Transplantation: Twenty-fifth Official Adult Lung and Heart/Lung Transplantation Report. J Heart Lung Transplant. 2008; 27:957–69. [PubMed: 18765187]

2. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit Care Med. 2002; 166:440–4. [PubMed: 12186817]
3. Hartwig MG, Appel JZ, Li B, Hsieh CC, Yoon YH, Lin SS, et al. Chronic aspiration of gastric fluid accelerates pulmonary allograft dysfunction in a rat model of lung transplantation. J Thorac Cardiovasc Surg. 2006; 131:209–17. [PubMed: 16399314]
4. Lau CL, Palmer SM, Howell DN, McMahon R, Hadjiliadis D, Gaca J, et al. Laparoscopic antireflux surgery in the lung transplant population. Surg Endosc. 2002; 16:1674–8. [PubMed: 12140642]
5. Hadjiliadis D, Davis RD, Steele MP, Messier RH, Lau CL, Eubanks SS, et al. Gastroesophageal reflux disease in lung transplant recipients. Clin Transplant. 2003; 17:363–8. [PubMed: 12868994]
6. Cantu E, Appel JZ III, Hartwig MG, Woreta H, Green C, Messier R, et al. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg. 2004; 78:1142–51. [PubMed: 15464462]
7. Burton PR, Button B, Brown W, Lee M, Roberts S, Hassen S, et al. Medium-term outcome of fundoplication after lung transplantation. Dis Esophagus. 2009; 22:642–8. [PubMed: 19515194]
8. Spechler SJ, Castell DO. Classification of esophageal motility abnormalities. Gut. 2001; 49:145–51. [PubMed: 11413123]
9. Tutuian R, Vela MF, Balaji NS, Wise JL, Murray JA, Peters JH, et al. Esophageal function testing with combined multi-channel intraluminal impedance and manometry: multi-center study in healthy volunteers. Clin Gastroenterol Hepatol. 2003; 1:174–82. [PubMed: 15017488]
10. Streets CG, DeMeester TR. Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do. J Clin Gastroenterol. 2003; 37:14–22. [PubMed: 12811203]
11. Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. Am J Gastroenterol. 1993; 88:25–9. [PubMed: 8420269]
12. Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Hum Pathol. 1988; 19:166–78. [PubMed: 3343032]
13. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. Chest. 2003; 124:1689–93. [PubMed: 14605036]
14. D'Ovidio F, Mura M, Ridsdale R, Takahashi H, Waddell TK, Hutcheon M, et al. The effect of reflux and bile acid aspiration on lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. Am J Transplant. 2006; 6:1930–8. [PubMed: 16889547]
15. Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, et al. Nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients. J Heart Lung Transplant. 2009; 28:141–8. [PubMed: 19201339]
16. Jones MP, Sloan SS, Rabine JC, Ebert CC, Huang CF, Kahrilas PJ. Hiatal hernia size is the dominant determinant of esophagitis presence and severity in gastroesophageal reflux disease. Am J Gastroenterol. 2001; 96:1711–7. [PubMed: 11419819]
17. Patti MG, Goldberg HI, Arcerito M, Bortolasi L, Tong J, Way LW. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996; 171:182–6. [PubMed: 8554137]
18. Gasper WJ, Sweet MP, Hoopes C, Leard LE, Kleinhenz ME, Hays SR, et al. Antireflux surgery for patients with end-stage lung disease before and after lung transplantation. Surg Endosc. 2008; 22:495–500. [PubMed: 17704875]
19. Au J, Hawkins T, Venables C, Morritt G, Scott CD, Gascoigne AD, et al. Upper gastrointestinal dysmotility in heart-lung transplant recipients. Ann Thorac Surg. 1993; 55:94–7. [PubMed: 8417718]
20. Berkowitz N, Schulman LL, McGregor C, Markowitz D. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. Chest. 1995; 108:1602–7. [PubMed: 7497768]
21. Sodhi SS, Guo JP, Maurer AH, O'Brien G, Srinivasan R, Parkman HP. Gastroparesis after combined heart and lung transplantation. J Clin Gastroenterol. 2002; 34:34–9. [PubMed: 11743243]

22. Reid KR, McKenzie FN, Menkis AH, Novick RJ, Plug-felder PW, Kostuk WJ, et al. Importance of chronic aspiration in recipients of heart-lung transplants. Lancet. 1990; 336:206–8. [PubMed: 1973771]

23. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology. 2004; 127:1592–622. [PubMed: 15521026]

24. Winters C Jr, Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL, Hacker JF III, Johnson DA, et al. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology. 1987; 92:118–24. [PubMed: 3781178]

25. Campos GM, DeMeester SR, Peters JH, Oberg S, Crookes PF, Hagen JA, et al. Predictive factors of Barrett esophagus: multivariate analysis of 502 patients with gastroesophageal reflux disease. Arch Surg. 2001; 136:1267–73. [PubMed: 11695971]

26. Oka M, Attwood SE, Kaul B, Smyrk TC, DeMeester TR. Immunosuppression in patients with Barrett's esophagus. Surgery. 1992; 112:11–7. [PubMed: 1621218]

27. Saleh W, Duranceau A, Martin J, Noiseux N, Poirier C, Ferraro P. Rapid progression of Barrett's esophagus into adenocarcinoma in a combined lung and kidney transplant recipient. J Thorac Cardiovasc Surg. 2010; 139:217. [PubMed: 19660251]

Table I

Characteristics of patients with and without GERD after lung transplantation

	Patients with GERD	Patients without GERD	P value
Patients	51%	49%	
Gender			.404
Males	28%	41%	
Females	72%	59%	
Age (yrs)*	55 (46–60)	59 (52–63)	.165
Race			.615
Caucasian, non-Hispanic	90%	94%	
Caucasian, Hispanic	5%	0	
African American	5%	6%	
BMI*	24 (20–29)	26 (24–31)	.085
Lung disease			
Obstructive	67%	76%	.521**
AAT deficiency	11%	6%	
Cystic fibrosis	22%	6%	
COPD	22%	52%	
Scleroderma	11%	0	
Bronchiectasis	0	6%	
Chronic obstructive asthma	0	6%	
Restrictive			
IPF	33%	24%	

* Data are presented as median (interquartile range).

** Obstructive versus restrictive lung disease.

AAT, α_1-Anti-trypsin; *BMI*, body mass index (expressed in kg/m^2); *COPD*, chronic obstructive pulmonary disease; *IPF*, idiopathic pulmonary fibrosis.

Table II

Manometric and pH-metric profile

	Patients with GERD	Patients without GERD	P value
Manometric profile			
LES			
LES pressure (mm Hg)	25 (16–35)	30 (24–36)	.317
LES total length (cm)	2 (2–3)	3 (3)	.052
LES abdominal length (cm)	2 (1–2)	2 (2–3)	.084
Esophageal body			
DEA (mm Hg)	46 (32–81)	90 (53–137)	.029
pH metric profile			
Total time pH <4 (%)	9 (6–18)	1 (1–2)	.000001
Upright	8 (6–12)	2 (1–3)	.0004
Supine	9 (4–18)	0 (0)	.000003
Episodes >5 min	6 (4–11)	1 (0–1.1)	.000001
Longest episode (minutes)	24 (16–38)	6 (3–11)	.00004
Total episodes	57 (35–84)	13 (11–26)	.0001
DeMeester score (normal: <14.7)	31 (22–65)	5 (4–9)	.000001
Esophageal clearance (sec)			
Total mean acid clearance time	181 (132–280)	52 (30–106)	.0002
Upright	105 (87–149)	52 (30–106)	.101
Supine	236 (183–419)	0 (0–10)	.00002
Proximal pH sensor data			
Total time pH <4 (normal: <1%)	0.9 (0.5–2.2)	0.2 (0–1.9)	.0004
Upright	0.4 (0.2–2.4)	0.3 (0–2.9)	.238
Supine	0.7 (0–1.9)	0	.0034

Data are presented as medians (interquartile ranges).

DEA, Distal esophageal amplitude; *GERD*, gastroesophageal reflux disease; *LES*, lower esophageal sphincter.

Table III

Relationship between type of transplant and GERD, or underlying end-stage lung disease

Transplant type	Patients with GERD	Patients without GERD*
Unilateral	31%	69%
Bilateral	56%	44%
Retransplant	100%	0

*$P = .047$.

GERD, Gastroesophageal reflux disease.