Esophageal Acid Perfusion, Airway Function, and Symptoms in Asthmatic Patients with Marked Bronchial Hyperreactivity*

Tommy Ekström, M.D.; and Lita Tibbling, M.D., Ph.D.

It is believed that GER can trigger asthma by the stimulation of acid-sensitive receptors in the esophagus. The aim of this study was to determine whether esophageal acid stimulation in asthmatic patients can provoke clinically detectable bronchospasm and if a possible response is correlated to bronchial reactivity. Eight patients with chronic asthma and GER disease were investigated on three occasions with a histamine challenge test followed by acid provocation of the esophagus. Assessment of bronchial function was made by FEV₁, chest auscultation, and respiratory symptoms. While symptoms and signs of bronchoconstriction induced by esophageal acid stimulation were not detected clinically on any occasion, there was a significant correlation between histamine reactivity and the subclinical bronchospasm following acid provocation. It is concluded that esophageal acid stimulation during daytime in the majority of asthmatic patients is not a strong and immediate trigger of asthma. (Chest 1989; 96:995-98)

Gastroesophageal reflux has been suggested as a possible trigger of bronchospasm in asthmatic patients. Some authors believe that bolus- or microaspiration of stomach contents into the tracheobronchial tree is the most likely mechanism by which GER triggers asthma.¹ ² Proof of aspiration, however, has been hard to obtain despite the use of sensitive radiolabeled isotopic scintigraphic techniques.³ In a few studies aspiration has been demonstrated in a minority of asthmatic patients with GER.¹ ⁴ ⁵

Esophagobronchial reflexes triggered by acid stimulation of vagal receptors in the esophageal mucosa is another possible way by which GER may induce bronchospasm. In animals as well as in patients with asthma, acid perfusion of the esophagus has been shown to provoke mild bronchoconstriction especially if esophagitis is present.⁵ ¹² However, patients rarely experience symptoms of bronchospasm and real attacks of asthma have not been seen.⁵ ⁷ ¹² In a study by Davis et al¹³ acid perfusion of the esophagus during nighttime, however, caused severe bronchospasm in four children with asthma. A direct causal relationship between episodes of reflux and bronchial symptoms could not be demonstrated in the studies by Hughes et al¹⁴ or by Ekström and Tibbling,¹⁵ but Pellegrini and coworkers¹ reported a correlation between episodes of GER and attacks of asthma.

The contradictory results obtained by different authors could be explained by a difference in the severity of asthma in various patients studied.

Like any other trigger of asthma, bronchial susceptibility to esophageal acid stimulation should be related to the severity of asthma and to the degree of underlying airway hyperresponsiveness. In asthmatic subjects the sensitivity of the airways to acid stimulation of the esophagus might vary considerably from time to time depending on whether the patient is being influenced by aggravating factors such as airway infections, bad weather, or mental stress.

The aim of this study was to determine whether clinically significant bronchospasm and respiratory symptoms can generally be provoked in patients with asthma and marked bronchial hyperreactivity during prolonged esophageal acid stimulation in the daytime. Further, we wanted to study whether a bronchial response to esophageal acid stimulation is correlated to the degree of bronchial reactivity.

For editorial comment see page 963

PATIENTS AND METHODS

In this study eight patients with moderate to severe intrinsic asthma and a history of airway hyperresponsiveness to various types of airbone irritants, emotional stress, weather fluctuations, and exercise were evaluated. The diagnosis of asthma was based on the criteria established by the American Thoracic Society. All patients required daily medication of oral and inhaled β₂-agonists, theophylline, and inhaled steroids. Six patients took oral steroids in addition. No patient had anticholinergic medication. All had a known GER disease, an history of heartburn and regurgitation, pathologic GER with a 24-h pH-monitoring in the esophagus. GER reflux in more than 1 percent during the day, and a positive acid perfusion test. The 24-h pH-monitoring test and an acid perfusion test were performed prior to the present study without changing regular asthma medication. Four patients had a history of RARS, a vague feeling of respiratory distress when having heartburn or symptoms of regurgitation. Patients with RARS

GER = gastroesophageal reflux; RARS = reflux-associated respiratory symptoms

*From the Departments of Lung Medicine and Otolaryngology, University Hospital, Linköping, Sweden. This study was supported by a grant from the Swedish Medical Research Council (project no. 17X-04260-15C). Manuscript received June 23; revision accepted February 21. Reprint requests: Dr. Ekstrom, Department of Lung Medicine, University Hospital, S-581 85 Linköping, Sweden.
Table 1—Clinical Data on Eight Patients with Asthma, Pathologic GER and a Positive Acid Perfusion Test*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Asthma Duration (yr)</th>
<th>RARS Percentage (%)</th>
<th>Night FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Day FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>PC&lt;sub&gt;20&lt;/sub&gt;</th>
<th>GER, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>3</td>
<td>0</td>
<td>0.09</td>
<td>7.5</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>8</td>
<td>0</td>
<td>0.13</td>
<td>9.9</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>5</td>
<td>0</td>
<td>0.87</td>
<td>5.3</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>24</td>
<td>0</td>
<td>0.05</td>
<td>7.6</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>M</td>
<td>50</td>
<td>0</td>
<td>0.01</td>
<td>8.4</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>12</td>
<td>0</td>
<td>0.06</td>
<td>3.2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>F</td>
<td>44</td>
<td>0</td>
<td>0.13</td>
<td>4.9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>F</td>
<td>10</td>
<td>0</td>
<td>0.04</td>
<td>2.4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*RARS = reflux-associated respiratory symptoms (+) or not (−). FEV<sub>1</sub> and PC<sub>20</sub> before acid provocation (mean values of three test occasions) are given.

had asthma of longer mean duration and more pronounced impairment of lung function than patients without RARS (Table 1). There was no difference as regards asthma medication, predominance of either daytime or nighttime attacks of asthma or severity of reflux disease between patients with and without RARS. Oral medication was withdrawn at least 12 h prior to each acid perfusion test and β<sub>2</sub>-inhalants were withdrawn at least 4 h prior to testing. Serum levels of theophylline and β<sub>2</sub>-agonists were not analyzed on different study days.

To study the patients at different levels of bronchial reactivity esophageal acid provocation was performed three times in each patient at six-week intervals, during at least two seasons for each subject (winter-spring or spring-summer). Before each acid provocation, a histamine challenge test was done. Assessment of bronchial function before and after acid perfusion was made by FEV<sub>1</sub>. The clinical evaluation was composed of chest auscultation for rhonchi and prolonged expiration and observation of cough, and the patients were asked to report the occurrence of any respiratory distress and dyspnoea.

**Histamine Inhalation Test**

A modification of the 2-min tidal breathing method of Cockcroft and coworkers<sup>a</sup> was used. Normal saline solution and then doubled concentrations of histamine chloride were administered for 2 min by an Aiolos nebulizer (Aiolos System), with a constant output of 0.7 ml/min and an average particle size of 4 μ. The patient response was measured by FEV<sub>1</sub>, 2 min after each inhalation. The next concentration was then administered, with no recovery period. The test was continued until the patient's FEV<sub>1</sub> had fallen 20 percent or more below the highest post-saline solution value. The results were expressed as the histamine concentration causing a fall in FEV<sub>1</sub>, of 20 percent (PC<sub>20</sub>). This was obtained by linear interpolation of the last two points on the log dose-response curve. The error of the method in the histamine challenge test in our laboratory is estimated to be ± one dose-step.

**Acid Provocation Test**

Esophageal acid provocation was performed 2 to 3 h after the histamine inhalation when the patients' FEV<sub>1</sub> spontaneously had returned to baseline. The provocation was performed with the patient in a sitting position. Standard manometry catheters were introduced transnasally, and via a catheter outlet 15 cm above the lower esophageal sphincter, 0.1-M hydrochloric acid was instilled at a rate of 2 to 4 ml/min. The acid instillation was continued for 10 min after the onset of symptoms of heartburn.

The FEV<sub>1</sub> was measured with a dry spirometer (Vitalograph, Maids Moreton House). Measurements were performed three consecutive times and the highest value was recorded. Baseline FEV<sub>1</sub> was measured after insertion of the nasogastric tube but before the acid instillation. The FEV<sub>1</sub> was repeated after a 10-min period of symptoms of heartburn. The error of the method in our laboratory is estimated to be ± 0.21.

**Statistical Methods**

Student's t test was used for significance testing between patients with RARS and without and for interval estimation. The Spearman rank correlation coefficient and the associated exact test was employed when judging interindividual association between variables. Rank correlation methods were also used when considering association of variables within the same individual. This study was approved by the Human Research Ethic Committee and informed consent was obtained from each subject.

**RESULTS**

Respiratory symptoms or attacks of asthma were not noted in any of the patients during or immediately after acid provocation. The change in FEV<sub>1</sub> over 24 test occasions was -0.01 L and the SD between patients' averages was 0.07. A 95 percent confidence interval for average change is obtained as -0.01 ± 0.06 L. The average change in FEV<sub>1</sub> for each patient over the three tests was more negatively positioned in patients with RARS than in those without RARS (t = 3.96; df = 6; p<0.01; Fig 1). Patients with RARS also had a greater histamine reactivity than those without (p<0.05). There was a significant correlation between average histamine reactivity over...
DISCUSSION

Clinically significant bronchospasm, respiratory symptoms, or attacks of asthma during daytime acid provocation of the esophagus could not be demonstrated in this study. Changes in FEV₁ in response to esophageal acid stimulation on different occasions was small and not consistent in any of the patients. Histamine reactivity was so pronounced in most patients on every test occasion that if a high degree of airway responsiveness is the only factor that influences esophagobronchial reflexes in a clinically important way, it should have been detected.

The prerequisite for proper testing of the "reflex theory"9,10 should have been fulfilled, as all patients had pathologic GER and an acid-sensitive esophagus as indicated by the positive acid perfusion test. Further, 12 to 20 min of acid stimulation and 10 min of intensive heartburn should be a long and strong enough stimulus to be comparable with reflux periods seen in GER disease, although the duration of a GER episode may occasionally be longer.19,21 We expected that at least the four patients with a history of RARS should have experienced respiratory symptoms during the acid provocation test. However, patients with RARS had a greater subclinical bronchoconstrictor response than those without, which implies that a history of RARS rather than the severity of reflux disease identifies patients who are susceptible to esophageal acid stimulation. Supportive of this view is a study by Ekström and Tibbling,22 which showed that a history of RARS is the only factor that predicts an improvement in asthma control following ranitidine treatment. The experience of RARS is probably related to severity of asthma, since patients with RARS had the most impaired lung function and pronounced histamine reactivity. The reason why acid provoked asthma could not be demonstrated may be that some gastric factors are of importance for eliciting respiratory symptoms during GER. The acid perfusion test is not analogous to endogenous reflux which may include gastric distention and, or contractions.

It is not likely that asthma medication influenced the results, since all drugs were withdrawn before testing during a period that can be regarded as ethically acceptable with respect to the severity of the patients' asthma. Previous studies5-7,11 have shown that the bronchial response to esophageal acid perfusion is about the same regardless of the presence or absence of asthma medication. It can also be argued that too few patients have been studied to test the hypothesis. But as all patients were observed on three separate occasions and the SD between average FEV₁ measurements obtained in different patients is quite small, the number of observations should be large enough to achieve statistically significant results if acid stimulation is a strong trigger factor in most asthmatic subjects with GER. There is, of course, a possibility that esophageal acid stimulation is of importance in a minority of the population and that the minority has not happened to be represented among the eight patients in our study. The probability of such an omission in a random sample of eight patients is, however, less than 5 percent if every third patient with asthma and GER is supposed to have reflexly induced asthma. Our findings are in agreement with other authors,5,7,11 who in total have evaluated over 100 patients without demonstrating clinically significant bronchospasm during daytime acid stimulation of the esophagus, although respiratory distress has been reported by a few patients.11
Despite the fact that the patients did not show clinical signs of asthma, there was a statistically significant correlation between histamine reactivity and the subclinical bronchoconstriction following acid provocation. This implies that esophagobronchial reflexes may be of importance in extreme degrees of airway hyperresponsiveness that may be present at night. Since it has been demonstrated that nocturnal intraesophageal acid perfusion causes severe bronchospasm,13 our observation may be limited to the conscious patient in the upright posture during the daytime. In the recumbent position and during sleep, lack of gravitational forces and reduced esophageal peristalsis impair acid clearance,16-21 which prolongs acid mucosal contact time, and consequently increases the possibility for an esophagobronchial pathway to operate. Further, a small increase in bronchomotor tone through acid irritation of the esophagus may add to the diurnal decline in lung function often seen and could therefore precipitate an attack of asthma. In the aforementioned study by Ekström and Tibbling22 and in a study by Goodall et al23 effects of antireflux treatment were predominantly seen on nocturnal respiratory symptoms. Since recumbency at night increases the likelihood of aspiration, nocturnal asthma may also be caused by aspiration.

We could find no direct or clinically detectable effect of daytime esophageal acid provocation on bronchial asthma in conscious patients in the upright posture. It therefore seems likely that esophagobronchial reflexes do not provoke attacks of asthma in asthmatic patients in general, although this may occur in individual patients or at night.

REFERENCES


3 Ghaed N, Stein MR. Assessment of a technique for scintigraphic monitoring of pulmonary aspiration of gastric contents in asthmatics with gastroesophageal reflux. Ann Allergy 1979; 42:306-08


6 Mansfield LE, Hameister HH, Spaulding HS, Smith NJ, Glab N. The role of the vagus nerve in airway narrowing caused by intra-esophageal hydrochloric acid provocation and esophageal distension. Ann Allergy 1981; 47:431-34

7 Mansfield LE, Stein MR. Gastroesophageal reflux and asthma: a possible reflex mechanism. Ann Allergy 1978; 41:224-26


21 Orr WC, Johnson LF, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis, and acid clearing. Gastroenterology 1984; 86:814-19
