PAPER

# Antireflux Surgery Preserves Lung Function in Patients With Gastroesophageal Reflux Disease and End-stage Lung Disease Before and After Lung Transplantation

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**Background:** Gastroesophageal reflux disease (GERD) is common in patients with end-stage lung disease (ESLD). GERD may cause obliterative bronchiolitis after lung transplantation (LTx), represented by a decline in forced expiratory volume in 1 second ($FEV_1$).

**Objectives:** To identify the patterns of reflux in patients with ESLD and to determine whether antireflux surgery (ARS) positively impacts lung function.

**Design:** Retrospective review of prospectively collected data.

**Setting:** Tertiary care university hospital.

**Patients:** Forty-three patients with ESLD and documented GERD (pre-LTx, 19; post-LTx, 24).

**Interventions:** Antireflux surgery.

**Main Outcome Measures:** Reflux patterns including laryngopharyngeal reflux as measured by esophageal impedance, and $FEV_1$, and episodes of pneumonia and acute rejection before and after ARS.

**Results:** Before ARS, 19 of 43 patients (44%) were minimally symptomatic or asymptomatic. Laryngopharyngeal reflux events, which occurred primarily in the upright position, were common in post-LTx (56%) and pre-LTx (31%) patients. At 1 year after ARS, $FEV_1$ significantly improved in 91% of the post-LTx patients ($P < .01$) and 85% of the pre-LTx patients ($P = .02$). Of patients with pre-ARS declining $FEV_1$, 92% of post-LTx and 88% of pre-LTx patients had a reversal of this trend. Episodes of pneumonia and acute rejection were significantly reduced in post-LTx patients ($P = .03$) or stablilized in pre-LTx patients ($P = .09$).

**Conclusions:** There should be a low threshold for performing objective esophageal testing including esophageal impedance because GERD may be occult and ARS may improve or prolong allograft and native lung function.

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LUNG TRANSPLANTATION (LTx) has been established as an accepted treatment strategy for end-stage lung disease (ESLD). However, mean 5-year survival is 55%, mainly because of bronchiolitis obliterans syndrome (BOS),[1] which manifests as progressive and irreversible decreases in expiratory air flow caused by small airway obstruction.[2] BOS can occur at any time after LTx, and it has a variable course. Lung function may decrease rapidly, leading to respiratory failure and death in some patients, whereas other patients may survive for years with either stable or slowly progressive loss of lung function. Because the presence of BOS is difficult to establish pathologically using transbronchial biopsy specimens (sensitivity, 28%; specificity, 75%[3,4]), the diagnosis is made based on a downward trend in pulmonary function criteria using forced expiratory volume in 1 second ($FEV_1$) and mid-expiratory flow rate as indirect measures.[2]

Although the pathogenesis of BOS is not well understood, hypotheses of alloantigen-dependent[5,6] and alloantigen-independent mechanisms[7] have been reported. Given that there has been no significant therapeutic effect on BOS during the past 20 years despite the use of novel immunosuppressive strategies,[8,9] the strong association between BOS and gastroesophageal reflux disease (GERD) has been suggested as a potential cause and, thus, a target for prevention and therapy.[10] A high prevalence of GERD in patients with ESLD awaiting LTx has been reported; most patients with idiopathic pulmonary fibrosis (87%)[11] and cys-

tic fibrosis (90.9%)[12] have GERD. Furthermore, it has been established that GERD after LTx is extremely common, with up to 75% of patients having abnormal esophageal acid exposure and possible microaspiration as a cause of progressive lung damage or repetitive acute rejection,[13] for which 40% to 50% of recipients are treated during the first year after LTx, and BOS.[10,14] However, despite these strong associations, the causal relationship between GERD and the development of BOS has yet to be definitively established.

Antisecretory therapy using proton pump inhibitors (PPIs) or $H_2$ blockade has been routinely implemented after LTx. However, this therapy has not been shown to be effective in preventing weakly acid or nonacid reflux in the clinical setting, and patients may continue to have microaspiration of caustic agents.[15,16] Recent uncontrolled studies have demonstrated the positive impact of antireflux surgery (ARS) on lung function[17] and on the prevention or delay in the onset of BOS.[14,18] No consensus exists between transplantation centers regarding the proper management of GERD in patients with ESLD. The purposes of this study were to examine the patterns of reflux disease in patients with ESLD before and after LTx and to evaluate the effect of ARS on pulmonary function in this population.

## METHODS

### STUDY DESIGN AND PATIENTS

This is a retrospective review of prospectively collected data under the approval of the Institutional Review Board of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. Eligible individuals included patients with ESLD and documented GERD who were being evaluated as possible candidates for LTx (pre-LTx) or had undergone LTx (post-LTx) and subsequently underwent ARS.[19] Detailed demographic data (age, sex, and race), medical comorbidities, current or previous use of antisecretory medications, and body mass index were recorded. GERD symptom type and duration (typical and atypical) were assessed at the time of evaluation for ARS. Hypertension, pulmonary hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, allergies, and occupation-related lung injury were recorded as medical comorbidities. The cause of ESLD and details of LTx (single vs double, ischemic time, and others) were recorded.

Patients were referred for the evaluation of GERD by the transplant pulmonology service because they were either symptomatic or having declining pulmonary function of unknown etiology. All patients referred underwent objective esophageal testing, including upper endoscopy, barium esophagram, high-resolution manometry, 48-hour pH testing, and 24-hour multichannel intraluminal impedance–pH (MII-pH) at the University of Pittsburgh Medical Center. GERD was considered present when laryngopharyngeal reflux (LPR) (on impedance testing) (abnormal: $\geq$1 daily])[19] was present or when proximal reflux (on impedance testing) (abnormal: $\geq$5 daily [unpublished data]) was present in addition to any 1 of the following signs: esophagitis, Barrett esophagus, hypotensive lower esophageal sphincter, or PPI dependence. Each reflux event during the MII-pH study was analyzed to establish the number of reflux events, proximity of the event to the larynx, clearance time, and predominant body position at the time the reflux events occurred.

Pulmonary function tests are routinely performed every 3 months from the date of evaluation by the LTx team and continued at this interval after LTx is performed. Therefore, pre-ARS trends in lung function were established in all patients by recording pulmonary function test results 1 year before ARS and immediately before this intervention. The most recent post-ARS $FEV_1$ (% predicted), forced vital capacity (% predicted), and mid-expiratory flow rate FEF (% predicted) were obtained, and the trends were examined to determine the impact of this intervention on lung function. The number of pneumonia and acute rejection episodes in the year before ARS and during follow-up after ARS were counted. Pneumonia was considered present when the chest radiograph showed infiltration with clinical symptoms, such as productive cough, fever, and shortness of breath. Acute rejection was confirmed pathologically as perivascular or bronchiolar mononuclear inflammation from tissue obtained via routine bronchoscopy.

### ESOPHAGEAL OBJECTIVE TESTING

All the patients underwent endoscopic evaluation of the esophagus, stomach, and duodenum. Observed mucosal changes, such as esophagitis and suspected Barrett esophagus, were recorded. Before gastric insufflation, the location of the anatomical gastroesophageal junction (GEJ) and the squamocolumnar junction were measured. Barrett esophagus was suspected when the squamocolumnar junction was variegated and located proximal to the anatomical GEJ. The presence of esophagitis was documented using the Los Angeles Classification.[15] A hiatal hernia was defined as the presence of the GEJ proximal to the crural pinch.

High-resolution manometry was performed using a solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan; Sierra Scientific Instruments Inc, Los Angeles, California) to evaluate the function of the lower and upper esophageal sphincters and esophageal body motility. Abnormal esophageal motility was defined as failed contractions of greater than 20% or low mean wave pressure amplitudes of less than 30 mm Hg. Aperistaltic esophagus was defined when no contractions were propagated with deglutition.

Twenty-four–hour MII-pH was performed using a specialized impedance catheter configured to detect either acid LPR (model ZAI-BL-28E) or any LPR (model CZAI-BL-55) (Sandhill Scientific Inc, Highlands Ranch, Colorado). Both catheters have 2 pH probes located in the hypopharynx and distal esophagus. The ZAI-BL-28E catheter has impedance electrode pairs located 3, 5, 9, 15, and 17 cm proximal to the GEJ, whereas those of the CZAI-BL-55 catheter were located in the hypopharynx, the proximal esophagus (2 and 4 cm below the upper esophageal sphincter), and the distal esophagus (3 and 5 cm proximal to the GEJ) (**Figure 1**). Laryngopharyngeal reflux was considered present when retrograde bolus transit moved across all ring sets and both esophageal and hypopharyngeal pH dropped less than 4 (acid LPR, ZAI-BL-28E catheter) or when retrograde bolus transit ultimately reached the hypopharynx regardless of whether there was a change in pH (any LPR, CZAI-BL-55 catheter). Full-column reflux (ie, proximal esophageal reflux) was defined as reflux that reached the impedance site 2 cm distal to the upper esophageal sphincter of the CZAI-BL-55 catheter or the proximal electrode pairs of the ZAI-BL-28E catheter. The CZAI-BL-55 catheter was developed specifically with the goal of detecting LPR and was introduced during the time of this study.

### ARS AND PERIOPERATIVE MANAGEMENT

For patients with normal esophageal motility, laparoscopic Nissen fundoplication was performed. For patients with severe esophageal dysmotility defined by aperistaltic esophagus or failed swallows greater than 50%, laparoscopic Dor fundoplication was performed.

Laparoscopic fundoplication was performed using a 5-port technique. The stomach was mobilized by dividing the short gastric vessels. A 3-cm length of tension-free intra-abdominal esophagus was obtained by extensive circumferential mediastinal dissection. The diaphragmatic crura were approximated with interrupted sutures, and the fundoplication was created over a 60F bougie. A 2.5-cm floppy Nissen fundoplication was performed with 3 stitches, incorporating the anterior esophageal wall. A satisfactory fundoplication was confirmed intraoperatively based on the endoscopic findings of a properly configured valve.[20] All the patients with scleroderma underwent "modified Dor" fundoplication, which included reconstruction of the acute angle of His and anterior fundoplication with more than 15 fundus-to-crura sutures placed from the 4- to 9-o'clock positions over a 60F bougie. Patients were scheduled to stay in the intensive care unit overnight. Prophylactic anticoagulation in conjunction with sequential compression stockings was routinely performed to prevent deep vein thrombosis–related pulmonary embolism. Aggressive pulmonary toileting and early ambulation were routinely implemented to maximize pulmonary and physical function. For post-LTx patients, a liquid form of immunosuppressive medication was started on the same day of surgery. An intravenous corticosteroid was administered intraoperatively and postoperatively for patients with long-term corticosteroid use. On postoperative day 1, a chest radiograph was obtained, a clear liquid diet was started, and patients were sent home from the intensive care unit if they were voiding, ambulatory, and without nausea. With any new increase in oxygen demand, patients were kept in the hospital until this was treated and resolved. Patients were instructed to follow a liquid diet for 1 week and a soft diet for 2 months and to avoid heavy lifting of greater than 10 kg for 2 months. Patients were seen in the clinic at 2 and 6 weeks for follow-up. Perioperative complications were recorded.

### DATA HANDLING AND STATISTICAL ANALYSIS

Data were tested for normality to aid in the selection of the appropriate statistical test. Values are expressed as mean (SD) or median (interquartile range) for each end point wherever appropriate. Continuous variables were compared using the 2-tailed paired *t* test, and categorical variables were compared using the $\chi^2$ test. Two post-LTx and 6 pre-LTx patients have not undergone pulmonary function tests after ARS. These patients were excluded from the post-ARS analysis. An $\alpha < .05$ was used as the threshold for statistical significance.

## RESULTS

### PATIENT DEMOGRAPHICS AND PROCEDURE DATA

From May 1, 2008, to February 28, 2011, 43 patients with ESLD and GERD (19 pre-LTx and 24 post-LTx) underwent ARS (**Table 1**). The etiology of ESLD for the entire cohort included chronic obstructive pulmonary disease (n=11), idiopathic pulmonary fibrosis (n=14), cystic fibrosis (n=6), scleroderma (n=7), and others (n=5). The mean age and body mass index were comparable between the groups. Lung transplantation included single-lung (n=4) and double-lung (n=20) allografts, and ARS was performed at a mean (SD) of 31 (24) months after LTx. Most patients underwent laparoscopic fundoplication (Nissen: n=24 and Dor: n=17) with comparable procedure times between pre- and post-LTx patients. One pre-LTx patient with idiopathic pulmonary fibrosis was diagnosed as having a paraesophageal hernia, which was repaired. Another pre-LTx patient had complicated GERD and chronic aspiration due to gastric dilation proximal to a vertical banded gastroplasty, and this patient underwent esophagojejunostomy. The mean length of hospital stay was 2 days (range, 1-9 days) for both groups. There was no operative mortality in this series.

One pre-LTx patient with idiopathic pulmonary fibrosis developed acute pulmonary failure after ARS and required an emergency LTx. All in-hospital complications in post-LTx patients were treated nonoperatively. One patient with cystic fibrosis required reoperation (Nissen fundoplication) 12 months after primary ARS secondary to recurrent symptoms. Another patient with cystic fibrosis developed malnutrition that required hospitalization. Six patients had severe diarrhea with (n=1) or without (n=5) *Clostridium difficile*.

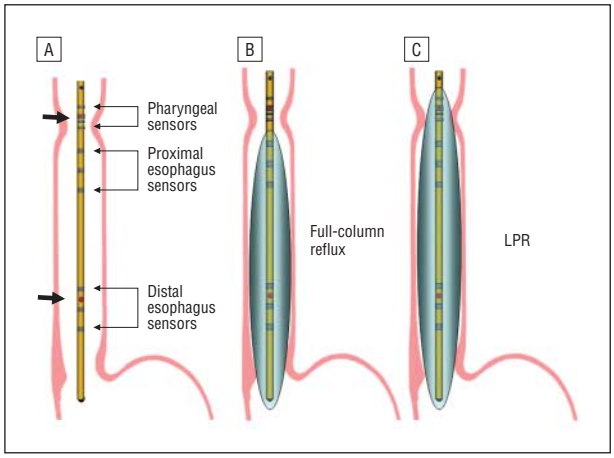


**Figure 1.** Configuration of a specialized impedance catheter (ZAI-BL-55 catheter) to detect laryngopharyngeal reflux and full-column reflux. A, The catheter has proximal and distal pH probes located in the hypopharynx and the distal esophagus, respectively (bold arrows). The impedance electrode pairs are located in the hypopharynx, the proximal esophagus (2 and 4 cm distal to the upper esophageal sphincter), and the distal esophagus (3 and 5 cm proximal to the gastroesophageal junction). B, Full-column reflux was defined as reflux that reached the impedance electrode pairs located 2 cm distal to the upper esophageal sphincter. C, Laryngopharyngeal reflux (LPR) was considered present when retrograde bolus transit ultimately reached the hypopharynx regardless of whether there was a change in pH (acid and nonacid LPR).

### PATTERNS OF REFLUX IN PATIENTS WITH ESLD

All the patients were receiving antisecretory therapy (PPIs or $H_2$ receptor blockers) at the time of referral for GERD evaluation. Nineteen of 43 patients (44%) were minimally symptomatic or asymptomatic, and only 8 of 43 patients (19%) had purely typical GERD symptoms (heartburn, regurgitation, or both) (**Table 2**). Six pre-LTx and 8 post-LTx patients did not undergo MII-pH because of previous positive pH testing before referral. Multichannel intraluminal impedance–pH demonstrated that LPR events were more common in post-LTx patients (56% vs 31%), although full-column reflux events were common in post- and pre-LTx patients (78% vs 86%). The mean number of total reflux events was 32 in pre-LTx patients and 33 in post-LTx patients, and reflux events

**Table 1. Demographic and Procedure Data for 43 Patients With End-Stage Lung Disease**

| Variable | Pre-LTx Patients (n=19) | Post-LTx Patients (n=24) |
|---|---|---|
| Sex, No. | | |
| Female | 8 | 16 |
| Male | 11 | 8 |
| Age, mean (range), y | 57 (22-77) | 53 (21-70) |
| BMI, mean (range) | 27.7 (17.4-37.3) | 26.2 (17.8-38.7) |
| Lung disease, No. | COPD, 3; IPF, 11; CF, 2; scleroderma, 1; eosinophilic lung disease, 1; complicated GERD, 1 | COPD, 8; IPF, 3; CF, 4; PPH, 2; scleroderma, 6; bronchoalveolar cancer, 1 |
| LTx, No. | NA | Single, 4; double, 20 |
| Interval between LTx and ARS, mean (SD), mo | NA | 31 (24) |
| Ischemic time, mean (SD), min | NA | 348 (82) |
| Antireflux surgery, No. | Nissen, 10; Dor, 7; others, 2[a] | Nissen, 14; Dor, 10 |
| Procedure time, mean (range), min | 163 (64-479) | 126 (70-193) |
| Hospital stay, mean (range), d | 2 (1-9) | 2 (1-9) |
| In-house complications, No. | Acute pulmonary failure requiring emergency LTx, 1 | Postoperative bleeding and tacrolimus toxicity, 1; pneumonia, 1; UTI, 1; nausea, 1 |
| Perioperative complications, No. | Diarrhea, 2; SOB, 1 | Redo Nissen, 1; diarrhea, 4; malnutrition, 1 |
| Follow-up, median (range), mo | 13 (1-33) | 10 (1-20) |

Abbreviations: ARS, antireflux surgery; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis; LTx, lung transplantation; NA, not applicable; PPH, primary pulmonary hypertension; SOB, shortness of breath; UTI, urinary tract infection.

[a] Others included a repair of paraesophageal hernia (n=1) and an esophagojejunostomy (n=1).

**Table 2. Reflux Pattern in Patients With ESLD**

| Variable | Pre-LTx Patients (n=19) | Post-LTx Patients (n=24) |
|---|---|---|
| Preoperative symptoms, No./total No. | Only typical, 1/19; minimal typical ± atypical, 5/19; asymptomatic, 3/19 | Only typical, 7/24; minimal typical ± atypical, 6/24; asymptomatic, 5/24 |
| MII-pH, No. | 28 catheter, 6; 55 catheter, 7; no MII-pH, 6 | 28 catheter, 7; 55 catheter, 9; no MII-pH, 8 |
| LPR events, both catheters, No./total No. (%) | 4/13 (31) | 9/16 (56) |
| LPR events, mean (range), No. | 1 (1-3) | 3 (1-8) |
| Full-column reflux, 55 catheter, No./total No. (%) | 6/7 (86) | 7/9 (78) |
| Full-column reflux, 55 catheter, mean (range), No. | 5 (3-6) | 11 (1-20) |
| Total reflux events, mean (range), No. | 32 (0-127) | 33 (2-135) |
| Only or primarily in upright position, No./total No. | 12/13 | 13/16 |
| LESP, mean (SD), mm Hg | 12.4 (6.6) | 9.3 (7.2) |
| Esophageal motility, No. | Normal, 10; abnormal, 5; aperistalsis, 4 | Normal, 11; abnormal, 3; aperistalsis, 7 |
| Hiatal hernia, No./total No. (%) | 11/18 (61) | 7/21 (33) |
| Esophagitis, No./total No. (%) | 7/11 (64) | 8/13 (62) |

Abbreviations: ESLD, end-stage lung disease; LESP, lower esophageal sphincter pressure; LPR, laryngopharyngeal reflux; LTx, lung transplantation; MII-pH, multichannel intraluminal impedance–pH.

occurred primarily in the upright position in most patients (25 of 29). The mean lower esophageal sphincter pressure of post-LTx patients was lower than that of pre-LTx patients. The distribution of esophageal motility was comparable between the groups. Half of the patients had abnormal esophageal motility, including aperistaltic esophagus (n=11, 27.5%). Although all the patients underwent upper endoscopy and barium esophagram before ARS at either the University of Pittsburgh Medical Center or referring hospitals, endoscopic and radiographic findings were available in 24 and 39 patients, respectively, at the time of review because some results of testing performed at referring hospitals were unable to be obtained. Based on the available data, hiatal hernia was more common in pre-LTx patients, although the presence of either esophagitis (n=12) or intestinal metaplasia (n=3) was comparable.

## IMPACT OF ARS ON LUNG FUNCTION

Nearly all measurements of lung function improved after ARS in both groups (**Table 3**). The $FEV_1$ improved in 91% of post-LTx patients (20 of 22) and in 85% of pre-LTx patients (11 of 13) (**Figure 2**). Of patients with declining $FEV_1$ before ARS, 92% of post-LTx patients (11 of 12) and 88% of pre-LTx patients (7 of 8) had a reversal of this trend. In addition, the pneumonia and acute rejection episodes were significantly reduced for post-LTx patients ($P=.03$) and seemed to be stabilized for pre-LTx patients ($P=.09$). The presence of LPR on impedance testing before ARS (n=9) was associated with more episodes of acute rejection compared with those without LPR (n=7) (56% vs 14%, $P=.30$). In addition, patients with LPR on impedance testing had a pre-ARS declining $FEV_1$ that was more likely to be reversed by ARS

**Table 3. Pulmonary Function Test Results Before and After ARS in Patients With ESLD**

| Variable | Before ARS | After ARS | *P* Value |
|---|---|---|---|
| Post-LTx patients (n=22) | | | |
| $FEV_1$, % predicted[a] | 81.5 (61.3-92.8) | 92.5 (65.8-102.5) | <.01[b] |
| FVC, % predicted[a] | 77.5 (63.5-87.3) | 81.5 (70.5-94.5) | .04[b] |
| $FEF_{25-75}$, % predicted[a] | 53.5 (31.3-100.3) | 58 (44.5-118) | .03[b] |
| Pneumonia, No./total No. (%) | 7/24 (29) | 1/24 (4) | .03[b] |
| Rejection, No./total No. (%) | 8/24 (33) | 1/24 (4) | .03[b] |
| Pre-LTx patients (n=13) | | | |
| $FEV_1$, % predicted[a] | 55 (44.3-76.3) | 68 (49-82) | .02[b] |
| FVC, % predicted[a] | 61 (50-71) | 71 (52-75) | <.01[b] |
| $FEF_{25-75}$, % predicted[a] | 49.5 (19.3-78.8) | 70 (23-81) | .26 |
| Pneumonia, No./total No. (%) | 6/16 (38) | 3/16 (19) | .09 |

Abbreviations: ARS, antireflux surgery; ESLD, end-stage lung disease; $FEF_{25-75}$, midexpiratory flow rate; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LTx, lung transplantation.

[a] Measurements immediately before ARS and the most recent post-ARS measurements are expressed as median (interquartile range).

[b] $P<.05$.

compared with those without LPR (6 of 9 [67%] vs 1 of 5 [20%], $P=.1$). On the other hand, $FEV_1$ worsened after ARS in 2 of 22 post-LTx patients (9%) and 2 of 13 pre-LTx patients (15%). Of them, 1 post-LTx patient with cystic fibrosis was found to have a herniated, disrupted fundoplication probably due to severe coughing after ARS, although the repair seemed to be intact on endoscopic examination in the other 3 patients, who did not undergo repeated pH or impedance testing to confirm the absence of reflux.

## COMMENT

GERD, suggested as a potential cause of ESLD,[17,21] is extremely common after LTx, possibly because of intraoperative vagal nerve damage, impaired cough, and mucociliary clearance of transplanted lungs secondary to immunosuppressive medication adverse effects or the preexisting presence of GERD.[14,22-24] A recent study demonstrated an association between pseudomonal colonization and the presence of bile acids in bronchoalveolar lavage and suggested that epithelial defects by bile acids might predispose patients to colonization with *Pseudomonas* and airway neutrophilia, which potentially leads to BOS.[25,26] Treatment with PPIs effectively neutralizes gastric acid but cannot control nonacid reflux containing bile acids and activated enzymes. Antireflux surgery leads to the successful re-creation of an anatomical barrier to reflux[27] and has been identified as a possible approach to defend patients with ESLD (pre- or post-LTx), who may be entirely asymptomatic,[11,21] against occult pulmonary injury and resultant decompensation of lung function.

Although previous studies have demonstrated that ARS potentially provides a survival benefit and delays the onset of BOS, particularly with early intervention (<90 days after LTx),[14,18] the true benefit and optimal timing of ARS remains controversial. Davis et al[14] reported that $FEV_1$ significantly improved by an average of 24% in 80% of post-LTx patients who underwent ARS (n=43). In a follow-up to this study (n=76), survival was significantly better for patients who underwent early (<90 days) vs late fundoplication (100% vs 69%-86%, $P=.03$).[18] These results may represent a lead time bias. Burton et al[28] reported that fundoplication did not reverse any decline in lung function when performed a mean of 768 days (range, 145-1524 days) after LTx in patients with documented GERD. More recent data[29] (abstract form) demonstrated a 15.9% incidence of BOS in the early (<90 days) fundoplication group (n=67) compared with 47.7% in the late group (n=117) ($P<.001$), although there was no significant difference in survival at 1-year follow-up between groups (97.0% vs 97.2%, $P=.93$).

The present data demonstrate that ARS had a positive impact on the lung function of LTx patients, with the $FEV_1$ improving in 91% overall. Perhaps more importantly, a preintervention declining $FEV_1$ was reversed in 92% of post-LTx patients (11 of 12) after ARS. No correlation was noted between time after LTx and responsiveness to ARS, although all the patients except 1 in the present study underwent ARS more than 90 days after LTx. Based on these data, evaluation for GERD and possible ARS should be considered at any time point after LTx and even more so if $FEV_1$ has declined. Because all the patients in this study were taking antisecretory medication at the time of evaluation for GERD, these data lend support that an anatomical reconstruction of the esophagogastric junction is superior to acid suppression alone and that the caustic effects of nonacid reflux are likely related to microaspiration.

Because of the shortage of organs available for transplantation, the use of ARS to preserve native lung function in patients with ESLD should be considered. However, these patients have little pulmonary reserve and should be counseled that an emergency LTx may be required should they develop perioperative pulmonary failure. Our selection for pre-LTx ARS was individualized and was based on pulmonary function, functional status, and comorbid conditions. Patients with pulmonary hypertension were not candidates for ARS before LTx. The patient who required an emergency LTx in this study had borderline pulmonary hypertension (systolic pulmonary arterial blood pressure, 39 mm Hg) and a history of abdominal surgery requiring a longer

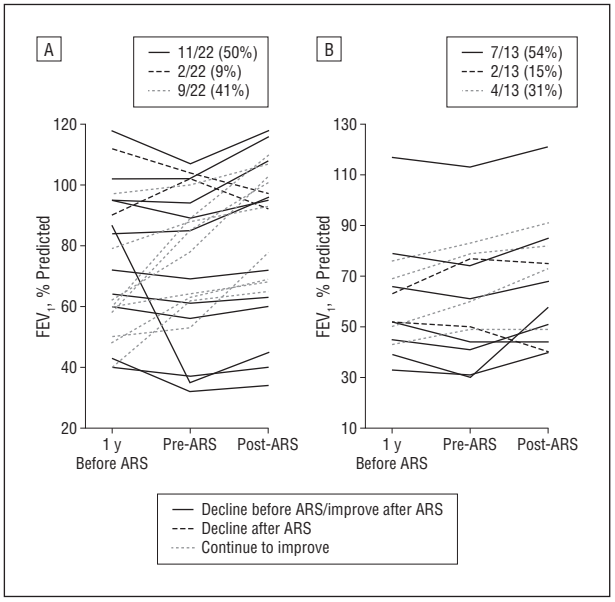


**Figure 2.** Impact of antireflux surgery (ARS) on forced expiratory volume in 1 second ($FEV_1$) (% predicted) for individual patients after lung transplantation (post-LTx) (A) and before LTx (pre-LTx) (B) 1 year before ARS, pre-ARS, and post-ARS. Overall, $FEV_1$ improved in 20 of 22 post-LTx patients (91%) and in 11 of 13 pre-LTx patients (85%). Of patients with a declining $FEV_1$ before ARS, 92% of post-LTx patients (11 of 12) and 88% of pre-LTx patients (7 of 8) had a reversal of this trend. In contrast, $FEV_1$ declined after ARS in 2 of 22 post-LTx patients (9%) and in 2 of 13 pre-LTx patients (15%).

procedure time due to intra-abdominal adhesions. Laryngopharyngeal reflux has been reported to cause atypical symptoms, asthma, and pulmonary fibrosis.[30] However, the clinical presentation of LPR is nonspecific, and there has been no way to definitively measure laryngeal exposure to refluxate. Multichannel intraluminal impedance–pH has been introduced as a promising tool to determine the proximal extent and composition of reflux. In this study, we used a specialized impedance catheter configured to detect LPR. Full-column reflux and LPR were common in this population, especially in post-LTx patients. Given the fact that as few as 3 episodes of LPR per week can cause severe laryngeal inflammation and injury,[30] LPR may be causing continuous lung injury via occult microaspiration. The number of total reflux events was often normal even if patients had documented LPR and full-column reflux. Many of these patients had a normal DeMeester score and would not otherwise have been selected for surgery using current criteria. In addition, patients with LPR tended to be minimally symptomatic or asymptomatic (compared with those without LPR) but had more episodes of acute rejection before ARS. In the present study, the presence of LPR as measured with MII-pH is sensitive for a response to ARS in patients with ESLD especially after LTx; MII-pH should likely be performed in all patients with ESLD regardless of symptoms.

Previous studies[14,17,18,28,31,32] have demonstrated that ARS can be performed safely in this population. In this study, there were 3 major perioperative complications in post-LTx patients. One post-LTx patient with chronic obstructive pulmonary disease had postoperative intra-abdominal hemorrhage after resumption of anticoagulation therapy, which was treated nonoperatively; this was followed by tacrolimus toxic effects in the same patient. The tacrolimus level is highly variable and should be checked if patients cannot resume an appropriate oral intake the day after surgery. A post-LTx patient with cystic fibrosis was complicated by disruption of the fundoplication with recurrent symptoms likely due to postoperative coughing. Patients with ESLD can have friable, edematous tissue because of long-term corticosteroid use and immunosuppressive medications. Note that a prolonged tissue-healing period is required, especially in patients who require immunosuppression. In addition, the reduced gastric volume after fundoplication can lead to early satiety and may cause malnutrition in patients with cystic fibrosis who have pancreatic insufficiency and secondary malabsorption. A temporary feeding tube may need to be placed at the time of fundoplication in these patients. Postoperative diarrhea with or without *C difficile* is common and can cause tacrolimus toxicity. Treatment with metronidazole should be started before the diagnosis is confirmed. All patients are given probiotics before surgery and should be cared for as an immunocompromised host. In addition, strict hand washing and early discharge are emphasized to decrease exposure to pathogens. Dor fundoplication was successfully performed on 7 patients with scleroderma without postoperative dysphagia. Based on the early outcomes presented in the present study, the risk associated with ARS in this population is low.

In conclusion, ARS improves objective measurements of lung function, reducing rejection episodes and preventing pneumonia in patients pre- or post-LTx. Patients with ESLD and GERD have atypical patterns of reflux that may be entirely asymptomatic. There should be a low threshold for performing objective esophageal testing including MII-pH (with a catheter configured to detect LPR) in patients with ESLD before and after LTx because reflux and microaspiration may be occult. To determine whether ARS can prevent BOS and lead to improved survival, a controlled trial with long-term follow-up is required.

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