A Critical Review of the Studies of the Effects of Simulated or Real Gastroesophageal Reflux on Pulmonary Function in Asthmatic Adults*

Stephen K. Field, MD

Objective: To identify and critically review the published peer-reviewed, English-language studies of the effects of both spontaneous and simulated gastroesophageal reflux (GER) on pulmonary function in asthmatic adults.

Design: Using the 1966 to 1997 MEDLINE database, the terms asthma and lung disease were combined with GER to identify studies of the effects of GER and acid perfusion (AP) of the esophagus on pulmonary function. The bibliographies were also reviewed. Studies of asthmatics with and without symptomatic GER were analyzed both together and separately.

Results: A total of 254 citations, including 180 published in English, were identified. Among these were 18 studies of GER and AP in asthmatic adults. These reports, which contain data on 312 asthmatics, found that the FEV1 and the midexpiratory rate did not change during AP and GER in the studies containing 97% and 94% of the asthmatics, respectively. Flow volume loop indexes, including the flow at 50% of the vital capacity (V˙50), flow at 25% of the vital capacity, and the peak expiratory flow rate, did not change during AP or GER in the studies with 77%, 60%, and 65% of the asthmatics, respectively. Small changes in the resistance were reported in the studies containing 42% of the asthmatics. Among asthmatics without symptomatic GER, no changes in spirometry, resistance, and flow volume indexes were found, except for a 10% decline in V˙50 in one study with seven subjects.

Conclusions: In asthmatics with GER, the effects of AP on pulmonary function are minimal, and only a minority are affected. The literature does not support the conclusion that asymptomatic reflux contributes to worsening lung function.

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Key words: airway resistance; asthma; atypical chest pain; bronchial reactivity; cough; dyspnea; gastroesophageal reflux; heartburn; pulmonary function

Abbreviations: AP = acid perfusion; FEF25–75% = midexpiratory flow rate; GER = gastroesophageal reflux; PEF = peak expiratory flow rate; Raw = airway resistance; Rrs = total respiratory resistance; sGaw = specific airway conductance; V˙25 = flow at 25% of the vital capacity; V˙50 = flow at 50% of the vital capacity

Since Kennedy first reported the association between gastroesophageal reflux (GER) and lung disease 36 years ago,1 a number of publications have reported improvement and even cure of asthma with successful antireflux surgery.2,3 Perrin-Fayolle et al,4 reported asthma improvement or cure in 29 of 44 asthmatics 5 years after successful antireflux surgery. GER was reported to be the most common cause of difficult-to-control asthma, and its diagnosis and treatment, even if asymptomatic, were important for improved asthma control.5 These and similar reports led investigators to study the effects of spontaneous and simulated GER in asthma. The results of these studies have been conflicting. GER has variably been reported to have an important effect,6 small effect,7 or no effect on pulmonary function.8 The two proposed mechanisms are vagally mediated bronchospasm and microaspiration.9 Bray10 introduced the idea of a vagally mediated esophagobronchial reflex. The foregut and the respiratory tract have common embryological origins with a number of shared functions and reflexes. Upper airway reflexes protect the respiratory tract from aspiration during deglutition. The diaphragm contributes to lower esophageal sphincter function11, and a vagally mediated reflex relaxes the crural diaphragm to allow passage of a food bolus into the stomach.12 The afferent limb of this reflex

*From the Foothills Medical Centre, Calgary, Alberta, Canada.

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Correspondence to: Stephen K. Field, MD, Foothills Medical Centre, 1403 29th St NW, Calgary, Alberta, Canada, T2N 2T9; e-mail: sfield@acs.ucalgary.ca.
originates in the esophagus. In a dog model, Mansfield et al. showed that specific airway conductance (sGaw) fell during acid perfusion (AP) of the esophagus and that the response was abolished after bilateral cervical vagotomy. Microaspiration is another mechanism that has been suggested in order to explain the relationship between GER and asthma. In cats, tracheal instillation of 0.05 mL of 0.2 N HCl increased airway resistance to a greater extent than did 10 mL instilled in the esophagus. Donnelly et al. demonstrated evidence of aspiration in asthmatics monitored with a tracheal probe. Other studies designed to demonstrate the presence of aspiration have been disappointing, however. Asthmatics with GER were fed radiolabeled meals in the evening and then underwent nuclear scanning the following morning. Tracer activity over the lung fields was presumed to represent evidence of GER and aspiration. However, less than one half of those studied had positive tracer studies. Either the low prevalence of aspiration in asthmatics caused these results, or the technique was not sensitive enough to document the presence of aspiration. Harding et al. measured esophageal pH with a dual probe monitor and peak expiratory flow rate (PEF) during AP. It was assumed that if microaspiration had an important effect on airway tone, falls in the pH in the upper esophagus would correlate with falls in the PEF. However, PEF did not correlate with pH changes in the upper esophagus, leading them to conclude that microaspiration was not important. Gastal et al. also found that proximal reflux was not a specific etiological factor in asthma.

An obvious question is whether the data from these apparently conflicting studies can be reconciled and provide insight into the nature of the relationship between GER and asthma. The purpose of this report is to critically review the available literature to determine the importance of GER in asthma.

**Materials and Methods**

The MEDLINE 1966 to 1997 database was used to identify studies of the effects of spontaneous reflux and AP in adult asthmatics. Searches were conducted on GER in combination with asthma, lung disease, and bronchospasm. Since only 18 references were identified, we included all 18 citations regardless of whether the reports included objective data confirming the diagnoses of asthma and GER, or whether the diagnoses were based on history alone. The reference lists of these papers were reviewed to identify studies not included in the MEDLINE search. The effects of AP and GER on spirometry, flow-volume loop, and resistance and bronchial reactivity indexes were included, when available. Where possible, information about asthma severity, asthma medication use, pulmonary function, and demographics were collected. The location of the esophageal catheter, rate, and duration of AP were also noted. The studies were reviewed to determine which objective esophageal investigations were done to document the presence of GER. The studies were grouped according to whether the asthmatics had symptomatic GER. The results of all of the studies were also combined for analysis.

**Results**

The MEDLINE search identified 254 papers, including 150 published in English. Among these were 17 papers on the effects of AP and GER in adult asthmatics. One other study was published only as an abstract but was included in the analysis. These studies were published between 1978 and 1995.

Comparisons between studies are limited by the heterogeneity of asthma and GER severity in the different reports. The following variables have differed among the studies: number of patients, age, gender mix, patient position during AP (whether seated, supine, or semirecumbent), diagnostic criteria for GER, whether esophagitis was present, esophageal catheter position, and rate and duration of AP.

Subjects were divided by GER criteria in some reports, whereas in others, asthmatics with and without abnormal GER were analyzed together. In these studies, most asthmatics with GER had reflux symptoms, and most had GER documented by at least one objective investigation. Objective tests included ambulatory pH monitoring, endoscopy, motility studies, upper GI contrast radiography, scintiscans, and Bernstein testing. Since the studies were done over 17 years, the tests used to document the presence of abnormal GER varied considerably. Earlier studies were more likely to have included upper GI contrast radiography and scintiscans, and the more recent studies were more likely to have included motility studies and ambulatory pH monitoring to document the presence of abnormal GER.

Unfortunately, the data were not complete enough to allow a more detailed analysis of the effects of AP or spontaneous GER on the basis of the different objective reflux parameters or GER severity.

In most studies, the definition of asthma severity was arbitrary. Baseline pulmonary function data were included in 13 of the 18 reports. Among the studies that included baseline pulmonary function data, it did not appear that asthma severity influenced the response to AP. Asthma medication use was reported in 12 of the studies. Among these, theophylline was prescribed for the majority of patients. In most of the studies, the average age of the subjects was between 40 and 55 years, and most had been asthmatic for > 10 years.
Published Studies

Mansfield reported 15 asthmatics, including one child with symptomatic GER who underwent a controlled study of AP.20 Except for the flow at 25% of the vital capacity (V_{25}) being reduced by 20%, spirometry and flow-volume indexes did not change during AP. Total respiratory resistance (Rrs) increased approximately 20% during AP. In a second study, the observations were extended to a larger group of asthmatics with symptomatic GER, normal subjects, asthmatics without symptomatic GER, and nonasthmatics with symptomatic GER.6 None of the pulmonary function parameters changed in any of the four groups during AP. However, when asthmatics with GER were divided by their Bernstein test results, a 10% increase in Rrs was noted in those with a positive Bernstein test.6 None of the other parameters changed during AP in the subgroup with positive Bernstein tests.

Kjellen et al21 reported the effects of AP on 15 asthmatics with symptomatic GER. The vital capacity decreased an average of 0.21 L, and the slope of the alveolar plateau increased without a change in the closing volume. No other pulmonary function changes were reported.

Jakes et al23 studied 10 asthmatics without esophageal disease. No changes in spirometry occurred during AP. This study was never published as a complete paper.

The report by Perpina et al27 was the only one that indicated that AP had any effect on spirometry. Their report showed that FEV_{1} decreased by 8% in six asthmatics with symptomatic GER. Resistance, the flow at 50% of vital capacity (V_{50}), and the midexpiratory flow rate (FEF_{25–75%}) also decreased. However, 15 asthmatics without GER did not demonstrate any changes in spirometry, V_{50}, or airway resistance (Raw).7

Herve et al22 studied 12 asthmatics, including 7 with abnormal pH monitoring studies. Acid perfusion did not have a significant effect on V_{50} in asthmatics with normal pH studies. In those with abnormal pH studies, V_{50} was measured at 5-min intervals during AP and eventually declined by 17.5% after 25 min.

Other indexes including V_{25}, PEF, and spirometry were measured but not reported. Herve et al22 also compared the effects of AP to the effects of saline perfusion of the esophagus on bronchial reactivity during isocapnic hyperventilation challenge testing. They found that AP caused significantly greater declines in V_{50} during challenge testing. They did not report the effects of AP on FEV_{1} during challenge testing. When the patients were grouped by GER status, they found that the greater response to AP was limited to the asthmatics with GER. They also found an increased response to methacholine challenge testing in five asthmatics during AP.22

Andersen et al23 studied the effects of AP in asthmatics with and without esophagitis. Measured parameters included PEF by flowmeter and Raw by plethysmography. Asthmatics without esophagitis did not experience any changes during AP. Those with esophagitis experienced a 12% fall in PEF and a 19% increase in Raw. The other flow-volume and spirometric parameters were not reported.23

Ducolone et al24 studied asthmatics with and without GER. Neither group experienced a significant decline in FEV_{1} during AP. During AP, V_{25} but not V_{50} fell in asthmatics with GER. In asthmatics without GER, V_{50} declined, but V_{25} did not. The other spirometric and flow-volume indexes were not reported.24

Harper et al25 did not find any change in spirometry during AP in 15 asthmatics with symptomatic GER. Thirteen had objective evidence of abnormal GER.

Ekstrom and Tibbling26 compared the PEF during periods with and without spontaneous GER and did not find significant differences. Limiting the analysis to patients with greater amounts of GER or to those with positive Bernstein tests did not change their findings.26 Ekstrom and Tibbling27 also studied the effects of AP in asthmatics with GER. Eight moderate to severe asthmatics underwent AP on three different occasions. They were studied at different times to see if there was a seasonal effect in the response to AP. They were unable to demonstrate that AP had a significant effect on FEV_{1} ([mean ± SD] 10 ± 70 mL).27

Rauscher et al28 were unable to demonstrate that drinking orange juice (pH 2.7) changed bronchial reactivity in either 15 asthmatics or 10 nonasthmatics with bronchial hyperreactivity during methacholine challenge testing. Obviously, the duration of acid mucosal contact was shorter than that in the AP studies with HCl.

Wright et al29 conducted the largest study of the effects of AP on lung function. Findings in 136 normal subjects, asthmatics, and chronic bronchitics were reported. The FEV_{1} was not lower during AP (91.5 ± 2.9%) than during saline perfusion of the esophagus (90.9 ± 2.9%). Other spirometric and flow-volume parameters were not reported. Unfortunately, the results of the different patient categories were not reported separately.

Tan et al30 studied the effects of spontaneous GER and AP on 15 sleeping asthmatics. The asthmatics developed progressively worsening airway obstruction through the night. In comparison to saline perfusion, neither spontaneous GER nor AP caused
a greater change in FEV₁ or pulmonary resistance. Limiting the analysis to patients with positive Bernstein tests did not alter their findings of a lack of response to AP.⁴⁰

Wesseling et al⁸ studied the effects of AP in mild asthmatics. None of the reported parameters including FEV₁, PEF, Rrs, and reactance changed significantly. Schan et al³¹ studied seated asthmatics both with and without abnormal pH monitoring studies and compared them to normal controls and nonasthmatics with GER.

There were no significant changes in FVC, FEV₁, FEV%, or FEF 25–75% in any of the four groups during AP. The PEF's were lower in the asthmatics with GER than in the other three groups across all treatment phases. Surprisingly, the changes in the PEF's were greater in normal subjects and nonasthmatics with GER than in asthmatics. The specific Raw increased approximately 10% in asthmatics with GER but not in those without it.³¹

The same group conducted a similar study in semirecumbent subjects.¹⁸ They studied 20 asthmatics and 10 nonasthmatics with GER. Similar to the previous study, spirometric indexes did not change during AP. The PEF declined 6% in asthmatics but not in nonasthmatics. Specific Raw increased slightly during AP in the asthmatics.¹⁸

Jack et al¹⁵,³² developed a technique for intratracheal pH monitoring to determine whether aspiration may affect lung function in asthmatics. A pH probe was inserted transtracheally, via the cricothyroid membrane, under general anesthesia and guided by rigid bronchoscopy to allow the tip to be positioned 2 cm above the carina. The location of the probe was subsequently confirmed by fiberoptic bronchoscopy. Four patients were studied in this fashion with simultaneous esophageal pH monitoring.³² During the monitoring period, the four patients experienced 37 episodes during which esophageal pH declined for a minimum of 5 min. Five of these episodes were temporally related to episodes in which tracheal pH declined to < 5.5, and these were associated with a > 20% decline in PEF (84 ± 16 L/min; mean ± SE). The average decline in PEF during the other 32 episodes of spontaneous GER was 8 ± 4 L/min (mean ± SE).³²

The studies of the effects of AP in adult asthmatics without and with symptomatic GER are shown in Tables 1 and 2, respectively. The results in all asthmatics are shown in Table 3 and Figure 1. The results are summarized by symptomatic GER status in Table 4.

**Discussion**

The strong association between GER and asthma and the reported beneficial effects of antireflux surgery on asthma control led most investigators to hypothesize that GER would worsen airway obstruction. The AP studies were conceived with this expectation, and they were designed to maximize the chance that the effects on pulmonary function would be identified. To accomplish this, the most sensitive spirometric and flow-volume indexes were measured. Various measures of Raw were also made. The AP studies were almost evenly split between those that did and those that did not report changes in pulmonary function. Among those reporting an adverse effect, usually one or two of the more sensitive but less specific indexes such as V₅₀, V₃₅, PEF, or resistance demonstrated modest changes.

Only one study reported a small change in FEV₁ in asthmatics with GER.⁷ Even though the changes during AP were greater than those in the other studies, the investigators concluded that the response was small and not clinically significant.⁷ In contrast, no changes were found in the nine other studies with FEV₁ data in asthmatics with symptomatic GER (Table 2). Moreover, none of the studies in

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**Table 1—Effects of AP in Asthmatics Without Symptomatic GER**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>FVC</th>
<th>FEV₁</th>
<th>FEV₁%</th>
<th>FEF</th>
<th>PEF</th>
<th>V₅₀%</th>
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<th>Raw/sGaw</th>
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<td>10</td>
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<td>NS</td>
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<tr>
<td>Spaulding et al⁶</td>
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<tr>
<td>Perpina et al²⁷</td>
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<td>NS</td>
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<tr>
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<td>NS</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>79</td>
<td>0/26</td>
<td>0/48</td>
<td>0/17</td>
<td>0/26</td>
<td>0/28</td>
<td>7/24</td>
<td>0/11</td>
<td>0/52</td>
</tr>
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</table>

*FEV₁ % = ratio of FEV₁ to FVC; NS = not significant.
†Statistically significant.
‡No. of asthmatics in studies showing an effect/No. not affected.
asthmatics without symptomatic GER showed changes in FEV\textsubscript{1} during AP (Table 1). Whether or not the data were segregated by GER status, spirometric and flow-volume loop indexes did not change in the majority of asthmatics during real or simulated reflux (Table 4).

Resistance was variably measured as Rrs,\textsuperscript{6,8,20} pulmonary resistance,\textsuperscript{30} Raw,\textsuperscript{23} specific Raw,\textsuperscript{18,31} or sGaw.\textsuperscript{7}

These measures are sensitive and may be affected by other factors, including changes in lung volume and upper airway tone.\textsuperscript{30} Glottic closure due to GER has been reported and could cause a measured increase in resistance.\textsuperscript{35}

The studies reporting changes in PEF as evidence of airway obstruction require comment. Three studies in asthmatics without GER\textsuperscript{22,23,31} and four in asthmatics with GER did not show a fall in PEF during AP.\textsuperscript{8,20,22,26} Decreases in PEF occurred in four studies of asthmatic individuals with GER.\textsuperscript{18,23,31,32} One group reported two of the four studies with PEF declines during AP.\textsuperscript{18,31}

Abnormal GER was documented both by symptoms and by esophageal pH studies. None of the spirometric parameters changed in either paper.\textsuperscript{18,31} Although statistically significant, the PEF decreases were only in the range of 5% in both papers. Moreover, PEF changed more in normal subjects and in nonasthmatics with GER than in the asthmatics during AP.\textsuperscript{31} The authors concluded that their data on asthmatics and nonasthmatics with and without GER might be explained by the presence of a vagally mediated esophagobronchial reflex, which prevents the aspiration of caustic agents.\textsuperscript{31}

The study by Jack et al\textsuperscript{32} also requires further comment. The four patients they reported on were studied soon after undergoing general anesthesia, which may interfere with glottic closure and could explain an abnormally large volume of gastric contents being aspirated during GER.\textsuperscript{15}

The episodes of aspiration were large enough to decrease the pH to 5.5 at a point 2 cm above the carina.\textsuperscript{32} Mendelsohn\textsuperscript{36} reported the development of wheezing in the syndrome named after him, due to massive acid aspiration after general anesthesia. Whether the episodes reported by Jack et al\textsuperscript{32} have more in common with Mendelsohn’s syndrome or whether they are comparable to the episodes of microaspiration proposed to play a role in asthmatics with GER is unclear.

Peak expiratory flow is the most effort dependent of the spirometric and flow-volume loop indexes.\textsuperscript{37} Retrosternal discomfort during AP may have inhibited expiratory effort. However, Harding et al\textsuperscript{18} and Schan et al\textsuperscript{31} did not show a relationship between the decline in PEF and the presence of a positive Bernstein test in their studies. Glottic closure has been demonstrated during episodes of GER.\textsuperscript{35} It could explain a reduction in PEF without a decline in FEV\textsubscript{1}, as reported by Schan et al\textsuperscript{31} and Harding et al.\textsuperscript{18}

**Bronchial Reactivity**

Only two papers reported the effects of AP on bronchial reactivity. Herve et al\textsuperscript{22} found that it caused a greater decline in V\textsubscript{50} during isocapnic hyperventilation challenge testing in 12 asthematics. When subjects were divided by GER status, the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>FEV\textsubscript{1}, %</th>
<th>FEF\textsubscript{25–75}, %</th>
<th>PEF, %</th>
<th>V\textsubscript{50}, %</th>
<th>V\textsubscript{25}, %</th>
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<td>Total</td>
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<td>6/75</td>
<td>52/69</td>
<td>13/41</td>
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*In each table cell, the magnitude of the effect of AP on pulmonary function is shown. NS = not significant.
†Statistically significant.
‡Presence of GER determined by pH monitoring rather than by symptoms.
§Results of the patient’s Bernstein tests were positive.
||No. of asthmatics in studies showing an effect/No. not affected.
response was limited to the seven with GER. Presumably the authors chose to report the more sensitive but less specific $\dot{V}\varepsilon_{50}$ rather than FEV$_1$ because of the lack of effect on the latter. They also found that AP increased the response to methacholine challenge testing in five asthmatics. However, Rauscher et al$^{28}$ did not find that drinking orange juice (pH 2.7) increased sensitivity to methacholine in 25 subjects.

Ekstrom and Tibbling$^{27}$ found a correlation between changes in FEV$_1$ during AP and bronchial reactivity. Although bronchial reactivity correlated with the change in FEV$_1$, the findings are hard to interpret because the changes in FEV$_1$ were $< 100$ mL/s. Even those asthmatics whose FEV$_1$ improved during AP experienced an increase in bronchial reactivity, and there were only eight subjects in the study.

Possible Explanations Why the AP Studies Failed to Show an Effect

There are several reasons why the AP studies may have been unable to show an effect on lung function. First, asthmatics have different sensitivities to a variety of triggers, such as allergens, exercise, and cold air. It would be reasonable to expect that some might respond to GER whereas others might not.$^{38}$

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**Table 3—The Effects of AP on Asthmatics With and Without Symptomatic GER**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>FVC, %</th>
<th>FEV$_1$, %</th>
<th>FEF, %</th>
<th>PEF, %</th>
<th>$\dot{V}\varepsilon_{50}$, %</th>
<th>$\dot{V}\varepsilon_{25}$, %</th>
<th>Raw/sGaw, %</th>
<th>PC$_{20}$, %</th>
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<tbody>
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*In each table cell, the magnitude of the effect of AP on pulmonary function is shown.
†PC$_{20}$ = provocative concentration of substance causing 20% fall in FEV$_1$; NS = not significant.
‡Statistically significant.
§Each of these subjects was studied three different times.
¶Values not included in total.
¶¶No. of asthmatics in studies showing an effect/No. not affected.

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Figure 1. Effect of AP of the esophagus on pulmonary function. The pairs of bars indicate the number of asthmatics in studies that do and do not show a significant change in FEV$_1$, FEF$_{25-75}$, $\dot{V}\varepsilon_{50}$ and PEF during AP.
Asthma medications were continued in some of the studies and may have blunted potential changes in lung function due to GER. Acid perfusion of the esophagus increases the sensitivity to capsaicin. Rather than having a direct effect on lung function, AP may increase the sensitivity to other triggers. Herve et al investigated this possibility but, as noted above, were unable to show any further decline in FEV₁ due to bronchoprovocation during AP. Both Schan et al and Harding et al also reported that the effects of AP persisted into the recovery period after the acid had been cleared from the esophagus. This suggests that GER may have a prolonged or delayed effect on pulmonary function. Hamamoto et al reported that intraesophageal HCl increased plasma extravasation in the trachea and large bronchi in a guinea pig model. This airway response to AP was abolished by vagotomy. Neurogenic inflammation could explain why a delayed effect on lung function might occur.

Most of the AP studies were designed to detect an immediate effect and could have missed later changes in lung function. Neither Tan et al, who studied the effects of both spontaneous GER and AP overnight, nor Ekstrom and Tibbling, who monitored the effects of spontaneous GER for 24-h periods, found evidence of a late effect on lung function, however.

Statistical Considerations

In general, the sample sizes in the AP studies were small, and the possibility of type II error cannot be excluded. Moreover, the reported effects of AP were small and, although sometimes statistically significant, too small to be clinically significant.

Some of the studies that reported statistically significant changes had serious methodological problems. Most changes were reported to be statistically significant at the p < 0.05 level. However, a number of parameters were measured in these studies, and the p levels were calculated without a statistical correction for multiple comparisons. If one measures a number of parameters and tests each for significance at the 5% level, the chance that at least one will be significant at the 5% level increases with the number of tests performed. Some of these changes would no longer be statistically significant if a correction for multiple comparisons, such as Bonferroni’s, had been made to control for a type I error.

In the study by Herve et al, V₅₀ was tested at 5-min intervals and was reported to have changed significantly at 25 min by a paired t test. However, a more rigorous test such as analysis of variance or Dunnett’s multiple range test should have been used to account for repeated measurements.

In some studies, patients were grouped by whether esophagitis or GER was present. Theoretically, those with esophagitis might have a heightened response to AP. In other studies, however, they were divided subjectively according to their Bernstein test response. The rationale for dividing these patients by symptomatic response rather than by an objective parameter to identify the presence of a reflex is unclear.

Spaulding et al found no changes in Rrs, spirometry, or flow-volume indexes in 20 asthmatics with symptomatic GER. When asthmatics were divided by symptomatic response to AP, an isolated 10% increase in Rrs was found in the group with positive Bernstein tests. They concluded that a vagally mediated reflex accounted for the increased resistance during AP based on their findings in dogs.

Association Between GER and Asthma

Clearly, the data do not support the hypothesis that GER-induced bronchospasm accounts for pulmonary function worsening in asthmatics with GER. Yet asthmatics with GER frequently experience reflux-associated respiratory symptoms, including shortness of breath. The obvious problem, then, is how to best explain the strong association between GER and asthma and the high prevalence of reflux-associated respiratory symptoms if GER does not cause worsening pulmonary function. Two groups have reported that GER may cause dyspnea in nonasthmatics with normal pulmonary function and methacholine challenge test results. In one of these studies, episodes of dyspnea correlated with esophageal pH changes and improved after successful antireflux therapy.
These reports demonstrate that GER can cause shortness of breath without changes in pulmonary function. Moreover, some asthmatics with esophageal disease experience respiratory symptoms during AP with only a trivial effect on lung function, and medical antireflux therapy may improve asthma symptoms without improving lung function.

Pain may cause changes in ventilation. Although the literature is not extensive, several reports have addressed the relationship between pain and ventilation. Sarton et al found that pain increased minute ventilation in normal volunteers. Both Bourke and Borghjert et al found that painful stimuli enhanced the ventilatory response to CO₂.

A possible explanation of GER-induced respiratory symptoms is that discomfort increases ventilation, and the greater respiratory effort may be experienced as shortness of breath. To test this hypothesis, nonasthmatics with normal lung function underwent AP following manometric testing for esophageal disease.

Patients who experienced discomfort during AP increased their minute ventilation. Despite having normal lung function, the pain-induced increases in minute ventilation correlated with an increased awareness of respiratory effort. The subjects with the greatest increases in minute ventilation complained of shortness of breath. Discomfort-induced changes in ventilation may account for some of the reflux-associated respiratory symptoms in asthma. Both hypocarbia and increasing minute ventilation may cause worsening bronchospasm in asthmatic individuals. It is possible that symptomatic GER may indirectly cause worsening lung function in some asthmatics by increasing minute ventilation. However, this hypothesis has not been investigated.

The recently published study findings by Vincent et al are consistent with my conclusions. Ninety-four outpatients who met the American Thoracic Society criteria for the diagnosis of asthma were surveyed for GER symptoms. They also underwent detailed esophageal testing including 24-h ambulatory pH monitoring, motility testing, and endoscopy. One half of the patients surveyed had regular GER symptoms, and one third had abnormal pH monitoring study findings. Patients were grouped by different asthma and GER criteria in an attempt to demonstrate that GER had an adverse effect on lung function or bronchial reactivity. When the analysis was limited to the six patients with the highest number of reflux episodes, they found a correlation with the dose of methacholine required to cause a 20% decrease in FEV₁, but not with any other parameter. However, a correlation could not be demonstrated when the other patients were included. Whether patients were compared by subjective or objective GER criteria, pulmonary function, including spirometric, flow-volume, and bronchial reactivity indexes were the same in those with and without GER. Moreover, asthma medication use, including theophylline, β-agonists, and inhaled corticosteroids, was similar in those patients with and without GER.

In summary, despite the strong association between GER and asthma, and intensive study by a number of investigators, there is little evidence to support the hypothesis that either spontaneous GER or AP has an effect on lung function in asthmatics. Small changes have been reported in a minority of asthmatics with symptomatic GER (Table 2). Although statistically significant in some cases, the changes were small and unlikely to be clinically important. The data on asthmatics without GER suggest that AP does not affect pulmonary function (Table 1).

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