Severe Gastroesophageal Reflux Is Associated With Reduced Carbon Monoxide Diffusing Capacity*

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Objective: To assess whether severe gastroesophageal reflux (GER) is associated with abnormalities in lung function including measures of lung volume and gas diffusion.

Methods: Data from 147 patients with obesity (body mass index [BMI] range, 31.7 to 70 kg/m²) who presented for obesity surgery was analyzed retrospectively. A questionnaire was completed preoperatively that included a history of GER, frequency and severity of symptoms, investigations, and medications used. A history of lung disease, sleep-disordered breathing, and smoking also was obtained. A physician who was blinded to lung function graded GER severity prospectively by the results of pH monitoring and/or gastroscopy, and medication use. Spirometry, lung volumes, and gas transfer were measured preoperatively.

Results: Patients with severe GER had reduced levels of the diffusing capacity of the lung for carbon monoxide (DLCO) [21.1 mL/min/mm Hg; 95% confidence interval (CI), 18.9 to 23.2], as measured by CO transfer, compared with those patients without GER (26.3 mL/min/mm Hg; 95% CI, 24.4 to 28.2; p = 0.001). This remained significant after adjusting for age, gender, BMI, and smoking history. Gas transfer corrected for lung volume also was reduced in the group with severe GER (4.6 mL/min/mm Hg per L; 95% CI, 4.3 to 4.9) compared to the group without GER (5.3 mL/min/mm Hg per L; 95% CI, 5.1 to 5.5; p = 0.001). There was no significant difference in other measures of lung function.

Conclusions: Severe GER is associated with an impairment of gas exchange. This may be due to microaspiration of gastric acid or fluid into the airways.

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Key words: diffusing capacity; gastroesophageal reflux; lung function

Abbreviations: ANOVA = analysis of variance; BMI = body mass index; CI = confidence interval; DLCO = diffusing capacity of the lung for carbon monoxide; ESS = Epworth sleepiness scale; GER = gastroesophageal reflux; Hb = hemoglobin; TLC = total lung capacity; VA = alveolar volume; V˙/Q˙ = ventilation/perfusion ratio

Gastroesophageal reflux (GER) is known to be associated with many forms of respiratory disease, including asthma, pulmonary fibrosis, cystic fibrosis, scleroderma, and obstructive sleep apnea syndrome. It is frequently coexistent, and may be causative or may exacerbate, preexisting lung disease.

The potential mechanisms for GER affecting lung function are aspiration of acid or bulk fluid into the airways and potentially then aspiration into the lung parenchyma or alveolar tissue causing chronic inflammation. Chronic inflammation in the lung parenchyma may progress to pulmonary fibrosis with airway obstruction and gas exchange impairment. In the airways, it may also cause airway hyperresponsiveness. Any preexisting lung disease may be exacerbated by GER or potentially GER may be a causative factor in the development of chronic lung disease. Animal studies have shown that the continuous aspiration of acid into animal lungs causes pulmonary inflammation and pulmonary fibrosis.

Other important explanations for a positive association between lung disease and GER may include lung disease itself, exacerbating GER particularly in those patients in whom chronic cough is a major symptom. Some systemic diseases, such as scleroderma or connective tissue diseases, also may affect both the respiratory and GI systems, therefore sug-
gesting that lung disease and GER coexist rather than one or the other being causative.\textsuperscript{10}

It would therefore be expected that an improvement in GER might either improve or slow deterioration in patients with chronic lung conditions. Studies have shown an improvement in asthma symptoms and lung function associated with medical or surgical treatment for severe GER.\textsuperscript{3,11–13} In children with cystic fibrosis who have symptomatic GER, changing from postural drainage with positive expiratory pressure chest physiotherapy to upright positive expiratory pressure physiotherapy improved GER symptoms, reduced the amount of GER, improved lung function for > 6 months, decreased the deterioration in lung function, and reduced hospital admissions over 18 months.\textsuperscript{3}

Both lung disease and GER have a high prevalence worldwide.\textsuperscript{14,15} These conditions are frequently coexistent. Although it is known that massive GER may cause pulmonary fibrosis,\textsuperscript{16} or may exacerbate asthma and cystic fibrosis, it is unknown whether moderate-to-severe GER may cause or exacerbate milder forms of lung disease, or whether they are causative of lung function changes in the absence of overt symptomatic lung disease.

Few studies have compared the severity of GER with changes in lung function or have included measures of gas diffusion. The aim of our study was to assess the correlation between the severity of GER and lung function measures of lung volume and gas diffusion.

**Materials and Methods**

**Samples and Selection Criteria**

Data on 147 consecutive patients who presented for weight loss surgery were assessed retrospectively. Patients are considered for obesity surgery if they present with a body mass index (BMI) of > 35 kg/m\textsuperscript{2} and are experiencing significant medical, physical, or psychosocial disabilities.

Preoperatively, a full medical history was taken and a physical examination was performed. Information on GER included history, previous investigations, and medication usage. Patients completed a questionnaire preoperatively of respiratory disease history, previous investigations, and medication usage. Patients with cystic fibrosis who have symptomatic GER, changing from postural drainage with positive expiratory pressure chest physiotherapy to upright positive expiratory pressure physiotherapy improved GER symptoms, reduced the amount of GER, improved lung function for > 6 months, decreased the deterioration in lung function, and reduced hospital admissions over 18 months.\textsuperscript{3}

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Preoperatively, a full medical history was taken and a physical examination was performed. Information on GER included history, previous investigations, and medication usage. Patients completed a questionnaire preoperatively of respiratory disease and symptoms, which was a modified form of the International Union against Tuberculosis.\textsuperscript{17} None of the patients had significant lung disease other than asthma, and none were excluded from the series because of a history of respiratory disease or symptoms. Routine preoperative laboratory tests were performed. These included hemoglobin (Hb), fasting insulin, plasma glucose, and liver function tests.

**Lung Function**

Lung function was assessed in all patients preoperatively (Vmax C22 system; SensorMedics; Yorba Linda, CA). A respiratory scientist who was blinded to the presence or severity of GER performed these measures. Spirometry was measured using a calibrated mass flow sensor with the flow signal digitally integrated to calculate volume. Values for FEV\textsubscript{1} and FVC are reported as percent predicted values.\textsuperscript{18}

Single-breath diffusing capacity of the lung for carbon monoxide (DL\textsubscript{co}) was measured using a rapid carbon monoxide and methane analyzer, which was calibrated prior to each measurement. Values for DL\textsubscript{co} and DL\textsubscript{co} corrected for alveolar volume (VA) [DL\textsubscript{co}/VA] were obtained and are reported as percent predicted values.\textsuperscript{19}

Lung volumes were measured using the inert gas (ie, nitrogen washout) technique. All instrumentation met American Thoracic Society standards, and tests were performed following them. Lung volumes were obtained and are reported as percent predicted values.\textsuperscript{20}

**Definitions**

A physician, who was blinded to lung function, graded GER prospectively according to severity. Patients with grade 3 GER had a history of severe GER that had been diagnosed using pH monitoring and/or gastroscopy. All patients with grade 3 GER were receiving daily therapy with proton pump inhibitors and had ongoing symptoms. Patients with grade 2 GER had reported symptoms that were consistent with GER and often were receiving regular anti-GER therapy, but had not undergone any investigation or had only mild or moderate GER based on the findings of gastroscopy or pH monitoring. Patients with grade 1 GER had no symptoms, and no medication was being used for the treatment of GER. If there was any doubt about the severity of the disease, or if the subjects had been inadequately investigated, they were placed into grade 2.

Asthma was defined as having a history of physician-diagnosed asthma with wheeze in the last 12 months. Excessive daytime somnolence was defined as an Epworth sleepiness scale (ESS) score of > 10.\textsuperscript{21,22}

Patients with a history of smoking were divided into those who had never smoked (ie, 0 pack-years), those with a mild history of smoking (ie, > 0 to 10 pack-years), those with a moderate history of smoking (ie, > 10 to 20 pack-years), and those with a history of heavy smoking (ie, > 20 pack-years).

**BMI**

BMI was calculated, and all patients were obese (BMI range, 31.7 to 70 kg/m\textsuperscript{2}). Anthropometric measurements included waist, hip, and neck circumference.

**Statistical Analysis**

Data were analyzed using a statistical software package (SPSS; SPSS Inc; Chicago, IL). Prevalence rates and mean values are reported with 95% confidence intervals (CIs). One-way analysis of variance (ANOVA) with the Tukey method of post hoc analysis was used to analyze the means of grouped data based on preoperative GER grades 1 to 3. The Student t test was used to compare the mean values of those patients in grades 1 and 3, where indicated. Kruskal-Wallis analysis was used when the data distribution was nonparametric (eg, number of pack-years previously smoked). \(\chi^2\) statistics were used to determine the significance of the differences in prevalence. A stepwise linear regression analysis was used to control for age, gender, BMI, smoking history, and Hb.

**Results**

Data from 147 consecutive obese patients (BMI range, 31.7 to 70 kg/m\textsuperscript{2}) were analyzed retrospec-
tively. Patient demographics are in Table 1. The patients with grade 3 GER were significantly older (p = 0.006).

The group with grade 3 GER (n = 21) did not have an increased prevalence of current smoking (Table 1), although there was a difference between groups in the number of pack-years previously smoked (p < 0.001). This increase in pack-years smoked was present in the grade 2 (mild GER) group only and not in the grade 1 and grade 3 GER groups. There was also a trend toward a reduced Hb in the group with grade 3 GER (p = 0.09). Smoking history, current smoking status, and Hb level were allowed for in all further analyses. When smoking history was divided into four groups according to the number of pack-years previously smoked, there was no difference in DLCO (p = 0.61), DLCO/VA (p = 0.89), and DLCO percent predicted (p = 0.17) between these groups.

There were no differences in FEV1, FVC percent predicted, FEV1/FVC ratio (Fig 1), or lung volumes between patients with grade 1 GER and those with grade 3 GER. Flow rates also were analyzed, and there was no difference in the maximal mid-expiratory flow percent predicted (Table 2). There was a significant reduction in DLCO (Fig 2), DLCO/VA, and DLCO percent predicted in those patients with grade 3 GER (21 patients) when compared with patients with grade 1 GER (66 patients) [Table 2]. GER category explained the significant variance in DLCO, DLCO/VA, and DLCO percent predicted when modeled with age, gender, BMI, smoking history, and Hb level. Total lung capacity (TLC) VA was assessed for gas trapping, and there was no significant difference across the groups (p = 0.63).

Patients with grade 2 GER were those who reported symptoms consistent with GER and were receiving regular GER therapy and had not undergone any investigations or had only mild or moderate GER shown on findings of gastroscopy or pH monitoring. If there was any doubt about the severity of GER, or if the patients had been investigated inadequately, they were placed into the grade 2 group. This group represents the presence of a mixed severity of GER, and therefore the significance of the results in this group is unclear.

Results are shown as percent predicted. With many of the prediction equations, the normal values are not inclusive of severe obesity. However, there was no difference in BMI (p = 0.48), waist/hip ratio (Table 1), or neck circumference (p = 0.8) across the three groups of GER severity.

To determine whether these differences in gas diffusion could be due to differences in sleep-disordered breathing, we looked at all known factors associated with sleep apnea. There was no difference in male gender, BMI, or body habitus, including waist/hip ratio (Table 1), neck circumference, or prevalence of hypertension (p = 0.29). There were also no differences in the incidence of self-reported snoring or witnessed apneas (Table 1). There was, however, an increase in daytime somnolence in the group with grade 3 GER when compared with those in the group with grade 1 GER, as measured by the mean ESS (p = 0.03 [t test]).

Liver disease may also influence DLCO by increasing the hepatic pulmonary shunt. Obese subjects have an increase in the prevalence of steatohepatitis, which is associated with insulin resistance. There was no significant difference in levels of aspartate aminotransferase (p = 0.32), alanine aminotransferase (p = 0.78), diabetes (p = 0.93), or insulin resistance (p = 0.68) across the GER groups.

Table 1—Patient Demographics vs GER Severity

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Reflux (n = 66)</th>
<th>Intermittent Reflux GER 2 (n = 60)</th>
<th>Severe Reflux GER 3 (n = 21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender† %</td>
<td>27.3</td>
<td>16.7</td>
<td>14.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Age‡ yr</td>
<td>40.3 (37.9–42.5)</td>
<td>41.0 (38.7–43.3)</td>
<td>47.8 (44.0–51.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI†</td>
<td>46.9 (45.0–48.8)</td>
<td>45.4 (43.5–47.3)</td>
<td>45.5 (43.0–47.9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Physician-diagnosed asthma†</td>
<td>36.4</td>
<td>46.7</td>
<td>42.9</td>
<td>0.50</td>
</tr>
<tr>
<td>Current smokers†</td>
<td>9.2</td>
<td>21.3</td>
<td>4.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Snoring†</td>
<td>39.4</td>
<td>53.3</td>
<td>47.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Witnessed apneas†</td>
<td>22.7</td>
<td>23.0</td>
<td>28.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean ESS†</td>
<td>6.5 (5.2–7.8)</td>
<td>8.1 (6.7–9.5)</td>
<td>9.5 (7.2–11.8)</td>
<td>0.056</td>
</tr>
<tr>
<td>Waist/hip ratio†</td>
<td>0.91 (0.89–0.93)</td>
<td>0.88 (0.85–0.92)</td>
<td>0.89 (0.86–0.93)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Values given as mean (95% CI) or percentage, unless otherwise indicated.
†Assessed by χ² statistic.
‡Differences between groups were assessed using ANOVA by the Tukey method of post hoc analysis.
§Differences were significant.
The principle finding of this study was that severe GER, defined by the findings of pH monitoring and/or gastroscopy, is associated with a reduction in gas diffusion. This effect was not due to differences in obesity, weight distribution, spirometric function, or lung volumes. Furthermore, there did not appear to be any other relevant medical history to account for these gas exchange abnormalities.

The current series is the largest to date assessing GER and diffusing capacity. No previous studies have compared a control group with a group of patients with severe GER for changes in lung function including DLCO. Only one previous study has shown an improvement in DLCO at 6 and 12 months after Nissen fundoplication surgery for severe GER.

The patient demographics in this study are not representative of the general population. These patients were obese, and the majority of patients were female, with a lower prevalence of current smoking than in the general population, and all were presenting for obesity surgery. The changes in lung function may be influenced by the comorbidity of obesity. However, the degree of obesity and weight distribution was not different across the groups, and an independent association between GER and gas diffusion impairment persisted after controlling for BMI.

**Table 2**—Lung Function Test Results vs GER Severity

<table>
<thead>
<tr>
<th>Variables</th>
<th>GER Group 1</th>
<th>GER Group 2</th>
<th>GER Group 3</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, % predicted</td>
<td>87.0 (83.4–90.6)</td>
<td>93.6 (90.0–97.1)</td>
<td>88.0 (81.1–94.8)</td>
<td>0.024</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>91.7 (87.9–95.6)</td>
<td>97.7 (94.4–101.1)</td>
<td>94.7 (88.3–101.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>FEF_{50} % predicted</td>
<td>82.8 (76.6–88.9)</td>
<td>87.1 (79.4–94.7)</td>
<td>76.8 (64.7–89.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>67.9 (61.1–74.7)</td>
<td>68.6 (62.9–74.2)</td>
<td>68.1 (59.6–76.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>0.21 (0.18–0.25)</td>
<td>0.23 (0.20–0.26)</td>
<td>0.26 (0.22–0.29)</td>
<td>0.32</td>
</tr>
<tr>
<td>DLCO, mL/min/mm Hg</td>
<td>26.31 (24.4–28.2)</td>
<td>24.6 (22.9–26.2)</td>
<td>21.1 (18.9–23.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td>5.32 (5.12–5.51)</td>
<td>5.04 (4.81–5.27)</td>
<td>4.61 (4.30–4.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>102.5 (97.2–107.8)</td>
<td>93.91 (89.3–98.5)</td>
<td>88.9 (80.7–97.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Values given as mean (95% CI), unless otherwise indicated. RV = residual volume; FEF_{50} = midexpiratory phase of forced expiratory flow.*

Values were significantly different. Differences between groups were assessed using ANOVA with the Tukey method of post hoc analysis.
The group with severe GER (grade 3) reported increased daytime somnolence with an increase in the mean ESS score. Sleep-disordered breathing may be associated with an increase in DLco and the degree of obesity. Our patients did not undergo polysomnography, however, all known factors associated with sleep-disordered breathing were assessed, and there was no difference in male gender, degree of obesity, or body composition as measured by neck circumference, waist/hip ratio, or hypertension, and no difference in the prevalence of snoring or self-reported witnessed apneas. It is likely that the increase in daytime somnolence was due to GER causing an increase in arousals rather than to a difference in the prevalence of sleep-disordered breathing. This can be further supported by data concerning the lack of correlation between ESS scores and apnea-hypopnea index in severely obese patients.

The potential mechanisms that are responsible for the impairment in gas diffusion include microaspiration into the tracheobronchial tree, causing airway inflammation with subsequent ventilation/perfusion ratio (V/Q) maldistribution. Previous studies have shown the occurrence of microaspiration in patients with asthma, scleroderma, and cystic fibrosis. Acidification or irritation of the airways could cause an increase in airway inflammation and may exacerbate preexisting lung disease. Both mechanisms also may be operative. Although the residual volume/TLC ratio was not increased, we did not perform other measures of airway function that may have been relevant to V/Q maldistribution. The relative assessment of the gas diffusion matched for change in V/Q and the reduction in DLco/VA, however, suggests an element of alveolar capillary membrane dysfunction.

In this study, gas diffusion impairment in subjects with severe GER in the absence of spirometric abnormality suggests that we may be looking at the earliest measurable dysfunction in a progressive pathway in the evolution of progressive pulmonary fibrosis. A case can then be put forward for sorting severity of subjects with severe GER with lung function tests, including DLco, and if these findings are deteriorating, in the absence of another cause, then more aggressive treatment of the GER may be warranted to prevent lung damage.

Smoking is associated with lung function impairment and, through the relaxant effects of smoking on lower esophageal sphincter tone, also with GER. The possibility of smoking confounding the association between GER and lung function impairment needs to be addressed. We obtained an extensive medical history that included the number of previous pack-years smoked and current smoking status. Patients...
with severe GER had a greater smoking history, as previously has been found in other studies. The differences in DLCO between GER groups, however, remained significant after a multivariate linear regression was performed adjusting for smoking history, number of pack-years smoked, and current smoking status. The fact that there was no significant difference in the prevalence of current smokers among the GER groups suggests that cessation of smoking may not affect the severity of GER, once it is established. With the difference in smoking history, potentially we are noting changes to the alveolar capillary membrane in the absence of airway obstruction or lung volume changes due to smoking.

The cross-sectional nature of this study did not allow us to address issues of temporality in the relationships between GER and impairment in gas diffusion. Nevertheless, if GER can exacerbate or cause lung disease, either treatment of GER may be improved with regular treatment.

Other potential associations include the possibility that lung disease may exacerbate GER. However, in our study none of our patients had significant lung disease, other than asthma, and the prevalence of doctor-diagnosed asthma or airway obstruction did not differ between groups.

Other factors that may cause a reduced diffusing capacity also may confound these results, however, none of our patients had significant cardiac, pulmonary vascular, or connective tissue disease, and anemia, renal disease, and hepatic disease were assessed in the routine preoperative laboratory tests. It seems unlikely that another cause of significant morbidity was present in this group of otherwise well obese subjects who were presenting for obesity surgery.

Our findings are significant in that GER and lung diseases are both very common, and frequently coexist. If GER may exacerbate or cause lung disease, it needs to be closely addressed in all patients complaining of respiratory symptoms, particularly those with preexisting lung conditions. In patients with chronic lung disease, the treatment of GER may be an important aspect of overall management.

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