

Maximizing Outcome of Extraesophageal Reflux Disease

Based on a presentation by Peter J. Kahrilas, MD

Presentation Summary

Gastroesophageal reflux disease (GERD) accompanied by regurgitation and aspiration has been suggested as the cause of many conditions, but the strongest evidence exists for a relationship between asthma and GERD and posterior laryngitis and GERD. The exact mechanism of the tracheopulmonary damage has not been determined, but studies show that proton pump inhibitor therapy can ameliorate to some extent the laryngeal symptoms in laryngitis as well as asthma symptoms, asthma medication use, and lung function. Antireflux surgery appears to be more effective than antireflux medication in asthma patients with GERD symptoms. The role of tracheopulmonary damage in patients with chest pain is less clear, and the difficulty lies in determining which patients have gastroesophageal etiology.

Gastroesophageal reflux disease (GERD) is often accompanied by regurgitation and aspiration. Given the acidic nature of the refluxate, it is not surprising to find damage to the trachea and pulmonary system. Although it has taken time to convince the medical community that these tracheopulmonary complications exist (extraesophageal reflux disease), they are now well established, and the challenge is to determine their cause and to identify their mechanism.

In theory, 2 possible ways exist to cause tracheopulmonary manifestations of reflux disease. First, a gastroesophageal reflexive mechanism stimulates chemoreceptors in the distal esophagus and activates a vagovagal reflex. Most often, this reflex causes bronchospasm.

The other potential and more direct pathway occurs when the microaspirate of the refluxate contacts the pharynx directly. Evidence most strongly supports the latter event as the most common etiology of laryngopulmonary changes.

Gastroesophageal reflux accompanied by regurgitation and aspiration has been suggested as the cause of many conditions, including asthma, posterior laryngitis, chronic coughing, recurrent pneumonitis or nocturnal choking, chronic hoarseness, pharyngitis, and dental disease. However, establishing unequivocal causality is difficult. The most compelling evidence exists for laryngitis and asthma.

Posterior Laryngitis

Pharyngeal injury caused by acid

reflux was first described in 1968. Before that time, the injury was considered a manifestation of voice abuse.^{1,2} The initial presentation is subtle and is usually caused by erythema spilling onto the vocal folds. When a patient is referred with such a presentation, it is often because he or she complains of persistent hoarseness. Only some of those cases are the result of acid, so the challenge is to determine which ones, particularly if the squamocolumnar junction is intact and no good evidence of reflux disease exists.

There are several possible causes for this type of lesion. First, during sleep the upper esophageal sphincter tone is practically absent. GERD appears to be mainly a nocturnal injury to the larynx. Eating late at night causes reflux and directly exposes the larynx to the refluxate. Second, there is no reflex contraction of the upper esophageal sphincter as it responds to acidification, so it does not protect itself in any way. Third, the esophagus responds to abrupt distension by relaxing and facilitating the flow of whatever material is in the proximal esophagus. Because it does not contract, as might be expected, it is not a protective sphincter but may be considered to act as a respiratory muscle.³⁻⁵

Given these findings, a clinician would expect that if these were acid-related injuries, acid exposure would be observed proximal to or close to the larynx. However, dual-channel pH studies (of the distal esophagus and the very proximal esophagus) in individuals who had reflux disease without laryngitis, reflux disease with laryngeal symptoms, or reflux disease with both laryngeal symptoms and laryngoscopic findings that were believed consistent with reflux laryngitis show that most reflux events are limited to the distal esophagus.⁶ Whereas there was no difference among the groups in the distal pH values, the proximal pH values showed a

significant increase in acid exposure among those with laryngoscopic findings and laryngoscopic symptoms.

When these measurements were done only at night (when the patients were supine), the differences became even more profound. In fact, individuals with laryngeal symptoms and findings had significantly more nocturnal acid exposure. However, these data do not support using pH monitoring as a diagnostic modality, because several participants with laryngeal symptoms and laryngitis had no acid exposure in the proximal esophagus. As a result, this test can provide supportive data for this diagnosis, but all treatment decisions cannot be based on these findings because the results for many individuals will be false negatives.

Proton pump inhibitor (PPI) therapy would be expected to improve reflux laryngitis symptoms, and studies support this theory. In a study of 16 patients with persistent posterior laryngitis, PPI therapy (40 mg/day of omeprazole) was given for 6 to 24 weeks. Omeprazole significantly reduced laryngeal symptoms after 6 weeks of therapy, but the symptoms recurred after discontinuation, suggesting that reflux is the underlying etiology (Figure 1).⁷

Similarly, 182 patients with chronic laryngitis symptoms (edema or erythema only) were treated with nocturnal antireflux precautions (eg, not eating late). The study results showed that simple lifestyle modifications cured most of the mild cases. Pharmacotherapy was progressively introduced to patients who did not respond to antireflux precautions alone: first famotidine 20 mg at bedtime, then omeprazole 20 mg at bedtime, and finally omeprazole 40 to 80 mg or antireflux surgery. The final results showed that 96% of the patients responded to lifestyle changes and/or PPI therapy. Those with refractory symptoms had a partial response or chose fundoplication.⁸

The data suggest that the pathophysiology of reflux laryngitis is caused by intermittent contact of the laryngeal mucosa by gastric refluxate. Exposure appears to be more common at night, probably because of the physiologic properties of the upper sphincter (diminished upper esophageal sphincter pressure and poor esophageal clearance). Although PPI therapy appears to be beneficial, its benefits are not complete so other cofactors are probably involved (eg, excessive voice use, viral laryngitis, or smoking). Therefore, the recommended treatment is PPI therapy in addition to identifying and modifying the cofactors when possible.

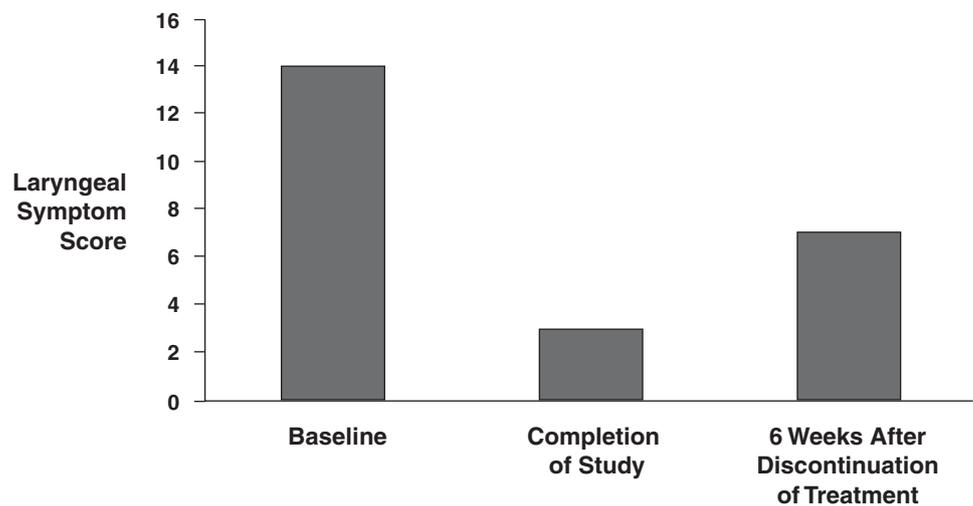
Atypical GERD Symptoms

The data for treating atypical GERD symptoms are limited. In a recent study of 150 patients who were referred for laparoscopic antireflux surgery, 35 of whom had atypical symptoms, 16 had pulmonary symp-

toms (eg, asthma or chronic cough), 12 had atypical chest or epigastric pain (excluding cardiovascular etiology of pain), and 9 had pharyngeal or laryngeal symptoms (eg, hoarseness, halitosis, or sore throat). The outcomes were measured by independent observers.⁹

The results show a significant improvement in the symptom score for those with atypical symptoms: 48% of the patients with pulmonary symptoms, 58% of atypical chest pain patients, and 78% of patients with pharyngo/laryngeal symptoms improved. Those with typical symptoms showed substantially greater improvement after the surgery: heartburn was relieved in 93% of patients with typical symptoms. However, improvement is less satisfactory and more difficult to predict in patients with atypical symptoms. In fact, the response to acid suppression was the only predictor of outcome for those with atypical symptoms. Therefore,

Figure 1. Effect of PPI Therapy on Symptoms of Reflux Laryngitis



Laryngeal symptom scores were based on 2 scales: severity parameters were graded from 0 to 3, and the frequency was graded from 0 to 4. The symptom score was the sum of the severity x frequency for the worst 2 symptoms.

PPI = proton pump inhibitor.

Source: Adapted from reference 7.

the authors conclude that because laparoscopic Nissen fundoplication can have undesirable side effects, realistic expectations are important in optimizing patient satisfaction.⁹

Cough is also a poor predictor of outcome after surgery, even though it is recognized as a reflux-related symptom. In a study of 195 consecutive patients treated with laparoscopic antireflux procedures, 133 were treated for inadequate control of reflux and 62 were treated primarily for refractory respiratory symptoms. With independent observer assessment, the results showed improvement in cough score in those with respiratory symptoms (but with a large confidence interval) and a significant improvement in cough score in those with esophageal symptoms who had a complete resolution of cough. The evidence indicates that antireflux surgery, with or without esophageal symptoms, has an impact on cough as a symptom of reflux disease, however, the result was better for those with esophageal symptoms as well.¹⁰

Asthma and GERD

The data for patients with asthma and its relationship to GERD are not clear cut. In a study of patients with adult-onset wheezing who had no history of allergy, 90% had GERD with mild or absent symptoms. Patients were randomized to receive either placebo or antireflux surgery. At the 6-month and 7-year endpoints, there was no significant change in the asthma medication score (an indicator of the severity of bronchospasm) for those who took placebo, and the range of medication scores in this group was broad. Those who received antireflux surgery had a fairly similar spectrum of asthma medication scores at baseline compared with the placebo group. At 6 months, 30% to 40% of the patients in this group had com-

plete resolution of asthma, which was maintained for 7 years.¹¹

Although encouraging, the data have not been replicated. A survey of 8 randomized, controlled trials shows significant improvement in the asthma response (ie, asthma symptoms and asthma medication use) to medical reflux treatment (Figure 2). However, there was less significant improvement in asthma medication use, and the peak expiratory flow rate indicated that fewer patients were improved than not improved. Similarly, spirometric measurements (the most objective measure of asthma) indicated no improvement.¹²

Looking at the asthma response to antireflux surgery (summarized from controlled trials in the literature), asthma symptoms, medication use, and pulmonary function improved in the majority of patients (Figure 3).¹³

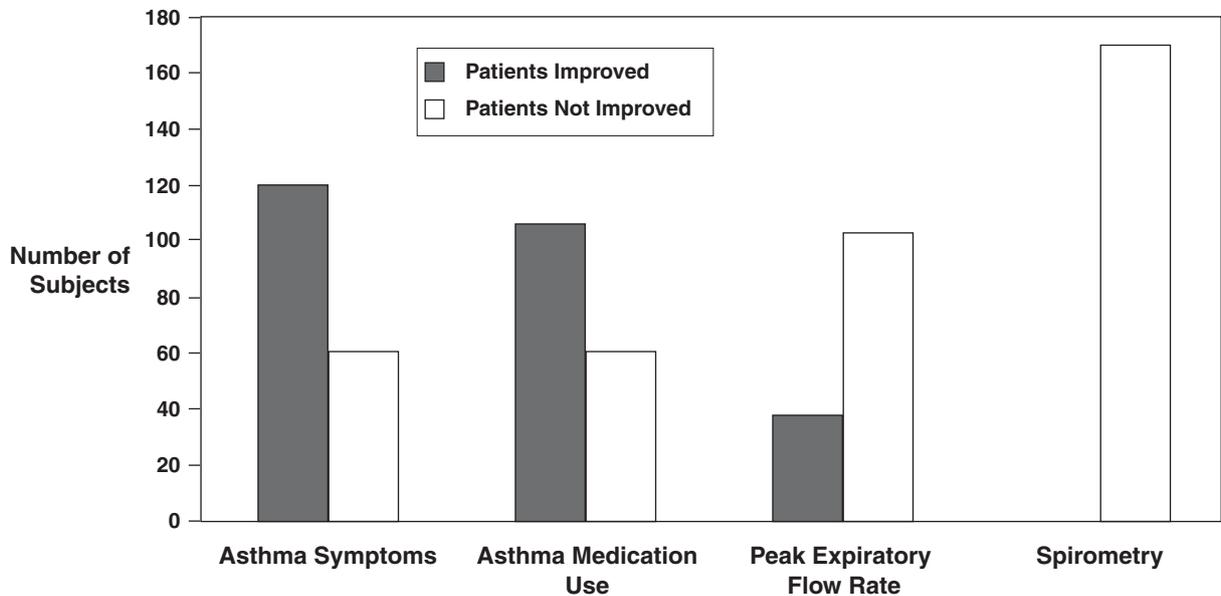
Together, these data reveal that whereas medical GERD treatment can produce some symptomatic improvement, it does not produce functional improvement. With surgical GERD treatment, a large subset of patients experienced functional improvement as well. Unfortunately, no way to select these patients currently exists.

Patients With Chest Pain

In analyzing the symptom of chest pain, the history taking is most important. Patients with chest pain are divided into 3 groups: 1) those with concomitant esophageal symptoms, 2) those with isolated chest pain without any concomitant symptoms, and 3) those with anxiety and somatization neurosis. The last group is often easy to identify, although there may be some overlap with the other 2 groups.

As expected, the approach to treatment for each group is different. If patients have chest pain with esophageal symptoms (eg, heartburn, regurgitation, dysphasia, water

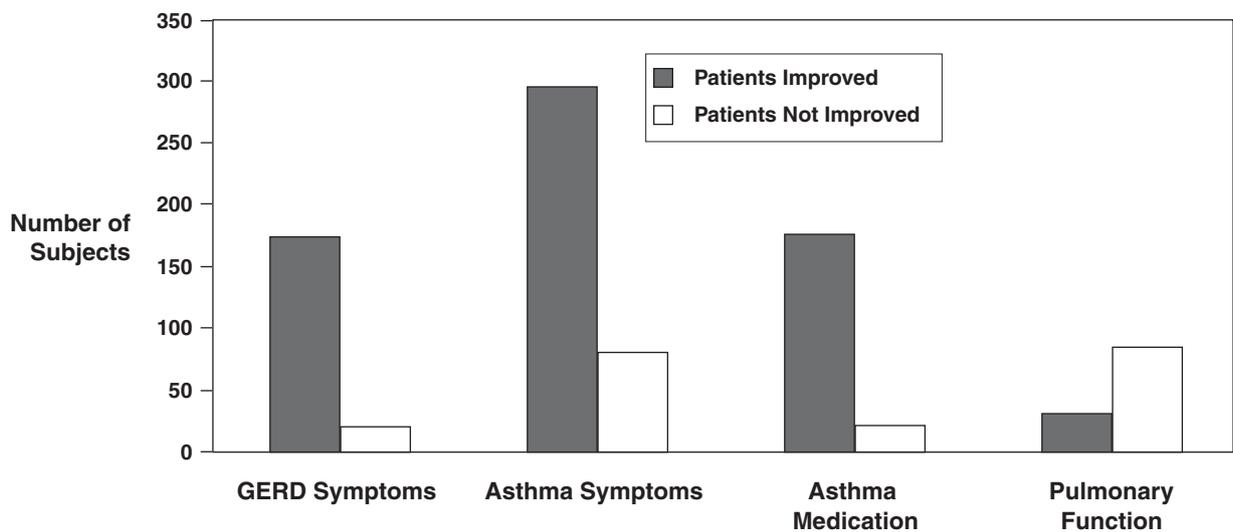
Figure 2. Asthma Response to Medical GERD Treatment: Summary Data from 8 Randomized Controlled Trials



GERD = gastroesophageal reflux disease.

Source: Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux? A critical review of the literature. *Chest* 1998;114:275-283. Reprinted with permission.

Figure 3. Asthma Response to Antireflux Surgery: Literature Review



GERD = gastroesophageal reflux disease.

Source: Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999;116:766-774. Reprinted with permission.

brash, nausea, or vomiting), they should be treated as if they have only GERD, and their chest pain will invariably improve.

It is very rare to have an esophageal etiology in those who experience isolated chest pain. Evaluating other noncardiac causes is just as valid as considering an esophageal cause of pain. A useful approach is to scrutinize the cardiologic evaluation and monitor and reassure the patient. It is not prudent to extensively pursue esophageal etiologies in the absence of any evidence. Those with anxiety and neuroses may best be referred to a psychiatrist.

Evaluating Esophageal Disorders in Patients With Chest Pain

Endoscopy or a barium swallow and manometry will detect an esophageal etiology most of the time. The quagmire exists in endoscopy-negative reflux disease that may lead to chest pain, which has led to some support for a PPI test for noncardiac chest pain.

A recent study evaluated the ability of a short course of omeprazole to identify the cause of noncardiac chest pain in 37 patients who had daily chest pain and a negative cardiovascular evaluation. They were randomized to receive either omeprazole 40 mg every morning and 20 mg for every hour of sleep or placebo for 7 days. A positive response was defined as a 50% decrease in symptoms. Of the 37 patients, 23 were GERD positive, as documented by pH monitoring or endoscopy, and 14 were GERD negative. Seventy-eight percent of the GERD-positive group had a response to the PPI trial; 14% of the GERD-negative group responded. This "omeprazole test" did identify GERD in noncardiac chest pain patients, but its value is questionable, because the patients were already identified as having GERD. The real challenge is to identify a GERD etiol-

ogy in patients who have no available evidence of reflux disease.¹⁴

Summary

Extraesophageal reflux disease presents unique clinical challenges, primarily because the treatment regimens are not formally outlined. They are determined empirically, and a review of the etiology of this disease can explain why. In the 1990s, the greatest challenge regarding extraesophageal manifestations of reflux disease was convincing the medical community that they really existed. In 2000, we accept that they exist and are now trying to define the disease and its diagnosis. In the future, physicians will be faced with the difficult issue of how and when to treat the disease when the response to standard treatment is not obvious or immediate.

... REFERENCES ...

1. Jackson C. Contact ulcer of larynx. *Ann Otol Rhinol Laryngol* 1928;37:227-230.
2. Cherry J, Margulies SI. Contact ulcer of larynx. *Laryngoscope* 1968;78:1937-1940.
3. Kahrilas PJ, Dodds WJ, Dent J, Haerberle B, Hogan WJ, Arndorfer RC. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. *Gastroenterology* 1987;92:466-471.
4. Vakil NB, Kahrilas PJ, Dodds WJ, Vanagunas A. Absence of an upper esophageal sphincter response to acid reflux. *Am J Gastroenterol* 1989;84:606-610.
5. Kahrilas PJ, Dodds WJ, Dent J, Wyman JB, Hogan WJ, Arndorfer RC. Upper esophageal sphincter function during belching. *Gastroenterology* 1986;91:133-140.
6. Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with "reflux laryngitis." *Gastroenterology* 1991;100:305-310.
7. Kamel PL, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med* 1994;96:321-326.
8. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. *Ann Otol Rhinol*

Laryngol 1995;104:550-555.

9. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. *Surgery* 1998;124:28-32.

10. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax* 1998;53:963-968.

11. Larrain A, Carrasco E, Galleguillos F, Sepulveda R, Pope CE II. Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. *Chest* 1991;99:1330-1335.

12. Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux? A critical review of the literature. *Chest* 1998;114:275-283.

13. Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999;116:766-774.

14. Fass R, Fennerty MB, Ofman JJ, et al. The clinical and economic value of a short course of omeprazole in patients with noncardiac chest pain. *Gastroenterology* 1998;115:42-49.