Increased Prevalence of Gastroesophageal Reflux Symptoms in Patients With COPD*

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Study objectives: To determine the prevalence of gastroesophageal reflux (GER) symptoms in patients with COPD and the association of GER symptoms with the severity of airways obstruction as assessed by pulmonary function tests (PFTs).

Design: Prospective questionnaire-based, cross-sectional analytic survey.

Setting: Outpatient pulmonary and general medicine clinics at a Veterans Administration hospital.

Patients: Patients with mild-to-severe COPD (n = 100) were defined based on American Thoracic Society criteria. The control group (n = 51) consisted of patients in the general medicine clinic without respiratory complaints or prior diagnosis of asthma or COPD.

Intervention: Both groups completed a modified version of the Mayo Clinic GER questionnaire.

Results: Compared to control subjects, a greater proportion of COPD patients had significant GER symptoms defined as heartburn and/or regurgitation once or more per week (19% vs 0%, respectively; p < 0.001), chronic cough (32% vs 16%; p = 0.03), and dysphagia (17% vs 4%; p = 0.02). Among patients with COPD and significant GER symptoms, 26% reported respiratory symptoms associated with reflux events, whereas control subjects denied an association. Significant GER symptoms were more prevalent in COPD patients with FEV₁ < 50%, as compared with patients with FEV₁ > 50% of predicted (23% vs 9%, respectively; p = 0.08). In contrast, PFT results were similar among COPD patients with and without GER symptoms. An increased number of patients with COPD utilized antireflux medications, compared to control subjects (50% vs 27%, respectively; p = 0.008).

Conclusions: The questionnaire demonstrated a higher prevalence of weekly GER symptoms in patients with COPD, as compared to control subjects. There was a trend toward higher prevalence of GER symptoms in patients with severe COPD; however, this difference did not reach statistical significance. We speculate that although GER may not worsen pulmonary function, greater expiratory airflow limitation may worsen GER symptoms in patients with COPD.

(CHEST 2001; 119:1043–1048)

Key words: COPD; FEV₁; gastroesophageal reflux disease; questionnaire

Abbreviations: GER = gastroesophageal reflux; H₂-RA = histamine 2-receptor antagonists; PFT = pulmonary function test; PPI = proton pump inhibitor

The association between gastroesophageal reflux (GER) symptoms and respiratory symptoms is well recognized in the setting of asthma.¹,² In the US adult population, it has been estimated that GER symptoms occur at frequencies of 7% daily, 14 to 19% weekly, and 40% monthly.³–⁵ The prevalence of weekly GER symptoms in patients with asthma is much higher (39 to 70%).⁶–⁸ However, the mechanisms accounting for the strong relationship between GER symptoms and asthma are not well established. Two explanations have been proposed. One mechanism suggests that reflux induces microaspiration of gastric contents that irritate airways.⁹ Other studies⁹–¹² suggest that asthma symptoms may be induced without direct exposure of the airways to refluxant material. Some studies⁹–¹² have demonstrated bronchoconstriction with distal esophageal acid perfusion (pH < 4) in patients with asthma. These results support the notion that acid reflux into the distal esophagus induces vagally mediated reflex broncho-
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constriction. Based on these mechanisms, a recent review emphasized that patients with asthma be aggressively treated for GER.

In contrast to asthma, the prevalence of GER symptoms is not well established in patients with COPD. Anderson and Jensen noted an increased prevalence of benign esophageal disease (e.g., GER, insufficiency of the lower esophageal sphincter, esophageal dysmotility, hiatal hernia, esophagitis) in patients who self-reported COPD. El-Serag and Sonnenberg performed a retrospective review of a large group of veterans and demonstrated an increased risk of pulmonary diseases, including COPD, in patients with reflux esophagitis, as compared to control subjects. Unlike asthma patients, esophageal acid perfusion did not increase bronchoconstriction in patients with COPD.

Thus, the relationship between GER symptoms and COPD is unclear. To further explore this association, we assessed the prevalence of GER symptoms in a large, veteran-patient population with COPD.17,18 Thus, the relationship between GER symptoms and COPD is unclear. To further explore this association, we assessed the prevalence of GER symptoms in a large, veteran-patient population with COPD, as compared to a control group of internal medicine outpatients without COPD from the same medical center. Our findings suggest an association between GER symptoms and COPD.

MATERIALS AND METHODS

Patient Selection

We consecutively enrolled 100 eligible patients with a diagnosis of COPD as defined by the American Thoracic Society, who were attending the outpatient pulmonary clinic at the Veterans Administration Chicago Health Care System, Lakeside Division. Inclusion criteria for COPD patients consisted of (1) age ≥ 50 years, (2) ≥ 30 pack-year smoking history, and (3) abnormal findings on pulmonary function tests (PFTs) demonstrating nonreversible airways obstruction based on American Thoracic Society criteria (<200 mL and 12% improvement in FEV1 or FVC after inhaling albuterol). To meet the criteria for COPD, the FEV1 and the FEV1/FVC had to be ≤ 70% of predicted. Exclusion criteria included the following: (1) respiratory disorders other than COPD; (2) normal PFT results after bronchodilator therapy; (3) known esophageal disease such as cancer, achalasia, stricture; (4) active peptic ulcer disease; (5) Zollinger-Ellison syndrome; (6) mastocytosis; (7) scleroderma; or (8) current abuse of alcohol (more than three alcoholic drinks a day).

Control Group

The control group included patients attending general medicine clinics at the same institution who denied having respiratory symptoms such as dyspnea or chronic sputum production, or had a previous diagnosis of asthma or COPD or any respiratory illnesses.

Protocol

Both COPD patients and control subjects completed a modified version of a previously validated, self-reported questionnaire developed by Locke and associates at the Mayo Clinic. This questionnaire is simple, understandable, and well accepted by patients. Our modified version contained 50 of the 80 original questions. The first 33 questions examined four symptoms in detail: heartburn, acid regurgitation, dysphagia, and chronic cough. The first question for each symptom served as a branch point, such that subjects who indicated “no” proceeded to the next symptom. The next two questions for each symptom addressed the frequency and severity of the symptom in the last year. Further questions assessed specific attributes of each symptom. Eight questions were added to assess the effect of heartburn and acid regurgitation on shortness of breath, cough, wheezing, and increased inhaler use. The remainder of the questions assessed patient’s demographic data, alcohol use, smoking history, use of over-the-counter antacids, and prescription antireflux medications. The terminology of the questionnaire was understandable at a fourth-grade reading level. In general, the questionnaires were completed in < 20 min.

The study was approved by the Institutional Review Board of Northwestern University and the Veterans Administration Chicago Healthcare System, Lakeside Division.

Statistical Analysis

Statistical analysis consisted of tests for comparing continuous variables between two groups. The associations between binary variables were tested using χ2. These associations were verified by using Bonferroni’s multiple comparison adjustments.

RESULTS

The demographic data of the 100 consecutively eligible patients with COPD and the 51 control subjects are presented in Table 1. All control subjects and 99 of 100 COPD patients were men. COPD patients and control subjects were matched for body mass index and alcohol consumption. Patients in the COPD group were slightly older than control subjects (mean age [± SD], 69.8 ± 7.6 years vs 65.8 ± 12.7 years, respectively; p = 0.04). As expected, the smoking pack-year exposures were greater in the COPD group (57 ± 49 pack-years vs 50 ± 43 pack-years; p < 0.001). The pack-year data were obtained by multiplying years of smoking by number of packs of cigarettes used per day. Coffee consumption was also greater in COPD patients, as

![Table 1—Demographics of Control Subjects and Patients With COPD](http://journal.publications.chestnet.org/pdfsaccess.ashx?url=/data/journals/chest/21961/)

*p Data are presented as mean ± SD.
†Score of 1 indicates none or less than one drink per day.
compared to control subjects (2.3 ± 2.3 cups per day vs 1.4 ± 1.5 cups per day; p = 0.01). The was no significant difference in the amount of smoking, coffee, and alcohol consumption between the 19 COPD patients with significant GER symptoms and the 81 COPD patients without GER symptoms.

Figure 1 summarizes the data concerning the prevalence of significant heartburn and/or regurgitation (once or more per week), chronic cough, and dysphagia. The prevalence of infrequent heartburn (less than once per week) was similar among patients with COPD and control subjects (26% and 25%, respectively; p = 0.95). However, COPD patients had an increased prevalence of infrequent regurgitation as compared to control subjects (29% vs 10%; p = 0.01), significant heartburn and/or regurgitation (19% vs 0%; p < 0.001), dysphagia (17% vs 3%; p < 0.02), and chronic cough (32% vs 9%; p < 0.03). None of the patients with significant GER symptoms were current smokers. These results suggest that GER symptoms were more common in veterans with COPD, compared to a control-patient cohort attending internal medicine clinics.

Measures of spirometry and lung volume were similar among the 19 patients with COPD and significant GER symptoms and the 81 patients with COPD without significant GER symptoms, as shown in Table 2. By comparison, Table 3 and Figure 2 illustrate that significant GER symptoms were more prevalent in patients with FEV₁ ≤ 50%, compared to FEV₁ > 50% without achieving statistical significance (24% vs 9%; p = 0.08). Thus, the results suggest that patients with more severe COPD may also have more frequent symptoms of GER.

Reflux-Associated Respiratory Symptoms and Inhaler Use

Among the 19 patients with significant GER symptoms, 5 patients (26%) reported increased respiratory symptoms (e.g., cough, shortness of breath, or increased wheezing) associated with heartburn and/or acid regurgitation (Fig 3). Of the five patients with worse reflux-associated respiratory symptoms, four patients noted increased use of β₂-agonist inhalers when they experienced reflux symptoms. Among control subjects, no association between respiratory symptoms and reflux events was detected. Thus, these results suggest a greater association between reflux events and the worsening of respiratory symptoms in COPD.

Antacids and Antireflux Medication Use

Next, we assessed the prevalence of acid-suppressive medication use in these two groups. Data in Figure 4 indicate that the use of any antireflux medication was greater in COPD patients than in control subjects (50% vs 27%, respectively; p = 0.008). Among patients with COPD, 43% reported using over-the-counter antacids (excluding over-the-counter histamine 2-receptor antagonists [H₂-RAs]) at least once a week, compared to 25% in control subjects (p < 0.05). Proton pump inhibitors (PPIs) and H₂-RAs were used in 28 patients with COPD (6 patients and 22 patients, respectively). Of these 28 patients, only 12 patients were receiving

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**Table 2—PFT Results in the COPD Group**

<table>
<thead>
<tr>
<th>Spirometry and Lung Volumes</th>
<th>GER Disease Symptoms (n = 19)</th>
<th>No GER Disease Symptoms (n = 81)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>1.2 ± 0.34</td>
<td>1.3 ± 0.48</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>41 ± 11</td>
<td>45 ± 16</td>
<td>0.26</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.30 ± 0.51</td>
<td>2.36 ± 0.63</td>
<td>0.73</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>62.0 ± 9.8</td>
<td>64.3 ± 16.4</td>
<td>0.41</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>137 ± 36 (n = 13)</td>
<td>141 ± 34 (n = 60)</td>
<td>0.71</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>111 ± 19 (n = 13)</td>
<td>111 ± 15 (n = 60)</td>
<td>0.94</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>176 ± 53 (n = 13)</td>
<td>172 ± 47 (n = 60)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. FRC = functional residual capacity; TLC = total lung capacity; RV = residual volume.

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*Figure 1. Higher prevalence of significant GER symptoms in patients with COPD. The prevalence of significant GER symptoms (heartburn and/or regurgitation once or more per week), chronic cough, and dysphagia in patients with COPD (gray bars) are compared to control subjects (open bars). GER symptoms were assessed by a modified version of the Mayo Clinic GER questionnaire (see “Materials and Methods” section). *p < 0.05 COPD patients vs control subjects.
PPI and H$_2$-RA medications for GER disease. The rest were either treated for inactive peptic ulcer disease or other reasons (e.g., empiric therapy, gastritis). Only three of the control subjects (5.7%) were receiving H$_2$-RA or PPI therapy, and none had significant GER symptoms. Taken together, these results indicate that the use of acid-suppressive medication was greater in COPD patients, compared to control subjects in outpatient clinics at a veterans’ hospital. This finding supports the increased prevalence of GER symptoms in patients with COPD.

Intensive Therapy of GER Symptoms

Nine patients who had significant respiratory and GER symptoms were receiving a medical regimen (five patients were receiving H$_2$-RA, and four patients were receiving PPIs) and were considered treatment failures. Two of nine patients agreed to receive high-dose PPI: lansoprazole, 30 mg bid for 1 month, followed by repeat PFTs and completion of the GER questionnaire. In both patients, GER symptoms and chronic cough resolved with no change in PFT results.

Discussion

The goals of this study were to determine the prevalence of GER symptoms in patients with COPD and to address the relationship between severity of airways obstruction and GER symptoms. The most important finding of this study is that significant GER symptoms (heartburn and/or acid regurgitation once or more per week) are more prevalent in patients with COPD when compared with control subjects at the same institution. We utilized a GER symptoms questionnaire that accurately reflects the presence of GER disease. The utility of this questionnaire is supported by the finding that heartburn and acid regurgitation are specific symptoms of GER. We also noted a trend

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**Table 3—Association of Symptoms With FEV$_1$ in Patients With COPD Compared With Control Subjects**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Control Subjects (n = 51)</th>
<th>COPD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FEV$_1$ $\leq$ 50% (n = 67)</td>
<td>FEV$_1$ $&gt;$ 50% (n = 33)</td>
</tr>
<tr>
<td>Any HB</td>
<td>13 (25)</td>
<td>22 (33)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Any RG</td>
<td>5 (10)</td>
<td>22 (33)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Significant HB and/or RG</td>
<td>0</td>
<td>16 (24)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>8 (16)</td>
<td>22 (33)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (4)</td>
<td>14 (21)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%). HB = heartburn; RG = regurgitation.
†Control subject group was significantly different than FEV$_1$ $\leq$ 50% group.
‡Control subject group was significantly different than FEV$_1$ $>$ 50% group.
considerably less than in previous reports. In this study, we demonstrated that significant GER symptoms occur in 19% of patients with COPD, as compared to those with an FEV1 > 50%. It is possible that a larger study may confirm this observation and reach statistical significance.

There are several mechanisms by which GER can induce symptoms in patients with COPD and asthma. One mechanism suggests that reflux induces microaspiration, whereas other studies suggest that acid reflux induces reflex bronchoconstriction. Severe hyperinflation, vigorous cough, and bronchospasm may increase intra-abdominal pressure and change the relationship between the diaphragm and lower esophageal sphincter. Acid reflux induces reflex bronchoconstriction. Medications such as β2-agonists, anticholinergics, and theophylline may increase GER by lowering esophageal sphincter pressure. However, results of several studies have questioned the association between reflux and these medications. Furthermore, several studies have demonstrated that esophageal acid perfusion does not induce bronchoconstriction in patients with COPD.

It has been difficult to demonstrate if GER triggers bronchoconstriction. A recent critical review of the effects of both simulated or real GER on pulmonary function in adult asthmatic patients failed to demonstrate a direct relationship. However, asthmatics with GER do report reflux-associated dyspnea, and this phenomenon has been reported in nonasthmatics with normal PFT and methacholine challenge findings. It is possible that symptoms of dyspnea occur without significant worsening in PFT results. Reflux-associated dyspnea may increase minute ventilation, promoting air trapping and hyperinflation in patients with obstructive airways disease who have expiratory limitation to airflow. However, the mechanism whereby reflux causes dyspnea has not been fully elucidated.

In summary, significant GER symptoms are more prevalent in patients with COPD, as compared to control subjects. There was a trend toward higher prevalence of GER symptoms in patients with more severe airflow obstruction than in COPD patients with and without GER symptoms. Thus, the data suggest that COPD may increase GER symptoms in this study population. Although GER symptoms are commonly associated with asthma and COPD, an important causal relationship has not been fully elucidated.

Figure 4. Higher use of antireflux medications by COPD patients. The proportion of patients with COPD (gray bars) compared to control subjects (open bars) receiving over-the-counter antacids once or more per week, daily H2-IRAs, or PPI therapy is indicated. Some patients were receiving multiple therapeutic regimens (eg, antacids and other prescription strength antireflux medications). *p < 0.05 COPD patients vs control subjects.
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