

Original Article

Bronchial hyperreactivity in patients with gastroesophageal reflux disease*

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ABSTRACT

Objective: To identify this vagal reflex using bronchial provocation tests in patients with gastroesophageal reflux disease. **Methods:** The study group was composed of 10 patients presenting endoscopic evidence of hiatal hernia or gastroesophageal reflux disease, and the control group consisted of 11 patients presenting no evidence of either condition. All subjects were submitted to bronchial provocation with carbachol. **Results:** The provocation test was positive in 5 (50%) of the study group patients and 3 (27%) of the control group patients ($p = 0.64$). **Conclusion:** The hypothesis that the airways of patients with gastroesophageal reflux disease (and no history of asthma-like respiratory symptoms) might be more responsive than those of individuals without the disease remains unproven.

Keywords: Asthma/complications; Gastroesophageal reflux/complications; Hernia hiatal; Peak expiratory flow rate; Bronchial hyperreactivity; Forced expiratory volume; Carbachol/diagnostic use

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INTRODUCTION

Asthma is a disease of the upper airways that occurs in susceptible individuals and presents three main characteristics: obstruction of the upper airways that is either spontaneously reversible (although not completely in some individuals) or reversible with treatment; inflammation of the airways; and hyperreactivity of these airways to a large number of stimuli.⁽¹⁾

There are a few factors that predispose to bronchial hyperreactivity (BHR): allergens, infections, gastroesophageal reflux, air pollution, inhaled irritants, physical exercise, pharmacological stimulants and emotional factors.⁽²⁾

Gastroesophageal reflux disease (GERD) may present in several forms, some including extra-esophageal symptoms. In the respiratory tract, GERD may manifest as a simple persistent cough, voice alteration or even severe clinical profiles such as chronic bronchitis, recurrent pneumonia and asthma-like manifestations.⁽³⁻⁵⁾ The incidence of GERD among asthmatic patients (ranging from 40% to 80%) exceeds the incidence in the general population. Therefore GERD constitutes an important instability factor in BHR.⁽⁶⁻⁷⁾

It is believed that gastroesophageal reflux may aggravate or even cause BHR in certain patients.⁽⁸⁻¹⁰⁾ The possible mechanisms involved in triggering BHR in such individuals include microaspiration of refluxed acid^(8,11) and activation of a vagal reflex from the esophagus to the lung (resulting in bronchoconstriction),⁽¹¹⁻¹³⁾ as well as sensitization of the vagal system (acid-sensitive receptors in the esophageal wall), which can induce or accentuate BHR.^(6, 14-16)

In cases of chronic cough of undefined etiology, the bronchial provocation test is used to define whether the cough is asthma-related. Upper digestive endoscopy and contrast-enhanced radiological examination of the esophagus, stomach and duodenum are used to diagnose GERD, asymptomatic or not. Although considered the gold standard exam for the diagnosis of GERD, pHmetry often presents false-negative results does not yet have a standardized value of normality. This was demonstrated in a doctoral thesis,⁽¹⁴⁾ in which only 72% of the patients with biopsy-confirmed esophagitis tested positive for GERD.

Chronic cough and bronchial asthma can be caused by gastroesophageal reflux. The main consequence of such reflux in the lung is the stimulus

of an esophagobronchial and tracheal vagal reflex which could lead to diffuse bronchoconstriction. However, the intensity and the significance of this vagal reflex in individuals with GERD who do not present respiratory symptoms is unknown. Asymptomatic patients may present BHR alteration detectable only by bronchoprovocation. One published study, the only one on this issue, revealed that gastroesophageal reflux is correlated with increased BHR in patients without pulmonary symptoms.⁽¹⁷⁾

Since gastroesophageal reflux is an important causal factor of BHR, and its main mechanism of action is through an esophagobronchial vagal reflex, the objective of this study was to assess, through bronchoprovocation with carbachol, whether patients with GERD present more BHR than do normal individuals, and to reveal, through bronchoprovocation, the existence of esophagobronchial reflex in patients who do not present pulmonary disease.

METHODS

A group of 10 patients with GERD and a control group of 11 individuals without GERD were studied during the 1998-2000 period. The patients were volunteers from the Gastroenterology Outpatient Clinic and the Endoscopy Department of the Faculdade de Medicina do ABC (ABC School of Medicine).

We used the following inclusion criteria: presenting esophagitis, hiatal hernia or gastroesophageal reflux confirmed by digestive endoscopy; presenting gastritis or normal endoscopic examination (in control patients); being a nonsmoker or having quit smoking more than eight years prior; presenting pulmonary function tests within patterns of normality; having no history of respiratory symptoms.

The exclusion criteria were as follows: being over 70 years of age (since most patients in this age bracket presented considerable difficulty in performing this test); having undergone endoscopy more than three months prior to the date of the test; presenting more than two comorbidities.

The patients were initially submitted to a pulmonary function test to confirm the pattern of normality. The test was carried out using a Collins spirometer, the use of which was duly explained to the patient. Forced vital capacity (FVC) maneuvers were performed. Volume-time and flow-volume curves were also recorded. From these curves, forced expiratory volume in one second (FEV₁), FVC and the relationship

between the two (FEV_1/FVC) were determined.

Bronchoprovocation was performed if the pulmonary function was within normality patterns, that is, if the FEV_1/FVC ratio was higher than or equal to 75% or if FEV_1 was higher than 80% of predicted.

Bronchoprovocation was performed with carbachol at the following dilutions: 0.25; 0.50; 1.00; 2.00 and 4.00 mg/ml. Inhalation was sustained for 120 seconds, followed by new spirometric curve measurements, until the total dose or a 20% drop in FEV_1 was achieved. If there was a drop in FEV_1 of 20% or more, the test was considered positive. The cumulative dose that determined the test as positive was 2.5 mg.

The study was approved by the ABC School of Medicine Ethics Committee. All patients gave written informed consent.

The results obtained from the two groups were statistically compared using the paired Student's t-test. Calculations were made using the Statistical Analysis System.

RESULTS

We performed 29 pulmonary function tests and 21 bronchoprovocation tests with carbachol. Eight patients presented abnormal pulmonary function test results, which contraindicated the bronchoprovocation test.

Of the 21 bronchoprovocation tests performed, 17 were performed in women and 4 in men; 10 were performed in patients with GERD, reflux esophagitis or hiatal hernia, as shown in Tables 1 and 2. We observed that 6 of these patients presented gastroesophageal reflux, 3 presented reflux

esophagitis, and 3 presented hiatal hernia (all diagnosed by digestive endoscopy). Six patients were being treated with a proton pump inhibitor. Two patients presented a history of treatment for rhinitis, and 5 of the 10 patients reacted positively to the bronchoprovocation test (drop in $FEV_1 > 20\%$).

In the control group, 9 patients had gastritis and the remainder presented endoscopic exams within normality patterns. Three presented a positive bronchoprovocation test. Two patients (1 of whom was a former smoker) had a history of treatment for rhinitis, 1 had rheumatoid arthritis, and 2 had systemic arterial hypertension. Of the 2 patients with systemic arterial hypertension, one admitted being a smoker prior to the test, and the other had had pneumonia three months prior to the test (Tables 3 and 4).

We chose not to exclude the smokers from the study since they presented negative bronchoprovocation, and the final result of the study would therefore not be affected.

Ages ranged from 23 to 64 in the group with GERD and from 17 to 63 in the control group (Tables 1 and 3).

Figure 1 summarizes the results of the tests in the two groups. There were no statistical differences regarding age. Mean age in the GERD group was 45.09 (± 13.52), and mean age in the control group was 45.27 (± 14.24) ($p = 0.95$). The bronchoprovocation test was positive in 27% of the individuals of the control group ($n = 3$) and in 50% of the patients with GERD ($n = 5$). However, this difference was not found to be statistically significant using Fisher's exact test ($p = 0.22$).

TABLE 1

Patients with gastroesophageal reflux, hiatal hernia or reflux esophagitis

Patient N ^o	Age/gender	Diagnosis	Accompanying disease(s)	Drugs used
1	61/F	GERD	None	None
2	23/M	GERD	History of rhinitis	Omeprazole (1 week)
3	47/F	RE stage II	None	Omeprazole (4 months)
4	64/F	GERD	None	Omeprazole (3 months)
5	47/F	HH	History of rhinitis/sinusitis	None
6	50/F	GERD/RE	None	Omeprazole (1 month)
7	52/F	HH/RE stage IV	Clinical profile of sinusitis for six years	Gentamicin Omeprazole (3 months) Cisapride
8	37/F	HH stage II/Gastritis	History of sinusitis/Smoking	None
9	41/M	GERD	None	Omeprazole on the test day
10	28/M	GERD	None	None

F: female; M: male; GERD: gastroesophageal reflux disease; RE: reflux esophagitis; HH: hiatal hernia

TABLE 2
Bronchoprovocation with carbachol in patients with gastroesophageal reflux, hiatal hernia or reflux esophagitis

Patient N ^a	FEV ₁ Baseline	FEV ₁ After drug	FEV ₁ (%)	Conclusion Carbachol dose (mg)
1	1.96	1.92	2	Negative Carbachol 2.5
2	3.92	2.85	27	Positive Carbachol 0.37
3	3.13	3.00	4	Negative Carbachol 3.0
4	1.95	1.78	8	Negative Carbachol 3.2
5	3.28	2.23	32	Positive Carbachol 2.16
6	2.26	1.79	20	Positive Carbachol 1.50
7	2.11	1.56	26	Positive Carbachol 0.37
8	3.37	3.16	6	Negative Carbachol 2.8
9	4.09	3.74	8	Negative Carbachol 3.25
10	4.15	2.84	32	Positive Carbachol 0.4

FEV₁: forced expiratory volume in one second (in liters)

DISCUSSION

Approximately 90% of all patients with nonallergic asthma present GERD. To date, the relationship between gastroesophageal reflux and respiratory diseases remains under debate.⁽⁷⁾

One group of researchers suggested that gastroesophageal reflux causes asthma symptoms but does not significantly affect the pulmonary function.⁽¹⁸⁾ The authors attributed the asthma-like symptoms to the retrosternal discomfort that increases minute ventilation and the respiratory sensation. This contradicts the findings of another study which showed a drop in FEV₁ at up to 90 minutes after instillation of hydrochloric acid in the esophagus of asthmatic patients.⁽¹⁴⁾

It is currently believed that there are three mechanisms through which gastroesophageal reflux may induce or aggravate asthma: microaspirations of refluxed acid;^(8,11) activation of vagal reflex from the esophagus to the lung;⁽¹¹⁻¹³⁾ and sensitization of the vagal reflex, which would induce or accentuate BHR.^(6,14-16)

Scintigraphic studies, together with pHmetry in the esophagus and trachea, as well as double pHmetry in the esophagus, demonstrated that 20% of the patients with GERD presented microaspiration.⁽¹⁹⁾ However, other studies revealed that microaspiration is not a significant cause of gastroesophageal reflux-induced bronchoconstriction. The significance of aspiration as a causative factor of asthma remains uncertain.⁽¹⁵⁾

Some authors have demonstrated that acid infusion into the esophagus of asthmatic patients causes increased airway resistance, which was totally reversed by the use of antacids.⁽¹²⁾ In studies involving dogs, it has been demonstrated that acid infusion into the esophagus produced a drop in respiratory conductance, which disappeared with the bilateral section of the vagal nerve.⁽¹³⁾

TABLE 3
Control group

Patient N ^a	Age/gender	Diagnosis	Accompanying disease(s)	Drugs used
1	30/F	Gastritis	None	None
2	42/F	Normal endoscopic exam	Rhinitis (treatment for six months)	Diazepam
3	60/M	Pangastritis	None	None
4	62/F	Gastritis	None	None
5	49/F	Normal endoscopic exam	Smoking/Pemphigus/SAH	Prednisone/ Methyldopa/ Chlorthalidone
6	4/F	Pangastritis	None	None
7	47/F	Gastritis	None	None
8	36/F	Pangastritis	History of rhinitis/former smoker	None
9	63/F	Gastritis	SAH/pneumonia three months before	Methyldopa
10	17/F	Gastritis	None	None
11	52/F	Gastritis	Rheumatoid arthritis	NSAID

F: female; M: male; SAH: systemic arterial hypertension; NSAID: nonsteroidal anti-inflammatory drug

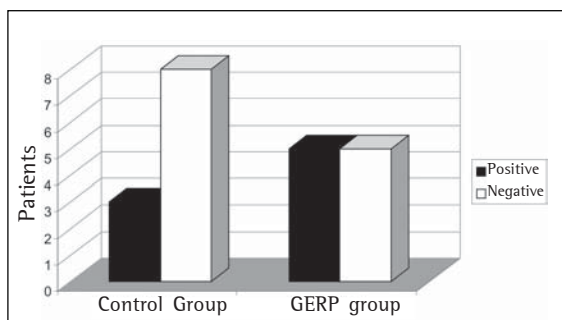


Figure 1 - Results of bronchoprovocation tests carried out in the control group and in the group of patients with gastroesophageal reflux, hiatal hernia or reflux esophagitis; GERD: gastroesophageal reflux disease

Hyperreactivity of the airways seems to be altered by gastroesophageal reflux. Esophageal instillation of acid or acid reflux resulted in a decrease in the peak expiratory flow in asthmatics with GERD, or even in patients who presented only asthma or patients who presented only gastroesophageal reflux. This alteration was prolonged beyond the clearance of the acid in the asthmatic patients with GERD. However, the same did not occur in the other groups.⁽¹⁵⁻¹⁶⁾ This may result from a prolonged vagal stimulus or may be associated with the release of inflammatory mediators, which would result in bronchoconstriction.⁽¹⁴⁻¹⁶⁾

If the presence of acid in the esophagus causes a vagal reflex and this, in turn, results in bronchoconstriction, why is it that only certain nonasthmatic patients with GERD present this alteration? Why do some asthmatic patients with reflux present no improvement in their pulmonary clinical profile after treatment with proton pump inhibitors? The studies reviewed did not reveal how this vagal reflex could act in patients with reflux only. Would its existence depend on preexisting BHR?

In the general population, BHR seems to present a normal distribution. Approximately 20% of individuals without pulmonary disease present mild BHR. Although the significance of this BHR in patients without pulmonary disease is uncertain, studies suggest that these patients are in a latent phase of asthma.⁽¹⁷⁾ In this particular study, 36% of the patients with GERD and no respiratory symptoms presented BHR ($p < 0.01$), suggesting that gastroesophageal reflux is associated with increased BHR.

In the present study, 50% of the patients with GERD had BHR, whereas only 27% of the control

group tested positive. The results were not statistically relevant, making it impossible to confirm the relationship.

In patients with BHR, the effects of treating GERD with proton pump inhibitors (such as omeprazole), or even through surgical procedures, are unknown. Some studies have shown a lessening of respiratory symptoms, although with no alteration in pulmonary function. A study carried out by one group of authors is consistent with this assertion.⁽²¹⁾ The study involved 36 asthma and chronic obstructive pulmonary disease patients with severe obstruction and BHR, as well as gastroesophageal reflux. These patients were treated with high doses of omeprazole (80 mg/day) for twelve weeks and did not present alteration in pulmonary function. The opposite was observed by other researchers who assessed patients with (mildly obstructive) asthma and GERD. The patients who used omeprazole at 20 mg/day and domperidone at 10 mg three times a day for six weeks presented significantly improved pulmonary function.⁽²²⁾ In our study, there was no difference in BHR between the patients using omeprazole and the untreated patients.

TABLE 4

Bronchoprovocation with carbachol in control group patients

Patient N°	FEV ₁ Baseline	FEV ₁ After drug	FEV ₁ (%)	Conclusion Carbachol dose (mg)
1	2.68	1.94	27	Positive Carbachol 2.19
2	2.22	1.54	30	Positive Carbachol 2.09
3	2.64	2.31	12	Negative Carbachol 2.8
4	2.23	1.83	18	Negative Carbachol 2.5
5	1.95	1.70	12	Negative Carbachol 2.83
6	2.25	1.99	11	Negative Carbachol 3.0
7	2.12	1.77	16	Negative Carbachol 2.75
8	2.94	2.93	13	Negative Carbachol 3.0
9	1.76	1.70	21	Positive Carbachol 0.829
10	2.45	1.96	19	Negative Carbachol 3.20
11	2.08	1.95	6	Negative Carbachol 3.01

FEV₁: forced expiratory volume in one second (in liters)

Some patients diagnosed with GERD were using omeprazole upon examination, which may increase the number of false-negative results. However, these patients were not excluded since, in the literature, there is no consensus regarding GERD treatment and decreased BHR. Of the 10 patients with GERD, omeprazole was taken by 6, 3 of whom tested positive (1 had been using the drug for a week, another for three months and the other for a month). Two patients who had been using the medication for three to four months tested negative.

One notable limitation of the study is that, due to a lack of equipment at the facility, the method used to diagnose GERD was not pHmetry, which is considered the gold standard. Had we been able to use pHmetry, this would probably have increased the number of diagnoses. However, one of the authors of the present study previously conducted a study in which only 72% of the diagnoses of GERD made through biopsy were confirmed by pHmetry,⁽¹⁴⁾ demonstrating that even using the method considered the gold standard, some diagnoses are not confirmed.

The hypothesis that the lungs of GERD patients with no history of asthma-like symptoms may be more responsive than those of patients without GERD remains unproven. However, it has been suggested that GERD constitutes a risk factor for bronchoconstrictive diseases.

This study has not provided statistical evidence that gastroesophageal reflux causes hyperreactivity in patients without respiratory symptoms. New studies on the issue are needed in order to obtain more conclusive results and to assess the importance of the use of proton pump inhibitors in patients with BHR.

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