Esophageal disease in lung transplant patients

John S. Young, Antonio Coppolino

Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, MA, USA

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Correspondence to: Antonio Coppolino. Division of Thoracic Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Email: acoppolino@bwh.harvard.edu.

Abstract: There is a very well-established and complex interplay between gastroesophageal reflux and lung disease. This is particularly true in end-stage lung disease and post-lung transplant patients. Numerous studies have shown that in patients who are undergoing pre-lung transplant evaluations for diseases such as idiopathic pulmonary fibrosis (IPF), emphysema, connective tissue disease, there is a high prevalence of gastroesophageal reflux and esophageal dysmotility. Post-lung transplant, many of the reflux issues persist or worsen, and there is some evidence to suggest that this leads to worsened long-term allograft function and bronchiolitis obliterans. Anti-reflux operations in patients with lung disease have been shown to be safe in both the pre and post-lung transplant setting and lead to improved reflux symptoms, as well as protecting against reflux induced allograft dysfunction in the post-lung transplant patients. Barrett's esophagus and esophageal malignancy are also not unheard of in these patients, and select patients may benefit from operative intervention. This review discusses the links between gastroesophageal reflux and lung transplant patients in both the pre and post-transplant setting. We also review the approach to the workup of esophageal disease in the pre-lung transplant setting as well as the surgical management of this unique group of patients.

Keywords: Lung transplant; gastroesophageal reflux; esophagus; fundoplication

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Introduction

The relationship between gastroesophageal reflux and lung disease has been well established and described in the literature. Pulmonary diseases such as pulmonary fibrosis, cystic fibrosis, pneumonia, asthma, and bronchitis all have clear correlations with gastroesophageal reflux (1-4). Esophageal disease frequently plays a role in end stage lung disease, of which lung transplantation is a lifesaving therapy with one-year survival of over 90%. The interplay between the esophagus and the lungs persists post lung transplant. This review explores esophageal disease in the lung transplant population and discusses some of the treatment strategies targeting the esophagus both pre and post-transplant.

Gastroesophageal reflux and lung disease

Gastroesophageal reflux plays a major role in pulmonary disease and specifically in end-stage lung disease patients who are undergoing evaluation for lung transplantation. Numerous papers have been published describing the prevalence of gastroesophageal reflux in this patient population.

In a 2005 study from Toronto, D'Ovidio and colleagues examined 78 consecutive end-stage lung disease patients who were being assessed for lung transplantation. They had 26 patients with idiopathic pulmonary fibrosis (IPF), 21 with emphysema, 10 with scleroderma, 5 with cystic fibrosis, and 16 others with miscellaneous diseases. All of the patients underwent esophageal manometry, 76 of the

78 patients had two-channel esophageal 24-hour pH testing, and 36 patients had gastric emptying studies performed. Gastroesophageal reflux related symptoms were seen in 63% (49 of 78) of the patients. Seventy-two percent of patients had a hypotensive lower esophageal sphincter (LES), 44% of patients had prolonged gastric emptying, and 38% had abnormal pH testing. An elevated DeMeester score was seen in 32% of patients and abnormal proximal pH probe readings were seen in 20% of patients (5).

Sweet and colleagues reported in the same year a total of 109 patients with end-stage lung disease who were awaiting lung transplantation at University of California San Francisco had symptom assessment, esophageal manometry, and pH monitoring. Seventy-four (68%) patients had reflux as defined by an elevated DeMeester score. Out of 104 patients who completed the symptom assessment, 72 patients (69%) had at least one typical symptom of gastroesophageal reflux disease (GERD). Notably, symptoms were not a good predictor of reflux with a sensitivity and specificity for distal reflux of 67% and 26%, respectively, and 62% and 26% for proximal reflux, respectively. In patients with reflux, many of the patients had a hypotensive LES (55%) and impaired esophageal peristalsis (47%). Distal reflux was present in 68% of patients and proximal reflux was present in 37% of patients (6).

More recent studies utilizing high resolution manometry have confirmed that esophageal motor dysfunction and gastroesophageal reflux are prevalent in lung transplant candidates. Basseri and colleagues looked at 30 consecutive lung transplant patients and compared them to a healthy control group of 10 patients. The lung transplant patients underwent 24-hour pH monitoring and high-resolution esophageal manometry whereas the control group underwent only high-resolution esophageal manometry. The lung transplant candidate group was older (64.0 *vs.* 53.4 years, P value 0.005). In the lung transplant group, there were 16 patients with chronic obstructive pulmonary disease (COPD), 10 with IPF, 2 with pulmonary artery hypertension, 1 with bronchiolitis obliterans with organizing pneumonia, 1 with severe scleroderma, and 1 with severe bronchiectasis. Lung transplant candidates had higher residual upper esophageal and LES pressures compared with the control group (3.9 *vs.* 3.1, P=0.015; 13.4 *vs.* 8.3, P=0.015 respectively). Twenty-three of the 30 (76.7%) lung transplant candidates had peristaltic dysfunction compared to none of the control patients (P<0.001). Of those lung transplant candidates with peristaltic dysfunction, ten had frequent dysfunction (>7 swallows with either failed peristalsis or a >3 cm defect in 30-mmHg isobaric contour of distal esophageal segment). Eighty percent of those patients with frequent dysfunction also had a hypotensive LES. Abnormal acid exposure time was seen in the proximal and distal esophagus in 25% and 36% of lung transplant candidates, respectively, which was consistent with prior studies. When compared with those patients with COPD, those with IPF had more aperistaltic contractions, more negative minimum intrathoracic pressure, and a higher frequency of abnormal distal esophagus acid exposure (7).

A more recent study looked specifically at the role of thoracoabdominal pressure gradient in GERD. This is the gradient across the LES between a positive intraabdominal pressure and a negative-pressure chest cavity. While things that cause an increased intraabdominal pressure (such as an increased body mass index) are clearly linked with GERD, the role of the chest is less understood. A recent retrospective 2018 study looked specifically at the thoracoabdominal pressure gradient (intraabdominal pressure minus the intrathoracic pressure during inspiration) as well as the adjusted thoracoabdominal pressure gradient (thoracoabdominal pressure gradient minus the resting LES pressure) in lung transplant candidates. They looked at 77 lung transplant patients who had undergone pre lung transplant manometry and pH studies. For a control group, they selected 22 patients with no lung disease and normal esophageal function tests. They found that GERD was more common in patients with restrictive lung disease than obstructive lung disease (24.2% *vs.* 47.6%, P=0.038). The thoracoabdominal pressure gradient was similar between the obstructive lung disease group and the controls (14.2 *vs.* 15.3 mmHg, P=0.850) but patients with restrictive lung disease had a higher thoracoabdominal pressure gradient than the control group (24.4 *vs.* 15.3 mmHg, P=0.002). They found that while the thoracoabdominal pressure gradient did not correlate with reflux parameters in the 77 end stage lung disease patients, the adjusted thoracoabdominal pressure gradient was positively correlated (DeMeester score, rs=0.256, P=0.024; total reflux time, rs=0.259, P=0.023; total number of reflux episodes, rs=0.268, P=0.018). An adjusted transabdominal pressure gradient of gradient >0 mmHg (i.e., when the transabdominal pressure gradient exceeds the lower esophageal pressure) was seen in 22/77 patients (28.6%). These patients had higher DeMeester greater prevalence of pathological reflux, higher total time pH <4, and more total number of reflux episodes compared with patients who had adjusted thoracoabdominal pressure gradient

≤0 mmHg (15.2 *vs.* 6.3, P=0.006; 59.1 *vs.* 30.9%, P=0.022; 4.5 *vs.* 1.5%, P=0.003; 66.5 *vs.* 23.4, P=0.012, respectively). The study supported the claim that especially in patients with restrictive lung disease, that ventilator mechanics and an elevated adjusted thoracoabdominal pressure gradient play a role in the development of GERD (8).

Others had previously looked at the role of gastroesophageal reflux in specific etiologies of end stage lung disease, particular in IPF. Sweet and colleagues looked at 30 patients with a diagnosis of IPF who had undergone esophageal testing (symptom assessment, esophageal manometry, and 24 hr pH monitoring) prior to lung transplantation. 20 of the 30 (67%) patients had abnormal esophageal reflux. They found that, similar to prior studies, typical reflux symptoms were not reliable as a screening test (sensitivity 65%, specificity 71%). 65% of patients with abnormal reflux had a hypotensive LES, abnormal esophageal peristalsis was more common in those with reflux (50% *vs.* 10%, P=0.03) and in 9 (30%) of patients, acid refluxed into the proximal esophagus for over 1% of the study time. These findings support the link between pathologic reflux and IPF (9).

Recognizing that the studies linking IPF to reflux relied on the dual-channel pH probe (which detects proximal reflux events up to 20 cm proximal to the LES), Hoppo and colleagues performed a retrospective review of 28 patients undergoing evaluation for reflux who carried a diagnosis of IPF. They utilized 24-hour hypopharyngeal multichannel intraluminal impedance with a specialized catheter to measure laryngopharyngeal reflux and full column reflux (reflux 2 cm distal to the upper esophageal sphincter). Twenty-seven of the patients had symptoms; 23 (82%) of whom had typical GERD symptoms, whereas 4 (14%) had isolated pulmonary symptoms. Abnormal proximal exposure which occurred almost exclusively in the upright position, was present in 54% (15/28) of patients. They did not find a difference in clinical symptoms, objective findings of GERD, and pulmonary functions between patients with and without abnormal proximal exposure. Many patients had a normal DeMeester score regardless of the presence of abnormal proximal exposure (80% in patients with, 85% in patients without). Patients with abnormal proximal exposure were more likely to have a defective LES compared to those without (93% *vs.* 75%), and 14 (56%) patients had an abnormal esophageal motility study. The group concluded that GERD and particularly proximal reflux are common in IPF patients despite a negative DeMeester score (10).

IPF is not the only pulmonary disease linked with esophageal disease. Connective tissue diseases are commonly associated with pulmonary disease as well as esophageal disease. A retrospective review from University of California San Francisco looked at 26 patients with connective tissue disease referred for lung transplantation. Twenty-three patients had esophageal manometry and ambulatory 24-h pH monitoring. Nineteen (83%) patients had pathologic distal reflux and 7 (30%) also had pathologic proximal reflux. There were 18 patients (78%) who had impaired or absent peristalsis (11).

Gastroesophageal disease has also been linked with cystic fibrosis and its progression. In a study from Button and colleagues, 11 adult patients with cystic fibrosis awaiting lung transplantation were evaluated with a symptom questionnaire and 24-hour esophageal pH monitoring. The group had an average DeMeester score of 36.6±22.3 (normal value is <14.7) and a mean reflux index of 2.4%±1.9% (normal value is 0.4%). The mean symptom score was 5.8±6.5 (a score of ≥4 indicates symptomatic reflux). Ten out of the 11 (90.9%) had significant gastroesophageal reflux on monitoring, among whom 4 (40%) had reflux symptoms. The authors concluded that gastroesophageal reflux is a significant problem in patients with cystic fibrosis (12).

A common theme throughout these studies in pre lung transplantation patients is that symptoms are not sufficient to determine who should undergo esophageal function testing. Posner and colleagues at Duke focused on this specific issue in their 2018 study. They retrospectively reviewed 226 patients who had undergone high resolution manometry and pH testing as part of their lung transplant evaluation over a 12-month period in 2015. Interstitial lung disease was the most common diagnosis (131 patients, 58%), with COPD being next most common (49 patients, 21.7%). An abnormal pH study was seen in 116 (51%) patients and the presence of symptoms was significantly associated with an abnormal study (P<0.01). They found dysmotility in 93 (43%) of patients. Forty-five (20%) of these patients had major peristaltic or esophageal outflow disorders. Importantly symptoms did not correlate with findings on esophageal manometry. Fifteen of 25 (60%) asymptomatic patients had an abnormal manometry or pH study. Given these findings, they supported esophageal studies (high-resolution manometry and pH study) in all patients being evaluated for lung transplant (13).

The practice at our institution is to evaluate all potential lung transplant candidates regardless of the presence of symptoms with high resolution manometry as well as 24-hour pH monitoring given the proportion of

asymptomatic patients with abnormal studies and the significant post-transplant risk.

Esophageal disease after lung transplantation

Post lung transplant many reflux issues persist and are in fact exacerbated. A 2003 study from Duke University Medical Center reviewed 23 patients who had undergone pre-transplant and post-transplant reflux studies with 24 hour pH studies, esophageal manometry and gastric-emptying studies. Thirty-five percent (8 of 23 patients) had abnormal acid contact times before transplant, and 65% (15 of 23 patients) had abnormal acid contact after transplant. After lung transplantation, the total acid contact time increased by a mean of 3.7% (P=0.03) and the supine acid contact time increased by a mean of 6.4% (P=0.019). Notably, these findings were not linked with changes in manometry or gastric emptying. Of the 15 patients with reflux, only 5 patients had delayed gastric emptying (33%) and 2 had incomplete relaxation of the LES. Furthermore, many (12 of 15) of the patients with abnormal post-transplant pH studies were asymptomatic. The authors concluded that gastroesophageal reflux increased after lung transplantation (14).

A more recent 2010 study of 35 post lung transplant patients who underwent a combination of esophageal function testing, upper endoscopy, barium swallow, and gastric emptying looked at the prevalence and extent of GERD in this population. The prevalence of GERD was 51% in patients who had undergone lung transplantation and the type of transplantation also played a role. 31% of patients undergoing unilateral transplantation, 56% of patients undergoing bilateral lung transplantation and 100% of patients undergoing retransplantation had GERD (P=0.047). Of patients with GERD, 36% had ineffective esophageal motility, compared with 6% of patients without GERD (P=0.037). The manometric profile of the LES was similar between patients with and without GERD by LES pressure, LES total length, and LES abdominal length. Delayed gastric emptying was seen in 36% of patients and Barrett's esophagus was seen in 12% (15).

Other studies have tried looking at specific esophageal motility disorders after lung transplantation. A recent retrospective cohort study from Massachusetts General Hospital and Brigham and Women's Hospital reviewed 57 patients without jackhammer esophagus pre-lung transplant with high resolution manometry. Fifteen (25.4%) patients were found to have new jackhammer esophagus post-transplant. Patients with newly diagnosed jackhammer esophagus after lung transplant were older (61.3±5.3 *vs.* 51.6±15.6; P=0.02) and had more COPD (47.6% *vs.* 16.6%; P=0.03). There was no significant difference between body mass index, opioid use, pre-transplant esophageal manometry findings, surgical ischemic time, occurrence of gastroparesis, or measured post-transplant outcomes between the 2 groups (16).

A major question regarding esophageal motility is whether it leads to worse outcomes after lung transplantation. Posner and colleagues looked at 76 patients who underwent lung transplantation and had high resolution and pH studies before and after transplant. Post-transplant, there was a significant increase in esophageal contractility; median distal contractile integral increased from 1,470 to 2,549 mmHg cm s (P<0.01). Nineteen of 76 patients had Jackhammer esophagus post-transplant; notably 15 of these patients had normal motility pre-transplant. They did not see an increase in gastroesophageal reflux—35 (46%) of patients pre-transplant had an abnormal pH study compared with 29 (38%) of patients post-transplant (P=0.33). That said, patients with GERD post-transplant had less improvement in their pulmonary function at one year as measured by forced expiratory volume over 1 second (FEV1) (P=0.04) (17).

A number of other studies have looked at the link between gastroesophageal reflux in post lung transplant patients and allograft dysfunction. A study by Tangaroonsanti and colleagues looked at 50 post lung transplant patients who had undergone manometry and 24-hour pH/impendence studies looked at the development of obstructive chronic lung allograft dysfunction. They found that esophagogastric junction outflow obstruction alone, incomplete bolus transit, and proximal reflux were risk factors for obstructive chronic lung allograft dysfunction (P=0.01, P=0.006, P=0.042, respectively). Patients with esophagogastric junction outflow obstruction alone were more likely to develop chronic lung allograft dysfunction versus those with normal motility (77% *vs.* 29%, P<0.05). Interestingly, patients with esophagogastric junction outflow obstruction alone were less likely to exhibit an abnormal number of reflux events and had a lower total reflux bolus time compared to those with normal motility (10% *vs.* 64%, P<0.05; 0.6% *vs.* 1.5%, P<0.05). Post-reflux swallow-induced peristaltic wave index was found to be associated with obstructive chronic lung allograft dysfunction. The authors concluded that esophageal dysmotility and inefficient clearance of swallowed bolus or refluxed contents, rather than gastroesophageal reflux alone were risk factors in the development of obstructive chronic lung allograft

dysfunction (18).

The Chicago classification version (v3.0 *vs.* v2.0) used also makes a difference in identification of dysmotility in post lung transplant patients. In particular, in things like peristaltic breaks as defined by Chicago v2.0 can lead to prolonged esophageal clearance, but are deemed as normal by Chicago v3.0. Tangaroonsanti and colleagues looked again at their group of 50 patients post-lung transplant and found that reclassification from Chicago classification v3.0 to v2.0 resulted in 7 patients with normal motility being reclassified to hypo-contractility (n=6) or hyper-contractility (n=1). Two patients who had been labelled with hypo-contractility were reclassified to normal motility, and 3 patients with esophagogastric junction outflow obstruction without hyper-contractility were reclassified as esophagogastric junction outflow obstruction with hyper-contractility. Importantly, the sub-group exhibiting hypo-contractility became more likely to have abnormal numbers of reflux events (P=0.025) and incomplete bolus transit (P=0.002) than those with normal motility using Chicago classification v2.0. These associations were not seen using Chicago classification v3.0. Regardless of the Chicago classification version used, only patients with esophagogastric junction outflow obstruction showed an increased risk of developing obstructive chronic lung allograft dysfunction compared with normal motility (P<0.05). Irrespective of Chicago Classification used, only patients with esophagogastric junction outflow obstruction appeared more likely to develop allograft dysfunction than those with normal motility (P<0.05). Thus, the identification of more subtle abnormalities of hypocontractility (and therefore incomplete bolus transit and increased reflux) highlighted in Chicago classification v2.0 may have important consequences of allograft failure post-lung transplantation (19).

Others have looked at the link between esophageal motor disorders and the development of chronic lung allograft rejection. Ciriza-de-Los-Rios and colleagues in Spain studied 57 patients who underwent high resolution manometry both pre-lung transplant and six months post-lung transplant. They found esophageal motor disorders in 33.3% of patients pre-lung transplant and 49.1% of patients post-lung transplant with abnormal peristalsis more frequent in post-lung transplant patients (P=0.018). Hypercontractile esophagus was frequently found post lung-transplant (19.3% post-lung transplant *vs.* 1.8% pre-lung transplant). Importantly, esophageal motor disorders were more frequently seen post-lung transplant, in both patients without rejection and patients with rejection, but more so in the patients with rejection (43.2% and 69.2%, respectively; P=0.09). The esophagogastric junction was more frequently classified as normal (type I) in the non-rejection group compared to the rejection group (86.4% *vs.* 69.2%, respectively). Esophageal motor disorders such as distal spasm, hypercontractile esophagus and esophagogastric junction outflow obstruction were also observed more frequently post-lung transplant in the rejection group. This study supports the role of esophageal motor disorders leading to impaired esophageal clearance in the development of lung transplant rejection (20).

An earlier study from 2008 explored a putative link between gastroesophageal reflux and nighttime obstructive sleep apnea with bronchiolitis obliterans syndrome. Shepherd and colleagues had fourteen lung transplant patients undergo overnight polysomnography with simultaneous dual esophageal pH monitoring. The patients were on average 59±6 years old and were 38±47 months post-transplant. They had an average FEV1 of 84%±15%. Six out of fourteen patients were in various stages of bronchiolitis obliterans syndrome. The average proportion of time spent overnight with a pH of <4 was 1.7%±3.1%. Increased gastroesophageal reflux was evident in 8/14 patients during the postprandial period and/or overnight in the distal and/or proximal esophagus. All patients had obstructive sleep apnea with (Apnea Hypopnea Index >5 events per hour) with 50% of patients having severe obstructive sleep apnea (Apnea Hypopnea Index >30 events per hour). The researchers found that while gastroesophageal reflux and obstructive sleep apnea were common, they were not linked. Notably, they did not see a relationship between nocturnal gastroesophageal reflux or obstructive sleep apnea and the severity of bronchiolitis obliterans (21).

Others have investigated the role that the type of lung transplantation performed has on GERD. A Loyola University Medical Center study from 2012 retrospectively reviewed 61 lung transplant patients who underwent esophageal function tests and divided them into unilateral (n=25), bilateral (n=30), or retransplantation (n=6) recipients. Patients who had unilateral transplant were less likely to have GERD compared to those with bilateral lung transplant and retransplant (24% *vs.* 63% and 100%, respectively). Patients who received a unilateral lung transplant were also less likely to have proximal GERD, compared to those with a bilateral lung transplant or retransplant (24% *vs.* 52% *vs.* 50%; P<0.05). They found

that the prevalence of hiatal hernia, Barrett esophagus, and the manometric profile were similar in all groups of patients. The authors speculated that the extent of dissection places bilateral and retransplant patients at higher risk of GERD compared with unilateral lung transplant patients (22).

In a 2019 study, Tangaroonsanti and colleagues also studied the effect of unilateral versus bilateral lung transplantation on esophageal motility and gastroesophageal reflux and development of obstructive chronic lung allograft dysfunction. Forty-eight patients post lung transplant underwent high resolution manometry and 24-hour pH/impedance. Those patients who had a unilateral lung transplant were more likely to have esophagogastric junction outflow obstruction (47% *vs.* 18%, P=0.046) and less likely to have hypocontractility (0% *vs.* 21%, P=0.058) compared with those who had bilateral lung transplant. There was no difference between the groups in gastroesophageal reflux (33% *vs.* 39%; P=0.505). However, those who had bilateral lung transplantation were more likely to exhibit proximal reflux (8% *vs.* 37%; P=0.067). There was no difference between unilateral and bilateral lung transplantation in the development of obstructive chronic lung allograft dysfunction (hazard ratio =1.17; 95% confidence interval, 0.48–2.85; P=0.723), although the authors recognized the limitation of their small sample size (23).

Heart-lung transplantation has also been purported to play a role in upper gastrointestinal dysmotility. The recipient pneumonectomy and need for meticulous hemostasis is thought to lead to consequent delay in gastric emptying due to vagus nerve injury. Au and colleagues looked at 10 patients who had undergone heart-lung transplantation. Esophageal manometry, 24-hour pH monitoring, and radioisotopic gastric emptying were performed. Three patients had grossly delayed liquid and solid emptying compatible with complete vagotomy. Six other patients had delayed liquid but normal solid emptying. Two of these 9 patients had esophageal dysmotility. Interestingly, no patients had gastroesophageal reflux. Two patients had radiologic changes of bronchiectasis, and 3 had biopsy proven bronchiolitis obliterans. The researchers found no association between these sequelae and vagotomy, esophageal dysmotility, or gastroesophageal reflux. This was a small study but showed that while evidence of gastric emptying abnormalities after heart-lung transplantation exists, they were not linked with reflux and the development of pulmonary complications (23).

The lung transplant population has a heterogeneous mix of etiologies, many with different risk factors for esophageal dysfunction as demonstrated in a number of studies (8,9). Connective tissue disease such as systemic sclerosis and scleroderma are commonly linked with pulmonary disease and can affect multiple systems including the gastrointestinal system. Some have been reluctant to perform lung transplantation in this patient population in part because of these concerns. In their 2008 study on connective tissue disorders and esophageal dysmotility in lung transplant patients, Gasper and colleagues reported that 11 of the 26 patients with connective tissue disorders underwent lung transplantation. Ten were alive at a median follow-up of 26 months, and 1 patient died of a sudden unknown cause 1 month post-transplant. One of the 11 patients had bronchiolitis obliterans syndrome (11).

Miele and colleagues looked specifically at patients with systemic sclerosis who had undergone lung transplant. They compared their lung transplant patients with systemic sclerosis (n=35) to all non-systemic sclerosis lung transplant patients (n=527), non-systemic sclerosis lung transplant patients with diffuse fibrotic lung disease (n=264), and non-systemic sclerosis lung transplant patients that were matched (n=109). Pre lung transplant, systemic sclerosis patients had significantly more severe esophageal dysfunction by CT morphometry criteria (55%) versus the diffuse fibrotic lung disease group (8%, P<0.001). They found that the 1-, 3-, and 5-year post-lung transplant survival for systemic sclerosis patients was 94%, 77%, and 70%, respectively, and similar to the other groups. Primary graft dysfunction, acute rejection, as well as bronchiolitis obliterans syndrome were also similar between patients with systemic sclerosis and those without. They concluded that while esophageal dysfunction was prevalent in patients with systemic sclerosis, their outcomes are no worse to others in lung transplant (24).

Treatment with fundoplication

Given the prevalence of gastroesophageal reflux, the issues with esophageal dysmotility, and its effects on lung transplant recipients, is there a role for surgical treatment with a fundoplication?

Fisichella and colleagues retrospectively compared 29 consecutive lung transplant patients with 23 consecutive patients without lung transplant who had laparoscopic antireflux surgery for GERD. They found that there were similar prevalences of endoscopic esophagitis and Barrett's esophagus, manometric profiles, and prevalence of abnormal peristalsis. That said, lung transplant patients

were more prone to proximal GERD (65% *vs.* 33%, P=0.04) than their non-lung transplant counterparts. Importantly, the outcomes between the two groups were comparable. There was no difference in 30-day length of stay (P=0.75), complications (P=0.57), or readmissions (P=1). This was in spite of the higher surgical risk of lung transplants (median American Society of Anesthesiologists classification 3 versus 2, P<0.001). The authors concluded that laparoscopic antireflux surgery can be performed in lung transplant recipients with comparable safety to non-lung transplant patients (22).

Others have shown that fundoplication may have beneficial effects on symptoms and quality of life after lung transplant. A 2009 study looked at 21 patients post-lung transplantation with proven reflux who had undergone fundoplication. The indication for fundoplication was for symptoms in 8 patients and microaspiration in 13. There was 1 perioperative death at day 17, and there were 3 other late deaths. While fundoplication did not affect progression to bronchiolitis obliterans syndrome stage 1, it may have slowed progression to stage 2 and 3. Patients appeared to be satisfied with the outcome of the fundoplication and the prevalence of GERD symptoms decreased significantly following surgery (11 of 14 *vs.* 4 of 17, P=0.002) (25).

A number of other studies have looked at whether performing antireflux surgery improves graft function in lung transplant patients. Biswas Roy and colleagues retrospectively reviewed patients who underwent fundoplication after lung transplantation and divided the patients into 2 groups: early fundoplication (<6 months after lung transplantation) and late fundoplication (≥6 months after lung transplantation). Of 251 patients who underwent lung transplantation with available pH data, 86 (34.3%) underwent post-transplantation fundoplication for gastroesophageal reflux. Thirty-six of 86 (34.9%) had an early fundoplication and 56 of 86 (65.1%) had a late fundoplication. The 5-year percent predicted FEV1 was lower in the late group by 40.7% (95% confidence interval, −73.66 to −7.69; P=0.019). A linear mixed model showed a 5.7% lower percent predicted FEV1 over time in the late fundoplication group (P<0.001). The authors concluded that early fundoplication may protect against GERD-induced lung damage in post lung transplant patients (26).

A recent metanalysis published in the *Journal of Cardiovascular and Thoracic Surgery* looked at articles where anti-reflux surgery was performed after lung transplant and where FEV1 was documented during the pre- and postoperative periods. They found that there was a small increase in FEV1 after anti-reflux surgery in studies reporting raw values (2.02±0.89 *vs.* 2.14±0.77 L/1 sec; n=154) and % of predicted (77.1%±22.1% *vs.* 81.2%±26.95%; n=45), with a small pooled Cohen d effect size of 0.159 (P=0.114). When they looked specifically at the rate of change of FEV1, there was a significant difference in pre-anti-reflux surgery compared with post-anti reflux surgery (−2.12±2.76 *vs.* +0.05±1.19 mL/day; n=103). The pooled effect size was 1.702 (P=0.013), with a large effect of anti-reflux surgery on the rate of change of FEV1 values. Thus, there may be benefit of anti-reflux surgery in lung transplant patients, in particular in those patients with a declining FEV1 (27).

The practice at our institution is to perform anti-reflux surgery either before or after lung transplantation with a preference for performing the surgery after transplant. The preference for performing the procedure after transplant is guided by efforts to avoid a potential exacerbation of the patients underlying lung disease secondary to positive pressure ventilation. Timing of anti-reflux surgery can vary based on the patient's post lung transplant recovery. Our goal is to perform the procedure as soon as clinically appropriate following the patient's transplant and usually within the first 90 days. In patients with significant reflux secondary to a large hiatal hernia we have considered fundoplication prior to lung transplant. The decision for post-lung transplant fundoplication and discussion with the transplant candidate is made prior to listing for transplant. Post-transplant anti-reflux surgery is a requirement in our program for patients with symptoms of reflux, a DeMeester of >14.7, abnormal "nonacid" reflux determined on impedance studies or evidence of aspiration.

Posttransplant esophageal malignancy after lung transplant

The immunosuppression required after transplantation has been linked to a variety of malignancies. There is a paucity of literature regarding esophageal adenocarcinoma post lung transplant.

A case report from 2016 described the anesthetic management of a bilateral lung transplant recipient undergoing an esophagectomy. The patient was a 52-year-old woman 2 years post bilateral lung transplant who underwent a thoracoscopic esophagectomy with radical lymph node dissection, hand-assisted laparoscopic gastric mobilization, and anastomosis of the gastric conduit to the cervical esophagus via posterior mediastinum. There

was concern that due to impaired lymphatic drainage, pulmonary edema or lymphangiogenesis could lead to a severe immunologic response against the transplanted lungs. The patient was managed with lung protective ventilation, minimization of transfusion volume, continued immunosuppressive agents, usage of volatile anesthetics and epidural anesthesia. The authors believed that these factors contributed to the patient ultimately doing well (28).

Another case report describes the management of a 42-year-old man with cystic fibrosis, a history of bilateral lung transplant 13 years prior, and a 20 year history of GERD who was found to have T1aN0 esophageal adenocarcinoma in the setting of Barrett's. An endoscopic mucosal resection was performed that showed submucosal invasion and he underwent a transhiatal esophagectomy with immediate postoperative extubation. Immunosuppressive therapy was resumed 3 days postoperatively. He was discharged on postoperative day 16. Final pathology was pT1bN0 esophageal adenocarcinoma and he remained well and disease free as of 2 years post-surgery (29).

A 2019 single center study from Norton Thoracic Institute in Phoenix, Arizona looked at 466 patients who underwent lung transplant. Fifty-four (11.59%) had Barrett's esophagus on pretransplant esophagogastroduodenoscopy. Sixteen of these patients (29.62%) underwent antireflux surgery after lung transplant. Low grade dysplasia or esophageal adenocarcinoma developed in 3 patients during posttransplant surveillance. One patient had a diagnosis of high-grade dysplasia 24 months after retransplant and had endoscopic ablation but ultimately underwent esophagectomy for invasive cancer. Two patients had a diagnosis of low-grade dysplasia 7 and 13 months after transplant and were treated with radiofrequency ablation. The rate of progression to dysplasia or adenocarcinoma was 2.3% per patient-year. This study supports the claims that Barrett's appears to be more prevalent in the lung transplant population and that there is an increased risk of progression to dysplasia or adenocarcinoma (30).

We have not performed an esophagectomy in a post lung transplant patient at our institution. Patients with GERD or Barrett's undergo aggressive surveillance with an EGD every 1–2 years. All esophageal cancer patients are discussed at our multi-disciplinary team which includes medical and radiation oncologists, gastroenterologists, as well as surgical oncologists and thoracic surgeons. In the case of a post lung transplant patient, these patients are followed closely by both the pulmonary transplant team as well as the transplant surgeons.

Conclusions

While we are better understanding the complex interplay between esophageal disease, lung disease, and the effect of lung transplantation, much remains to be clarified. Certainly gastroesophageal reflux has a role in the development of end stage lung disease across a wide spectrum of etiologies of lung disease. In assessing patients for lung transplant, regardless of symptoms, all patients should be screened for esophageal motility disorders and gastroesophageal reflux. Post lung-transplant, these patients appear to have a higher risk of esophageal dysmotility and this combined with gastroesophageal reflux may contribute to worsening of allograft function. Anti-reflux surgery appears to offer benefit in these patients. Barrett's esophagus and esophageal adenocarcinoma are not unheard of in this population and select patients are candidates for operative intervention.

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Footnote

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