Frequency and Site of Gastroesophageal Reflux in Patients With Chest Symptoms*  
Studies Using Proximal and Distal pH Monitoring

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Prolonged ambulatory pH monitoring was performed on 89 patients with previous diagnosis of asthma (27 patients), chronic cough (28 patients), noncardiac chest pain (34 patients), and on 27 healthy control subjects. The extent of gastroesophageal reflux (GER) was determined using a catheter containing two antimony pH electrodes positioned 5 cm and 20 cm above the superior border of the manometrically determined lower esophageal sphincter. Reflux was defined as a drop in pH to <4 in the distal esophagus. We compared both pH <4 and pH <5 as the beginning of reflux episodes for the proximal esophagus. Considering the confidence interval of 95% in healthy control subjects as a normality criterion, we found a prevalence of abnormal distal GER in 44% of asthmatics, 50% of patients with cough, and 53.8% of patients with noncardiac chest pain. Abnormal proximal acid exposure was found in 24% of asthmatics, 10.7% of patients with cough and 44.1% of patients with chest pain. Distal acid exposure was significantly longer than proximal esophageal acid exposure in all patient groups (p<0.05). There were no differences in the evaluation of proximal GER comparing pH <4 with pH <5. The data also indicate a tendency toward upright, rather than supine acid exposure. These results support the use of 24-h pH monitoring in patients with chest complaints and indicate that GER may frequently be involved in the pathogenesis. They do not support the theory that proximal GER is a specific etiologic factor in chronic cough or asthma.

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**GER=gastroesophageal reflux; LES=lower esophageal sphincter**

Key words: ambulatory pH monitoring; asthma; cough; gastroesophageal reflux

Gastroesophageal reflux (GER) is an extremely common clinical problem, classically manifested by heartburn or acid regurgitation. Other manifestations such as chronic cough, hoarseness, bronchoconstriction, and unexplained chest pain are being increasingly recognized; the so-called “atypical” or “extraesophageal” manifestations. The relationship between GER and pulmonary complications has been recognized since the 1960s when Kennedy observed pulmonary complications in patients with evidence of chronic reflux. More recently, several studies have shown the relief of chest symptoms and improvement in results of pulmonary function tests after surgical or medical antireflux treatment in selected patients. Until recent times, however, techniques to identify GER as the causative factor in these conditions have been limited, creating uncertainty about the actual role of reflux in the production of the symptoms. The recent development of portable, compact recorders that can be worn by the patient during normal everyday activities

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METHODS

Patients

We studied 87 patients referred to the esophageal diagnostic laboratory for evaluation of possible GER associated with asthma (25 patients; 9 male/16 female; mean age, 54 years), chronic cough (28 patients; 10 male/18 female; mean age, 58 years), noncardiac chest pain (34 patients; 15 female/19 male; mean age, 50 years), and compared the results with those obtained in asymptomatic volunteers (27 subjects; 13 male/14 female; mean age, 30 years). All patients with the diagnosis of chest pain had been evaluated to exclude the possibility of cardiac disease. The
diagnoses of chronic cough and asthma were established on clinical basis from the referring physicians. All patients had been referred to the esophageal laboratory because of the suspicion that their symptoms might be due to GERD. The patients with chest pain were included as a positive patient control group since recent data suggest that up to 50% of such patients have abnormal GER.

**Ambulatory pH Study**

All patients underwent 24-h pH monitoring using a catheter containing two pH electrodes. The location of the lower esophageal sphincter (LES) was identified manometrically using the stationary pull-through technique with a solid-state manometry catheter connected to a computerized recording system. Esophageal pH monitoring was performed with a catheter (2.1-mm diameter) containing two antimony pH sensors separated by a 15-cm interval. The antimony pH electrodes were calibrated in buffer solutions of pH 7 and pH 1. The catheter was introduced through the nose and into the stomach initially and then slowly withdrawn until it was positioned with the electrodes 5 cm and 20 cm above the superior border of the manometrically determined LES. A silver chloride reference electrode was attached to the skin and to the portable memory recorder. During the 24 h when esophageal pH was being recorded, subjects were encouraged to continue their usual daily activities, including to eat ad libitum. Treatment with acid-suppressing medications was withheld for at least 24 h (H2-receptor antagonists) or 5 days (omeprazole) before the test.

**Data Analysis**

The data recorded by the pH monitor (Digitrapper) were down-loaded into a computer and analyzed using a program (Synectics Esophasgram, Synectics Medical, Irving, Tex). Analysis was performed to determine the percent time below a pH level of 4.0 and total number of reflux episodes during 24 h, both in upright and recumbent positions, for both the proximal and distal electrodes. A reflux episode was defined as a fall in esophageal pH to <4. The end of a reflux event was defined as a return of esophageal pH to >5. In the proximal electrode, we also evaluated reflux by a fall in pH <5 and the return to pH >6.

Normal values were obtained using the 95% value of the 27 asymptomatic volunteers. The Kruskal-Wallis test was chosen, considering the nonparametric distribution of the data, to identify the statistical significant for comparisons of the patient groups and volunteers.

**RESULTS**

Figures 1 and 2 illustrate the percent time pH <4.0 at the distal and proximal pH electrodes for all groups.
during the study. Median values and quartiles for percent time pH < 4 distally (upright, supine, and total) and proximally (total) for all groups are contained in Table 1. All groups showed a statistically significant (p < 0.01) longer percent time of acid exposure in the distal esophagus than in the proximal esophagus. All patient groups showed a significant (p < 0.01) increase in distal acid exposure as compared with normal volunteers but did not differ significantly from each other. All patient groups also showed significantly more acid exposure (p < 0.05) in the proximal esophagus as compared with normal subjects. In addition, however, the patients with chest pain showed significantly more proximal acid exposure (p < 0.05) than the other patient groups. The evaluation of proximal acid exposure using pH < 5 to define reflux failed to show any differences not seen using pH < 4.

When distal reflux was evaluated in the upright position, all patient groups again showed significantly more reflux (p = 0.02) than the normal volunteers but did not differ from each other. The evaluation of distal reflux in the supine position showed a trend toward significance with p = 0.0513; only the patients with chest pain differed from normal.

To evaluate the prevalence of abnormal reflux in these groups of patients, values distributed at the 95% of asymptomatic controls were defined as normal. These included 5.3% for total acid exposure (pH < 4), 7.5% in upright position, and 3.4% in the supine position in the distal esophagus, and 1.5% total acid exposure (pH < 4) in the proximal esophagus. Considering the total percent time with pH < 4 in distal esophagus as the criterion for the diagnosis of GERD disease, the prevalence was as follows: asthmatic patients, 44 percent; patients with chronic cough, 50%; and patients with noncardiac chest pain, 50%. There was no significant difference between these prevalences. The prevalence of abnormal proximal acid exposure was as follows: asthma, 24%; cough, 10.7%; and chest pain, 44.1%. The prevalence in patients with cough was significantly (p < 0.05) lower than that in asthmatics and patients with chest pain.

Discussion

The effects of refluxed gastric contents may extend beyond the esophagus itself, and may include a number of remote manifestations through anatomic or neural connections to the esophagus. Often termed the “extraesophageal” or atypical manifestations of GER disease, these include asthma, chronic cough, and noncardiac chest pain.

The mechanisms by which GER might precipitate asthma, cough, or substernal chest pain have not been fully clarified. Experimental studies have suggested that there might be two mechanisms by which acid reflux into the esophagus could promote bronchospasm, leading to asthma or cough. The so-called “reflux mechanism” invokes the reflux of gastric contents into the proximal esophagus with some degree of aspiration promoting changes in airway resistance. This theory is well-supported by experimental data showing that even very small amounts of acid instilled into the airway can produce intense bronchospasm. Documentation of this phenomenon clinically has been much more difficult. Although occasional patients have been shown to have evidence of radio-labeled gastric contents appearing in the lungs overnight, this has not been commonly found. On the other hand, the so-called “reflex mechanism” suggests that the stimulation of sensory afferents in the distal esophagus from acid reflux can trigger a neural response, believed to be vagally mediated, which would result in bronchospasm and changes in airway resistance. Once again, experimental data support the potential for this mechanism to occur, but clinical proof remains to be found.

The results of our study indicate that acid reflux into the distal esophagus is commonly found in patients with chronic asthma or cough but that the amount of proximal acid exposure, while exceeding normal, is significantly less than that found in patients with chest pain but without pulmonary symptoms. These results would tend to support the concept that distal acid exposure and “reflex bronchospasm” is an important, if not the most important, mechanism by which asthma and cough are produced by GER. Thus, if asthma or chronic cough are related to GER, the reflex mechanism rather than the reflux mechanism would appear to be more likely. However, one cannot totally exclude the possibility that a small quantity of acid may be aspirated in these patients.

In conclusion, our data support the observations that GER is common in patients with the symptoms

Table 1—Percent Time pH < 4, Median (Quartiles)

<table>
<thead>
<tr>
<th>Group</th>
<th>Distal (Upright)</th>
<th>Distal (Supine)</th>
<th>Distal (Total)</th>
<th>Proximal (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.2 (1.1-6.1)</td>
<td>0 (0-1.3)</td>
<td>1.4 (0-2.8)</td>
<td>0.2 (0-0.5)</td>
</tr>
<tr>
<td>Asthmatics</td>
<td>4.6 (2.0-8.6)</td>
<td>0.2 (0-6.1)</td>
<td>3.6 (1.5-9.4)</td>
<td>0.6 (0-1.5)</td>
</tr>
<tr>
<td>Patients with cough</td>
<td>7.2 (2.5-11.1)</td>
<td>0.45 (0-4.4)</td>
<td>5.2 (1.9-9.0)</td>
<td>0.45 (0.1-1.1)</td>
</tr>
<tr>
<td>Patients with chest pain</td>
<td>6.4 (2.3-13.1)</td>
<td>2.6 (0-6.2)</td>
<td>5.0 (2.3-13.3)</td>
<td>1.2 (0.1-3.9)</td>
</tr>
</tbody>
</table>
of asthma, chronic cough, or unexplained chest pain. A prevalence approaching 50% was found in each of these patient groups. Our studies show that abnormal proximal esophageal acid exposure, possibly leading to aspiration, is uncommon in patients with pulmonary symptoms (asthma or cough) and, therefore, support the "reflex mechanism" for production of these symptoms secondary to distal esophageal acid irritation. Finally, patients with unexplained chest pain showed an unexpectedly high prevalence of proximal acid exposure. The importance of this finding remains to be elucidated.

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