Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease

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ABSTRACT

Objectives: Gastroesophageal reflux disease (GERD) is prevalent after lung transplantation. Fundoplication slows lung function decline in patients with GERD, but the optimal timing of fundoplication is unknown.

Methods: We retrospectively reviewed patients who underwent fundoplication after lung transplantation at our center from April 2007 to July 2014. Patients were divided into 2 groups: early fundoplication (<6 months after lung transplantation) and late fundoplication (≥6 months after lung transplantation). Annual decline in percent predicted forced expiratory volume in 1 second (FEV₁) was analyzed.

Results: Of the 251 patients who underwent lung transplantation during the study period with available pH data, 86 (34.3%) underwent post-transplantation fundoplication for GERD. Thirty of 86 (34.9%) had early fundoplication and 56 of 86 (65.1%) had late fundoplication. Median time from lung transplantation to fundoplication was 4.6 months (interquartile range, 2.0-5.2) and 13.8 months (interquartile range, 9.0-16.1) for the early and late groups, respectively. The median DeMeester score was comparable between groups. One-, 3-, and 5-year actuarial survival rates in the early group were 90%, 70%, and 70%, respectively; in the late group, these rates were 91%, 66%, and 66% (log rank $P = .60$). Three- and 5-year percent predicted FEV₁ was lower in the late group by 8.9% (95% confidence interval, -30.2 to 12.38; $P = .46$) and 40.7% (95% confidence interval, -73.66 to -7.69; $P = .019$). A linear mixed model showed a 5.7% lower percent predicted FEV₁ over time in the late fundoplication group ($P < .001$).

Conclusions: In this study, patients with early fundoplication had a higher FEV₁ 5 years after lung transplantation. Early fundoplication might protect against GERD-induced lung damage in lung transplant recipients with GERD. (J Thorac Cardiovasc Surg 2018;155:2762-71)

Significantly lower FEV₁ over time in late versus early fundoplication group ($P = .019$).

Central Message

Early fundoplication (ie, within 6 months of transplantation) might protect against GERD-induced lung damage in lung transplant recipients with GERD.

Perspective

GERD is prevalent in the lung transplantation population. Early surgical correction of GERD (ie, within 6 months of transplantation) might slow the rate of lung function decline after transplantation by protecting against reflux-induced lung damage. Lung transplant recipients might benefit from routine surveillance protocols for GERD early in the post-transplantation period.

See Editorial Commentary page 2772.

See Editorial page 2760.

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Lung transplantation is increasingly being offered as treatment for patients with end-stage lung disease. However, chronic lung allograft dysfunction (CLAD) remains the biggest limiting factor to prolonged

Scanning this QR code will take you to a supplemental video and figure for the article.

Abbreviations and Acronyms

BOS	= bronchiolitis obliterans syndrome
CI	= confidence interval
CLAD	= chronic lung allograft dysfunction
FEV ₁	= forced expiratory volume in 1 second
GERD	= gastroesophageal reflux disease
IQR	= interquartile range
LAS	= lung allocation score
LES	= lower esophageal sphincter
LESP	= lower esophageal sphincter resting pressure
N/A	= not applicable
SAP	= symptom association probability

post-transplantation survival. A common clinical equivalent of CLAD is bronchiolitis obliterans syndrome (BOS), which is defined as an obstructive defect in ventilation and a persistent decline in forced expiratory volume in 1 second (FEV₁) $\leq 80\%$ below post-transplantation baseline.¹ Several immune and nonimmune factors have been implicated in the pathogenesis of BOS.^{2,3} Gastroesophageal reflux disease (GERD) has been suggested as an important nonimmune contributor in BOS development (Video 1). The direct injury that results from prolonged exposure to acidic refluxate, which is laden with gastrointestinal digestive enzymes, has been proposed to intensify the immune pathway of BOS pathogenesis.⁴

GERD affects up to 20% of the general population, increasing by 4% to 5% per year over the past 2 decades. The prevalence of GERD in patients with end-stage lung disease who undergo lung transplantation is much higher—up to 63%.⁵ The incidence of GERD increases even more after transplantation because of vagal denervation, delayed gastric emptying, and immunosuppressive medications. Although proton pump inhibitors decrease the acidity of the refluxate, they have no effect on gastroesophageal motility, mucociliary function, or cough reflex, which are the mainstay mechanisms behind the development of GERD after lung transplantation.

Fundoplication has been the gold standard of GERD treatment after lung transplantation. Although a causal relationship has yet to be established between GERD and BOS, fundoplication has been shown to reduce the proinflammatory environment in lung parenchyma,⁶ and has also been shown to decrease biomarkers for aspiration in lung transplant recipients.⁷ Few studies have examined the effect of the timing of antireflux surgery on the progress of BOS.^{8,9} Early fundoplication (ie, within 6 months of transplantation) has resulted in improved rates of freedom from BOS.^{8,9} In the current study, we examined our single-center experience with prevalence of GERD and outcomes of fundoplication in lung transplant recipients, with a special

VIDEO 1. Senior author Jasmine Huang describes the findings in this study, namely, that early fundoplication (ie, within 6 months of transplantation) might protect against GERD-induced lung damage in lung transplant recipients with GERD. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(18\)30357-X/fulltext](http://www.jtcvsonline.org/article/S0022-5223(18)30357-X/fulltext).

focus on the timing of fundoplication post-transplantation. We also reviewed our current practice of GERD surveillance in this patient population. Our goal was to compare the effects of early (< 6 months) versus late (≥ 6 months) fundoplication on pulmonary function as well as survival in lung transplant recipients. We hypothesized that early fundoplication would be associated with stabilization of lung function and, subsequently, increased survival and freedom from BOS after lung transplantation.

METHODS

After approval from the Institutional Review Board at St. Joseph's Hospital and Medical Center (Institutional Review Board approval number: PHXA-17-0009-71-18, October 19, 2016), we retrospectively reviewed the charts of patients who underwent fundoplication after lung transplantation at Norton Thoracic Institute between April 2007 and July 2014. Patients were divided into 1 of 2 groups: early fundoplication (ie, within 6 months of lung transplantation) and late fundoplication (ie, 6 months or more after lung transplantation). The 2 groups were compared for demographic characteristics, lung allocation score (LAS), comorbidities, type of fundoplication, and postoperative outcomes. Pretransplantation GERD workup included high-resolution manometry, 24-hour pH

monitoring, esophagogastroduodenoscopy, and a gastric emptying study. In patients who were bedbound and who underwent lung transplantation on an urgent basis, the GERD workup was completed at the earliest opportunity post-transplantation. Post-transplantation GERD surveillance was initiated 3 months after transplantation; surveillance endoscopy was also performed at this time to look for stigmata of GERD.

Immunosuppression

The immunosuppressive regimen was uniform across the study period. Induction therapy included high-dose glucocorticoids (methylprednisolone) before perfusion of the lung allografts, with interleukin-2 receptor antibody (basiliximab) or anti CD-20 monoclonal antibody (rituximab), with or without antithymocyte globulin. Maintenance therapy consisted of a steroid, mycophenolate acid, and tacrolimus. Episodes of acute cellular rejection were treated with pulsed steroids, followed by steroid taper.

Surveillance

Clinic-based spirometry was used to record FEV₁ measurements to monitor lung function after transplantation. Pulmonary function was tested every 2 to 3 weeks in the first 6 months, every 4 weeks in the next 6 months to 2 years, and every 3 to 6 months after the 2-year mark. Additional measurements were obtained during sick visits or upon suspicion of clinical worsening.

pH Study

GERD was diagnosed on the basis of ambulatory 24-hour pH monitoring, which was carried out 10 days after antireflux medications were withheld. Esophageal pH monitoring was performed using a catheter-based dual electrode probe (ComforTEC; Sandhill Scientific, Milwaukee, Wis). DeMeester score was calculated using the standard variables.¹⁰ Symptom-reflux correlation was done using symptom association probability and symptom index scores. Normal values for acid contact times in the distal probe are: total >4.2%, upright <6.3%, and supine <1.2%. All studies were interpreted after clinical correlation by a thoracic surgeon. Because of the implications of proximal GERD on allograft function, our institutional protocol has evolved to incorporate routine GERD surveillance 3 months after transplantation.

Fundoplication

Patient selection for fundoplication was on the basis of diagnosis of persistent GERD in a 24-hour pH monitoring study with or without decline in lung function, or symptomatic GERD with a positive 24-hour pH monitoring study in the post-transplantation period. Laparoscopic reduction, repair of hiatal hernia, and fundoplication were performed in standard fashion. Wrap type (ie, 270° or 360°) was selected based on the results of esophageal motility studies. After adequate esophageal mobilization of approximately 4 to 5 cm of intra-abdominal length, the hiatus was closed posteriorly with interrupted polyethylene sutures and reinforced with onlay biodegradable mesh as needed.

Acute Rejection and BOS

Acute rejection was graded on the basis of pathologic examination of transbronchial biopsy specimens obtained from surveillance bronchoscopies post-transplantation using standard criteria.¹¹ Criteria set forth by the International Society for Heart and Lung Transplantation¹ were used to diagnose the onset of BOS; more specifically, BOS was defined as a persistent decline of 20% or greater in FEV₁ in the absence of confounding factors. No distinction was made in BOS severity, or in the presence or absence of restrictive allograft syndrome.

Statistical Analysis

Continuous variables were reported using median and interquartile range (IQR); categorical variables were reported as frequencies. The

Wilcoxon rank sum and Fisher exact tests were used for continuous and categorical variables, respectively. Freedom from BOS was determined using the Kaplan–Meier method. Actuarial survival at 1, 3, and 5 years was also estimated using the Kaplan–Meier method followed by the log rank test to ascertain any difference in probabilities. Survival in the study groups was further compared with 2 control groups: patients without evidence of GERD on pH monitoring, and patients with evidence of GERD who were managed medically. A linear mixed model was used to analyze decline in percent predicted FEV₁ over time after lung transplantation. The Wilcoxon rank sum was implemented to ascertain any difference in FEV₁% predicted at each time point. The Bonferroni correction was used to adjust for multiple comparisons. A *P* value of < .05 was considered significant. All analyses were performed using Stata 2015 software, release 14 (StataCorp LP, College Station, Tex).

RESULTS

In total, 273 lung transplantations were performed at Norton Thoracic Institute between April 2007 and July 2014. Of these, pH data were available for 251 patients; 86 of 251 patients (34.3%) underwent post-transplantation fundoplication for GERD during the study period. Thirty of these patients (34.9%) underwent early fundoplication; 56 patients (65.1%) underwent late fundoplication. Table 1 shows a summary of patient characteristics of the 2 groups. The 2 groups were comparable in terms of age and sex, but patients in the early group had higher median LASs and lower body mass indices. The median time from lung transplantation to fundoplication was 4.6 months (IQR, 2.0-5.2) and 13.8 months (IQR, 9.0-16.1) for the early and late groups, respectively. A greater proportion of patients in the early group had restrictive lung disease before transplantation. The 2 groups were comparable in terms of type of fundoplication (ie, Nissen wrap vs Toupet wrap). Patient outcomes are described in Table 2. The hospital length of stay for the procedure was a median of 2 days in both groups. There was no in-hospital or 30-day mortality in either group. The failure rate for fundoplication was 5.8%, with 5 patients requiring redo surgery for recurrent symptoms or for wrap-related complications. Another 5 patients required endoscopic dilation or pyloric injection of botulinum toxin for persistent postoperative gastroparesis.

pH Studies

Table 3 lists the results of the 24-hour pH monitoring study recorded at the time of evaluation for lung transplantation. The 2 groups were comparable in all pretransplantation and prefundoplication pH metrics and DeMeester scores; however, some differences were observed in manometric measurements and endoscopic findings prefundoplication (Table 4). A greater proportion of patients in the late group had evidence of reflux esophagitis (61% vs 40%) on esophagogastroduodenoscopy, indicating prolonged acid reflux; this difference was not statistically significant. On high-resolution manometry, the total lower esophageal sphincter length was shorter in the early group. Median acid exposure time in

TABLE 1. Baseline characteristics of the fundoplication groups

Variable	Overall (n = 86)	Early fundoplication (n = 30)	Late fundoplication (n = 56)	P*
Median age at transplantation, y	62.5 (54.0-66.0)	63.0 (56.0-67.0)	62.0 (53.5-66.0)	.86
Male sex, n (%)	47 (54.7)	15 (50.0)	35 (62.5)	.52
Median LAS at transplantation	34.7 (32.4-41.6)	38.5 (32.9-52.3)	33.7 (32.0-38.5)	.004
Median body mass index	25.4 (22.6-28.7)	23.9 (20.6-26.3)	26.1 (23.6-29.3)	.002
Diabetes mellitus before transplantation, n (%)	56 (65.9)	22 (73.3)	34 (61.8)	.28
Bilateral lung transplantation, n (%)	86 (100.0)	30 (100.0)	56 (100.0)	N/A
Underlying pulmonary diagnosis, n (%)				.02
Obstructive lung disease	53 (61.6)	13 (43.3)	40 (71.4)	
Restrictive lung disease	23 (26.7)	12 (40.0)	11 (19.6)	
Cystic fibrosis	7 (8.1)	3 (10.0)	4 (7.1)	
Retransplantation	1 (1.2)	0 (0.0)	1 (1.8)	
Other	2 (2.3)	2 (6.7)	0 (0.0)	
Median KPS at transplantation	70 (60-70)	60 (50-70)	70 (60-70)	.04
Median serum creatinine, mg/dL	1.1 (0.84-1.3)	1.0 (0.80-1.2)	1.1 (0.89-1.3)	.12
Positive smoking history before transplantation, n (%)	59 (70.2)	20 (68.9)	39 (70.9)	.85
Type of fundoplication, n (%)†				.19
Toupet	37 (43.5)	14 (46.7)	23 (41.8)	
Nissen	47 (55.3)	15 (50.0)	32 (58.2)	
Dor	1 (1.2)	1 (3.3)	0 (0.0)	
Median time from lung transplantation to hernia repair, mo	8.7 (5.0-15.2)	4.6 (2.0-5.2)	13.8 (9.0-16.1)	<.001

All values expressed as median (interquartile range), unless indicated otherwise. LAS, Lung allocation score; N/A, not applicable; KPS, Karnofsky performance score.

*Calculated using Wilcoxon rank sum for continuous variables and Fisher exact for categorical variables. †Calculated for 85 patients.

the distal pH channel increased from 99.5 minutes pretransplantation to 144.9 minutes prefundoplication in the early group, and from 58.6 minutes to 147 minutes in the

late group. Similarly, the median DeMeester score increased from 31.7 pretransplantation to 46.8 prefundoplication in the early group and 19.3 to 49.7 in the

TABLE 2. Outcomes of post-transplantation fundoplication procedures

Variable	Overall (n = 86)	Early fundoplication (n = 30)	Late fundoplication (n = 56)	P*
Median LOS after fundoplication, d	2 (2-3)	2 (2-4)	2 (1-3)	.13
Acute rejection grade, n (%)				.32
A0	42 (48.8)	18 (60.0)	24 (42.9)	
A1	22 (38.4)	9 (30.0)	24 (42.9)	
A2/B1R	11 (12.8)	3 (10.0)	8 (14.3)	
Acute rejections before fundoplication, n (%)				.35
0	65 (75.6)	26 (86.7)	39 (69.6)	
1 or more	21 (24.4)	4 (13.3)	17 (30.4)	
Acute rejections after fundoplication, n (%)				.10
0	61 (70.9)	22 (73.3)	39 (69.6)	
1 or more	25 (29.1)	8 (26.7)	17 (30.4)	
Total number of acute rejections, n (%)				.46
0	42 (48.8)	18 (60.0)	24 (42.9)	
1 or more	44 (51.2)	12 (40.0)	32 (57.1)	
Median survival, y	3.5 (2.4-4.7)	3.1 (2.4-4.0)	3.9 (2.4-4.8)	.20
BOS before fundoplication, n (%)†	16/84 (19.1)	5/30 (16.7)	11/54 (20.4)	.77
Alive at 1 y, n (%)	78 (90.7)	27 (90.0)	51 (91.1)	1.0
Alive at 3 y, n (%)	54/82 (65.8)	17/26 (65.4)	37/56 (66.1)	.95
Alive at 5 y, n (%)	16/43 (37.2)	4/12 (33.3)	12/31 (38.7)	1.0

All values expressed as median (interquartile range), unless indicated otherwise. LOS, Length of stay; BOS, bronchiolitis obliterans syndrome. *Calculated using Wilcoxon rank sum for continuous variables and Fisher exact for categorical variables. †Data missing for 2 patients.

TABLE 3. Pretransplantation 24-hour pH study

Variable	Overall (n = 86)	Early fundoplication (n = 30)	Late fundoplication (n = 56)	P*
Median DeMeester score	32.2 (9.6-43.5)	31.7 (15.5-48.5)	19.3 (5.1-40.3)	.10
Median proximal channel total time pH <4, min	4 (0.40-17.0)	4.1 (0.30-17)	2.8 (0.90-20.0)	.80
Median proximal channel upright time pH <4, min	2.0 (0.30-12)	3.5 (0.30-11.1)	2.0 (0.10-15)	.87
Median proximal channel supine time pH <4, min	0.0 (0.0-2.0)	0.0 (0.0-3.1)	0.0 (0.0-1.0)	.55
Median distal channel total time pH <4, min	70.9 (16.0-136.0)	99.5 (41.0-147.7)	58.6 (12.9-125.6)	.21
Median distal channel upright time pH <4, min	37 (10.3- 109.0)	52.8 (20.8-101.7)	31.5 (5.1-109.9)	.21
Median distal channel supine time pH <4, min	7.0 (1.0-41.0)	9.2 (1.0-43.6)	3.0 (0.65-31)	.41
Symptoms, n (%)				.74
Heartburn	29 (47.4)	11 (64.7)	18 (69.2)	
Regurgitation	1 (2.3)	1 (5.9)	0 (0.0)	
Chest	1 (2.3)	0 (0.0)	1 (3.9)	
Cough	12 (27.9)	5 (29.4)	7 (26.9)	
Median SAP symptom total (proximal), min	0.0 (0.0-8.2)	0.0 (0.0-32.0)	0.0 (0.0-6.6)	.50
Median SAP symptom total (distal), min	0.0 (0.0-94.0)	21.3 (0.0-99.5)	0.0 (0.0-64.0)	.08

All values expressed as median (interquartile range), unless indicated otherwise. SAP, Symptom association probability. *Calculated using Wilcoxon rank sum for continuous variables and Fisher exact for categorical variables.

late group. No pH studies were performed postfundoplication in either patient group.

Disease Subgroups

A greater proportion of patients who underwent fundoplication post-transplantation had obstructive lung disease as the underlying pulmonary diagnosis (53 of 86;

61.6%; Table 5). In a comparison of patients with obstructive and restrictive disease who underwent fundoplication for reflux, we found that patients with restrictive lung disease were more often men with higher LAS. Patients with restrictive lung disease had higher DeMeester scores and longer distal esophageal acid exposure times pretransplantation. However, DeMeester

TABLE 4. Prefundoplication metrics

Variable	Overall (N = 86)	Early fundoplication (n = 30)	Late fundoplication (n = 56)	P*
Median DeMeester score	48.2 (30.5-68.6)	46.8 (30.5-54.5)	49.7 (30.0-73.5)	.37
Median proximal channel total time pH <4, min	7.0 (0.5-21.2)	8.4 (3.0-19.0)	6.0 (0.2-25.0)	.91
Median proximal channel upright time pH <4, min	3.0 (0.1-11.9)	5.1 (1.8-8.9)	1.6 (0.1-14.3)	.54
Median proximal channel supine time pH <4, min	0.0 (0.0-11.0)	0.25 (0.0-12.9)	0.0 (0.0-11.0)	.84
Median distal channel total time pH <4, min	147.0 (87.5-215.6)	144.9 (87.5-173.9)	147 (86.0-244.8)	.61
Median distal channel upright time pH <4, min	66.4 (34.8-132.8)	55.5 (26.8-132.8)	77.6 (36.0-134.0)	.64
Median distal channel supine time pH <4, min	54.2 (12.8-97.6)	37.9 (24.0-73.3)	58 (7.2-106.0)	.53
Median SAP symptom total proximal	0.0 (0.0-79.9)	0.0 (0.0-96.0)	0.0 (0.0-11.9)	.54
Median SAP symptom total distal	0.0 (0.0-95.0)	1.7 (0.0-99.4)	0 (0.0-95.0)	.55
Median LES, mm Hg	23.4 (12.5-30.4)	25.5 (15.7-31.3)	22.1 (11.8-28.5)	.32
Median total LES, cm	3.4 (3.1-3.7)	3.3 (2.9-3.6)	3.5 (3.2-3.9)	.02
Median abdominal LES, cm	1.1 (0.6-2.4)	1.2 (0.7-2.6)	1.1 (0.5-2.1)	.76
Hiatal hernia size, n (%)				.58
Small	40 (47.6)	12 (40.0)	28 (51.9)	
Large	5 (5.9)	2 (6.7)	3 (5.6)	
EGD/Barrett pathology, n (%)	19 (22.6)	7 (23.3)	12 (22.2)	.90
EGD evidence of esophagitis, n (%)	45 (53.6)	12 (40.0)	33 (61.1)	.06

All values expressed as median (interquartile range), unless indicated otherwise. SAP, Symptom association probability; LES, lower esophageal sphincter resting pressure; LES, lower esophageal sphincter; EGD, esophagogastrroduodenoscopy. *Calculated using Wilcoxon rank sum for continuous variables and Fisher exact for categorical variables.

TABLE 5. Comparison of fundoplication patients according to major disease groups

Variable	Obstructive lung disease (n = 53)	Restrictive lung disease (n = 23)	P*
Median age at transplantation, y	63 (56-66)	63 (57-67)	.75
Median LAS	32.7 (31.9-34.1)	41.6 (37.6-55.4)	<.001
Male sex, n (%)	26 (49.1)	16 (69.6)	.13
Pretransplantation pH study			
Median DeMeester score	15.5 (4.6-34.1)	41.8 (26.9-56.3)	.001
Median proximal channel total time pH <4, min	2 (0.8-21.6)	4.5 (0.3-10.0)	.68
Median distal channel total time pH <4, min	49.4 (10.5-96.1)	125.9 (96.9-189.0)	<.001
Median time between lung transplant and hernia repair, mo	11.0 (6.1-15.3)	5.7 (2.4-16.1)	.10
Prefundoplication pH study†			
Median DeMeester score	48 (30.0-66.0)	48.2 (32.5-74.5)	.67
Median proximal channel total time pH <4, min	6 (0.5-21.2)	7.0 (0.0-41.0)	.83
Median distal channel total time pH <4, min	139.5 (86.0-215.6)	164.1 (96.9-244.8)	.59
Median total LES length, cm	3.5 (3.1-3.8)	3.2 (2.9-3.6)	.14
Median LESP, mm Hg	23.0 (10.4-31.3)	19.6 (15.3-31.4)	.62
Total number of acute rejection, n (%)			.09
0	29 (54.7)	9 (39.1)	
1 or more	24 (45.3)	14 (60.9)	

All values expressed as median (interquartile range), unless indicated otherwise. LAS, Lung allocation score; LES, lower esophageal sphincter; LESP, lower esophageal sphincter resting pressure. *Calculated using Wilcoxon rank sum for continuous variables and Fisher exact for categorical variables. †Data missing for 2 patients.

score and proximal acid exposure times recorded prefundoplication were comparable between disease groups. Patients with restrictive lung disease had fundoplication earlier in their post-transplantation course (median, 5.7 months) compared with patients with obstructive lung disease (median, 11 months).

Acute Rejection

We calculated the number and severity of acute rejection episodes in total, as well as before and after fundoplication in both groups (Table 2). Although the late fundoplication group had a higher incidence of 1 or more episodes of acute rejection in total, this was not significant. The 2 groups were also comparable in terms of incidence of acute rejection after fundoplication, and in severity of acute rejection episodes.

FEV₁ and BOS

The 2 groups differed in rate of lung function decline (Figure 1). The FEV₁% increased by 2.5% ($P = .22$) over time in the early group compared with a decrease of 5.7% in the late group ($P < .001$). The 5-year percent predicted FEV₁ was lower in the late group by 40.7% ($P = .019$). The adjusted linear mixed model showed that late fundoplication resulted in lower FEV₁% than early fundoplication (Table 6). After stratification of fundoplication study group, the subgroup analyses showed a statistically significant decrease in FEV₁% over time in both groups.

We further ascertained interactions via the linear mixed model between patient demographic and clinical

characteristics with timing of fundoplication. Patients older than 60 years of age, LAS >40, obstructive end-stage lung disease, DeMeester score >20, and fundoplication length of stay >2 days were found to be effect modifiers with respect to the association between fundoplication timing and FEV₁ decline over time (not shown).

In total, 19% of patients (16.7% early; 20.4% late) met criteria for BOS grade 0-p or higher prefundoplication.¹ Pulmonary function data were available for 83 of 86 patients for interpretation of freedom from BOS. Subgroup analysis showed comparable freedom from BOS in the early and late groups (log-rank $P = .50$; Figure E1).

FIGURE 1. Linear mixed model showing differences in rate of decline in percent predicted FEV₁ over time according to fundoplication group after transplantation. FEV₁, Forced expiratory volume in 1 second.

TABLE 6. Comparison of FEV₁ decline between study groups after adjusting for confounding variables

Study group	Overall	<i>P</i> *	Early fundoplication only	<i>P</i> †	Late fundoplication only	<i>P</i> †
	Coefficient (95% CI)		Coefficient (95% CI)		Coefficient (95% CI)	
Early fundoplication	Reference		Reference		Reference	
Late fundoplication	−3.64 (−25.1 to 5.80)	.22	N/A		N/A	
Time	−4.67 (−6.22 to −3.12)	<.001	−5.07 (−7.29 to −2.85)	<.001	−4.63 (−6.64 to −2.63)	<.001

CI, Confidence interval; N/A, not applicable. *Linear mixed model to assess the estimated mean difference in FEV₁ across time after adjusting for the interaction between time and fundoplication status, age, sex, LAS, BMI at surgery, UNOS lung diagnosis, Karnofsky score, serum creatinine, interval between lung transplantation and fundoplication, DeMeester score, SAP symptom score, LES length, esophagitis, fundoplication LOS, number of rejections, time between last PFT and transplantation. †Linear mixed model to assess the estimated mean difference in FEV₁ across time after adjusting for age, sex, LAS, BMI at surgery, UNOS lung diagnosis, Karnofsky score, serum creatinine, interval between lung transplantation and fundoplication, DeMeester score, SAP symptom score, LES, esophagitis, fundoplication LOS, number of rejections, time between last PFT and transplantation.

Survival

Survival was comparable in both fundoplication groups (log rank *P* = .63). One-year, 3-year, and 5-year survival rates in the early group were 90%, 70%, and 70%; in the late group, these rates were 91%, 66%, and 66%. Furthermore, compared with lung transplantation patients with normal pH studies and GERD patients without fundoplication, actuarial survival was not worse in either fundoplication group (log rank *P* = .63).

DISCUSSION

Gastroesophageal reflux is prevalent in patients with end-stage lung disease awaiting lung transplantation^{5,12,13} and in patients who have undergone lung transplantation.^{13,14} Some have reported worsening of GERD post-transplantation.¹³⁻¹⁵ The reported rates of abnormal proximal acid exposure post-transplantation vary widely, but are generally lower than those seen in lung transplantation candidates. In our study, the prevalence of post-transplantation GERD was high (59%). Fundoplication was performed for 1 of 2 reasons: symptomatic reflux corroborated on pH monitoring, or asymptomatic reflux at surveillance pH monitoring post-transplantation. Our rates of fundoplication post-transplantation were also higher (34.5%) compared with rates described in the published literature, which range from 11% to 20%.^{16,17} These differences could be attributed to variation in institutional policies on the timing of fundoplication (ie, pretransplantation or post-transplantation). Furthermore, most institutions reserve pH testing for lung transplantation patients with symptomatic reflux or suspicion of aspiration-induced allograft injury. Hartwig et al¹⁸ reported rates of post-transplantation fundoplication as high as 53% (including only patients who had pH testing pretransplantation). The high rates of fundoplication (34.5%) in our lung transplantation population can be attributed to deferring the fundoplication to the post-transplantation period in patients with abnormal pH studies pretransplantation.

We also routinely refer all lung transplantation patients to an esophageal clinic post-transplantation and, if warranted,

repeat a complete GERD evaluation (ie, endoscopy, 24-hour pH monitoring) 3 months after transplantation, regardless of whether GERD was evident during pretransplantation evaluation. All patients who underwent fundoplication had abnormal distal esophageal acid exposure times. Proximal acid exposure varied widely; fundoplication was offered in cases of abnormal distal acid exposure or abnormal DeMeester score (>14.72) with or without evidence of proximal acid exposure on 24-hour pH monitoring.

Recently, some researchers have debated the reliability of proximal esophageal acid exposure as a surrogate for predicting aspiration in lung transplantation patients. Presence of pepsin^{19,20} and bile acids^{5,19,21} in bronchoalveolar lavage fluid have been shown to be more accurate predictors of gastroesophageal and gastroduodenal reflux, respectively, in these patients. However, use of these biomarkers remains limited to select centers, and pH studies in combination with endoscopy act as a widely used surrogate in cases of clinically suspected GERD-related aspiration. The presence of GERD in a patient undergoing lung transplantation is concerning for 2 main reasons: risk of aspiration-related allograft injury (ultimately contributing to allograft rejection), and the morbidity associated with fundoplication post-transplantation, which remains the only effective treatment for preventing reflux-related aspiration in this patient population.¹⁹

Although an association between reflux and lung transplantation is clear, controversy remains as to its role in the pathogenesis of allograft injury and CLAD. Some have reported stabilization of,¹⁶ and sometimes, even improvement in lung function¹⁷ measured according to FEV₁ after surgical correction of reflux post-transplantation. FEV₁ decline is often used as a surrogate for BOS, which manifests pathologically as obliterative bronchiolitis. BOS is a common phenotype of CLAD in lung transplantation.²² Cantu et al⁸ showed that early fundoplication (within 90 days) was associated with a greater freedom from BOS. Fisichella et al⁷ showed that patients with any detectable pepsin in bronchoalveolar lavage fluid had quicker progression to BOS

and more episodes of acute rejection, although they did not find a significant difference in time to BOS on the basis of treatment by early (<6 months) or late antireflux surgery.

Lo et al,⁹ in their retrospective analysis of 48 patients, reported that patients who underwent late (>6 months) antireflux surgery had significantly higher rates of early allograft injury (ie, acute rejection or lymphocytic bronchiolitis) compared with patients in their early fundoplication group. Results from our large single-center experience of 86 patients show that early surgical intervention before the onset of BOS (<6 months post-transplantation) in patients with a positive 24-hour pH monitoring study is associated with slower decline in lung function over the long term. However, we did not find any significant differences in rates of freedom from BOS and severity and number of acute rejections on the basis of the time of fundoplication after transplantation. This might be because of limitations in our study design, the multifactorial pathogenesis of BOS, and the presence of confounding factors. Despite this, our study clearly shows the positive effects of early surgical correction of GERD on long-term lung function post-transplantation.

Although most transplant centers now screen for preexisting GERD at the time of lung transplantation evaluation, the diagnosis and management of GERD in lung transplantation patients remain widely variable among transplant centers. No established guidelines for GERD surveillance exist for transplant recipients. In general, indications for surgical intervention for GERD after lung transplantation include evidence of symptomatic reflux, severe reflux as documented on pH-monitoring or impedance study and/or endoscopy, bronchoscopic evidence of aspiration, and unexplained decline in pulmonary function. Patients with severe symptomatic reflux usually present early post-transplantation, necessitating surgical intervention. However, there remains a fraction of patients with proximal reflux and silent aspiration who undergo surgery only after a decline in lung function. It is the latter subgroup of patients that might benefit from routine, continued GERD surveillance post-transplantation. Furthermore, on the basis of recent data documenting improved pulmonary inflammatory milieu after surgical correction of GERD,^{6,15} and several single-center experiences showing an improvement in lung function from early fundoplication, a strong argument can be made for initiation of routine GERD surveillance early in the post-transplantation period (ie, within 3 months of transplantation).

Reported rates of mortality related to antireflux surgery have been historically low (1.4%).²³ Kilic et al,²³ in their review of the nationwide inpatient sample, showed that fundoplication in lung transplant recipients is associated with longer length of stay and higher costs than in

nontransplantation patients. However, previous lung transplantation was not an independent risk factor for in-hospital mortality postfundoplication. Although 5 of 86 patients in our study required revision surgery for failed fundoplication, we had no fundoplication-related mortality. Delayed gastric emptying requiring endoscopic dilation or pyloric injection of botulinum toxin occurred in 5 of 86 patients. There was no increased incidence of medical or wrap-related complications postfundoplication in our transplantation population. In light of our findings, and of others who have reported improved quality of life postfundoplication²⁴ with low morbidity, fundoplication appears to be a safe and effective treatment for GERD after transplantation.

Many authors have reported an association between underlying pulmonary diagnosis and incidence of GERD and esophageal motility disorders.^{12,25,26} In our study, most post-transplantation fundoplications were performed in patients who underwent transplantation for obstructive lung disease. Restrictive lung disease patients who required post-transplantation fundoplication had higher pretransplantation DeMeester scores compared with patients with obstructive lung disease. This is likely because patients with restrictive lung disease awaiting lung transplantation often have severe pretransplantation GERD and poor esophageal motility. Poor esophageal motility can exacerbate reflux because of inadequate acid clearance from the esophagus, which explains the differences in pretransplantation pH studies in the 2 disease groups. It is also likely that patients with restrictive disease had a lower threshold for post-transplantation fundoplication, as evidenced by the shorter time between transplantation and fundoplication. This is likely because of positive pH studies at the time of transplantation evaluation, continued symptoms, and/or concern for aspiration-related allograft injury because of concomitant esophageal dysmotility. We are currently undertaking further studies to objectively assess rates of esophageal motor disorders and their association with GERD in our post-transplantation population.

This study drives home the importance of early and routine referrals of lung transplant recipients to esophageal clinics. Our study has validated the importance of early surgical intervention for GERD and the ability of fundoplication to slow the pulmonary function decline post-transplantation. Although BOS is multifactorial, our data do indicate a slower decline in FEV₁ after early fundoplication. Despite intervention to prevent aspiration-related allograft injury, we have seen neither improvement in lung function after fundoplication nor a significant difference in the onset of BOS, contrary to observations made by Davis et al.¹⁷ A potential explanation for this would be our small sample size and the multifactorial etiology of BOS. Another potential explanation would be that even a short median intervention time of 4.6 months post-transplantation (as seen in our early fundoplication

group) might be too late in the continuum of irreversible events associated with allograft injury that ultimately result in BOS. Additionally, this study constitutes one of the largest modern single-center experiences with antireflux surgery in the lung transplantation population to date (after Hartwig et al,¹⁸ who described 157 patients over 8.5 years). We also report specific characteristics of patients (ie, lung transplant recipients older than 60 years, LAS >40, obstructive lung disease, and DeMeester score >20) who stand to benefit the most from early fundoplication post-transplantation. We believe our current practice of esophageal surveillance beginning 3 months post-transplantation is a protocol worth adopting, because of the high prevalence of GERD and its implications on allograft function after lung transplantation. In a recent study, Ehrsam et al²⁷ reported GERD as an independent predictor of mortality in lung transplant recipients aged 60 years or older. This also raises the question of whether patients should be considered for fundoplication earlier than 6 months, especially in older recipients.

This study is limited by its retrospective nature and lack of a control arm. The biggest confounder in this study was the presence of unaccounted variables that could affect decline in lung function and freedom from BOS differently in the 2 patient groups. Another is the delay in fundoplication because of unforeseen complications in some patients in the late fundoplication group. As shown by Chan et al,²⁸ one might argue that some patients in the late fundoplication group were doomed to have worse allograft outcomes as a result of the “ripple effect” from immediate post-transplantation complications unrelated to GERD. Furthermore, some antireflux procedures offered to patients in the late fundoplication group might be construed as “too little, too late” in the continuum of BOS development. We do not have objective studies that have yet investigated bronchoalveolar aspiration markers (eg, pepsin, bile acid) or persistent reflux (24-hour pH study) in patients postfundoplication. Finally, because of the limited number of patients in our study, our 3- and 5-year survival numbers might be somewhat skewed.

CONCLUSIONS

GERD appears to become more severe after lung transplantation, but early fundoplication might slow the rate of lung function decline after transplantation. In this study, patients who underwent early fundoplication had a higher FEV₁ 5 years after transplantation. Early fundoplication might protect against GERD-induced lung damage in transplant recipients with pretransplantation GERD.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44:1479-503.
2. Belperio JA, Weigt SS, Fishbein MC, Lynch JP III. Chronic lung allograft rejection: mechanisms and therapy. *Proc Am Thorac Soc*. 2009;6:108-21.
3. Weigt SS, Wallace WD, Derhovanessian A, Saggar R, Saggar R, Lynch JP, et al. Chronic allograft rejection: epidemiology, diagnosis, pathogenesis, and treatment. *Semin Respir Crit Care Med*. 2010;31:189-207.
4. Bobadilla JL, Jankowska-Gan E, Xu Q, Haynes LD, Munoz del Rio A, Meyer K, et al. Reflux-induced collagen type V sensitization: potential mediator of bronchiolitis obliterans syndrome. *Chest*. 2010;138:363-70.
5. D'Ovidio F, Singer LG, Hadjiliadis D, Pierre A, Waddell TK, de Perrot M, et al. Prevalence of gastroesophageal reflux in end-stage lung disease candidates for lung transplant. *Ann Thorac Surg*. 2005;80:1254-60.
6. Fisichella PM, Davis CS, Lowery E, Pittman M, Gagermeier J, Love RB, et al. Pulmonary immune changes early after laparoscopic antireflux surgery in lung transplant patients with gastroesophageal reflux disease. *J Surg Res*. 2012;177:e65-73.
7. Fisichella PM, Davis CS, Lundberg PW, Lowery E, Burnham EL, Alex CG, et al. The protective role of laparoscopic antireflux surgery against aspiration of pepsin after lung transplantation. *Surgery*. 2011;150:598-606.
8. Cantu E III, 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; discussion 51.
9. Lo WK, Goldberg HJ, Wee J, Fisichella PM, Chan WW. Both pre-transplant and early post-transplant antireflux surgery prevent development of early allograft injury after lung transplantation. *J Gastrointest Surg*. 2016;20:111-8; discussion 8.
10. Richter JE, Pandolfino JE, Vela MF, Kahrilas PJ, Lacy BE, Ganz R, et al. Utilization of wireless pH monitoring technologies: a summary of the proceedings from the Esophageal Diagnostic Working Group. *Dis Esophagus*. 2013;26:755-65.
11. Stewart S, Fishbein MC, Snell GI, Berry GJ, Boehler A, Burke MM, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant*. 2007;26:1229-42.
12. Basseri B, Conklin JL, Pimentel M, Tabrizi R, Phillips EH, Simsir SA, et al. Esophageal motor dysfunction and gastroesophageal reflux are prevalent in lung transplant candidates. *Ann Thorac Surg*. 2010;90:1630-6.
13. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. *Chest*. 2003;124:1689-93.
14. Hadjiliadis D, Duane Davis R, Steele MP, Messier RH, Lau CL, Eubanks SS, et al. Gastroesophageal reflux disease in lung transplant recipients. *Clin Transplant*. 2003;17:363-8.
15. Fisichella PM, Davis CS, Gagermeier J, Dilling D, Alex CG, Dorfmeister JA, et al. Laparoscopic antireflux surgery for gastroesophageal reflux disease after lung transplantation. *J Surg Res*. 2011;170:e279-86.
16. Abbassi-Ghadi N, Kumar S, Cheung B, McDermott A, Knaggs A, Zacharakis E, et al. Anti-reflux surgery for lung transplant recipients in the presence of impedance-detected duodenogastroesophageal reflux and bronchiolitis obliterans syndrome: a study of efficacy and safety. *J Heart Lung Transplant*. 2013;32:588-95.
17. Davis RD Jr, Lau CL, Eubanks S, Messier RH, Hadjiliadis D, Steele MP, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg*. 2003;125:533-42.
18. Hartwig MG, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. *Ann Thorac Surg*. 2011;92:462-8; discussion 8-9.
19. Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J*. 2008;31:707-13.
20. Stovold R, Forrest IA, Corris PA, Murphy DM, Smith JA, Decalmer S, et al. Pepsin, a biomarker of gastric aspiration in lung allografts: a putative association with rejection. *Am J Respir Crit Care Med*. 2007;175:1298-303.
21. D'Ovidio F, Mura M, Ridsdale R, Takahashi H, Waddell TK, Hutcheon M, et al. The effect of reflux and bile acid aspiration on the lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. *Am J Transplant*. 2006;6:1930-8.
22. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2014;33:127-33.

23. Kilic A, Shah AS, Merlo CA, Gourin CG, Lidor AO. Early outcomes of antireflux surgery for United States lung transplant recipients. *Surg Endosc.* 2013;27:1754-60.
24. Robertson AG, Krishnan A, Ward C, Pearson JP, Small T, Corris PA, et al. Anti-reflux surgery in lung transplant recipients: outcomes and effects on quality of life. *Eur Respir J.* 2012;39:691-7.
25. el-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology.* 1997;113:755-60.
26. Seccombe J, Mirza F, Hachem R, Gyawali CP. Esophageal motor disease and reflux patterns in patients with advanced pulmonary disease undergoing lung transplant evaluation. *Neurogastroenterol Motil.* 2013;25:657-63.
27. Ehrsam JP, Benden C, Seifert B, Opitz I, Schneider D, Weder W, et al. Lung transplantation in the elderly: influence of age, comorbidities, underlying disease, and extended criteria donor lungs. *J Thorac Cardiovasc Surg.* 2017;154:2135-41.
28. Chan EG, Bianco V III, Richards T, Hayanga JW, Morrell M, Shigemura N, et al. The ripple effect of a complication in lung transplantation: evidence for increased long-term survival risk. *J Thorac Cardiovasc Surg.* 2016;151:1171-9.

Key Words: fundoplication, gastroesophageal reflux, lung transplantation

FIGURE E1. Cumulative incidence of BOS at follow-up, constructed using the competing risk extension of the Kaplan–Meier method where death is regarded as a competing risk. *BOS*, Bronchiolitis obliterans syndrome.