Lung Transplantation Exacerbates Gastroesophageal Reflux Disease*

Lisa R. Young, MD; Denis Hadjiliadis, MD, MHS; R. Duane Davis, MD, FCCP; and Scott M. Palmer, MD, MHS, FCCP

Introduction: A high prevalence of gastroesophageal reflux (GER) has been reported in lung transplant recipients and is possibly linked to the development of bronchiolitis obliterans syndrome. The etiology of posttransplant GER remains unknown but may occur due to the transplant operation or posttransplant medications, or represent preexisting GER disease. We evaluated these possibilities by studying the nature and severity of GER in a cohort of patients before and after lung transplantation.

Methods: Total, upright, and supine acid contact times were recorded in lung transplant recipients who underwent 24-h pH studies before and after transplantation. Patients also underwent esophageal manometry and gastric-emptying studies. Medications for acid suppression and gastric motility were discontinued before testing. Paired comparison between pretransplant and posttransplant results was performed using a paired t test.

Results: Twenty-three patients were included in the analysis. The mean age was 51.5 years, and native diseases included emphysema (n = 11), cystic fibrosis (n = 4), pulmonary fibrosis (n = 3), and others (n = 5). Posttransplant studies occurred a median of 100 days after transplantation. After lung transplantation, the total acid contact time increased a mean of 3.7% (p = 0.03) and the supine acid contact time increased a mean of 6.4% (p = 0.019). Thirty-five percent (8 of 23 patients) had abnormal acid contact times before transplant, and 65% (15 of 23 patients) had abnormal acid contact after transplant. Changes in acid contact times were not explained by changes in esophageal or gastric motility. Only 20% (3 of 15 patients) with abnormal posttransplant pH studies were symptomatic.

Conclusions: There is a significant increase in GER after lung transplantation, as measured objectively by 24-h pH studies, despite a lack of symptoms in most patients. Further research is needed to determine the physiologic mechanisms of posttransplant GER and its impact on long-term allograft function.

Key words: bronchiolitis obliterans syndrome; gastroesophageal reflux; gastroparesis; lung transplantation

Abbreviations: CF = cystic fibrosis; GER = gastroesophageal reflux; IPF = interstitial pulmonary fibrosis; LES = lower esophageal sphincter; OB = obliterative bronchiolitis

Gastroesophageal reflux (GER) is recognized as an important contributor to many pulmonary diseases, including bronchitis, asthma,1 and pneumonia.2 Patients with advanced lung disease such as pulmonary fibrosis3 and cystic fibrosis (CF)4 have also been shown to have a high prevalence of GER. GI complications are common after lung transplantation.5,6 They have included gastroparesis, diverticulitis, and GI bleeding.5,6 We have observed a high prevalence of GER in selected lung transplant recipients.7 It has previously been suggested that GER is associated with bronchiolitis obliterans syndrome.7–10 Most reports have focused on the prevalence of esophageal dysmotility and delayed gastric emptying, with inadvertent partial or total surgical vagotomy as the suspected mechanism.10,11 We have also observed that treatment of GER improved chronic allograft dysfunction in a patient with bronchiolitis obliterans syndrome.8 In order to determine whether posttransplant GER is due to a high prev-
alence of disease prior to transplantation or if it represents an effect of transplant surgery and medications, we compared pretransplant and posttransplant reflux studies in a cohort of lung transplant recipients. The study was retrospective, but the data were collected prospectively.

**Materials and Methods**

The transplant population included all patients undergoing lung transplantation at Duke University Medical Center. From 1992 to January 2001, there were 320 lung transplant operations performed. Standardized surgical techniques were used for the operations, and these are described elsewhere. Patients generally received postoperative immunosuppression with cyclosporine A (5 to 10 mg/kg/d), azathioprine (1 to 2 mg/kg/d), and corticosteroids (methylprednisolone, 125 mg q12h for the first 48 h, followed by prednisone, 20 mg/d). Since October 2000, tacrolimus (0.05 to 0.1 mg/kg/d) was used instead of cyclosporine A. Some patients received induction with rabbit antithymocyte globulin or mycophenolate mofetil instead of azathioprine as part of studies. Since January 1999 patients also received a monoclonal interleukin-2 receptor antibody (daclizumab) as induction immunosuppression. Episodes of acute allograft rejection were treated with methylprednisolone, 500 mg/d for 3 days, followed by a 2-week oral prednisone taper.

All patients at risk for cytomegalovirus infection (positive donor or recipient serology) received prophylaxis with ganciclovir. All patients received *Pneumocystis carinii* prophylaxis indefinitely. Fungal infection prophylaxis consisted of nystatin swish and swallow for the first 6 months after transplantation. In addition, aerosolized amphotericin B (either liposomal or conventional) was administered for at least 2 weeks after transplant. Vancomycin and ceftazidime were used for bacterial infection prophylaxis the first 2 weeks after transplant. In patients with septic lung disease, antibiotic choice was individualized and guided by pretransplant culture results. Further information is provided in previous studies.

Twenty-four-hour pH testing, esophageal manometry, and gastric-emptying studies both before and after transplantation were performed. Medications for acid suppression and gastric motility were appropriately discontinued prior to testing. Esophageal motility and pH studies were performed in standard fashion. Ambulatory esophageal pH monitoring was carried out using a monopolar antimony electrode with a single pH sensor as positioned by manometry. Results were based on values from this distal esophageal probe, as this correlated well with the results from the proximal probe in a selected sample of patients. Patients strictly recorded any symptoms of heartburn, dyspnea, cough, nausea, or chest pain, and recorded their position as upright or supine during the study. The percentage of time the esophageal probe measured a pH of < 4 was recorded for each patient over the 24-h study period. Symptoms of reflux and cough that were reported during the study were correlated with events on the pH probe. Solid gastric emptying was evaluated scintigraphically, using oral administration of radioactive oatmeal, containing technetium-99mTc-labeled sulfur colloid. Normal studies were defined by at least 50% emptying within 90 min. Abnormal acid contact was defined by pH < 4 in the distal esophagus, with normal values defined as < 3% for supine acid contact time, < 8% for upright acid contact time, and < 5% for total acid contact time. The normal values for our laboratory were determined by locally testing normal healthy subjects. Total acid contact time is a composite of the supine and the upright contact times. The percentages of times spent at each position for each patient are not reported individually.

All adult lung transplant recipients who underwent pretransplant and posttransplant testing within the past 2 years were included in the analysis. Because of transplantation prior to scheduling of pretransplant reflux studies, patient refusal to undergo testing, or postoperative death prior to repeat studies, approximately only 20% of all patients who underwent transplantation during this time were eligible for analysis. All patients were tested while in stable condition without ongoing infection or rejection, and were receiving prednisone, 15 to 20 mg/d.

Descriptive studies were used for demographic data. The χ² test was used for categorical variables. Comparison between pretest and posttest results was performed using paired difference t test because the data appear to be normally distributed. Subgroup analysis of the upright and supine acid contact times was performed because the differences in total acid contact times were significant.

**Results**

A total of 23 of 137 patients (16.8%) underwent both pretransplant and posttransplant reflux studies at the time of this analysis. The demographic characteristics of the patient population are displayed in Table 1. The mean patient age was 51.5 years, and a majority of the patients were female and underwent bilateral lung transplantation. Pretransplant studies were performed a median of 66 days prior to transplant (range, 1 to 443 days), and posttransplant studies occurred a median of 100 days after transplantation (range, 47 to 248 days). The patients who did not undergo reflux studies had the following baseline characteristics: (1) age, 47.1 ± 14.4 years (mean ± SD); (2) bilateral lung transplant (38 of 114 patients; 33.3%); (3) male gender (51 of 114 patients; 44.7%); and (4) pretransplant diagnosis of COPD (56

### Table 1—Patient Characteristics, Symptoms of GER, and Timing of GER Studies*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean recipient age, yr</td>
<td>51.5 ± 11.9</td>
</tr>
<tr>
<td>Female gender</td>
<td>14/23 (61)</td>
</tr>
<tr>
<td>Native disease</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>12 (52)</td>
</tr>
<tr>
<td>CF</td>
<td>4 (17)</td>
</tr>
<tr>
<td>IPF</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Others (LAM, PVOD, bronchiectasis, sarcoidosis)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Type of transplant</td>
<td></td>
</tr>
<tr>
<td>Single lung</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Bilateral lung</td>
<td>18 (76)</td>
</tr>
<tr>
<td>Median time of posttransplant testing (range), d</td>
<td>100 (47–248)</td>
</tr>
<tr>
<td>Patients with asymptomatic GER pretransplant</td>
<td>6/8 (75)</td>
</tr>
<tr>
<td>Patients with asymptomatic GER posttransplant</td>
<td>12/15 (80)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD, No./total (%), or No. (%) unless otherwise indicated. LAM = lymphangioleiomyomatosis; PVOD = pulmonary venoocclusive disease.
of 114 patients; 49.1%), CF (23 of 114 patients; 20.2%), idiopathic pulmonary fibrosis (IPF) [13 of 114 patients; 11.4%], and other (22 of 114 patients; 19.3%). The two groups of patients (with and without GER studies) were not statistically different in their baseline characteristics.

Acid contact time by 24-h pH probe was compared for each patient before and after transplantation. As shown in Table 2, the total acid contact time increased a mean of 3.7% after transplantation (interquartile range, −1.8% to +8%; p = 0.035) for the cohort of patients. The greatest increase in acid contact time occurred when patients were in the supine position (mean, 6.3%; interquartile range, −0.8% to +16.7%; p = 0.019). The mean supine acid contact time was abnormal before transplant (5.1%) and it doubled after transplant (11.4%). In contrast, mean upright acid contact time only increased slightly. There were no differences on acid contact time change based on the timing of the reflux studies.

Figures 1, 2 display the change in supine and upright acid contact times, respectively, before and after transplantation, for each of the patients in the cohort. Eight of the 23 patients (34.8%) had abnormal acid contact times prior to transplantation. The number of patients with abnormal acid contact times increased to 15 of 23 patients (65.2%) on 24-h pH probe study after lung transplantation (p = 0.075). The presence of GER before transplantation appeared to predict posttransplant GER, as all patients with pretransplant GER still had abnormal acid contact times after lung transplantation. An additional seven patients had completely normal pH studies before transplantation but acquired GER after transplantation.

These findings were not explained by changes in esophageal or gastric motility, as based on manometry and gastric-emptying studies. Of the 15 patients with posttransplant reflux, only 5 patients had delayed gastric emptying (33%), and only 2 others had incomplete relaxation of the lower esophageal sphincter (LES) on manometry testing. However, of the seven patients who had no evidence of GER before or after transplantation, four patients (57%) did have posttransplant gastroparesis. One of these four patients even had abnormal manometry and delayed gastric emptying prior to lung transplantation, but no evidence of GER either before or after transplantation. Another patient had nutcracker esophagus and incomplete LES relaxation, but a normal 24-h pH study after transplantation.

Table 2—Mean Acid Contact Times Before and After Transplant

<table>
<thead>
<tr>
<th>Position</th>
<th>Pretransplant, %</th>
<th>Posttransplant, %</th>
<th>Mean Change, Interquartile Range</th>
<th>p Value</th>
<th>Normal Values, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.6 ± 7.2</td>
<td>9.3 ± 9.2</td>
<td>3.7 ± 8.0</td>
<td>0.035</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Supine</td>
<td>5.1 ± 8.9</td>
<td>11.4 ± 15.5</td>
<td>6.3 ± 12.0</td>
<td>0.019</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Upright</td>
<td>6.2 ± 6.6</td>
<td>7.8 ± 7.4</td>
<td>1.6 ± 8.8</td>
<td>&gt; 0.200</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
The type of transplant (single vs bilateral) also did not appear to be correlated with presence of post-transplant GER. Fourteen of the 18 bilateral lung transplant recipients (77.8%) had posttransplant GER. Four of the five patients (80%) who received single lung transplants had posttransplant GER. In this cohort, age and underlying diagnosis also did not appear to be associated with presence or absence of posttransplant GER.

Only one of eight patients (12.5%) had classic GER symptoms prior to transplantation, but five of eight patients (62.5%) had cough that correlated with acid contact. GER was asymptomatic in the majority of our patients after lung transplantation, as well. Twelve of the 15 patients (80%) with abnormal acid contact time after transplantation did not report symptoms of GER. Four patients had no classic GER symptoms, but did have episodes of cough that correlated with reflux on the pH probe study.

**Discussion**

Lung transplantation has become an accepted treatment modality for end-stage lung disease, but long-term outcomes remain limited, with 5-year survival at approximately 50%. The entity of chronic rejection, which is very common, has been difficult to define, but histologic obliterative bronchiolitis (OB) is considered indicative of chronic allograft rejection. The pathogenesis of OB remains poorly understood, though many mechanisms including immunologic, infectious, and perioperative factors have been postulated.

GI complaints are common after lung transplantation, and several researchers have suggested a relationship between GI dysfunction and the development of OB. In addition, foreign body material has been described previously in the airways or alveolar spaces of patients with OB by several groups, leading to speculation that two forms of chronic allograft dysfunction may occur, one related to immunologic factors and another related to chronic aspiration. In a series of 10 heart-lung transplant recipients reported by Au and colleagues, all of the patients had varying degrees of GI dysfunction, but the presence of gastroparesis did not correlate with the presence of GER by pH probe study. Finally, a recent report suggests that treatment of GER with Nissen fundoplication leads to improved lung function in lung transplant recipients.

In our study, supine acid reflux contact times were very abnormal. They were abnormal before transplant and they almost doubled after transplant (four times the normal level). Supine GER can be very damaging to the esophagus. In addition, gravity is not helpful in clearing acid reflux. Future studies will be needed to assess whether supine acid reflux, in particular, leads to lung damage in lung transplant recipients.

Given the increased prevalence of GER in patients with advanced lung disease such as IPF and CF, it has been speculated that reflux might be common in lung transplant recipients largely due to a high incidence in the patients prior to transplantation. To address this question, we chose to compare GI function in a cohort of patients before and after lung transplantation. We have found a significant increase in GER after lung transplantation, especially as reflected in supine acid contact time. The presence of reflux prior to transplantation was indeed strongly associated with posttransplant reflux, suggesting that this subset of patients with pretransplant GER continue to have GER despite the removal of the abnormal lungs. These patients should be more carefully followed in the early postoperative period if evidence of aspiration and allograft dysfunction are noted. Our findings would not support the exclusion of these patients from transplantation, however, given than an equally large subset of patients acquired GER after transplantation.

Posttransplant GER is likely only part of the explanation for the high prevalence of GER in lung transplant recipients. The mechanism of posttransplant GER still remains poorly understood. For our patient cohort, the changes in acid contact time were not explained by changes in esophageal manometry or gastric-emptying studies. This finding is intriguing, given the general speculation that vagal injury is responsible for delayed gastric emptying, esophageal dysmotility, and thus reflux. In earlier reports, where gastroparesis was more commonly found, the majority of patients had undergone heart-lung transplantation, therefore increasing the risk of vagal nerve injury. In addition, incomplete LES relaxation, which was found in a few patients, does not usually lead to increased GER. The importance of the posttransplant medications remains unknown. GER has not been commonly found in other solid-organ transplant recipients, but only a few studies have carefully and systematically examined the nature and severity of GER in other transplant populations.

In particular, steroids, which are frequently used after transplantation, are known to worsen GER. Another factor that needs to be explored in future studies is the effect of the transplant operation on the diaphragm mechanics and the competence of the LES.

An important finding of our study was the fact that the majority of our patients with posttransplant GER were asymptomatic. Tobin and colleagues have also reported GER in the absence of typical symptoms in
patients with IPF (half of the patients and the control group were receiving steroids), and also found a similar predominance of GER at night.

One limitation of the current study is the small sample size. However, this represents the largest cohort of lung transplant recipients to undergo pretransplant and posttransplant reflux testing. A larger cohort of patients would be needed to further address possible mechanisms of posttransplant reflux, including the effects of specific immunosuppressive medications. Further studies in other solid-organ transplant recipients and patients undergoing thoracic surgery would be helpful in separating surgical factors from other mechanisms of GER.

In conclusion, there is a significant increase in GER after lung transplantation. Changes in esophageal and gastric motility do not appear to explain the increase in GER after transplantation. Further research is needed to determine the physiologic mechanisms of posttransplant GER and its impact on long-term allograft function. Evaluation for GER in lung transplant recipients may be warranted, regardless of lack of GER prior to transplant or absence of symptoms.

REFERENCES

1 Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest 1997; 111:1389–1402

www.chestjournal.org