Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation

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Objective: There is a strong association between reflux and end-stage lung disease, especially idiopathic pulmonary fibrosis. The presence of reflux after lung transplantation might predispose to the development of bronchiolitis obliterans. We evaluated the risk and physiologic effect of laparoscopic fundoplication in patients on the lung transplant waiting list.

Methods: One hundred forty-nine patients on the lung transplant waiting list between March 2001 and January 2005 were evaluated. Nineteen were found to have a history of reflux, continued symptoms, and severe reflux by means of pH and manometric studies and underwent laparoscopic fundoplication. The postoperative course of these 19 patients, including lung function, was retrospectively reviewed. Postoperatively, the lung function of the 14 patients with idiopathic pulmonary fibrosis who underwent the laparoscopic Nissen procedure was compared with that of 31 patients with idiopathic pulmonary fibrosis on the transplant waiting list who did not undergo fundoplication.

Results: There were no perioperative complications and no decrease in lung function over the 15-month average follow-up. Exercise capacity remained stable, as determined on the basis of 6-minute walk distance. Patients with idiopathic pulmonary fibrosis treated with fundoplication had stable oxygen requirements, whereas control patients with idiopathic pulmonary fibrosis on the waiting list had a statistically significant deterioration in oxygen requirement.

Conclusions: Laparoscopic fundoplication can be performed safely in patients with end-stage lung disease awaiting lung transplantation. Overall, these patients maintained stable lung function during the follow-up period. When compared with a control group of patients with idiopathic pulmonary fibrosis not undergoing fundoplication, there was stabilization of oxygen requirement. A larger prospective trial evaluating the effect of laparoscopic fundoplication on underlying lung function in this patient population is warranted.

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There is an association between gastroesophageal reflux disease (GERD) and a wide range of pulmonary disorders, including pneumonia, asthma, bronchiectasis, and cystic fibrosis. More recently, an association between GERD and interstitial lung disease, especially idiopathic pulmonary fibrosis (IPF), has been proposed.¹ Several decades ago, the incidence of GERD and hiatal hernia was

Abbreviations and Acronyms

COPD	= chronic obstructive pulmonary disease
DLCO	= diffusing capacity of lung for carbon monoxide
FEV ₁	= forced expiratory volume in 1 second
GER	= gastroesophageal reflux
GERD	= gastroesophageal reflux disease
IPF	= idiopathic pulmonary fibrosis

reported to be higher in a group of patients with interstitial pulmonary fibrosis than in age-matched control subjects.² More recently, 17 consecutive patients with biopsy-proved interstitial pulmonary fibrosis were studied with ambulatory esophageal pH probes. Sixteen (94%) of the 17 patients were found to have abnormal esophageal acid exposure at significantly higher levels than that seen in control patients with other types of interstitial lung disease.³ It has been hypothesized that recurrent overt or silent regurgitation and aspiration might play a role in the progression of these and other pulmonary disorders.

It has also been proposed that GERD is a potential cause of allograft dysfunction after lung transplantation, and as a result, laparoscopic Nissen fundoplication might be a suitable method to prevent the development of bronchiolitis obliterans after transplantation. Davis and colleagues⁴ showed a 76% incidence of GERD documented by means of pH-probe analysis in a series of patients who underwent lung transplantation. Surgical fundoplication after lung transplantation in these patients resulted in improved forced expiratory volume in 1 second (FEV₁) and a decrease in the incidence of bronchiolitis obliterans compared with that seen in historical control subjects. Moreover, fundoplication early (approximately 1 month) after transplantation resulted in a higher freedom from development of bronchiolitis obliterans and better survival when compared with late fundoplication (2 years) after transplantation.⁵ This report represents the largest series of surgical fundoplication after lung transplantation.

We reasoned that fundoplication might best be performed in selected patients before lung transplantation to potentially reduce morbidity and in some cases to stabilize the patient's end-stage pulmonary status. We show here that laparoscopic fundoplication in patients with end-stage lung disease can be safely accomplished before lung transplantation.

There might be several advantages to performing the antireflux procedure before transplantation. First, it allows for the earliest degree of protection from the negative effects of reflux on the transplanted lung. Second, it might offer protection from aspiration around the time of transplantation. Third, there is the potential for improvement of

native lung function and alteration of progression of underlying disease.

Patients and Methods

One hundred forty-nine patients listed on the lung transplant waiting list between March 2001 and January 2005 at Brigham and Women's Hospital were evaluated for a history of GERD and symptoms of heartburn or regurgitation. Nineteen were found to have a history of GERD, continued classical symptoms of GERD, and severe reflux documented by means of pH studies and underwent laparoscopic fundoplication. A retrospective analysis of these patients was performed with the approval of the institutional review board (approval date: June 30, 2004). All patients were referred for pulmonary rehabilitation at the time of consideration for lung transplantation.

Esophageal Assessment

Before selection as lung transplant candidates, patients were interviewed for a history of GERD and symptoms of heartburn or regurgitation. If any of these were present, they were referred for esophageal testing, which consisted of esophageal manometry, 24-hour ambulatory pH testing, and endoscopy. Evidence of pathologic reflux was considered to be increased esophageal acid exposure relative to normal values and was specifically defined as total acid exposure of greater than 4.0% or a composite Demeester reflux score of greater than 14.72 (95th percentile). Secondary data in support of the diagnosis of GERD included abnormalities on endoscopy, such as the presence of erosions, ulceration, or stricture or hiatal herniation on endoscopy, or abnormalities on esophageal manometry, such as reduction of resting lower esophageal sphincter pressure. Those with evidence of pathologic esophageal acid exposure and continued symptoms with medical therapy were referred for laparoscopic fundoplication.

Preoperative and Perioperative Pulmonary Assessment

Preoperative characteristics, including age, sex, underlying pulmonary disease, immunosuppressive medications, oxygen dependence, pulmonary function testing, and 6-minute walk distance, were collected (Table 1). The perioperative course of each patient, including length of stay and any complications, was reviewed. The postoperative course of these 19 patients, including oxygen dependence, 6-minute walk distance, and pulmonary function testing, and any symptoms of heartburn or regurgitation were retrospectively reviewed, with a mean overall follow-up of 15 months. Not all patients had preoperative or postoperative 6-minute walk distances, preoperative or postoperative diffusion capacity, or postoperative pulmonary function test results available.

Fourteen of the patients undergoing laparoscopic Nissen fundoplication had IPF. Their postoperative course, including FEV₁, forced vital capacity, diffusing capacity of lung for carbon monoxide (DLCO), 6-minute walk distances, and oxygen requirement, were retrospectively compared with those of patients with IPF on the waiting list who did not undergo fundoplication.

Technique of Laparoscopic Nissen Fundoplication

Laparoscopic fundoplication was performed through 5 ports. Complete division of the majority of the short gastric vessels was

TABLE 1. Preoperative patient characteristics (n = 19)

Average age	53 ± 10 y
Underlying lung disease, n	
Interstitial pulmonary fibrosis	14
Cystic fibrosis	1
COPD	3
Immotile cilia	1
Severity of GERD	
Average Demeester index	97.5 (<14.72, 95th percentile)
Average resting LES	3.7 ± 1.7 mm Hg
Lung function	
Average FEV ₁	55% ± 24%
Average FVC	62% ± 18%
Average adjusted DLCO	35% ± 15%
Immunosuppression	12 (63%)
Oxygen dependence	12 (63%)

COPD, Chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease; *LES*, lower esophageal sphincter; *FEV₁*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *DLCO*, diffusing capacity of lung for carbon monoxide.

performed. The diaphragmatic crurae were approximated with interrupted Ethibond sutures (Ethicon, Inc, Somerville, NJ). If there was any tension on the necessary 4 cm of intra-abdominal esophagus, then the esophagus was deemed short, and a Collis-Nissen procedure was performed. With a 56F to 60F (depending on the patient's body mass) bougie in place along the lesser curve of the stomach, an endoscopic GIA stapler was used to remove a triangular portion of fundus, essentially lengthening the intra-abdominal portion. A 2½-cm calibrated Nissen fundoplication was typically performed with 3 stitches, the first 2 incorporating esophagus. Patients were not allowed anything by mouth overnight and were started on clear liquids the next day. After tolerating full liquids on postoperative day 2, they were sent home on a full liquid diet for 2 weeks.

Statistical Analysis

The ± notation is used to report the sample standard deviation. The Spearman rank-order correlation coefficient was used as the measure of association between Demeester score and mean lower esophageal sphincter pressure with preoperative lung function and walk distance. The *P* value was computed by means of the Monte Carlo method for a 1-sided test that reflects the prior hypothesis of a positive correlation between the severity of gastroesophageal reflux (GER) and the severity of underlying lung disease. The comparison of preoperative and postoperative lung function or walk distance was based on the Wilcoxon signed-rank test. The exact *P* value is reported as 1 sided to rule out significantly decreasing lung function. The nonparametric tests were performed with StatXact 6 (Cytel Software Corp, Cambridge, Mass).

The patients with IPF who underwent laparoscopic fundoplication were compared with a control group with the same diagnosis on the transplant waiting list during the same period in terms of their changes in lung function, exercise capacity, and oxygen requirement over time. Each change was standardized by the time interval between the initial and follow-up tests to account for the varying intervals of follow-up testing among the patients, and

therefore the outcome is expressed as a rate. The rates derived for each test were analyzed by using the Wilcoxon rank sum test to determine whether a difference was present between the fundoplication and control groups. The 2-sided *P* values were computed by using the exact algorithm in SAS 8.2 (SAS Institute Inc, Cary, NC).

Results

Patient Population and Perioperative Events

Of 149 patients on the lung transplant waiting list between March 2001 and January 2005 at Brigham and Women's Hospital, 19 (12.8%) were found to have a history of significant GERD, continued symptoms on full medical therapy, diminished lower esophageal sphincter tone, and severe esophageal acid exposure, as determined by means of ambulatory pH study. These patients underwent laparoscopic Nissen fundoplication. Fourteen had IPF, 3 had chronic obstructive pulmonary disease (COPD), 1 had immotile cilia syndrome, and 1 had cystic fibrosis. The average patient age was 53 ± 10 years. Twelve of the 19 patients were on immunosuppressive regimens (6 were receiving corticosteroids) before the laparoscopic Nissen procedure. The incidence of complications was not higher for this group of patients.

Mean patient follow-up was 15 ± 8 months among the 13 patients who had undergone any of the lung function tests or 6-minute walk postoperatively. For the evaluation of the effect of laparoscopic Nissen fundoplication on native lung function, the follow-up interval of patients undergoing transplantation was terminated at the time of transplantation. The 4 patients undergoing transplantation were further observed during the perioperative transplantation period for episodes of aspiration. The patient who underwent a laparoscopic Toupet fundoplication experienced an episode of aspiration 5 days after transplantation but recovered and was discharged home on postoperative day 20. No other patient undergoing transplantation had aspiration or symptoms of recurrent reflux. Of the 4 patients undergoing transplantation, 1 had new symptoms of nausea and early satiety after transplantation. The patient was found to have significantly delayed gastric emptying, which improved with metoclopramide.

Four of the patients who underwent laparoscopic Nissen fundoplication died before being offered lung transplantation at 2, 6, 12, and 19 months after the antireflux procedure. All deaths were a result of progressive respiratory failure and were unrelated to the surgical procedure. Three of these 4 patients had the lowest DLCO value among the 19 patients (adjusted DLCO = 9% [died 2 months after Nissen fundoplication], 12% [died 6 months after Nissen fundoplication], 19% [died 19 months after Nissen fundoplication], and 46% [died 12 months after Nissen fundoplication]).

Of 45 patients with IPF on the transplant waiting list, 14 (31%) had symptoms and severe GERD confirmed by means of pH study and underwent laparoscopic Nissen

Figure 1. Correlation of preoperative oxygen dependence with Demeester Score.

fundoplication. Thirty-one patients with IPF on the waiting list did not undergo laparoscopic Nissen fundoplication.

pH, Manometric Studies, and Endoscopic Findings

The average Demeester score before fundoplication was 97.5 ± 81.1 (normal is considered ≤ 14.72 , 95th percentile). The mean resting lower esophageal sphincter pressure (above gastric pressure) was 3.7 ± 1.7 mm Hg. One patient was found to have significantly diminished esophageal body contractility with swallows, manifesting as reduced contraction incidence and amplitude. He underwent a Toupet (partial) fundoplication. The remainder showed no significant impairment of motility. The severity of preoperative GER, as determined on the basis of the Demeester score, correlated positively with preoperative oxygen requirement (correlation coefficient, 0.49; $P = .028$; Figure 1).

All patients undergoing Nissen fundoplication underwent preoperative endoscopy. No patients were found to have stricture or Barrett’s esophagus. Three were seen to have evidence of esophagitis. It should be noted that the majority of these patients had been receiving long-term proton-pump inhibitors until 1 week before their pH study and endoscopy.

Patients did not undergo routine postoperative pH/manometric testing. Because all those who underwent fundoplication had current symptomatic reflux, they were followed postoperatively for symptoms. Only one patient underwent postoperative pH/manometric testing because of symptoms of nausea. Her postoperative Demeester score was 20 (preoperative value, 86.8), and her nausea resolved spontaneously. Although none of the patients complained of recurrent heartburn or regurgitation, 13 of the 19 patients were restarted on acid-suppressive therapy to reduce the risk of gastritis or peptic ulcer associated with corticosteroid therapy.

Surgical Results

Fifteen patients underwent laparoscopic Nissen fundoplication, 3 underwent laparoscopic Collis-Nissen fundoplication, and 1 underwent laparoscopic Toupet fundoplication. Average length of stay was 3.5 ± 1.2 days (range, 2-6 days). One of the patients undergoing laparoscopic Nissen fundoplication required conversion to open Nissen fundoplication because of body habitus and gastric perforation. This patient required 2 dilations as an outpatient for recurrent stricture and is now swallowing without difficulty. This patient and 2 others experienced superficial wound infections requiring antibiotics. One patient had transient postoperative gastric dilation. A single patient had symptoms of nausea 6 months after the Nissen procedure and was evaluated with postoperative pH studies (see above). None of the patients had recurrent symptoms of either heartburn or regurgitation.

Lung Function

Table 2 shows the comparison among patients who had each type of assessment evaluated both preoperatively and postoperatively. Thus the preoperative summaries in Tables 1 and 2 reflect some fluctuations but are not significantly different. The overall follow-up interval was 15 months, as measured from the date of Nissen fundoplication. Overall,

TABLE 2. Average lung function and exercise capacity in those patients who had both prefundoplication and postfundoplication indices measured: All diagnoses

Parameter	N (number with both pre and post measurements)	Pre, median $\pm$ SD	Post, median $\pm$ SD	Median interval, mo	P value
Oxygen requirement (L/min)	15	2.4 $\pm$ 2.2	2.4 $\pm$ 2.2	12.7	.500
6-Min walk (ft)	10	1283 $\pm$ 344	1231 $\pm$ 199	7.1	.500
FVC (% predicted)	11	65 $\pm$ 15	61 $\pm$ 16	9.5	.093
FEV ₁ (% predicted)	11	54 $\pm$ 19	54 $\pm$ 24	9.5	.167
DLCO (% predicted, adjusted)	8	43 $\pm$ 14	40 $\pm$ 18	6.8	.242

$P \geq .05$ indicates no statistically significant change. Pre, Prefundoplication; Post, postfundoplication; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide.

TABLE 3. Comparison of sequential oxygen requirement, walk distance, and pulmonary function of patients with IPF undergoing Nissen fundoplication with values in those not undergoing Nissen fundoplication (control group)

Parameter	N	Pre, median (range)	Post, median (range)	Median (range) interval, mo	P value
Oxygen requirement (L/min)	Control group: n = 23 Nissen group: n = 11	2.0 (0-10) 3.0 (0-8)	3.0 (0-15) 2.5 (0-8)	13 (1-57) 11 (1-23)	.002
6-Min walk (ft)	Control group: n = 12 Nissen group: n = 8	1324.5 (618-1955) 1283 (691-2005)	989 (180-1908) 1241.5 (790-1479)	14 (4-24) 8 (1-15)	.664
FVC (% predicted)	Control group: n = 14 Nissen group: n = 8	56.5 (42-79) 57.5 (45-81)	63 (33-76) 54 (40-84)	12 (4-65) 6 (4-16)	.881
FEV ₁ (% predicted)	Control group: n = 14 Nissen group: n = 8	59.5 (42-84) 62 (49-80)	62 (32-81) 56 (44-103)	12 (4-65) 6 (4-16)	.973
DLCO (% predicted, adjusted)	Control group: n = 8 Nissen group: n = 6	30.5 (25-50) 36 (27-45)	26.5 (11-56) 35 (11-50)	12 (4-65) 4.5 (4-9)	.755

P < .05 indicates a statistically significant difference between the change in parameters between the Nissen and control groups. *Pre*, prefundoplication; *Post*, postfundoplication; *FVC*, forced vital capacity; *FEV₁*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity of lung for carbon monoxide.

the average percent predicted FEV₁, forced vital capacity, DLCO, and 6-minute walk distances showed no statistically significant decreases over the follow-up intervals. Twelve patients were oxygen dependent before the procedure, and there was no significant change in the degree of oxygen dependence after the procedure.

One patient with IPF had significant improvements in his FEV₁ (77% to 103%), decrease in supplemental oxygen requirement, and subjective reduction of shortness of breath. He elected to be taken off the transplant waiting list.

Comparison of Patients With IPF Undergoing Nissen Fundoplication With Control Patients With IPF

In an attempt to determine whether the stability of lung function and exercise capacity noted overall in the patients undergoing Nissen fundoplication represented a difference from that expected in patients with IPF overall, we retrospectively compared patients with IPF undergoing laparoscopic Nissen fundoplication (14 patients) with those not undergoing fundoplication (31 patients). The results, including initial and follow-up values, intervals, and 2-sided *P* values are listed in Table 3. The results indicate that there is a statistically significant difference in the oxygen requirements over time between the patients with IPF undergoing Nissen fundoplication and those not undergoing Nissen fundoplication.

Discussion

The incidence of severe GERD in patients with end-stage lung disease awaiting lung transplantation is high. One study of a subset of patients undergoing transplantation estimated the incidence of pretransplantation GERD at 35% and the incidence of posttransplantation reflux at 65%.⁶ All patients with reflux before transplantation continued to have reflux after transplantation. In addition, a high incidence of GERD has been reported in a variety of patients with

end-stage lung disease, including patients with COPD, asthma, and interstitial lung disease.^{7,8} In a study of 17 consecutive patients with IPF, 16 (94%) were found to have abnormal esophageal acid exposure. Only one quarter had symptoms of heartburn or regurgitation.³

Although numerous publications have documented an association between lung disease and GERD, the underlying mechanism is still not well understood.⁹ Patients with COPD and asthma have similar physiologic factors that might exacerbate reflux. During exacerbations, more negative intrathoracic pressure and correspondingly higher abdominal pressures are produced, favoring increased reflux. Furthermore, with lung hyperexpansion, the diaphragm is flattened, potentially interfering with the ability of the crura to support the lower esophageal sphincter. Theophylline can increase gastric acid production and decrease lower esophageal sphincter pressure. β -Agonist medications might induce lower esophageal sphincter relaxation.¹⁰ Conversely, GERD might induce bronchoconstriction. Asthmatic subjects could have increased vagal responses to acid in the esophagus, resulting in bronchoconstriction.¹¹ Microaspiration might result in airway inflammation and bronchospasm. Several animal studies have shown greater effects on airway resistance to acid infused directly into the trachea as opposed to acid infused into the esophagus; however, a study on acid infusion in adults with COPD failed to detect any changes in airway resistance.¹²

Although there is a clear association between IPF and GERD, a causal relationship is not clear.¹³ IPF is characterized by inflammation and fibrosis of the alveolar septae and terminal bronchioles and is believed to be immune mediated, with activation of proinflammatory cytokines resulting in fibroblast proliferation and scarring. A variety of factors, such as smoking, occupational exposures, viruses, and GERD, have been associated with IPF. The lack of

inflammation or injury in more proximal airways suggests that direct contact with refluxed material does not result in alveolar injury and inflammation. Rather, the refluxate might induce an immune response mediated by inflammatory cytokines targeting the alveoli.

Several studies have shown that antireflux medication or surgical intervention can alleviate respiratory disorders in certain patients. In patients with GERD (documented by means of pH probe) and respiratory symptoms consisting of chronic cough or asthma, 71% have good control of their respiratory symptoms after medical antireflux therapy.¹⁴ In a randomized controlled study of selected asthmatic patients, patients treated with medication or antireflux surgery required less asthma medication and had improved symptoms compared with those receiving placebo. Furthermore, there was evidence that those patients treated with surgical intervention had the greatest benefit. Fifty percent of patients treated with antireflux surgery in this study versus only 5% of patients treated with placebo had no respiratory symptoms at 6 years.¹⁵ In another study improvement in asthma was seen in 75% of patients who underwent Nissen fundoplication but in only 9% of patients who were treated medically. The asthma score improved 43% in the surgical group versus only 10% in the medical group.¹⁶

The greatest impediment to long-term survival after lung transplantation is chronic rejection consisting of inflammation and fibrosis of the small airways, a process termed obliterative bronchiolitis. This chronic bronchial injury is believed to be immune mediated. It is unclear what role chronic reflux of gastric contents, acid, or both into the bronchial tree might play in this process. A recent study of laparoscopic fundoplication after lung transplantation demonstrated a decrease in the incidence of bronchiolitis obliterans syndrome in patients who underwent the procedure after transplantation. Patients undergoing lung transplantation who had reflux determined by means of pH study and who underwent laparoscopic Nissen fundoplication demonstrated a 24% improvement in percent predicted FEV₁.⁴ Because the diagnosis of bronchiolitis obliterans syndrome is largely determined by a decrease in FEV₁ not attributable to other causes, the incidence of this clinical syndrome was lower in these patients, although it is not clear if the underlying process of chronic rejection was altered.

A follow-up retrospective study at the same institution noted that the incidence of posttransplantation reflux, as determined by means of pH probe, was 76%. They further divided the posttransplantation laparoscopic Nissen group into those antireflux procedures done early (ie, within 90 days) after transplantation and those done late after transplantation. In the 14 patients who underwent early fundoplication, 3-year survival was 100%, whereas 3-year survival was 86% in patients with reflux and late surgical intervention and 69% in patients with reflux and no surgical

intervention. Freedom from bronchiolitis obliterans syndrome at 3 years was 100% in the group undergoing early surgical intervention compared with 60% in patients with reflux and no surgical intervention and 47% in patients with reflux and late surgical intervention.⁵ Thus there is reasonable evidence to support the notion that prophylactic surgical fundoplication soon after transplantation or even before transplantation might prevent the decrease in lung function often seen after transplantation.

An antireflux procedure before transplantation might offer several advantages. First, this procedure offers immediate protection from the effects of reflux on the potential decrease in lung function after transplantation. Second, there is the potential benefit of reducing the risk of perioperative aspiration and pneumonia. In instances of perioperative aspiration and respiratory failure, some surgeons have even advocated performing a Nissen procedure before extubation. Our approach might avoid this difficult situation. Third, a large percentage of patients with IPF have reflux, and progression of their disease might, in part, be due to the effects of acid aspiration on the native lungs. Fundoplication in these patients or even in patients with early usual interstitial pneumonia might halt disease progression.

Although it has been argued that patients with GER and end-stage lung disease are at high risk for reflux surgery, our series demonstrates that laparoscopic Nissen fundoplication can safely be performed in this group of patients before transplantation. There were no serious complications after laparoscopic fundoplication in these 19 patients, despite their poor lung function (average preoperative FEV₁ of 55% of predicted value and average DLCO of 35% of predicted value). The average length of stay was 3.5 days, and no patient was in the hospital longer than 6 days. Four patients died before transplantation. There was no association between surgical intervention and their deaths. These patients had some of the lowest DLCO values in the group and clearly had advanced IPF. The variability in getting an appropriately matched lung allograft in time for a given patient with IPF is such that we are not able to recommend a cutoff as to who should not be offered fundoplication before surgical intervention.

There are isolated reports of improvement after antireflux procedures in patients with interstitial lung disease. Overall, the patients undergoing fundoplication in our series showed no significant decrease in lung function or increase in oxygen requirements. When the patients with IPF undergoing fundoplication (14 of the total 19 patients undergoing fundoplication) were retrospectively compared with patients with IPF on the transplant waiting list who had not undergone fundoplication, a highly statistically significant difference was seen in oxygen requirements over time. Patients with IPF undergoing Nissen fundoplication showed a decrease in the average oxygen requirement from 3.0 to 2.5

L/min, whereas the control patients with IPF showed an increase in the average oxygen requirement from 2.0 to 3.0 L/min ($P = .002$). No significant differences were noted in lung function tests or 6-minute walk distances, possibly because the follow-up interval for these tests to date is shorter, and it might take time for differences to become apparent. Further follow-up might or might not reveal differences in these parameters over time.

A limitation of this retrospective study is that not all patients had complete preoperative and postoperative pulmonary function test, 6-minute walk, and oxygen data recorded. It should be emphasized that this study is not randomized, and the experimental and control groups are not equal. The patients undergoing Nissen fundoplication were, for the most part symptomatic, whereas the control patients were largely asymptomatic. The patients undergoing Nissen fundoplication in all likelihood had a higher incidence of reflux and more severe reflux, but this cannot be known without 24-hour pH-probe testing in all patients.

Likewise, we are considering obtaining post-Nissen pH/manometric studies in all patients. Although no patients complained of postoperative heartburn or regurgitation, most were on acid-suppressive therapy because of associated corticosteroid use. This therapy can mask symptoms of an inadequate repair and allows for nonacid reflux. Any potential benefits of fundoplication on lung function will only be seen if the repair effectively reduces reflux.

We believe that because of prior reports of a high incidence of asymptomatic reflux in patients with IPF³ and because of the positive findings of this study, every patient with IPF on the waiting list should be considered for 24-hour pH-probe screening. There is reason to believe that if correction of reflux improves or stabilizes lung function in those with end-stage lung disease, correction earlier in the course of the disease (ie, at time of diagnosis of IPF) might be more effective in preventing deterioration of lung function. A prospective, randomized, 3-armed trial comparing maximal medical therapy, placebo, and surgical therapy would be necessary to evaluate the effect of intervention on underlying lung disease.

Conclusion

There is a high incidence of symptomatic and severe GERD in patients with IPF. The severity of GER correlates with the degree of preoperative oxygen dependence. Laparoscopic surgical fundoplication can be performed safely in these patients and patients with other end-stage lung diseases awaiting lung transplantation. No patient had recurrent symptoms of discomfort or reflux, and no patient who underwent complete fundoplication experienced aspiration around the time of lung transplantation. With a mean follow-up of 15 months, exercise capacity and lung function in those who underwent postoperative testing showed no significant decrease. When

compared with a control group of patients with IPF on the waiting list who did not undergo transplantation, there was an improvement in the oxygen requirement of the patients treated with fundoplication. The role of GER in the progression of underlying lung disease is not clear, and a randomized study is needed to define any benefit of surgical fundoplication in these patients.

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Discussion

Dr Pasquale Ferraro (Montreal, Quebec, Canada). Congratulations, Dr Linden, on a fine presentation. Your group certainly has to be commended on doing these types of operations in high-risk patients.

I have a number of comments before moving on to the questions. First of all, I reviewed this article not only from the per-

spective of an esophageal surgeon but also that of a lung transplantation surgeon. A number of recent studies have provided thought-provoking data on nonalloimmune injury with the possible association between reflux disease and bronchiolitis obliterans. We all know that 50% of our patients undergoing lung transplantation have bronchiolitis obliterans on long-term follow-up, despite improved immunosuppression, decreased incidence of acute rejection, and better lung preservation. The pioneering work of Davis and colleagues from Duke has provided fascinating insight. To date, however, much of the data have been incomplete or inconclusive for a number of reasons. Studies are retrospective in nature; sample sizes are small; data comparing preoperative and postoperative esophageal assessment, including endoscopic results, have not been provided; comparison with effective medical therapy has not been carried out; and long-term follow-up is not available. Nonetheless, the development of bronchiolitis obliterans and its devastating effect on the patient's quality of life and long-term survival certainly warrants a serious look at measures for controlling reflux disease after transplantation. Whether it should be done in patients on a waiting list before transplantation is a more important question rather than trying to establish its feasibility from a technical standpoint.

My first question is this. When looking at the data, the patients in your series do not appear to be severely compromised, with close to 40% not requiring oxygen and having a mean FEV₁ of 54%. How are patients selected with respect to the severity of their lung disease? Would high oxygen requirements or moderate pulmonary hypertension be a contraindication? Does this not represent an important selection bias?

Dr Linden. Thank you for your comments. We selected patients for operation as they were initially placed on the waiting list. They were evaluated for symptoms, and if they had persistent symptoms despite proton pump inhibitor therapy and were found to have a positive pH test result, they underwent laparoscopic fundoplication surgery. Therefore in a sense these represent patients at the end stage of lung disease but at the earliest stage on the waiting list. Some patients had significant oxygen requirements (ie, 4, 5, 6, and even 8 L/min for some), and they all met the criteria to be on the waiting list. Therefore they all did have significant impairments of lung function, even though they might have been just placed on the waiting list.

Dr Ferraro. How can you discuss surgical results of fundoplication without providing and comparing preoperative and postoperative data on pH studies, manometry, and endoscopic findings? Are symptoms alone a reliable indicator of reflux disease in this type of patient?

Dr Linden. You are correct in that the majority of patients with end-stage lung disease might actually have reflux without symptoms. We initially started out being as conservative as possible in picking out only those patients with the most severe reflux to fix. All of these patients were symptomatic before the operation, and after the operation, they did not have any classical symptoms of heartburn or regurgitation. Therefore I agree with you that it would be best to have prefundoplication and postfundoplication 24-hour pH-probe data, but because they were symptomatic preoperatively, we chose to follow symptoms postoperatively.

Dr Ferraro. In your conclusion you state, and I quote, "Lung function and exercise capacity showed no significant decrease after

fundoplication." Is it possible that the natural course of the disease, especially in COPD, or that a change in medical management, such as the use of prednisone or immunosuppressive agents, is responsible for this?

Second, 20% of the patients operated on still died before transplantation, which is not unlike the rate that is generally reported for patients on waiting lists in North America. How did the 130 patients who did not undergo fundoplication evolve?

Dr Linden. The vast majority of our patients had IPF. Immunosuppressive therapy, at least with steroid therapy, has been shown to have no effect on progression of underlying disease. This was really a feasibility study to show that it can be done safely in these patients. To really say that this operation improves the underlying lung function of the patient, one needs a randomized controlled study. Therefore I would agree with you in that regard.

Dr Steven R. DeMeester (*Los Angeles, Calif*). I congratulate you on a very interesting and nice presentation.

This certainly is a fascinating area. One thing that always is questionable, though, is whether we are looking at the chicken or the egg. We know that severe pulmonary disease can induce reflux; likewise, reflux can induce pulmonary disease. Do you have any insight into some of these patients? Is this chicken or egg in these patients? In other words, did you look and see how many had symptoms predating the onset of their significant pulmonary dysfunction in terms of reflux symptoms?

Dr Linden. That is a very good question. No, we did not try to elicit which symptoms came first. It is interesting to note that in the patients with IPF, it did not seem to be a motility problem in the esophagus. They all seemed to have normal manometric results, unlike some patients with scleroderma, in whom the esophagus and the lung might both be affected, and all of them had very low esophageal sphincter tone, maybe elucidating something about the mechanism, but we do not have any insights as to which causes what in patients with IPF.

Dr DeMeester. In terms of the mechanism, it is pretty well demonstrated, and we have some articles out, that the pressure gradient increases significantly when you have pulmonary disease in terms of the pressure gradient between thoracic and abdominal components, and therefore the difficult respiration leads to a large pressure gradient, which can induce reflux. Along those lines, one way also to get a sense of the severity or the longevity of the reflux disease is to look at complications of reflux disease in these patients. Did any of them have severe esophagitis, strictures, or Barrett's esophagus, which would suggest long-standing reflux disease?

Dr Linden. All patients underwent esophagogastroduodenoscopy, and Barrett's esophagus was not seen in any of the patients, I do not believe, nor was significant stricture. Probably a minority of them did have some evidence of esophagitis, but as far as severe sequelae of esophagitis, I do not think we found many with severe sequelae of esophagitis.

Dr R. Duane Davis, Jr (*Durham, NC*). I rise to congratulate you on an excellent presentation.

Again, I think the concern I have is just the appropriate control in terms of the fact that we know that the natural history in most of the patients who are referred with pulmonary fibrosis is fairly dismal, particularly once they get to an FEV₁ of about 50%. Anecdotally, I will say that when we have intervened earlier than

that, they seem to have a natural history completely different from the expected course. Therefore I would say that you really do need to kind of look at what your natural history is of the patients and try to do a case-control study.

The patient that you wrapped with a Toupet, I understand the rationale for doing it. Was the aspiration event actually something that you thought was coming from the stomach, or do you think this was something that was more of a primary esophageal problem?

Dr Linden. That is a very good question because aspiration can be a multifactorial event, and in fact, this patient underwent a video swallow after the event and was noted to have swallowing dysfunction. Therefore it is not clear in this patient whether his aspiration event was from swallowing dysfunction or from persistent reflux by an incomplete wrap. Both could have contributed.

Dr Toni Lerut (*Leuven, Belgium*). This was an excellent presentation.

You have 19 patients on whom you operated. How many of that series were receiving medical treatment? What was your policy? Did you operate on the basis of high-volume reflux with possible aspiration, or was it more on the symptomatic failure of the medical treatment? What is your policy in deciding between the indication for surgical intervention versus medical treatment?

Dr Linden. Well, to date, we have only operated on patients who were symptomatic and who were symptomatic despite proton pump inhibitor therapy and were shown to have a positive 24-hour pH study result. Therefore in a sense, all of these patients met the classical criteria for fundoplication. Now whether those criteria should be expanded in the future is something to think about and discuss.