Gastroesophageal Reflux-Induced Bronchoconstriction*
Is Microaspiration a Factor?

Susan M. Harding, MD, FCCP; Cathy A. Schan, PA-C1; Melany R. Guzzo, RN, BSN; Ronald W. Alexander, BA; Laurence A. Bradley, PhD; and Joel E. Richter, MD

Study objective: To evaluate the role of microaspiration in gastroesophageal reflux-induced bronchoconstriction.

Design: Prospective study blinded to the subject.

Setting: Outpatient laboratory of a 908-bed university hospital.

Participants: Thirty nonsmoking adults divided into two groups: asthmatics with reflux (AR), 20; and subjects with gastroesophageal reflux (R), 10.

Interventions: Dual esophageal pH probe placed. Esophageal infusions of normal saline solution, 0.1N hydrochloric acid, then normal saline solution, each lasting 18 min, were followed by two 20-min recovery periods. Subjects remained in the supine position throughout. Spirometry and specific airway resistance (SRaw) performed at baseline, after each esophageal infusion and recovery period. Proximal esophageal acid exposure, a requirement for microaspiration, was assessed by the proximal esophageal pH probe.

Results: Peak expiratory flow rate (PEF) decreased with esophageal acid in the AR group and did not recover immediately despite esophageal acid clearance with a significant main effect of subject groups (p<0.021) by repeated measures analysis of covariance. This decrease in PEF was not associated with the presence of proximal esophageal acid exposure (p=0.618). Specific airway resistance increased in the AR group with esophageal acid and worsened despite acid clearance, especially during the second recovery phase, with a significant phase (p<0.009) and group by treatment effect (p<0.009). The presence of proximal esophageal acid exposure was not associated with this deterioration in SRaw (p=1.0).

Conclusions: Esophageal acid infusions given in the supine position caused a decrease in PEF and an increase in SRaw in the asthma with reflux group, which did not improve despite acid clearance. These responses were not dependent on proximal esophageal acid exposure. Also, SRaw continued to worsen during the recovery phase in the AR group, which may represent a delayed bronchoconstrictor effect. These data suggest that microaspiration does not play a significant role in esophageal acid-induced bronchoconstriction.

(CHEST 1995; 108:1220-27)

Key words: asthma; bronchoconstriction; gastroesophageal reflux; microaspiration; pulmonary function

Asthma is exacerbated by multiple triggers, including gastroesophageal reflux (GER). The mechanism by which esophageal acid produces bronchoconstriction is debated and includes an esophagobronchial vagal reflex, reflux resulting in heightened bronchial reactivity, and microaspiration of acid into the larynx and upper airway.7-15

We have previously shown that peak expiratory flow rates (PEF) decreased with esophageal acid in normal control subjects, asthmatics with GER, asthmatics without GER, and patients with reflux alone. Esoph-
ageal acid clearance improved PEF in all groups except the asthmatic with reflux group, which had a further decrease in PEF. These effects were not dependent on a positive Bernstein test or evidence of proximal esophageal acid exposure, a prerequisite for microaspiration.

The purpose of this study was to prospectively examine whether microaspiration plays a significant role in reflux-induced bronchoconstriction by infusing esophageal acid while the patients are in the supine position and monitoring airway responses and proximal esophageal acid exposure. Two groups will be examined, asthmatics with GER and patients with GER alone.

**METHODS**

**Subjects**

Thirty adult subjects participated in this prospective study approved by the Human Use Committee at the University of Alabama at Birmingham on April 15, 1992. Two groups were studied: (1) asthmatics with GER disease (AR), 20 patients, and (2) patients with GER disease (R), 10 patients. All patients had a thorough history, baseline pulmonary function studies (PFTs), esophageal manometry, and ambulatory 24-h esophageal pH monitoring prior to entry into the study.

Asthma was defined by clinical symptoms and the American Thoracic Society's definition of asthma, including the following: (1) 20% improvement in FEV₁ after bronchodilators or a 20% decrease in FEV₁ with methacholine challenge, and (2) the absence of symptoms of chronic bronchitis or other forms of chronic lung disease.17

Gastroesophageal reflux was defined by symptomatic disease and abnormal amounts of acid reflux documented by 24-h pH monitoring. All patients with reflux complained of heartburn and/or regurgitation at least twice a month. Based on 110 normal control subjects using 95th percentile data in our laboratory, abnormal amounts of acid reflux were considered present in the distal esophagus, 5 cm above the manometrically defined lower esophageal sphincter (LES), if the total percent time pH <4 exceeded 5.45% during the 24-h study period, or upright acid exposure exceeded 8.05%, or supine acid exposure exceeded 2.98%.18 Based on studies in 20 healthy volunteers, abnormal amounts of proximal reflux occurred if the total percent time pH <4 exceeded 1.10%, or upright acid exposure exceeded 1.70%, or supine acid exposure exceeded 0.60% at the proximal pH probe placed just below the manometrically defined upper esophageal sphincter (UES).19,20

Patients in the reflux only group had normal pulmonary spirometry and denied pulmonary symptoms.

Exclusion criteria are those younger than 18 years old, smokers, inability to give informed consent, history of scleroderma, esopha-

gal, gastric, or pulmonary surgery, asthma exacerbation within 2 weeks of the study, or the presence of other pulmonary, cardiac, or systemic disorders that would increase the patient's risk or interfere with the execution or interpretation of the study.

Treatment with all prescription medications was continued as prescribed except antireflux medications (H2-blockers, omeprazole, metoclopramide, cisapride or bethanecol) and ipratropium bromide or atropine inhalation aerosols. Antacids were allowed up to 4 h before the study. Treatment with other antireflux drugs was held for 72 h, except omeprazole, which was held for 7 days.

**Study Design**

The flow diagram for our study is outlined in Figure 1. All subjects gave informed consent and presented after an 8-h fast. Based on previous manometric studies, a dual antimony esophageal pH probe was placed intranasally with pH electrodes 5 cm above the LES and just below the UES. To ensure that the proximal pH probe was 1 to 2 cm below the UES, probes of different sizes (ranging from 12 to 18 cm between the proximal and distal pH sensors) were used (Synectics Medical Inc; Irving, Tex). An external reference electrode was attached to the skin on the anterior part of the chest. The probe was connected to a data logger (Synectics Medical, Inc.) worn on a waist belt that continuously recorded esophageal pH at both locations. Before and after the study, the pH electrodes were calibrated using a neutral buffer and an acid buffer of pH 4. During all studies, electrode drift was <0.2 pH units.

Esophageal infusion tests were done by inserting an 8F feeding tube intranasally positioned at the midpoint between the UES and LES. In an order blinded to the patient, the following fluids were infused at a rate of 7 mL/min for 18 min: normal saline solution (pH, 5.5 to 6.0), followed by 0.1N hydrochloric acid (pH, 1.0 to 1.5), followed by normal saline solution. During the esophageal infusions, patients remained in the supine position, on a stretcher at a 30° angle, and spontaneously reported pulmonary and reflux symptoms. A patient was considered Bernstein test positive if reflux symptoms were reported during acid infusion, and abated with the second normal saline solution infusion (Fig 1).21 Patients remained in the supine position for two 20-min recovery periods in which no esophageal infusions were given.

Pulmonary function tests, including spirometry and airway resistance, were performed in the sitting position (using a SensorMedics 2800 Autobox; SensorMedics; Anaheim, Calif). At each time point, FVC, FEV₁, mean forced expiratory flow during the middle half of the FVC (FEF25-75%), PEF, and FEV₁/FVC (FEV₁%) were determined. To ensure reproducibility, flow volume curves were monitored with each effort. Multiple forced expiratory curves were obtained. At each time point, the test that gave the largest sum of FVC plus FEV₁ was used. Reference values were obtained using Morris/Polgar normal predicted equation sets based on height, age, weight, sex, and race.22-24 Airway resistance was determined using 2800 Autobox (SensorMedics) with manual shutter control using the panting technique. Panting airway resistance loops were analyzed using center tangent methods. Thoracic specific gas volumes (Vtg) were also edited. At least two efforts were

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Flow diagram of the study protocol along a time axis showing esophageal infusions, recovery periods, and PFT determinations. Patients remained in the supine position throughout except during the PFTs.
obtained and the lowest specific airway resistance thoracic volume (SRaw) value was used for data analysis since this measurement incorporates thoracic volume.

Pulmonary functions were performed after placement of the pH probe and SF feeding tube, after each infusion, and after two 20-min recovery periods while the subjects remained in the supine position (Fig 1). Esophageal infusions were interrupted only during measurements of specific airway resistance. Pulmonary function observations, except FEV1%, are expressed as percentage of the predicted value.

Statistical Analysis

A series of two-tailed Student’s t tests was performed in which the two subject groups’ mean values on the 24-h esophageal pH, esophageal manometry, baseline PFT variables, and esophageal pH values during the infusion and recovery periods were compared. In addition, χ² analyses were performed that compared the frequencies for the subject groups of a positive Bernstein test and the occurrence of proximal esophageal acid exposure during esophageal acid infusion.

During the next phase of the statistical analysis, the PFTs were entered in a series of 2 (subject group) × 4 (treatment phase: esophageal acid infusion, saline solution infusion 2, recovery phase 1, and recovery phase 2) repeated measures analysis of covariance (ANCOVAs). The covariate used for each analysis was the appropriate PFT parameter measured following supine esophageal saline solution infusion 1. Pulmonary function parameters measured after esophageal saline solution infusion 1 were used as covariates because they were the first parameters measured when the subjects were in the supine position. The ANCOVA suggested that the AR group, relative to the R group, had further worsening of SRaw during recovery phase 2, and χ² analysis was again performed.

Next, a χ² analysis was performed on each individual group (AR and R) to determine if the presence of proximal esophageal acid exposure was associated with a decrease in PEF in response to esophageal acid. A χ² analysis also was used to determine if a positive Bernstein test was associated with a decrease in PEF in response to esophageal acid infusion. Finally, χ² analysis was performed to assess whether proximal esophageal acid exposure during esophageal acid infusion was associated with an increase in SRaw seen during recovery phase 2. A separate χ² analysis was used to determine if a positive Bernstein test was associated with this SRaw response.

RESULTS

Demographics of Patient Groups

Twenty patients with asthma and gastroesophageal reflux (AR) participated. The mean age of the group was 44.8 years, ranging from 24 to 72 years, with 8 men and 12 women. The mean length of asthma symptoms was 13.7 years (range, 2 to 47 years). Eleven of 20 (55%) had nocturnal asthma symptoms. Five (25%) had mild, eight (40%) had moderate, and seven (35%) had severe asthma based on the National Asthma Education Program Expert Panel Report Executive Summary.25 Eighteen of 20 (90%) were receiving inhaled β₂-agonists, 4/20 (20%) were receiving oral β₂-agonists, 1/20 (5%) was receiving inhaled ipratropium bromide, 11/20 (55%) were receiving inhaled corticosteroids, 13/20 (65%) were receiving oral theophylline, and 7/20 (35%) were receiving oral corticosteroids. Specifically, all patients had heartburn and/or regurgitation at least twice monthly. Eleven of 20 (55%) had daily heartburn, 4 patients (20%) had heartburn at least weekly, and 4 patients (20%) had heartburn at least monthly. Five patients (25%) reported daily regurgitation, eight (40%) reported regurgitation at least weekly, and five (25%) reported daily regurgitation at least monthly. Twelve of 20 (60%) had a positive Bernstein test.

Ten patients with GER (R) participated. The mean age of this group was 43.7 years ranging from 26 to 61 years, with 6 men and 4 women. All patients had heartburn and/or regurgitation at least twice monthly.

Table 2—24-h Esophageal pH, Manometry, and Bernstein Tests: Mean ± Standard Error

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total distal (nl* &lt;2.5%)</td>
<td>Asthma+Reflex</td>
<td>Reflux</td>
</tr>
<tr>
<td>Supine distal (nl* &lt;2.98%)</td>
<td>12.28±1.87%</td>
<td>11.74±1.77%</td>
</tr>
<tr>
<td>Upright distal (nl* &lt;8.05%)</td>
<td>9.02±2.21%</td>
<td>12.18±3.26%</td>
</tr>
<tr>
<td>LESP, mm Hg (nl 29.0±12.1 mm Hg)</td>
<td>13.37±1.98%</td>
<td>10.95±2.07%</td>
</tr>
<tr>
<td>Amplitude, mm Hg (nl 99±40 mm Hg)</td>
<td>10.94±1.11</td>
<td>17.50±3.81</td>
</tr>
<tr>
<td>No. with positive Bernstein test</td>
<td>9/10</td>
<td>2/20</td>
</tr>
</tbody>
</table>

*nl=normal values based on 110 normal controls. 1Amplitude=amplitude of esophageal contraction.
Specifically, five of ten (50%) had daily heartburn, three (30%) had heartburn at least weekly, and two (20%) had heartburn at least once a month. Three patients (30%) reported daily regurgitation, three (30%) had regurgitation at least weekly, and four (40%) had regurgitation at least once a month. Nine of ten (90%) had a positive Bernstein test.

Table 1 summarizes baseline PFTs expressed as percent predicted (except FEV<sub>1</sub>%) in the two study groups. There was a significant difference in FEV<sub>1</sub> between the two groups with the AR group having a lower mean (±SE) FEV<sub>1</sub> (77.5±4.7%) than the R group (100.4±3.8%) (p<0.003). The same is true with FEV<sub>1</sub>% (<0.001). Asthmatics with reflux also had lower FEF25-75% (50.1±6.4%) (SE) than patients with reflux (102.5±6.5%) (SE) (p<0.001). There was no significant difference between the groups in baseline FVC, PEF, or SRaw. This may be due to the fact that asthmatics continued treatment with their bronchodilators prior to the study.

Table 2 summarizes 24-h esophageal pH acid exposure, esophageal manometry, and Bernstein test results in the two study groups. Both groups had abnormal amounts of esophageal acid contact time both in the supine and upright positions. There was no significant difference between the groups in total, supine, or upright distal esophageal acid contact time. Lower esophageal sphincter pressure (LESP) was reduced in both groups (normal >29.0±12.1 mm Hg (SE)); however, the asthmatic with reflux group had lower LESP (10.9±1.1 mm Hg) (SE) than the reflux group (17.5±3.8 mm Hg±3.8 mm Hg (SE) (p<0.036). The mean (±SE) amplitude of the distal esophageal contraction waves in both groups was in the normal range (normal, 99±40 mm Hg) and was not statistically different from each other. Likewise, the frequency of a positive Bernstein test was not significantly different between the two groups.

Esophageal acid clearance was assessed during the study by measuring the time required for esophageal pH to return to 4 during the second normal saline solution infusion. The asthma with reflux group had a mean (±SE) esophageal acid clearance time of 5.6±1.1 min compared with 6.6±1.8 min in the reflux alone group. There was no significant statistical difference in esophageal acid clearance between groups (p=0.621). There was also no significant difference between groups in esophageal acid contact times during the recovery periods (p=0.176).

Pulmonary Function Response to Esophageal Acid

Figure 2 shows the PEF response to esophageal infusions in the supine position as well as the PEF during the two recovery periods where patients remained in the supine position. The ANCOVA results show a significant main effect of subject groups (p<0.021) in which PEF decreased with esophageal acid in the AR group. With esophageal acid clearance, the R group had further improvement in PEF, whereas the AR group had no immediate improvement.

A χ² analysis examining the AR and R groups and the PEF response to esophageal acid show that 60% of participants in the AR group had at least a 5% decrease in PEF with esophageal acid vs 20% in the R group with p=0.038. When examining the PEF response to acid clearance (normal saline solution 2), 25% of the AR group and 40% of the R group had at least a 5% improvement in PEF; however, there was no significant difference in the way the two groups reacted to acid clearance (p=0.398). To further investigate this, Figure 3 shows the individual PEF responses in the AR and R groups before and after esophageal acid infusion and acid clearance. Figure 3, right, shows that three individuals in the R group had a marked increase in PEF with acid clearance, reflected in the mean value in Figure 2. When both groups are compared, however, there is no significant difference in the way the two groups reacted to acid clearance.

Figure 4 shows the SRaw response in the two groups during the esophageal infusions and the two recovery periods. The AR group shows a mild worsening in
SRaw in response to esophageal acid that does not improve despite acid clearance. During the second recovery phase (REC 2), the AR group had further deterioration in SRaw. The ANCOVA results show a significant phase effect (p<0.009) and group by treatment effect (p<0.009). A χ² analysis examining the AR and R groups and the SRaw response from the second normal saline solution phase (acid clearance) to the second recovery phase shows that the AR group relative to the R group had a continued increase in SRaw (p<0.018).

The ANCOVs for FEV₁, FEV₁%, and FEF25-75% showed no significant interactions between the variables during the esophageal infusions and recovery phases.

**Proximal Esophageal Acid Exposure During Esophageal Acid Infusion and Airway Responses**

Evidence of proximal GER during esophageal infusions was assessed by the proximal sensor of the dual pH probe positioned just below the UES. Twenty percent of patients in the AR group and 30% in the R group had evidence of proximal esophageal acid exposure without a significant difference between groups (p=0.657).

To evaluate if the presence of proximal esophageal acid was associated with at least a 5% decrease in PEF with esophageal acid infusion, a χ² analysis was performed. Proximal esophageal acid exposure was not associated with a decrease in PEF in the AR group (p=0.619) or the R group (p=0.067).

The effect of proximal esophageal acid exposure and SRaw responses to esophageal acid were also examined. A χ² analysis examining the frequency of proximal acid exposure and an increase in SRaw during the second recovery phase show no significant association in both the AR and the R groups (AR, p=1.0; R, p=1.0).

**Positive Bernstein Test and Airway Responses**

To determine if a positive Bernstein test was associated with a decrease in PEF during esophageal acid infusion, a χ² analysis was performed. The presence of a positive Bernstein test was not associated with a decrease in PEF (AR, p=0.648; R, p=1.0). A positive Bernstein test was likewise not associated with an increase in SRaw during the second recovery phase (AR, p=1.0; R, p=1.0).

**Discussion**

To our knowledge, this study is the largest to date examining airway responses to esophageal acid while in the supine position. The purpose was to examine the role of proximal esophageal acid exposure, a prerequisite for microaspiration, on airway responses and to examine the frequency of proximal esophageal acid exposure while in the supine position in a group of patients with well-documented GER disease. Asthma was defined by clinical and pulmonary function data. All participants were nonsmokers and had GER defined by 24-h esophageal pH monitoring and symptoms. We monitored airway responses by using spirometry and SRaw. Because we have previously shown that evidence of bronchoconstriction was still present despite acid clearance in asthmatics with GER, we...
Lower esophageal sphincter pressure in the AR group was reduced compared to the R group. This finding is in concert with the experience of Sontag et al who found that LESP was lower in 104 consecutive asthmatics vs a normal control population (13 mm Hg vs 19 mm Hg, p<0.001). Investigators have shown that theophylline lowers LESP, and 13 of 20 in our AR group were receiving theophylline during manometry. This may partially explain the lower LESP. Sontag et al point out that in their population, there was no significant difference in LESP in asthmatics receiving and not receiving bronchodilator medication.

Our results show that the asthma with GER group had a 6% decrease in PEF with esophageal acid that did not immediately recover despite esophageal acid clearance (Fig 2). This finding is in concert with our previous study in which esophageal infusions were performed in the upright position. Another finding is that SRaw increased by 7% in the AR group with esophageal acid that did not recover despite esophageal acid clearance (Fig 4). During the recovery phase, in which the subjects remained in the supine position for 40 min, there was a 27% increase in SRaw compared with the measurement taken before the esophageal acid infusion in the AR group. This effect was not seen in the R group (Fig 4). This particular finding suggests that there may be a delayed bronchoconstrictor effect in asthmatics with reflux or it may be related to the patients’ remaining in the supine position. It would have been optimal to follow airway responses over a 12-h recovery period looking for late asthmatic responses; however, it would have been difficult to control for spontaneous reflux episodes in our study population. Whether esophageal acid induces an airway inflammatory response in asthmatics with reflux still needs to be delineated, although Herve et al have shown that esophageal acid in asthmatic subjects caused a significant decrease in the provocative dose of methacholine that produced a 20% fall in FEV₁ (PD20), implying the presence of heightened airway hyperreactivity. Our entrance criteria included asthmatics who had a 20% change in FEV₁. We doubt that using a less stringent FEV₁ threshold (ie, 15%) would change our conclusions since Mansfield and Stein also showed significant airway responses to esophageal acid infusion in asthmatics without using a change in FEV₁ as part of their study criteria.

Our findings are in conflict with Wesseling et al who concluded that no direct effect on bronchomotor tone was found with esophageal acidification in 12 asthmatics with GER. Their conclusion was based on not finding significant changes in respiratory impedance or FEV₁ immediately and 30 min after esophageal acid infusion. We also found no change in FEV₁ with esophageal acid infusion and did not perform respiratory impedance. Wesseling et al presented their data.

---

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21724/)
in liters instead of percent predicted, which may have made it more difficult to compare individuals within the study group. Also, they did not discuss their PEF data.31 Our data from two studies, including 40 asthmatics with reflux, consistently show that esophageal acid infusion does cause an alteration in bronchomotor tone reflected as a decrease in PEF rate and an increase in SRaw.16

Our findings also suggest that microaspiration does not play a significant role in the pathophysiologic state of esophageal acid-induced bronchomotor responses. The presence of proximal esophageal acid exposure was not associated with worsening in PEF with esophageal acid infusion in both the asthma with reflux and the reflux groups. Also, proximal esophageal acid exposure was not associated with a worsening in SRaw in both groups. Over the entire study population, only 7 of 30 had any supine proximal esophageal acid exposure during the study period. This low frequency of supine proximal esophageal acid exposure during esophageal acid infusion may be partially explained by the observation that our study population had distal esophageal contraction amplitudes in the normal range; therefore, acid in the distal esophagus would be rapidly cleared distally and not reflux into the proximal esophagus. Esophageal acid clearance times were 6 min or less in both groups. Our study agrees with the findings reported by Gastal et al32 in that only 24% of asthmatics who presented to their esophageal diagnostic laboratory had abnormal proximal acid exposure, implying that proximal acid exposure plays a minor role in asthmatics. Proximal reflux with microaspiration may play a more significant role in asthma with reflux who have esophageal motility dysfunction, especially in the distal esophagus. Tuchman et al13 has shown in a cat model that if acid is instilled in the trachea, there is a 4.65-fold increase in total lung resistance from baseline; thus, microaspiration probably plays a role in a subgroup of patients.

Mansfield and Stein7 performed esophageal infusions on 15 asthmatics with reflux and found that total respiratory resistance increased and flow at 25% of vital capacity decreased significantly with acid infusion, suggesting a vagal reflex mechanism. To further support this theory, Mansfield et al8 performed esophageal acid infusions in dogs before and after bilateral vagal ablation and found that there was a significant fall in respiratory conductance with esophageal acid that disappeared after severing the vagal nerves. Our data support their finding, suggesting that a vagally mediated reflex arising from the esophagus could cause bronchoconstriction.

Our study also showed that a positive Bernstein test, a marker of esophageal mucosal disruption, is not associated with esophageal acid-induced bronchoconstriction. Our results disagree with Kjellen et al33 who concluded that a positive Bernstein test was necessary to elicit an airway response with intraesophageal acid; however, in their population, all 15 subjects with asthma and reflux had a positive Bernstein test.

Our study did not evaluate bronchomotor changes with esophageal acid during sleep. Our study was performed during daytime hours and patients remained awake during the esophageal infusions. Further studies performed in the sleep laboratory nocturnally on asthmatics with reflux would help further delineate the work of Tan et al.11

In conclusion, esophageal acid infusion with subjects in the supine position caused a decrease in PEF in asthmatics with reflux that did not fully recover despite esophageal acid clearance. There was also an increase in SRaw that continued to increase 40 min after esophageal acid clearance in asthmatics with reflux. This finding may represent a late-phase reaction reflecting inflammatory mediator release. The presence of proximal esophageal acid exposure was not associated with these bronchoconstrictor responses; thus, microaspiration did not play a significant role in esophageal acid-induced bronchoconstriction in our study population.

ACKNOWLEDGMENTS: The authors thank Drs. William C. Bailey and K. Randall Young for their support, Delancy Gardner, RPFT, Jean Price, MT (ASP), and Susan Irwin, RN, BSN, for assistance, and Jeannine A. Moore for her help in editing the manuscript.

REFERENCES
1 Harding SM, Richter JE. Gastroesophageal reflux disease and asthma. Semin Gastrointest Dis 1992; 3:139-50
2 Mays EE. Intrinsic asthma in adults associated with gastroesophageal reflux. JAMA 1976; 236:2696-28
6 Osler WB. The principles and practice of medicine. 8th ed. New York: D Appleton & Co, 1915; 628-31
7 Mansfield LE, Stein MB. Gastroesophageal reflux and asthma: a possible reflex mechanism. Ann Allergy 1978; 41:224-26
10 Ekström T, Tibbling L. Gastroesophageal acid perfusion, airway function, and symptoms in asthmatic patients with marked bronchial hyperreactivity. Chest 1989; 96:995-98
12 Herve P, Denjean A, Jian R, et al. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. Am Rev...
27 Sontag SJ, O'Connell S, Khandelwal S, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99:613-20

American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225-44

Respir Dis 1986; 134:986-89
17 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225-44