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The Prevalence and Extent of Gastroesophageal Reflux Disease Correlates to the Type of Lung Transplantation

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Abstract

Background—Evidence is increasingly convincing that lung transplantation is a risk factor of gastroesophageal reflux disease (GERD). However, it is still not known if the type of lung transplant (unilateral, bilateral, or retransplant) plays a role in the pathogenesis of GERD.

Study Design—The records of 61 lung transplant patients who underwent esophageal function tests between September 2008 and May 2010, were retrospectively reviewed. These patients were divided into 3 groups based on the type of lung transplant they received: unilateral (n=25); bilateral (n=30), and retransplant (n=6). Among these groups we compared: (1) the demographic characteristics (eg, sex, age, race, and body mass index); (2) the presence of Barrett esophagus, delayed gastric emptying, and hiatal hernia; and (3) the esophageal manometric and pH-metric profile.

Results—Distal and proximal reflux were more prevalent in patients with bilateral transplant or retransplant and less prevalent in patients after unilateral transplant, regardless of the cause of their lung disease. The prevalence of hiatal hernia, Barrett esophagus, and the manometric profile were similar in all groups of patients.

Conclusions—Although our data show a discrepancy in prevalence of GERD in patients with different types of lung transplantation, we cannot determine the exact cause for these findings from this study. We speculate that the extent of dissection during the transplant places the patients at risk for GERD. On the basis of the results of this study, a higher level of suspicion of GERD should be held in patients after bilateral or retransplantation.

Keywords

gastroesophageal reflux disease (GERD); laparoscopic antireflux surgery; esophageal function testing; lung transplantation

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The prevalence of gastroesophageal reflux disease (GERD) in lung transplant patients is twice that of the general population, yet it is unclear which pathophysiological factors play a role in the development or exacerbation of GERD in these patients.¹⁻⁴ It has been speculated that the lung transplantation itself might be causative in the pathogenesis of GERD after lung transplantation, probably by increasing the risk of esophageal or vagal nerve injury or by increasing the transdiaphragmatic gastroesophageal pressure gradient.^{1,2} For example, Young et al² demonstrated that GERD worsens after lung transplantation, reporting that the mean esophageal acid contact time in the supine position before and after transplant doubled from 5.1% to 11.4%. However, they failed to demonstrate that the type of transplant may be responsible for the deterioration of the reflux profile in these patients. Conversely, in a small study that we conducted to determine the prevalence and extent of GERD, as well as the frequency of risk factors and complications of GERD in lung transplant patients, we incidentally found that GERD was more common after bilateral transplantation and retransplantation than after a unilateral lung transplant.¹ Therefore, to understand if the type of transplant may lead more frequently to GERD and proximal reflux, we have investigated the prevalence of distal and proximal reflux, as well as the radiologic, endoscopic, and manometric characteristics, in a much larger series of lung transplant patients, which have been stratified according to the type of transplant received (unilateral, bilateral, or retransplant).

PATIENTS AND METHODS

Sixty-one consecutive patients underwent a combination of esophageal function testing (esophageal manometry and dual-sensor pH-monitoring), upper endoscopy, and barium swallow after unilateral lung transplantation, bilateral lung transplantation, or retransplantation.

Esophageal Manometry

From September 2008 to September 2009, lung transplant patients underwent esophageal high-resolution impedance manometry using a 32-channel solid state catheter (insight HRIM system with BioVIEW software; Sandhill Scientific Inc., Highlands Ranch, CO) with 4 active impedance channels located at 5, 10, 15, and 20 cm above the high pressure zone of the lower esophageal sphincter (LES). Since September 2009, all patients underwent esophageal function testing with a Koenigsberg 9-channel solid state catheter (Sandhill EFT catheter; Sandhill Scientific Inc.) with 5 pressure sensors spaced 5 cm apart. The LES was identified by using a pull-through technique (normal LES pressure: 10 to 45mm Hg); the esophageal body function was assessed after the patients performed 10 serial swallows with 5mL of normal saline (liquid swallows), each separated by 20 seconds. The amplitude, duration, and velocity of the peristaltic waves were recorded. Peristaltic wave amplitude was calculated for the distal esophagus [distal esophageal amplitude (DEA)] based on data from pressure sensors located 5 and 10 cm above the LES. Esophageal motility was considered normal on manometry if normal peristaltic waves were present in >80% of the swallows with DEA<180mm Hg. Ineffective esophageal motility (IEM) was defined when DEA was <30mm Hg or when >30% simultaneous waves were present in the distal esophagus.⁵

Ambulatory pH Monitoring

All patients were asked to stop proton pump inhibitors for 14 days and histamine H₂-receptor antagonists for 3 days before pH-monitoring. A dual-sensor pH catheter (Sleuth system with BioVIEW software; Sandhill Scientific Inc.) was passed through the nose and the 2 pH sensors were positioned 5 and 20 cm, respectively, from the manometrically determined upper border of the LES. This allowed for pH measurements in the distal (5cm above the LES) and proximal esophagus (20 cm above the LES). The DeMeester score was

calculated for the distal pH recordings and a score >14.7 was considered abnormal.⁶ Proximal reflux was defined as >1% total time that pH<4 as recorded at the proximal sensor (located 20 cm above the LES).⁷

Upper Endoscopy

An upper endoscopy with biopsies of the gastroesophageal junction was performed in patients with GERD. The definitive confirmation of Barrett metaplasia was obtained by pathologic interpretation of the endoscopic biopsies. The degree of dysplasia was classified as the following: negative for dysplasia, indefinite for dysplasia, lowgrade dysplasia, or high-grade dysplasia.⁸

Barium Swallow

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

Gastric Emptying Scan

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

Statistical Analysis

Tests of statistical significance were conducted with SPSS Statistical Software, version 16 (SPSS, Chicago, IL). The χ^2 test for association was used for differences in groups on categorical variables, and the Mann-Whitney *U* test was used for scaled variables. Results are reported as percentages for categorical variables and as median (with interquartile range) for scaled variables. A difference between observed variables was considered statistically significant when *P*<0.05. This study was approved by the Loyola University Medical Center Institutional Review Board.

RESULTS

The records of 61 consecutive lung transplant patients who underwent esophageal function tests between September 2008 and May 2010 were retrospectively reviewed. These patients were divided into 3 groups based on the type of lung transplant they received: unilateral (*n*=25), bilateral (*n*=30), and retransplant (*n*=6). Among these groups we compared: (1) the demographic characteristics (eg, sex, age, race, and body mass index); (2) the presence of Barrett esophagus, delayed gastric emptying, and hiatal hernia; and (3) the esophageal manometric and pH-metric profile.

Demographics

All groups were composed of patients with similar sex and race. Bilateral and retransplanted patients were younger and had a leaner body habitus than patients with a unilateral transplant (Table 1). Unilateral and bilateral transplant patients had a similar median time since transplant. Patients who were retransplanted predictably had a longer median time since their first transplant than those who received unilateral and bilateral transplant (Table 1). In addition, patients with unilateral and bilateral transplants with GERD had a shorter median time since their first transplant than those without GERD (Table 4). However, these

differences were not statistically different within and among the groups. The distribution of the underlying end-stage lung disease was similar among all groups (Table 2).

Relationship Between Prevalence and Extent of GERD and Type of Transplantation

The relationship between the prevalence and extent of GERD and the type of lung transplantation is illustrated in Figures 1 and 2. Patients who received a unilateral lung transplant were less likely to have GERD. Specifically, 24% of patients with a unilateral transplant had GERD compared with 63% of patients with a bilateral lung transplant and 100% of patients who had been retransplanted (Fig. 1). Figure 2 shows the prevalence of proximal GERD among groups. Patients who received a unilateral lung transplant were less likely to have proximal GERD, compared to those with a bilateral lung transplant or retransplant (24% vs. 52% vs. 50%; $P<0.05$).

Esophageal Manometry

Patients in all groups had a similar prevalence of hypotensive LES (12%, 14%, and 17% of those with unilateral, bilateral, and retransplants, respectively) and a similar prevalence of IEM (16%, 18%, and 33% of those with unilateral, bilateral, and retransplants, respectively). Although the DEA was lower in patients who had been retransplanted (median DEA: 47mm Hg) than in those with bilateral (median DEA: 63mm Hg) or unilateral transplants (median DEA: 83mm Hg), these differences were not statistically different (Table 3). Likewise, patients in all groups had similar LES resting pressures and total and abdominal LES lengths (Table 3). When we analyzed the manometric profile in patients with and without GERD stratified according to the type of transplant, we found similar LES-resting pressures in patients with or without GERD in each category of lung transplant (Table 4). However, we found a lower DEA and a higher prevalence of IEM in bilateral and retransplants with GERD compared with unilateral transplants with GERD. However, these differences were not statistically different.

Ambulatory pH Monitoring

The analysis of the pH-metric profile in patients with GERD stratified according to the type of transplant showed a worse DeMeester score and a greater total time $\text{pH}<4$ in retransplant patients compared with that of unilateral or bilateral transplants, although this difference was marginally significant ($P=0.06$) (Table 5). In addition, the analysis of the proximal reflux profile showed a higher severity of proximal GERD in retransplanted patients compared with those with unilateral or bilateral transplants, as shown by the greater total time $\text{pH}<4$ in retransplanted patients than in patients of other groups (Table 6).

Other Tests

Among those patients who had a barium swallow, only 1 patient with a unilateral transplant (or 12%), 3 patients with a bilateral transplant (or 19%), and 3 patients who had been retransplanted (or 50%) demonstrated a hiatal hernia. Only 1 patient with a bilateral transplant had a moderate size hiatal hernia, and the hernia was small in all other cases. These differences were not statistically different.

The prevalence of delayed gastric emptying was 32%. Specifically, among those patients who had a gastric emptying study, 1 patient with a unilateral transplant (or 20%), 4 patients with a bilateral transplant (or 35%), and 1 patient who had been retransplanted (or 33%) demonstrated delayed gastric emptying. Moreover, the prevalence of delayed gastric emptying was higher in bilateral and retransplants with GERD compared with unilateral transplants with GERD (Table 4). These differences were not statistically different.

The overall prevalence of biopsy-confirmed Barrett esophagus was 19%. Among those patients who had an upper endoscopy, 2 patients with a unilateral transplant (or 20%), 4 patients with a bilateral transplant (or 19%), and 1 patient who had been retransplanted (or 17%) demonstrated biopsy-confirmed Barrett esophagus. These differences did not vary significantly. Only 1 transplant patient who had been retransplanted had a long (5 cm) segment Barrett esophagus. None of the patients had dysplasia.

DISCUSSION

It has been speculated that lung transplantation might play a role in the pathogenesis of GERD in these patients. However, the literature on this topic is limited and inconsistent.

In 2003, Young et al² noted by 24-hour pH monitoring that the frequency of abnormal acid contact increased from 35% before lung transplantation to 65% after lung transplantation; yet, they could not explain these findings by esophageal manometry or gastric emptying studies. For example, the frequency of delayed gastric emptying posttransplantation was paradoxically higher in those with negative as opposed to positive testing for GERD (57% vs. 33%, respectively). The authors also reported that the type of lung transplant had no effect on the risk of posttransplant GERD, although this observation may have been limited by the smaller study size of 23 total patients, of which only 5 underwent a unilateral lung transplant.² Likewise, Davis et al,⁹ in their study directed at studying the impact of fundoplication on the pulmonary function of lung transplant patients with GERD, noted that the frequency of GERD seemed unaffected by the type of transplant, although there is no mention of patients having undergone a retransplant.

In contrast to the findings of Young and colleagues and Davis and colleagues, we have previously found that GERD seemed to be more frequent in those who had undergone bilateral or retransplantation.¹ The present study, which incorporates greater than twice the number of patients, confirms that those patients with a bilateral lung transplant or a retransplant more commonly have GERD than those with a unilateral lung transplant and shows that proximal reflux is more frequent and severe in those after bilateral or retransplantation. The importance of this finding is that proximal GERD may have profound implications for the lung transplant recipient as GERD and aspiration have been implicated in the development of bronchiolitis obliterans syndrome.^{3,4,9-11}

Unfortunately, the precise reasoning behind the observed discrepancy in prevalence of GERD in patients with different types of lung transplantation remains elusive. For instance, typical risk factors for GERD such as obesity, hypotensive LES, transient LES relaxations, and hiatal hernia seem less relevant to GERD in lung transplantation, and these factors do not explain the increased frequency of proximal and distal reflux after bilateral or retransplantation as evidenced by our study.^{1,2,4,12} Therefore, other mechanisms may be involved in the pathogenesis of GERD in these patients, such as iatrogenic vagal nerve disruption or an increased transdiaphragmatic gastroesophageal pressure gradient. Our study was not aimed at identifying a difference in gastroesophageal pressure gradients between types of lung transplants. Furthermore, our results do not rule out the possibility of vagal nerve damage in patients with a more extensive dissection (such as patients with bilateral transplants or retransplants), which is a concern previously raised as a risk factor for GERD in early studies on combined heart-lung transplantation.^{13,14} The authors of these studies concluded that there was evidence for vagal nerve disruption after heart-lung transplantation, manifesting itself as esophageal dysmotility and delayed gastric emptying. Along these lines, we have previously shown that lung transplant patients with GERD had lower amplitudes of esophageal contractions, worse esophageal motility, and more delayed

esophageal acid clearance as compared with lung transplant recipients without GERD, which may be suggestive of disrupted vagal innervation.¹

Our present study supports these earlier suspicions, as we have found that patients with GERD after bilateral or retransplantation tend to have more delayed gastric emptying, impaired esophageal motility, and delayed esophageal acid clearance than those who had received a unilateral lung transplant. For instance, the median DEA after bilateral and retransplantation was nearly 50% lower than that of unilateral lung transplant patients with GERD (47 vs. 81mm Hg, respectively). In addition, IEM was approximately twice as prevalent in those with GERD after bilateral and retransplantation as compared with unilateral transplants (32% and 40% vs. 17%, respectively), and delayed gastric emptying was also more common after bilateral and retransplantation. Although these results did not reach statistical significance after having stratified the patients into 6 groups, they are in line with the significant findings of our earlier study.

Taken together, the impact of these results may be greater in light of a recent study by Mertens et al.¹⁵ The authors of this study deduced a reduction in GERD and aspiration by restoring gastric and esophageal motility with azithromycin, a macrolide antibiotic. They reported that lung transplant patients receiving azithromycin had substantially less total reflux events ($P=0.012$), less proximal extent of reflux ($P=0.0086$), and less bile acids in their bronchoalveolar lavage fluid ($P=0.011$) than those not taking azithromycin. These findings may imply that iatrogenic vagal nerve injury, by way of impairing gastric and esophageal motility, might be causative of the differences in GERD frequency between the types of lung transplants.

This study confirms that all lung transplant recipients should be regarded as high risk for GERD, particularly those who have undergone bilateral or retransplantation. Given the growing body of literature suggesting a detrimental impact of GERD on pulmonary allograft function, the utility of laparoscopic antireflux surgery in these patients seems increasingly important. We recommend aggressive screening and early laparoscopic antireflux surgery in patients with objective evidence of GERD. Regarding the therapeutic value of proton pump inhibitors (PPIs) and motility agents before laparoscopic antireflux surgery, studies have shown that treatment with PPIs after lung transplantation reduced acid reflux but did not affect nonacid reflux.¹⁶ Moreover, gastric juice from patients “on PPIs” can still provoke a significant inflammatory reaction in bronchial epithelial cells.¹⁷ Therefore, PPIs may not be sufficient to prevent GER and aspiration in these patients. Conversely, motility agents (metoclopramide and azithromycin) might be helpful before surgery because of their different mechanism of action in preventing GERD. Motility agents can increase the gastric emptying rate and reduce weakly acidic GER especially during the night. However, it has been shown that bile acid aspiration reduces survival in lung transplant recipients with BOS despite azithromycin.¹⁸ Therefore, although advocated in the treatment of GERD, no recommendations on the use of motility agents can be made until further studies confirm their therapeutic value.

We acknowledge that our study is limited by the absence of pretransplant data for comparison. However, many of patients on the lung transplant list are very debilitated with a large oxygen requirement at rest and unable to tolerate esophageal function tests. Therefore, the collection of some data is often impractical before transplantation. Another limitation is lack of data on the prevalence and time to onset of bronchiolitis obliterans syndrome after each type of lung transplant. In addition, multiple levels of stratification limited the statistical analysis of manometric findings. Therefore, these assessments must be left to future studies with a larger cohort size and longer period of follow-up. Finally, as all patients in this study were “off PPIs,” we cannot predict if these findings were to be considered

clinically relevant if GERD was equal among groups and all patients had been “on PPIs.” The literature does suggest that there is a higher detection rate of reflux (acid and nonacid) with pH-impedance compared with pH monitoring.¹⁹ One study reported that 27% of lung transplant patients had exclusively increased nonacid reflux.¹⁶ However, like pH monitoring, pH impedance does not diagnose aspiration, but gives us only an imprecise estimate of its risk. Studies that have tried to correlate and quantify the predictive role of pH-impedance to the risk of aspiration are scarce. Only 1 study has shown that only nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients.²⁰

CONCLUSIONS

Our data show a discrepancy in prevalence of GERD in patients with different types of lung transplantation, although we cannot determine the exact cause for these findings from this study. We speculate that the extent of dissection during the transplant places the patients at risk for GERD and proximal reflux. As we conclude that all lung transplant recipients, especially those who have undergone bilateral or retransplantation, should be considered as high risk for GERD, we advocate screening with esophageal function tests and early laparoscopic antireflux surgery in patients with GERD on pH monitoring, as the usefulness of PPIs is limited and that of motility agents is largely unconfirmed.

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FIGURE 1.
Prevalence of gastroesophageal reflux disease among groups.

* $p < 0.05$, Bilateral vs. Unilateral

** $p < 0.05$, Re-transplant vs. Unilateral

FIGURE 2.

Prevalence of proximal gastroesophageal reflux disease among groups.

TABLE 1**Demographics**

	Unilateral	Bilateral	Retransplant
Patients (%)	25 (41%)	30 (49%)	6 (10%)
Sex (%)			
Males	10 (40%)	20 (67%)	3 (50%)
Females	15 (60%)	10 (33%)	3 (50%)
Age (y) *	61 (58–65) [†]	51 (38–62)	50 (44–57)
Race (%)			
White: non-Hispanic	22 (88%)	27 (90%)	6 (100%)
White: Hispanic	2 (8%)	2 (7%)	—
African American	1 (4%)	1 (3%)	—
BMI *	31 (28–31) [†]	24 (22–29)	21 (19–28)
Time since first transplant (mo) *	15 (5–24)	34 (7–62)	67 (44–134) [‡]

* Data are presented as median (interquartile range).

[†] $P < 0.05$, unilateral versus bilateral and unilateral versus retransplant.

[‡] $P < 0.05$, retransplant versus unilateral and retransplant versus bilateral.

BMI indicates body mass index expressed in kg/m².

TABLE 2**Causes of End-stage Lung Diseases Among Groups**

	Unilateral	Bilateral	Retransplant
	n = 25	n = 30	n = 6
AAT deficiency	2	3	1
Cystic fibrosis	—	5	3
COPD	15	8	1
Scleroderma	—	2	—
Bronchiectasis	—	1	—
Chronic obstructive asthma	—	2	—
LAM	1	—	—
IPF	7	9	1

AAT deficiency indicates α 1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis.

TABLE 3

Manometric Profile of Patients Stratified According to the Type of Transplant

	Unilateral	Bilateral	Retransplant
LES			
LES pressure (mm Hg)	31 (25–38)	23 (16–31)	31 (18–36)
LES total length (cm)	3 (2–3)	2 (2–3)	3 (2–4)
LES abdominal length (cm)	2 (1–2)	1 (1–2)	2 (1–3)
Esophageal body DEA (mm Hg)	83 (58–115)	63 (45–106)	47 (24–67)

Data are presented as median (interquartile range).

$P < 0.05$, unilateral versus bilateral versus retransplant.

DEA indicates distal esophageal amplitude; LES, lower esophageal sphincter.

Manometric Profile, Prevalence of Delayed Gastric Emptying, and Time Since First Transplant in Patients With and Without GERD Stratified According to the Type of Transplant

TABLE 4

	Unilateral		Bilateral		Retransplant	
	GERD+	GERD-	GERD+	GERD-	GERD+	GERD-
LES pressure (mm Hg) *	30 (23-33)	32 (25-41)	18 (15-30)	24 (22-31)	31 (18-36)	N/A
DEA (mm Hg) *	81 (65-81)	96 (53-130)	47 (41-115)	79 (53-93)	47 (24-67)	N/A
IEM (% of patients)	17%	12%	32%	0	40%	N/A
Delayed gastric emptying (% of patients)	20%	N/A	35%	N/A	33%	N/A
Time since first transplant (mo)	8 (3-17)	16 (6-25)	12 (7-61)	38 (19-61)	67 [†] (44-134)	N/A

* Data are presented as median (interquartile range).

[†] P<0.05, retransplant versus unilateral and retransplant versus bilateral.

DEA indicates distal esophageal amplitude; GERD, gastroesophageal reflux disease; IEM, ineffective esophageal motility; N/A, not applicable.

TABLE 5

pH-metric Profile in Patients With GERD Stratified According to the Type of Transplant

	Unilateral	Bilateral	Retransplant
Total time pH <4 (%)	9 (9–9)	9 (7–23)	18 (14–20)*
Upright	13 (8–14)	7 (6–12)	16 (7–21)
Supine	4 (2–10)	11 (7–44)	14 (8–35)
Episodes >5 min	7 (6–8)	7 (4–13)	14 (10–17)*
Longest episode (min)	18 (17–29)	24 (15–74)	33 (26–54)
Total episodes	50 (47–63)	73 (60–91)	61 (43–105)
DeMeester score	30 (27–35)	35 (24–95)	61 (43–85)*
Mean clearance time (s)	147 (120–157)	182 (124–294)	238 (176–289)
Upright	112 (107–141)	97 (65–125)	130 (101–208)
Supine	163 (96–242)	306 (194–418)	361 (196–499)

Data are presented as median (interquartile range).

* $P=0.06$, retransplant versus unilateral.

GERD indicates gastroesophageal reflux disease.

TABLE 6

pH-metric Profile in Patients With Proximal GERD Stratified According to the Type of Transplant

	Unilateral	Bilateral	Retransplant
Total time pH <4 (%)	2 (1–3)	2 (2–3)	6 (5–7) *
Upright	2 (1–3)	2 (2–4)	3 (0–6)
Supine	0 (0–1)	2 (0–4)	0 (0–1)

Data are presented as median (interquartile range).

Normal total time pH<4 is <1%.¹⁶

* $P<0.05$, retransplant versus unilateral.

GERD indicates gastroesophageal reflux disease.