Gastroesophageal reflux and asthma: Can the paradox be explained?

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BACKGROUND AND OBJECTIVE: The reported effects of asthma on gastroesophageal reflux (GER), effects of GER on asthma and the effects of antireflux therapy on asthma are conflicting. The purpose of this paper is to review the evidence for a relationship between the two conditions.
DESIGN: A search of the MEDLINE 1966 to 1999 database, combining the terms GER and asthma, was used to identify studies of the effects of acid perfusion of the esophagus, the physiological equivalent of GER and the effects of both medical and surgical antireflux therapy on asthma. Bibliographies of the identified papers were also reviewed.
MAIN RESULTS: The collected evidence suggests that GER causes asthma symptoms but has minimal effects on pulmonary function. Both medical and surgical antireflux therapy can improve asthma symptoms and asthma medication requirements without improving pulmonary function. The paradox of GER causing symptoms without affecting pulmonary function may be because of the retrosternal discomfort that accompanies GER increases minute ventilation and respiratory sensation.
CONCLUSIONS: Despite an extensive body of literature, many questions remain about the relationship between GER and asthma. A review of the data suggests a strong association between the two conditions, and that GER worsens asthma symptoms without affecting pulmonary function. Asymptomatic GER does not worsen asthma. Antireflux therapy may have a role in asthma patients with symptomatic GER, possibly being most beneficial for those with reflux-associated respiratory symptoms. Unfortunately, many studies contain flaws such as a lack of controls and small sample sizes. Further properly designed controlled trials, including ones that measure the effects of GER and antireflux therapy on quality of life, are needed to understand better the role of GER in asthma.

Key Words: *Bronchial reactivity; Chest pain; Cough; Dyspnea; Fundoplication; Heartburn; Vagal reflexes*

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The 1892 edition of Sir William Osler's (1) textbook of medicine included the caveat that people with asthma should not eat a large evening meal to avoid wheezing at night. Bray (2) proposed in 1934 that gastric distention causes bronchospasm by a vagally mediated reflex. It was the 1960s, however, before data demonstrating an association between asthma and gastroesophageal reflux (GER) were available (3,4). Several investigators reported that the people

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Reflux gastroœsophagien et asthme : pouvons-nous expliquer ce paradoxe ?

HISTORIQUE ET OBJECTIF : Les effets rapportés de l'asthme sur le reflux gastroœsophagien (RGO), des effets du reflux gastroœsophagien sur l'asthme et des effets du traitement antireflux sur l'asthme sont en contradiction. Le but du présent article est de rechercher les preuves d'une relation entre les deux affections.
MODÈLE : Une recherche dans la base de données Medline de 1966 à 1999 combinant les termes « GER » et « *asthma* » a permis d'identifier les études portant sur les effets d'une perfusion acide dans l'œsophage, l'équivalent physiologique d'un RGO, et les effets du traitement médical et chirurgical antireflux sur l'asthme. Les bibliographies des articles identifiés ont aussi été passées en revue.
PRINCIPAUX RÉSULTATS : Les preuves recueillies laissent à penser que le RGO cause les symptômes de l'asthme mais n'a que des effets minimes sur la fonction pulmonaire. Les traitements médical et chirurgical antireflux peuvent tous deux améliorer les symptômes de l'asthme et diminuer le besoin de médication contre l'asthme sans cependant améliorer la fonction pulmonaire. Le paradoxe du RGO causant des symptômes sans détériorer la fonction pulmonaire pourrait résider dans le fait que la douleur rétrosternale qui accompagne le RGO accroît la ventilation minute et la sensibilité respiratoire.
CONCLUSIONS : Malgré un nombre imposant d'articles, de nombreuses questions demeurent au sujet d'une relation entre RGO et asthme. Une revue des données laisse à penser qu'il existe une forte association entre ces deux affections, et que le RGO aggrave les symptômes de l'asthme sans détériorer la fonction pulmonaire. Le RGO asymptomatique n'aggrave pas l'asthme. Le traitement antireflux pourrait être indiqué chez les patients asthmatiques atteints d'un RGO symptomatique, et serait le plus bénéfique pour ceux dont les symptômes respiratoires sont associés au reflux. Malheureusement, de nombreuses études contiennent des failles comme le manque de témoins et la taille insuffisante des échantillons. D'autres essais comparatifs bien conçus, y compris ceux qui mesurent les effets du RGO et du traitement antireflux sur la qualité de vie, sont nécessaires pour mieux comprendre le rôle du RGO dans l'asthme.

with asthma in their large series of patients undergoing antireflux procedures experienced improvement and, in some cases, cure of their asthma after successful surgery. These observations stimulated research into the nature of the relationship between GER and asthma. Some investigators implicated GER as an important asthma trigger and reported that treating GER was important for good asthma control (5-7). Others, however, concluded that GER does not adversely affect asthma and that antireflux therapy is not beneficial for asthma control (8-10). This review presents the apparently conflicting data surrounding the relationship between the two conditions, offers an explanation for the strong association between them and suggests indications for investigating and treating GER in patients with asthma.

ASSOCIATION BETWEEN GER AND ASTHMA

Both asthma and GER are relatively common conditions in the general population. Twenty per cent of telephone survey respondents reported at least three episodes of symptomatic GER per month (11). Both the prevalence and severity of GER are greater in asthma (Figure 1). The prevalence of GER in asthma patients has ranged from 30% to 90% depending on which subjects were studied and the methods used to determine the presence of GER (12). In a controlled, questionnaire-based survey of consecutive patients attending a university asthma clinic, 45% had pyrosis regularly compared with only 10% of the patients in two control groups (13). Irwin et al (5) reported that two-thirds of patients referred to their university-based clinic with difficult to control asthma had symptomatic GER. Sontag and colleagues (14,15) evaluated outpatient asthma clinic attendees at a Veterans Administration hospital and found that more than 80% had abnormal esophageal pH monitoring studies, nearly 60% had a hiatus hernia and 40% had erosive esophagitis. Balson et al (16) reported that 75% of pediatric patients with severe asthma had abnormal pH monitoring studies. These reports suggest a strong association between the two conditions, but the nature of the relationship between them is controversial. The relationship may be because of asthma causing GER, bronchodilator medication causing GER or, as most investigators have assumed, GER causing asthma.

DOES ASTHMA CAUSE GER?

GER should be more prevalent in asthma because cough and the greater respiratory effort accompanying it increase the pressure gradient across the lower esophageal sphincter, which favours the retrograde movement of gastric contents (13). Singh and Jain (17) reported that treatment with ephedrine and the resulting improvement in five asthma patients reduced GER. Moote and colleagues (18) performed methacholine challenge tests in patients with mild asthma and in normal subjects while they were undergoing esophageal pH monitoring and found that GER was increased in people with asthma. In a similarly designed study, Ekstrom and Tibbling (19) were unable to demonstrate increased GER in asthma patients undergoing histamine challenge testing. The differences among the studies cannot be explained by the use of different bronchoconstricting agents because methacholine increases lower esophageal sphincter pressure and histamine increases gastric acid secretion.

DO BRONCHODILATORS CAUSE GER?

Both theophylline and beta agonists relax the lower esophageal sphincter, which should facilitate GER, and theophylline increases gastric acid production (20-22). Therapeutic doses of beta agonists, however, do not increase GER in asthma patients or normal subjects (23,24). The findings with theophylline are not consistent. Approximately

half of investigators have reported that theophylline increases GER, but the remainder were unable to demonstrate an effect (25-30). Two groups did not find an increased prevalence of GER in asthma patients receiving regular bronchodilator medication (13,14). In another study, bronchodilator medication use was similar in asthma patients with and without GER (31). These cross-sectional studies may have been unable to identify an association between theophylline use and more severe GER because patients who develop GER are more likely to discontinue its use.

GER AND RESPIRATORY SYMPTOMS

Several authors reported that asthma patients experience respiratory symptoms during episodes of symptomatic GER. Ekstrom et al (32) found that 56% of asthma patients with GER experienced reflux-associated respiratory symptoms (RARS), ie, cough, dyspnea or wheezing, during episodes of symptomatic GER. Field et al (13) found that 41% experienced RARS and 28% used their rescue beta agonist during episodes of symptomatic GER. Goodall et al (33) reported a correlation between the severity of GER and asthma symptoms. Harding et al (34) reported a temporal correlation between GER, documented by ambulatory pH monitoring, and respiratory symptoms in asthma patients. The relationship between GER and asthma symptoms led investigators to study the effects of simulated and real GER on pulmonary function.

ANIMAL STUDIES

The foregut and respiratory tract have common embryological origins and share a number of reflexes that coordinate breathing and deglutition. Diaphragmatic tone contributes to lower esophageal sphincter function (35,36). In both feline and canine models, esophageal distention stimulates mechanoreceptors in the afferent limb of a vagal reflex that relaxes the crural diaphragm, facilitating the movement of the food bolus through the lower esophageal sphincter (37,38). Harding and Titchen (39) reported that hydrochloric acid stimulates esophageal mechanoreceptors. Mansfield et al (40) showed that acid perfusion (AP) of the canine esophagus increased airway tone and that this response was abolished after bilateral cervical vagotomy. They postulated that the increase in airway tone during AP was because of a vagally mediated reflex. Hamamoto et al (41) reported that AP of the esophagus caused inflammatory changes in the guinea pig bronchial tree. They proposed that AP of the esophagus might trigger asthma by stimulating the production of neurogenic inflammatory mediators. A recent study of the composition of expectorated sputum found no difference in inflammatory mediators in asthma patients with and without GER (42).

Tuchman and colleagues (43) found that intratracheal instillation of 0.05 mL of 0.2 N hydrochloric acid increased airway resistance substantially more than 10 mL 0.2 N hydrochloric acid instilled into the feline esophagus, leading them to conclude that microaspiration could be the mechanism by which GER triggered asthma. Consistent with this hypothesis, Ishikawa and co-workers (44) recently reported that AP of the esophagus did not increase airway tone but laryngeal stimulation with hydrochloric acid did.

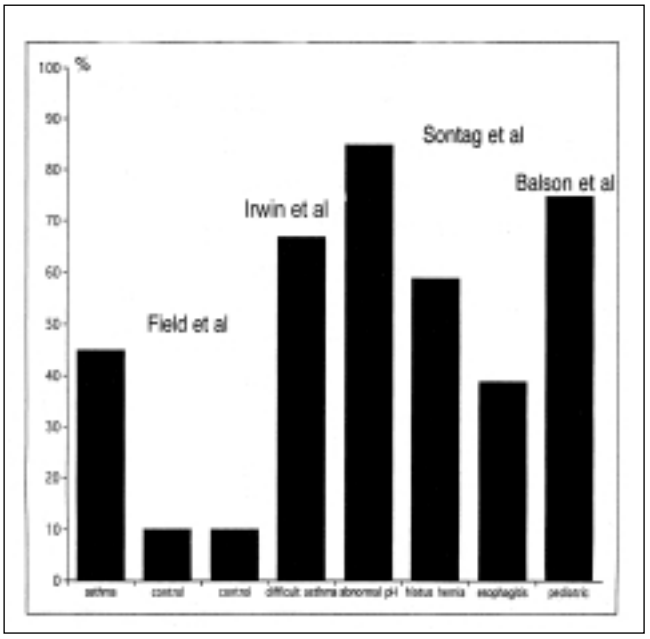

Figure 1) *The prevalence of gastroesophageal reflux (GER) in different groups of asthma patients. The first three histograms on the left are the percentage of asthma patients and subjects in two separate control groups with symptomatic GER, respectively. Data adapted from reference 13. The next column, fourth from the left, is the percentage of difficult to control patients with asthma with GER. Data adapted from reference 5. The next three columns are the percentage of asthma clinic attendees with abnormal ambulatory pH findings, hiatus hernia and erosive esophagitis, respectively. Data adapted from references 14 and 15. The column on the right is the percentage of children with severe asthma found with abnormal ambulatory pH monitoring findings. Data adapted from reference 16*

EFFECTS OF AP OF THE ESOPHAGUS ON PULMONARY FUNCTION IN HUMANS

Vagal reflexes originating in the esophagus are present in humans. Esophageal distention inhibits diaphragm function (45). Wright et al (46) reported the effects of AP of the esophagus on heart rate, forced expiration volume in 1 s (FEV_1) and arterial saturation in 136 subjects. FEV_1 and arterial saturation were the same during AP and saline perfusion of the esophagus, but the decline in heart rate was greater during AP of the esophagus. The reduction in heart rate suggests that AP increases vagal tone but does not cause a clinically significant decline in pulmonary function (46). Unfortunately, this study did not separate the results from the patients with asthma from those of normal subjects and patients with chronic bronchitis. Lodi et al (47) performed vagal testing in asthma patients with symptomatic GER and found that the majority displayed cardiovascular responses consistent with increased vagal activity compared with controls. Vagal activity, however, did not correlate with asthma severity.

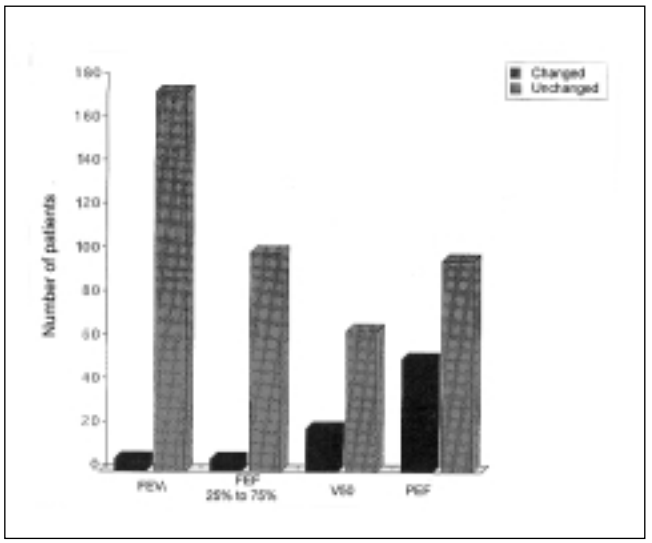

Figure 2) *The effect of acid perfusion (AP) of the esophagus on pulmonary function of people with asthma. The pairs of bars show the number of patients with asthma in studies that do (black bar) and do not (gray bar) show a significant change in forced expiration volume in 1 s (FEV_1), forced midexpiratory flow ($FEF_{25-75\%}$) and peak expiratory flow (PEF) during AP. V_{50} Flow at 50% vital capacity. Reproduced with permission from reference 63*

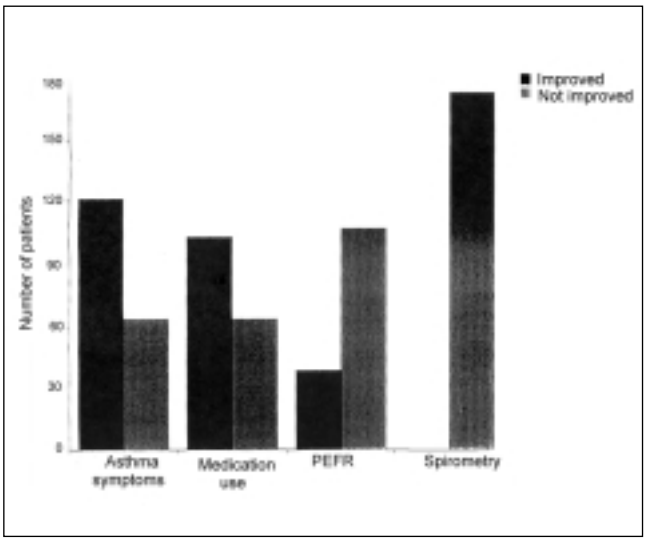

Figure 3) *Summarized data on the effects of medical antireflux therapy on asthma symptoms, asthma medication use, peak expiratory flow rate (PEFR) and spirometry in eight randomized, placebo controlled trials. Each pair of columns shows the number of patients in the studies who improved (black bar) and did not (gray bar) improve. Reproduced with permission from reference 76*

HUMAN STUDIES OF THE EFFECTS OF GER ON PULMONARY FUNCTION

Most investigators assumed that GER triggered asthma because of the effects of AP in animal studies, and the development of respiratory symptoms in asthma patients during symptomatic GER. A number of investigators have reported the effects of AP on pulmonary function in people with asthma (8,9,46,48-62). These studies were designed to maximize the likelihood that the effects of GER on pulmonary function would be identified. Investigators measured a number of spirometric, flow-volume loop and resistance indexes during AP. Twelve of 18 papers on the effects of GER or AP of the esophagus in asthma published in the English-language literature reported that one or two pulmonary function indexes declined during AP or GER (63). In general, these studies found small but statistically significant changes in the more sensitive and less specific parameters, but statistical corrections for multiple measurements were not included in the analysis. A critical review of these studies found that, for each parameter, only a minority of patients experienced any decline (Figure 2) (63). Segregating the data by whether asthma patients had symptomatic GER did not affect the findings (63).

Aspiration of gastric contents causes inflammatory changes in the airway (64). Mendelson (65) reported that wheezing was a feature of massive aspiration. Although acid aspiration that was severe enough to decrease tracheal pH at a location 2 cm above the carina caused a significant decrease in peak expiratory flow (PEF) in their patients with asthma, Jack et al (48) were unable to show that AP of the esophagus caused a significant decline in PEF. Relatively large amounts of aspirate can cause changes in pulmonary function; however, this is not typical in patients with GER. Several investigators reasoned that, if microaspiration, repeated aspiration of minute amounts of gastric contents, was a cause of bronchoconstriction, then GER into the proximal esophagus would be a better predictor of pulmonary function changes than GER limited to the lower esophagus (59). Proximal reflux, however, did not correlate with changes in lung function (66).

EFFECTS OF MEDICAL ANTIREFLUX THERAPY IN ASTHMA

Reports of asthma improving with successful antireflux surgery led investigators to study the effects of H2 receptor blockers in patients with asthma with GER (32,33,56,67-69). Initially, there were concerns that these medications may cause clinical worsening of asthma because of H2 receptor blockade in the bronchial tree (70-72). Although some investigators reported that H2 receptor blockers increase bronchial reactivity, their use in asthma appears to be safe (73-75). A recent critical review identified 12 English-language studies of the effects of medical antireflux therapy in people with asthma with GER (76). In the eight controlled studies, two used cimetidine, four ranitidine and two omeprazole (10,32,33,67-69,77,78). A critical review of the controlled studies indicates that medical antireflux therapy improved GER symptoms, asthma symptoms and asthma medication requirements (76). Medical antireflux therapy, however, did not improve PEF or spirometry (Figure 3). Since the publication of this report, two more controlled trials with omeprazole have been published (79,80). The addition of the results from these two studies to the critical review did not affect its conclusions (76). A recent study of the effects of lansopra-

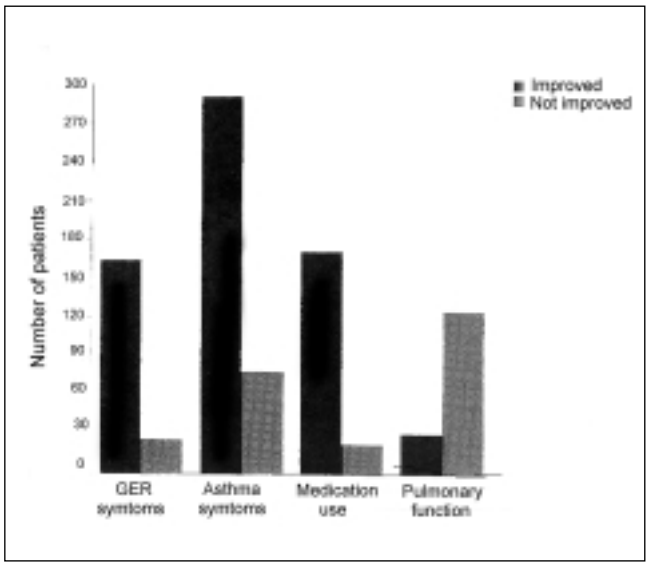

Figure 4) *The effects of antireflux surgery on gastroesophageal reflux (GER) symptoms, asthma symptoms, asthma medication requirements and pulmonary function testing. The dark bars indicate the number of subjects who experienced an improvement, and the lighter bars indicate the number of patients who did not improve. Reproduced with permission from reference 82*

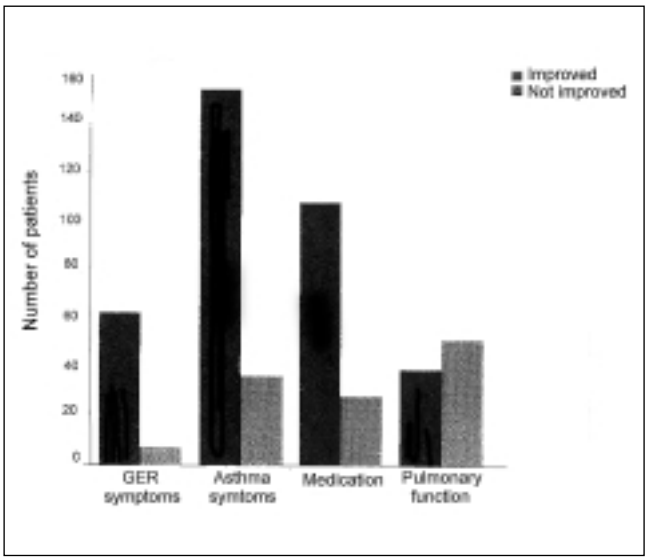

Figure 5) *The effects of open and laparascopic Nissen fundoplication on gastroesophageal reflux (GER) symptoms, asthma symptoms, asthma medication requirements and pulmonary function testing. The black bars show the number of patients who improved postoperatively, and the gray bars show the number of patients who did not improve in the nine reports in which Nissen fundoplication was used. Reproduced with permission from reference 82*

zole found that it also improved respiratory symptoms and quality of life, but neither PEF nor spirometry improved in asthma patients with GER (81).

EFFECTS OF SURGICAL ANTIREFLUX THERAPY

Since the 1960s, antireflux surgery has been reported to be beneficial in asthma patients with GER (3,4). A recent review identified 24 reports, with more than 400 patients, on the effects of antireflux surgery in asthma (82). The two controlled trials demonstrated that antireflux surgery improves asthma symptoms and asthma medication requirements but does not improve pulmonary function (67,83). The addition of the results of the open reports to the controlled trials does not change the conclusions. Antireflux surgery improves GER symptoms, asthma symptoms and asthma medication requirements but does not improve pulmonary function (Figure 4) (3,4,6,84-102). Limiting the analysis to the effects of Nissen fundoplication, the current gold standard surgical procedure, did not alter the findings (Figure 5) (82).

Several other reports of the effects of antireflux surgery have been described. Hunter and colleagues (103) reported symptomatic improvement in 25 of 30 asthma patients following fundoplication. Unfortunately, neither the effects on asthma medication requirements nor pulmonary function were reported. A retrospective study of 39 people with asthma among 600 patients undergoing antireflux surgery found that asthma symptoms and medication requirements improved postoperatively. Pulmonary function was not reported (104). Ruth et al (105) found that fundoplication improved asthma symptoms but did not improve pulmonary function or bronchial reactivity to methacholine. The additional data do not change the findings of the recent critical review on antireflux surgery (82). The effects of both surgical and medical antireflux therapy on asthma show a paradox. Antireflux therapy improves asthma symptoms and asthma medication requirements but does not improve pulmonary function (82).

CAN THE PARADOX BE EXPLAINED?

Previous investigators of the relationship between GER and asthma are divided into two opposing camps. Some believe that GER worsens asthma and treating GER improves it. Others have disagreed and interpreted the data to indicate that GER does not affect asthma. Another explanation is that GER does not affect pulmonary function but causes respiratory symptoms requiring asthma medication. An obvious question is whether this apparent paradox can be explained.

GER is a frequent cause of chronic cough that responds to antireflux therapy (106-108). Orringer (109) suggested that the chest discomfort associated with GER may produce a subjective feeling of shortness of breath in patients. There are several reports that GER can cause dyspnea in patients with normal pulmonary function and bronchial reactivity, and that treating GER relieves dyspnea (110,111).

The anesthesia literature contains several reports that pain can increase minute ventilation (112). Respiratory effort is the most important determinant of respiratory sensation (113). Retrosternal discomfort because of GER can increase minute ventilation that, in turn, increases the sensation of respiratory effort that is experienced as dyspnea in some

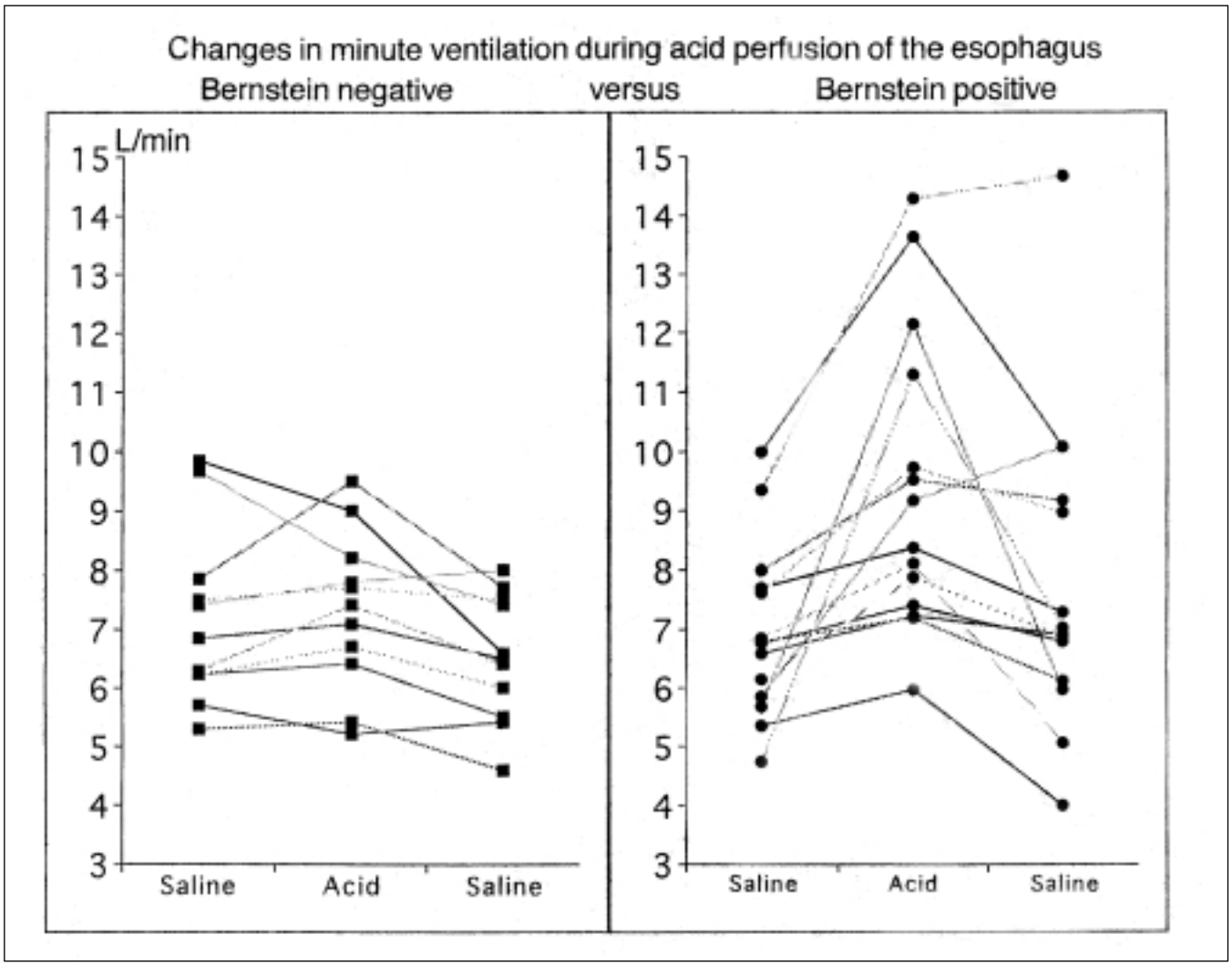

Figure 6) *Minute ventilation of individual patients during saline and acid perfusion periods. Patients are grouped according to whether they had a positive or negative acid perfusion test result. The minute ventilation for the Bernstein-positive patients was 7.0±1.6, 9.4±2.6 and 7.8±2.5 L/min in the first saline, acid and second saline perfusion periods, respectively. The minute ventilation for the Bernstein-negative patients was 7.2±1.5, 7.4±1.5 and 6.6±1.2 L/min in the first saline, acid and second saline perfusion periods, respectively. Reproduced with permission from reference 114.*

patients. To test this hypothesis, nonasthmatic patients with normal pulmonary function who were undergoing motility testing as part of their investigation for esophageal disease were given an acid reflux test (114). Patients who developed pain during the acid reflux test increased their minute ventilation, whereas those with negative acid reflux tests did not (Figure 6). The increase in respiratory sensation correlated with the increase in minute ventilation (114). The majority of subjects with a positive acid reflux test described the increased respiratory sensation as an awareness of their greater respiratory effort that was not unpleasant. The two subjects with the greatest increases in minute ventilation described their respiratory sensation as air hunger that was unpleasant (114). Similar increases in minute ventilation in asthma patients with abnormal pulmonary function may cause even greater changes in respiratory sensation.

Hyperventilation and hypocarbia are recognized triggers of bronchospasm (52). The increase in minute ventilation accompanying retrosternal discomfort in asthma patients with symptomatic GER may explain the reports of wheezing associated with symptomatic GER. GER, therefore, may serve as an indirect trigger of bronchospasm in sensitive individuals.

ALTERNATIVE EXPLANATIONS OF THE PARADOX

Other explanations have been offered to explain the inability to show consistently that GER worsens pulmonary function or that antireflux therapy improves it. Asthma patients are sensitive to a variety of triggers including allergens, exercise and cigarette smoke. The response to different triggers varies among asthma patients. Similarly, not all asthma patients are sensitive to GER. Nonasthmatic patients with respiratory symptoms may be diagnosed to be asthmatic and treated for

asthma (115). Inclusion of similar patients in studies would preclude showing an effect on pulmonary function because of GER or antireflux therapy. Pulmonary function testing was not routinely done in some of the investigations, increasing the likelihood that nonasthmatic patients were included. Moreover, asthma patients may experience reflux-like symptoms in the absence of physiological GER (31,32). The absence of either asthma or GER in some members of the study cohort may explain the inability to show an effect. Moreover, continuing asthma medications during the studies may have blunted the response to GER. AP of the esophagus increases cough sensitivity to capsaicin (116). Instead of a direct effect on airway tone, GER may indirectly increase the sensitivity to other triggers.

There are additional reasons why antireflux therapy failed to improve pulmonary function. Most studies did not confirm that antireflux therapy adequately suppressed GER in the study cohort. The study by Harding et al (117) was the exception, showing that GER remained abnormal in a third of their subjects receiving the standard dose of omeprazole, 20 mg once daily. Even if acid suppression is sufficient, inflammatory changes in the airway may take more than one year to heal (118). Most studies were relatively short, and Meier (77) reported persistent esophagitis even after six weeks of daily therapy with 40 mg of omeprazole. Most studies of the effects of both medical and surgical antireflux therapy contained small numbers of patients, and beta error cannot be excluded as the reason that a positive effect was not demonstrated (82).

Trigger avoidance is the recommended first line approach to asthma management (119). Irwin et al (5) reported that GER was the most common trigger in patients with difficult to control asthma. Some have advocated an aggressive approach to both the investigation and treatment of GER in asthma even in the absence of GER symptoms (5-7). Others reported that GER has no adverse effect on pulmonary function and treating it does not improve asthma management (9,10,56,58,60,68,80). The uncertainty surrounding the relationship between asthma and GER is reflected by the ambivalence in the recommendations for the evaluation and treatment of GER in the National Institutes of Health-sponsored asthma guidelines (120). Analysis of the available literature suggests that an approach that falls between the extremes of ignoring GER and aggressively investigating for and treating asymptomatic GER in asthma is appropriate.

Most physicians would agree that the presence of asthma should not affect the appropriate investigation and treatment of patients with symptomatic GER. The evaluation and treatment of GER should also be considered for asthma patients with less severe GER symptoms, especially if they have RARS (32). The literature available does not support the investigation for and treatment of GER in asthma patients lacking GER symptoms. A full discussion of the controversy surrounding the relative merits and cost effectiveness of medical versus surgical antireflux therapy is beyond the scope of this review. The available data, however, suggest that medical and surgical antireflux therapy have similar effects on asthma symptoms and asthma medication requirements in patients with symptomatic GER (76,82). The limited amount of available controlled data does not show that either medical or surgical antireflux therapy has a clinically significant effect on pulmonary function (76,82). Further properly controlled studies of the effects of antireflux therapy in asthma should be undertaken. It is mandatory that they be adequately powered with adequate numbers of subjects and measure GER and pulmonary function objectively, confirm that GER is controlled for an adequate treatment period and confirm the effects of antireflux therapy on pulmonary function. Future studies should also measure the effects of antireflux therapy with properly validated quality of life questionnaires (79,81). Quality of life measures may be the best way to assess the effects of antireflux therapy because it appears to affect asthma symptoms but not pulmonary function.

SUMMARY

There is a strong association between GER and asthma but the nature of the relationship remains controversial. Although GER causes respiratory symptoms in asthma patients, it does not appear to affect pulmonary function. Moreover, both medical and surgical antireflux therapy improve asthma symptoms and medication requirements but do not improve pulmonary function. The apparent paradox of the effects of GER and antireflux therapy in asthma patients may be explained by discomfort-induced changes in minute ventilation.

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