The Effects of Antireflux Surgery on Asthmatics With Gastroesophageal Reflux*

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Background: Antireflux therapy, including surgery, has been advocated for asthma patients with gastroesophageal reflux (GER). A recent review of medical antireflux therapy reported improvements in asthma symptoms and medication requirements but no improvement in pulmonary function. The purpose of this article is to review the available literature on the effects of antireflux surgery in asthma.

Method: Using the Medline 1966 to August 1998 database, lung disease, asthma, and pulmonary function were combined with GER and different antireflux surgeries, including fundoplication. Reference lists of identified articles were also reviewed.

Results: Combining the terms asthma and GER identified 271 articles, including 193 in English. Searching the term fundoplication identified 497 articles, including 413 in English. Twenty-four reports addressed the effects of antireflux surgery in asthma. Only two studies were controlled. Asthmatic data could not be distinguished from that of other subjects in five articles. The remainder were case series, retrospective reviews, or uncontrolled studies. Ten reports included data on ≤ 10 patients. Two studies were only published as abstracts. A total of 417 asthma patients were included in the identified reports. Antireflux surgery improved GER symptoms, asthma symptoms, asthma medication use, and pulmonary function in 90%, 79%, 88%, and 27%, respectively.

Conclusions: Antireflux surgery may improve GER and asthma symptoms and decrease medication requirements, but it has little effect on pulmonary function. The effects of antireflux surgery on asthma are similar to those of medical antireflux therapy. (CHEST 1999; 116:766–774)

Key words: asthma; bronchial reactivity; cough; dyspnea; esophageal surgery; esophagitis; fundoplication; gastroesophageal reflux; hiatus hernia; pH monitoring

Abbreviations: AP = acid perfusion; GER = gastroesophageal reflux; \( \dot{V}e \) = minute ventilation

Few topics in medicine are more controversial than the relationship between gastroesophageal reflux (GER) and asthma. Despite the uncertainty surrounding the nature of the relationship, there is a strong association between the two conditions. More than 30 years ago, thoracic surgeons recognized that asthma symptoms were common in patients with GER and often improved after successful antireflux surgery.1,2 Although most authors have assumed that GER aggravates asthma, the reported effects of GER or acid perfusion (AP) of the esophagus on pulmonary function, its physiologic equivalent, have been minor or nonexistent.3

The prevalence of symptomatic GER in asthma varies considerably, depending on the criteria used to define GER and asthma, and the populations studied. One controlled study found that 45% of the attendees at a university-based asthma clinic experienced at least one episode of symptomatic GER in
the previous week, compared to only 10% of the subjects in two control groups. Sontag and coworkers studied asthma clinic attendees and found that > 80% had abnormal reflux by pH-monitoring criteria. Approximately 60% had a hiatus hernia, and 40% had erosive esophagitis. During episodes of symptomatic GER, many asthma patients experience respiratory symptoms including dyspnea, wheezing, and cough, and require their β-agonist inhalers for asthma symptom relief.

The reported effects of medical antireflux therapy range from nothing to an improvement of asthma symptoms, medication requirements, and pulmonary function. A critical review of the controlled studies of medical antireflux therapy demonstrates an apparent paradox: asthma symptoms and medication requirements improved, but not pulmonary function.

Results of studies on the effects of antireflux surgery on asthma control published over the last 4 decades are conflicting. Some report that most patients experience cure or considerable improvement in asthma control postoperatively. The results of other studies have been disappointing. Although some asthma experts advocate antireflux surgery in asthma patients with GER, most of the experts remain skeptical about its role. The recommendations in asthma guidelines and recently published position papers by the National Institutes of Health reflect this ambivalence and the uncertainty in peer-reviewed literature regarding the relationship between GER and asthma.

Recently, studies of the effects of GER on pulmonary function, minute ventilation (Ve), and respiratory sensation, and the effects of medical and surgical antireflux therapy in asthma have been published. A review of the effects of antireflux surgery on asthma is needed to help clarify its role.

### MATERIALS AND METHODS

The Medline 1966 to August 1998 database was used to identify English language studies on the effects of antireflux surgery in asthma. The terms GER and fundoplication were each combined with the terms asthma and lung disease. Other surgical terms, including gastropexy, Belsey, Allison, Toupet, Lortat-Jacob, Boerema, and the Hill procedures, were combined with asthma and lung disease. Reference lists of these articles were reviewed to identify studies that were not located in Medline searches. The identified papers were reviewed to determine the effects of antireflux surgery on asthma control. Studies of antireflux surgery in patients with other respiratory diseases were also reviewed. The asthmatic data from studies that contained both asthma patients and patients with other respiratory diseases were included in the analysis. Since only 24 references reported the effects of antireflux surgery on asthma, all were included in the analysis, regardless of how the diagnoses of asthma and GER were made (Table 1). The surgical procedure(s) performed in each study and the duration of postoperative follow-up were noted (Table 1). Information about asthma severity, medication use, pulmonary function, and demographics were collected (Table 2). Studies were reviewed to determine which investigations were done to document GER preoperatively and postoperatively (Table 1). Reflux symptoms and their response to surgery were noted. The results of the available studies were combined for analysis (Table 2).

### RESULTS

Combining the terms GER and asthma identified 271 articles, 193 of which were in English. Searching the term fundoplication identified 497 articles, 413 of which were published in English. Twenty-four articles addressed the effects of antireflux surgery in asthmatics with GER.

Some articles focused on the effects of antireflux surgery in asthma. Others reported patients with a variety of respiratory diseases, including asthma. Asthma patients in these series were included in the analysis where possible. Other conditions reported in patients with GER included chronic bronchitis, bronchiectasis, pneumonia, pulmonary fibrosis, and respiratory diseases of infancy, including respiratory distress and apnea. Some studies concentrated on the effects of antireflux surgery on respiratory symptoms, including cough, sputum production, dyspnea, and wheezing. Studies were not included unless the subjects were asthmatic. Wheezing, in the setting of other diseases such as bronchitis, bronchiectasis, or aspiration pneumonia was not considered to be diagnostic of asthma. Other reports included patients with asthma who were treated with both medical and surgical antireflux therapy. Surgical data from these articles were incorporated into the analysis. One article advocated antireflux therapy, but it did not include any data to support the recommendation. In four reports, the data on patients with asthma could not be separated from the data on patients without it. Ten of the remaining studies included ≤ 10 subjects. Only two reports were controlled trials. The remainder were case series, retrospective reviews, or uncontrolled trials. Two were reported as abstracts only.

Data were available on 417 patients with asthma who underwent antireflux surgery (Tables 1, 2). Gastroesophageal reflux symptoms, asthma symptoms, asthma medication use, and pulmonary function improved in 90%, 79%, 88% and 27%, respectively (Fig 1).

### Controlled Studies of Antireflux Surgery in Asthma

Larrain and colleagues compared antireflux surgery to placebo and cimetidine therapy in a parallel design study. Asthma was assessed by medication...
requirements and spirometry, and GER was documented by pH monitoring, manometry, endoscopy, and upper GI radiography. At 6 months, the results with cimetidine and surgery were similar. Compared to the placebo group, both treated groups experienced an improvement in asthma symptoms and decreased medication requirements, but spirometry did not improve.

In a similarly designed study, Sontag et al compared Nissen fundoplication to treatment with ranitidine and to placebo in asthma patients with GER. Asthma symptoms and medication requirements improved postoperatively, but peak expiratory flow only improved by 10% in one third of the patients. This study was never published as a complete article.

**Open studies of antireflux surgery**

Overholt and Voorhees performed > 200 trans-thoracic hiatus hernia repairs between 1958 and 1964. Twenty-four patients had intractable asthma. Seventeen of 18 patients who were followed a minimum of 6 months postoperatively perceived an improvement or a cure of their asthma symptoms. Neither preoperative nor postoperative pulmonary function data were reported.

Urschel and Paulson reported that 104 of 636 patients referred for evaluation of GER or hiatus hernia had asthma or complained of wheezing. Initially, a modified Allison repair was used, although subsequently a modified Belsey repair was favored. Twenty-four of 27 asthmatics experienced complete symptom relief, leading the authors to conclude that asthma may be cured or improved by the surgical correction of GER. Neither preoperative nor postoperative pulmonary function data were mentioned.

Davis described 294 patients who were operated on for hiatus hernia and/or GER. Among these 294 patients, 40 underwent a modified Allison repair and 254 were repaired with the Belsey procedure or a modification thereof. Twenty-seven patients had asthma. They did not report whether asthma symptoms, medication requirements, or pulmonary function improved postoperatively. Interestingly, dyspnea was a presenting complaint in some of the nonasthmatic patients with GER.

Three articles reported that asthma symptoms improved in five of the six patients with asthma after antireflux surgery. Pulmonary function data were not reported. Among 372 hospitalized patients with hiatus hernia, Iverson and colleagues found 96 who suffered from respiratory conditions. Thirty others had asymptomatic abnormalities on chest radiograph. Most patients had pneumonia or bronchitis, but five had asthma. The authors did not report which patients with asthma underwent surgery nor their outcomes.
Lomasney reported respiratory symptoms in 129 of 300 patients prior to the surgical correction of GER. Sixteen patients had asthma and all improved postoperatively. Interestingly, Lomasney reported that “almost all of our 300 patients reported improvement in breathing postoperatively.” The antireflux procedure(s) used was not mentioned.

Henderson and Woolfe described 1,000 consecutive patients referred for evaluation of GER. Among these, 120 of 279 patients with historical evidence of aspiration underwent antireflux surgery and were reevaluated an average of 3.6 years postoperatively. No mention was made of the type of repair. Forty-four of 46 patients with chronic cough or hoarseness improved. None that presented with recurrent respiratory tract infections had problems postoperatively. Seventeen of the 28 asthmatics improved, but none were cured. Pulmonary function tests were performed but not reported.

Pellegrini and coworkers studied the prevalence of respiratory symptoms and their relationship to physiologic GER in 100 patients with abnormal 24-h ambulatory pH monitoring studies. One of four asthma patients had pH monitoring evidence suggesting that GER was triggered by asthma. The remaining three patients were in a group of eight patients whose respiratory symptoms followed documented episodes of GER. Five patients underwent antireflux surgery with improvement in both respi-
ratory and GER symptoms. Neither the type of repair nor the total number of asthma patients that underwent surgery were stated. Pulmonary function data were not reported.²³

There were 17 children with asthma among the 42 patients with chronic pulmonary disorders and GER who underwent Nissen fundoplication reported by Foglia et al.²¹ Thirteen patients who were available for follow up > 6 months after surgery reported improvement in asthma symptoms and medication use. Pulmonary function data were not reported.

Berquist and colleagues²² identified 82 children with chronic asthma and/or recurrent pneumonia among 283 children referred for evaluation of GER. The diagnosis of GER was based on the presence of abnormalities in at least two of the following tests: cine-esophagography, acid reflux, manometry, esophagoscopy, or esophageal biopsy. Seventeen asthma patients with documented GER underwent fundoplication. Asthma symptoms and medication use improved in 15 patients. Pulmonary function data were not reported. It is unclear whether patients in this series overlapped with those reported by Foglia et al.²¹

Johnson et al²³ reported 273 children with GER who underwent antireflux surgery. Three different antireflux procedures were used, most commonly a Nissen fundoplication (55%). The primary complaint was respiratory in 122 children. Ten children with asthma in whom GER was believed to be an exacerbating factor underwent antireflux surgery. Asthma symptoms improved in seven children. Pulmonary function data were not reported.

The series reported by Buts and coworkers³⁸ included five children with asthma or recurrent obstructive bronchitis who underwent fundoplication. Asthma symptoms and medication requirements improved. They did not report pulmonary function data.

Sontag and coworkers¹⁹ reported 13 asthma patients with GER who underwent antireflux surgery. Postoperatively, six patients experienced complete relief from wheezing, six achieved partial relief, and one was unchanged. Medication requirements improved in 10 of 11 patients. Peak expiratory flow improved in three of nine patients after Nissen fundoplication. Three patients died in the follow-up period, including one from status asthmaticus.¹⁹

Perrin-Fayolle et al¹³ reported 44 asthmatics who underwent a Nissen procedure for objectively documented GER. Thirty-two asthmatics had chronic airway obstruction, and 12 were normal between asthma exacerbations. Symptomatic GER was controlled in 42 patients postoperatively. Asthma symptoms and medication requirements were improved in 29 of 44 asthma patients a minimum of 5 years postoperatively. Pulmonary function was unchanged in 31 patients. In six patients, FEV₁ improved from 68.2 ± 4 to 72.7 ± 3% of predicted values. In seven others, FEV₁ improved, but the values were not reported.¹³

Ribet et al²⁴ reported the effects of the Hill antireflux procedure on 132 patients with respiratory disease, including 40 patients with asthma. Surgery cured GER in > 90% of their patients. Asthma symptoms improved in 21 patients. Three of the four deaths occurred in asthma patients. Pulmonary function data were not reported.

Tardif and colleagues³⁷ reported a reduction in asthma medication requirements in 5 of 10 asthma patients after antireflux surgery. They employed either a Toupet or Lortat-Jacob procedure.

DeMeester and colleagues³⁴ performed 24-h pH monitoring in 77 patients with respiratory complaints, including cough, dyspnea, and/or recurrent pneumonia. Seventeen patients who did not respond to medical antireflux therapy underwent either a Nissen fundoplication or a Belsey-Mark IV procedure. Nine of these patients experienced relief from their respiratory symptoms. It is unclear which of the patients who underwent antireflux surgery had asthma.

Bittner and colleagues²⁵ reported their experience with laparoscopic Nissen fundoplication. Among 35 patients with symptomatic GER, 14 had respiratory problems, including 9 with asthma. One half were reported to be satisfied with their surgical results.

Alexander and colleagues⁴⁰ reported 14 asthma patients who underwent laparoscopic Nissen fundoplication. Asthma symptoms improved in 9 patients, and medication requirements decreased in 11 patients. Pulmonary function results were not reported. This study was published only as an abstract.

Rothenberg and coworkers¹¹ reported the effects of laparoscopic fundoplication in 56 children with reactive airway disease and GER. Some had asthma, but others with bronchopulmonary dysplasia were included. Their ages ranged from 1 month to 19 years. Forty-eight of the children experienced prompt improvement in symptoms, 54 experienced improvement in medication requirements, and 16 had a documented improvement in FEV₁.

**Discussion**

Although the results from individual studies reported over 30 years vary considerably, the collected data demonstrate that antireflux surgery improves asthma symptoms and medication requirements, but usually does not improve pulmonary function (Table 2). Comparisons between studies are limited by
protocol and demographic differences. Antireflux procedures have varied between studies and sometimes within studies.\(^1,2,23,29,37\) In some patients, the presence of a hiatus hernia without documentation of GER was the indication for surgery.\(^2\) The anatomic correction of a hiatus hernia would not necessarily improve GER-associated asthma symptoms.

Among the 24 studies mentioned above, only 1 controlled study was published in the peer-reviewed medical literature. The skepticism about whether antireflux surgery has any role in asthma is understandable. Asthma is a chronic condition that may spontaneously wax and wane; therefore, a control group is essential to determine whether an apparent improvement is due to treatment. The expected improvement in the placebo group in asthma trials is approximately 33%.\(^41\) Other reasons besides a beneficial effect from treatment may explain why asthma patients in clinical trials improve. Patients in clinical trials are more likely to have the advantages of regular medical surveillance, instruction in proper medication delivery device use and trigger avoidance, and reinforcement of adhering to the prescribed regimen.\(^10\) Nonadherent patients are often excluded from the trial results. The decision to carry out a major intervention is often made when patients are at their worst, and the principle of “regression toward the mean” may also contribute to subsequent improvement.\(^42\) Undoubtedly, many surgical patients benefit from preoperative consultation by an asthma specialist; this also contributes to subsequent improvement.

Limits of the Studies

Both proponents and opponents of the role of antireflux therapy in asthma have valid criticisms of earlier studies. Skeptics point out that most studies were uncontrolled and that symptomatic improvements were often not confirmed by pulmonary function testing. Moreover, most studies lacked an adequate run-in period to optimize and assess asthma control preoperatively. Some studies did not report operative complications.

Despite these valid criticisms, the summarized results are strikingly similar to findings of controlled studies of medical antireflux therapy in asthma.\(^10\) Both medical and surgical antireflux therapy improve asthma symptoms and medication requirements, but not pulmonary function. This lack of an objective effect on lung function has been another reason for skepticism.

Inflammatory changes in the airway may occur if stomach contents are aspirated and may take a year to heal.\(^43,44\) In some studies, the assessment of asthma response was done early in the postoperative period and may not have allowed enough time for healing of the inflammatory airway changes to occur. The sample sizes of many studies were small, and \(\beta\) error could lead to a beneficial effect being missed.\(^10\) Small sample sizes are not unexpected and only likely to be addressed by large multi-institutional trials. However, if the response to surgery was as dramatic as some have stated, even small studies should have been sufficient to show a beneficial effect. Similar criticisms have been raised about the studies of medical antireflux therapy in asthma.\(^10\)

Some studies had other shortcomings, including a failure to confirm the presence and severity of GER and esophagitis by pH monitoring studies and endoscopy.\(^2,29,30,35\) Ekstrom et al.\(^7\) showed that GER was not confirmed by pH monitoring in approximately one third of asthma patients with typical symptoms. Vincent and coworkers\(^45\) also found that GER symptoms in asthma patients were often not confirmed by physiologic testing.

Most studies were not limited to those patients whose respiratory symptoms appeared to be triggered by GER. DeMeester and colleagues\(^34\) showed that the relationship between GER and respiratory symptoms may demonstrate three patterns: GER may be preceded by respiratory symptoms, it may precede or coincide with respiratory symptoms, or the two conditions may be unrelated. They proposed that GER may only trigger respiratory symptoms in those whose GER precedes or coincides with the respiratory symptoms. Antireflux therapy may only benefit these patients.

A wide variety of antireflux procedures were used in the different studies of the effects of antireflux surgery in asthma (Table 1). Currently, the Nissen fundoplication is the most commonly performed antireflux procedure, particularly since the advent of laparoscopy. Two earlier studies utilized surgical procedures that were used primarily to reduce a hiatus hernia or to restore the gastroesophageal angle, such as the Allison repair.\(^1,29\) Urschel and Paulson\(^1\) reported that it was not a satisfactory procedure, with a 25% failure rate. A number of studies did not specify which antireflux procedures were used. Some studies employed procedures that are much less frequently utilized, such as the Hill procedure and several types of gastropexy (Table 1). Studies did not always confirm that GER and esophagitis were controlled postoperatively by pH monitoring studies and endoscopy. The lack of asthma improvement may be due to persistent GER postoperatively. Limiting the analysis to those studies that objectively confirmed an improvement in GER suggests a postoperative improvement in asthma symptoms, but not pulmonary function (Table 2).
Limiting the analysis to patients who underwent Nissen fundoplication did not change the overall findings either (Fig 2).

**Improvement of Asthma Symptoms but not Pulmonary Function**

The paradox of asthma symptoms and medication requirements but not pulmonary function improving with antireflux therapy warrants consideration. Bronchospasm, either due to microaspiration of gastric contents or a vagally mediated bronchoesophageal reflex, is the most popular explanation of the relationship between asthma and GER. Accordingly, antireflux therapy should not improve asthma without improving pulmonary function. Previous authors have not considered that the apparent paradox reflected the nature of the relationship between the two conditions. They concluded that GER either had a greater effect or no effect on asthma based on their interpretation of negative results or very small changes in pulmonary function. The observation that antireflux therapy improves symptoms without improving pulmonary function may provide clues about the true nature of the relationship between GER and asthma. Two studies reported that GER can cause breathlessness in patients with normal pulmonary function and bronchial reactivity to methacholine. DePaso et al reported that treating GER improved dyspnea. Lomasney and Davis observed that many of their nonasthmatic patients experienced an improvement in their breathing after successful antireflux surgery. The most important determinant of breathlessness is respiratory effort. This has been shown in normal subjects during loaded breathing and in other conditions, including asthma. Increases in VE increase respiratory sensation and may cause breathlessness.

The recent anesthesia literature contains several reports of pain increasing VE. Retrosternal discomfort during AP increased VE and respiratory sensation in nonasthmatic individuals with normal pulmonary function. Those with the greatest increases in VE experienced shortness of breath despite having normal pulmonary function. Perhaps the major benefit from both medical and surgical antireflux therapy is to prevent increases in VE due to retrosternal discomfort accompanying GER. This could explain the apparent paradox of asthma symptoms and medication requirements improving without an improvement in pulmonary function. These findings may also help direct which asthma patients will benefit from antireflux therapy. A recent review of the effects of GER and AP failed to show an effect on pulmonary function in asthma patients without symptomatic GER. If discomfort-induced changes in ventilation explain worsening of asthma symptoms due to GER, there is little justification to treat or investigate asymptomatic GER. Some asthma patients may develop bronchospasm because of the GER-induced increase in VE. Hyperventilation and hypocapnia are known asthma triggers and can cause bronchoconstriction. Antireflux therapy may indirectly improve pulmonary function by preventing the GER-induced changes in ventilation. Another explanation of worsening airway obstruction that has been proposed is the development of GER-induced reflex glottic closure.

**Future Directions**

Clearly, the roles of medical and surgical antireflux therapy in asthma require further investigation. Although significant improvements in pulmonary function have not been consistently demonstrated, the data suggest that symptoms and medication requirements improve with effective antireflux therapy. It is essential to understand the nature of the relationship between GER and asthma to allow a more rational selection of asthma patients for antireflux therapy.

Investigators are becoming increasingly interested in the effects of treatment on “quality of life” in asthma. Although objective changes have been the traditional measures, small statistically significant changes in lung function do not necessarily predict a meaningful clinical effect. The ability of asthmatics to exert themselves, to minimize absences from school and work, and to avoid exacerbations that

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**Figure 2.** The effects of open and laparoscopic Nissen fundoplication on gastroesophageal reflux symptoms, asthma symptoms, asthma medication requirements, and pulmonary function testing. The black bars show the number of patients who improved postoperatively, and the gray bars show the number of patients who did not in the nine reports in which Nissen fundoplication was used.
disrupt lives, both day and night, are more important to them than small changes in pulmonary function. Antireflux therapy may have a major impact on quality of life measures in both the GER and asthma domains, by improving symptoms and decreasing the need for medications, including corticosteroids and theophylline, along with their serious and unpleasant side effects. To help understand rather than confuse, future studies should be controlled, they should be large enough to avoid β error, and they should objectively document the severity of both GER and asthma both preoperatively and postoperatively. Patients enrolled in these studies require adequate run-in periods to allow proper assessment and stabilization of their asthma, and they should be followed for an adequate time after surgery to ensure healing of esophagitis and airway inflammation. Since objective measures may not adequately reflect the impact on patients, properly evaluated quality of life tools should also be used to assess the effects of therapy. Studies should report the side effects of asthma and antireflux medications, as well as surgical and anesthetic complications.

In summary, 24 reports of the effects of antireflux surgery on asthma have been published over a 30-year period. Similar to medical antireflux therapy, surgical antireflux procedures improve asthma symptoms and medication requirements, but do not improve pulmonary function.

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