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Effect of Positions, Eating, and Bronchodilators on Gastroesophageal Reflux in Asthmatics

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Gastroesophageal reflux is common in asthmatics. To determine whether bronchodilators, the supine position, or eating affect gastroesophageal reflux, we performed ambulatory 24-hr pH monitoring on 44 controls and 104 unselected adult asthmatics. All asthmatics had discrete attacks of wheezing and documented reversible airway obstruction of at least 20%. The presence or absence of gastroesophageal reflux symptoms was not used as a criterion for patient selection. Chronic bronchodilator therapy was required by 71.2% of the asthmatics, and was continued during the test. Asthmatics had significantly worse GER than controls during the 3-hr postprandial period, which continued into the nonpostprandial period up to the next meal. Significant differences were present for esophageal mucosal acid contact time, frequency of reflux episodes, and clearance times. During the nonpostprandial periods asthmatics had four times the acid reflux as controls and 19-fold the frequency of prolonged reflux episodes. There were no differences between asthmatics on bronchodilators and those not on bronchodilators in any of the reflux parameters during the upright (postprandial, nonpostprandial) period or supine (sleep) period (P = NS). We conclude that: (1) regardless of the use of bronchodilator therapy, asthmatics have significant GER when asleep and after meals that continues beyond the postprandial period to the next meal; and (2) asthmatics receiving bronchodilators have similar gastroesophageal reflux patterns after eating, in the nonpostprandial period, and when asleep as asthmatics not receiving bronchodilators.

KEY WORDS: gastroesophageal reflux; asthma; bronchodilators; positions; eating.

Gastroesophageal reflux (GER) is common in asthmatics (1–3) and has been implicated in the precipitation of asthmatic episodes (4, 5). Mechanisms by which GER might invoke asthma include aspiration of gastric contents (1, 6–8) and triggering of a vagal reflex by acid reflux (9, 10). Either or both potential mechanisms might be activated by factors that promote GER, such as the use of bronchodilators (6, 11, 12), assuming the supine position (13, 14), and overeating (15).

We used 24-hr esophageal pH testing to determine the reflux patterns in asthmatics and to study the effects of positions, eating, and bronchodilators on GER.

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MATERIALS AND METHODS

Controls. Forty-four volunteers who were without gastrointestinal complaints and were asymptomatic for GER were recruited from the hospital outpatient population and the employee staff. Volunteers were considered asymptomatic for GER if they had less than two episodes of GER symptoms (heartburn, postprandial chest pain, regurgitation) per year for the previous five years. Forty-two males and two females, ranging in age from 19 to 70 years with a mean of 47.9 ± 1.9 years (mean ± SE) were studied.

Patients. One hundred four asthmatics were consecutively referred from the outpatient and pulmonary clinics and the inpatient hospital. The presence or absence of GER symptoms was not used as a criterion for patient selection.

Group I. Asthmatics Receiving Chronic Bronchodilator Therapy. Seventy-four asthmatics (70 males, 4 females; age range 21–73 years, mean 53 ± 13 years) were studied while taking their usual combinations of theophylline, terbutaline, inhalants (adrenergic, anticholinergic, corticosteroid), and prednisone: theophylline only (400–1200 mg daily), 19 patients; theophylline (400–1200 mg daily) with terbutaline (5–15 mg daily) with or without inhalants (4–6 puffs daily), 50 patients; inhalants (4–16 puffs daily) with or without terbutaline, 5 patients.

Group II. Asthmatics Not Receiving Chronic Pulmonary Medication. Thirty asthmatics (29 males, 1 female; age range 27–65 years, mean 47 ± 13 years) were studied while receiving no pulmonary medications. Although patients may have used intermittent bronchodilators in the past for control of asthma, none required them at the time of the studies.

Documentation of Asthma. Asthma was defined as discrete episodes of wheezing and either a 20% improvement in forced expiratory volume in 1 sec (FEV_1) (16) following bronchodilator administration or a 20% decrease in FEV_1 after methacholine bronchoprovocation, which was performed in accordance with the American Thoracic Society guidelines (17).

Esophageal Manometry. Esophageal manometry was performed through the nose using a Narco Bio-systems (Houston, Texas) motility transducer catheter and Physiograph recording system. The lower esophageal sphincter (LES) was identified by a sustained resting pressure area that relaxed with swallowing; it was measured in centimeters from the nose. When resting pressure was not elevated, the point of initial peristalsis, as determined on withdrawal of the catheter, was used to define the lower esophageal sphincter area.

Esophageal pH Testing. Twenty-four-hour esophageal pH testing was performed using standard methods with a Beckman pH electrode positioned 5 cm above the superior border of the manometrically determined LES and a Gastroreflux Data Analyzer (Del Mar Avionics). Supine or upright positions were recorded by the use of a switch on the recorder. Patients were instructed to remain upright (sitting, standing, or walking) during the day, to assume the supine position only when in bed at night; to eat their usual meals for breakfast, lunch, and dinner; to refrain from all other eating, including bedtime snacks; and to drink water at will. Monitoring was performed in a special hospital unit or at home depending on patient's preference. In addition, a detailed diary of all events including meal times and sleep time was kept. The patients were freely ambulatory throughout the test period.

Reflux data analysis. A reflux episode was defined as a drop in pH below 4 that lasted for more than 10 sec. The acid contact time (percent of time that the pH was less than 4), the frequency of significant reflux episodes, and two clearance values were determined for the total 24-hr period, the upright period, and the supine period. The two clearance values were determined as follows: (1) frequency of prolonged (greater than 5 min) reflux episodes per hour. (2) mean duration of each reflux episode [total time (minutes) pH was less than 4 divided by the number of reflux episodes].

The following definitions were used: (1) Upright period—postprandial and nonpostprandial time. (a) postprandial period—the 3-hr period following each meal. (b) nonpostprandial period—the time remaining after the postprandial period but before the next meal. (2) supine period—the period from lying down in bed at night until arising in the morning.

Consumption of tobacco and alcohol was recorded as follows: (1) quit smoking, quit drinking: abstinence for at least the previous 12 months; (2) active smoking, active drinking: presently consuming or consumed in the previous 12 months; (3) nonsmoker, nondrinker: never smoked or quit more than one year ago with a total of less than one pack per day for six months; never drank alcohol or quit more than one year ago with a total of less than one drink per day for six months.

Statistical Analysis. The Mann-Whitney U test was used to detect differences in GER parameters between groups:

TABLE 1. CHARACTERISTICS OF ASTHMATICS AND CONTROLS

			*Smoking history**		*Alcohol history**	
	Subjects (N)	*Age* (mean ± SD)*	*Present smoker (%)*	*Quit or never smoked (%)*	*Present drinker (%)*	*Quit or never drank (%)*
Asthmatics						
On bronchodilators	74	52.9 ± 13.3	32.3	67.7	53.3	46.7
Not on bronchodilators	30	47.1 ± 13.1	42.1	57.9	69.2	30.8
Controls	44	47.9 ± 12.9	23.7	76.3	51.4	48.6

*P = NS; there were no differences between any of these groups in regards to age, smoking, or alcohol consumption.

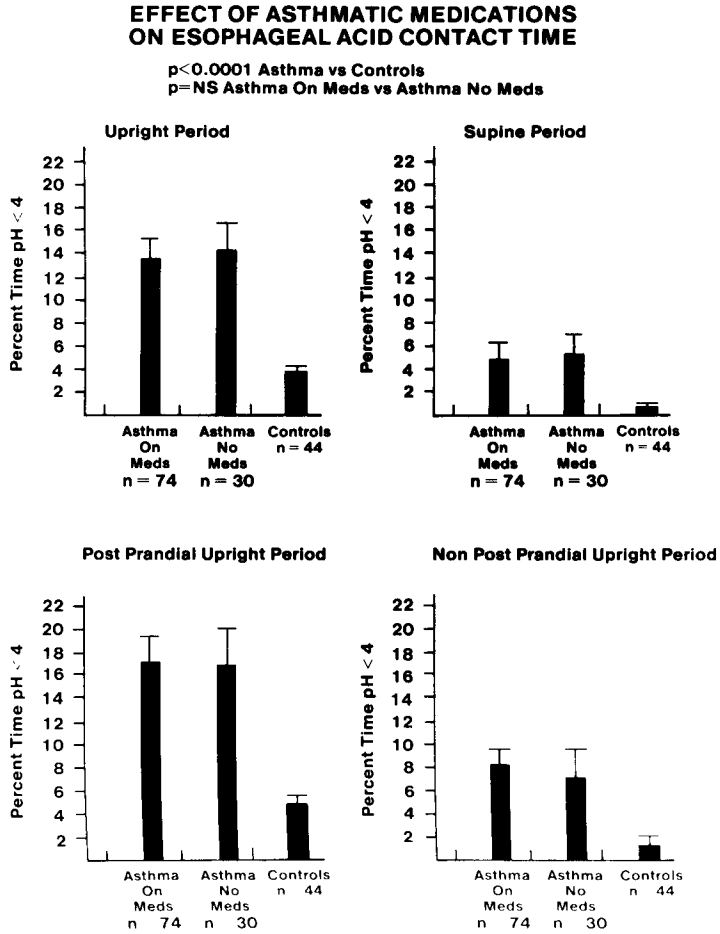

Fig 1. During the upright, supine, postprandial upright, and nonpostprandial upright periods, when compared to controls, asthmatics had significantly ($P < 0.0001$) greater esophageal acid contact time. During the nonpostprandial periods asthmatics had four times the acid reflux as controls. Bars indicate mean ± SE. There were no differences in any parameters (P = NS) between asthmatics on pulmonary medications and asthmatics on no pulmonary medications.

asthmatics vs controls; asthmatics on medications vs asthmatics on no medications.

RESULTS

The characteristics of asthmatics and controls are shown in Table 1. There were no statistically significant differences between any of the three groups in regards to age, smoking, or alcohol consumption.

The effect of asthmatic medications on the GER parameters is shown in Figures 1 through 4. There were no differences in any of the GER parameters between asthmatics on bronchodilators and those not on bronchodilators during either the upright or supine periods (Figures 1 through 4). When the upright period was divided into the postprandial and nonpostprandial periods, there was still no difference between asthmatics taking and those not taking bronchodilators (Figures 1 through 4; $P > 0.05$).

The effect of eating on the various GER parameters, as demonstrated in the postprandial and nonpostprandial sections of Figures 1 through 4, shows that asthmatics had significantly worse GER than controls during the 3-hr postprandial period that continued into the nonpostprandial period up to the next meal. Significant differences between asthmatics and controls were present for esophageal mucosal acid contact time (Figure 1), frequency of reflux episodes (Figure 2), and clearance times as shown by the mean duration of reflux episodes (Figure 3), and the frequency of prolonged reflux episodes (Figure 4) ($P < 0.0001$ for all parameters tested).

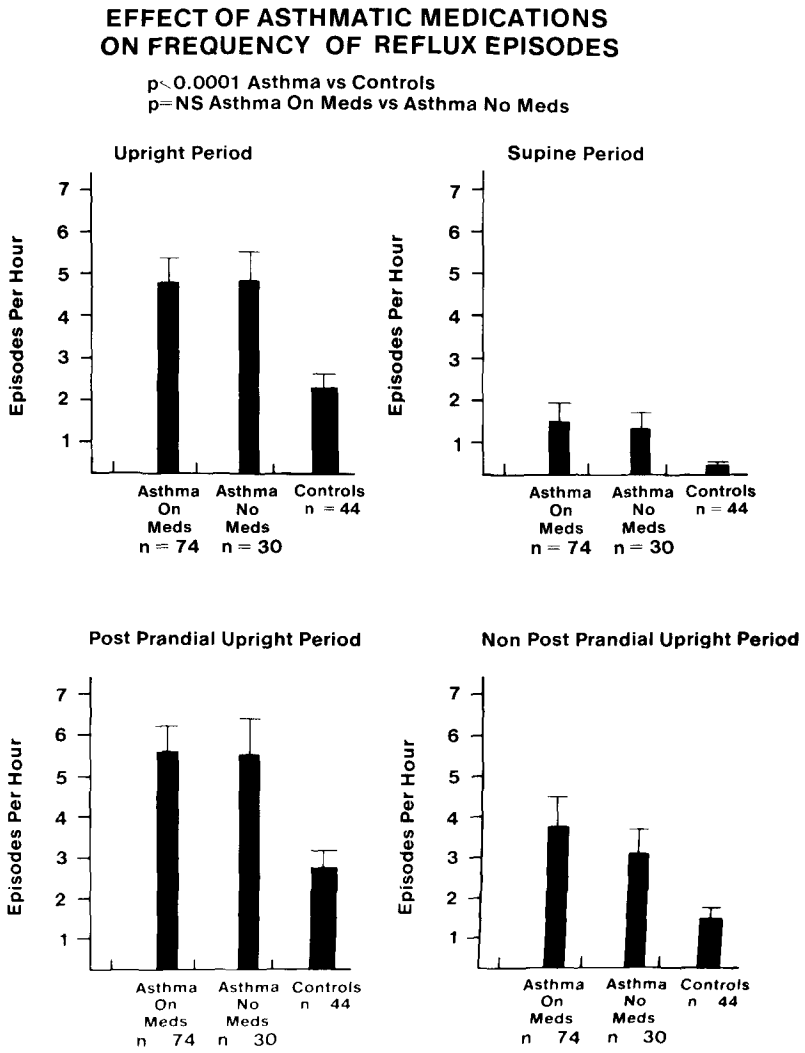

Fig 2. During all four periods, when compared to controls, asthmatics had significantly ($P < 0.0001$) greater frequency of reflux episodes. Bars indicate mean ± SE. There were no differences in any parameters (P = NS) between asthmatics on pulmonary medications and asthmatics on no pulmonary medications.

During the nonpostprandial periods asthmatics had four times the acid reflux as controls (Figure 1); asthmatics on medications and off medications had 20-fold and 11-fold, respectively, the frequency of prolonged reflux episodes (Figure 4, nonpostprandial period), but there was no difference between the two groups of asthmatics.

DISCUSSION

Three factors reported to promote GER in asthmatics are the use of bronchodilators (6, 11, 12), assuming the supine position (14, 19), and overeating (15, 20). The exact mechanism by which GER promotes the bronchospasm, however, still remains unknown. The results of our previous work (35) and of other published studies on mechanisms (14, 36–40) have failed to provide a diagnostic test with a degree of certainty high enough to identify patients with GER-induced asthma. However, it has been suggested that the occurrence of a GER-induced exacerbation of asthma is dependent on a number of factors. These factors include reflux of gastric acid into the esophagus, an acid-sensitive esophagus (positive Bernstein), and a low nocturnal threshold to bronchoconstrictive stimuli (14, 21), which may result from the normal circadian variations in bronchial reactivity and/or a waning of the effect of bronchodilator medications (22).

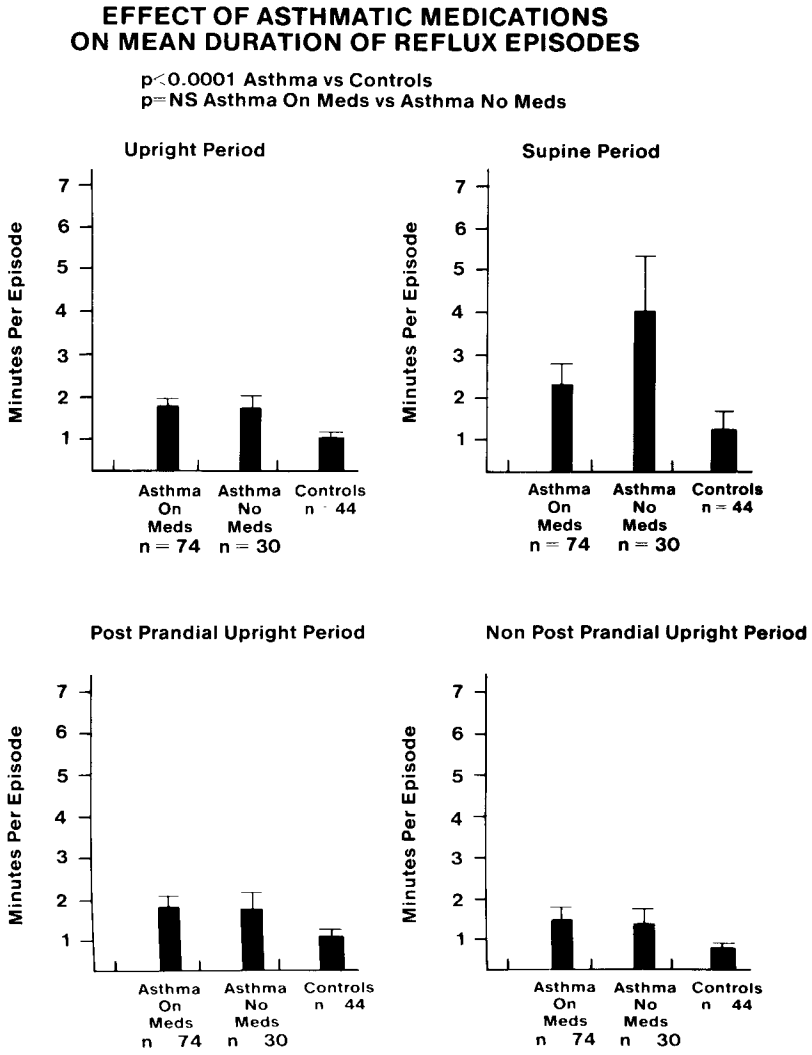

Fig 3. During all four periods, when compared to controls, asthmatics had significantly ($P < 0.0001$) longer clearance times as demonstrated by the mean duration of reflux episodes. Bars indicate mean ± SE. There were no differences in any parameters (P = NS) between asthmatics on pulmonary medications and asthmatics on no pulmonary medications.

Bronchodilators. Asthmatics who require bronchodilators might be expected to be at risk for nocturnal asthma because of increased drug-induced GER followed by decreased bronchodilating activity as the drug is eliminated throughout the night. Indeed, asthma drug therapy, by relaxing the LES, has been reported to adversely influence GER (11, 23–27) and potentially contribute to or worsen asthma (28, 29).

Our results, however, demonstrated similar reflux patterns both in the group receiving and in the group not receiving bronchodilators. There appeared to be no adverse effects of bronchodilators on any of the GER parameters during the upright, supine, postprandial, or nonpostprandial periods. Although we did not study GER parameters in each subject before and after administration of bronchodilators, we did demonstrate that asthmatics receiving bronchodilators had no worse reflux than those not receiving bronchodilators, suggesting that bronchodilators do not promote postprandial or nocturnal reflux. Indeed, two placebo-controlled studies also could not demonstrate an adverse effect of asthma medications on acid reflux or frequency of reflux episodes (12, 30).

Supine Position. The prevalence of night cough and nocturnal wheezing is significantly greater in asthmatics with GER than in asthmatics without

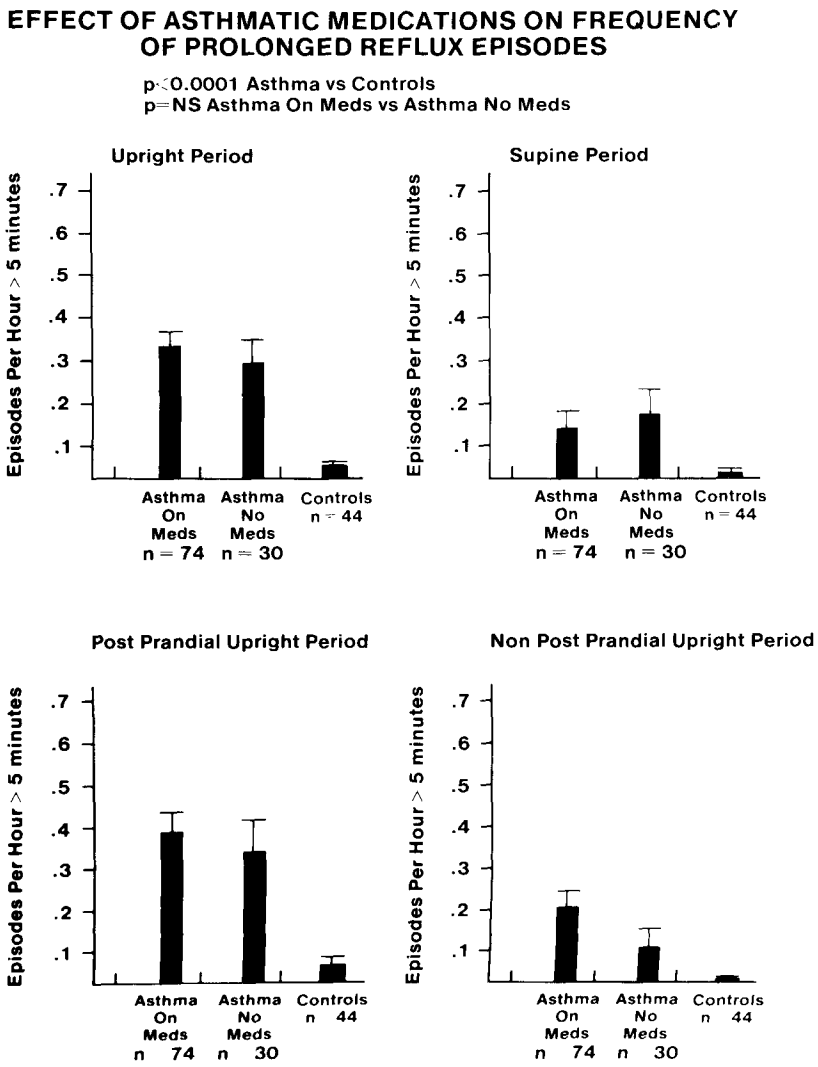

Fig 4. During all four periods, when compared to controls, asthmatics had significantly ($P < 0.0001$) longer clearance times as demonstrated by the increased frequency of prolonged reflux episodes. Asthmatics on medications had 20-fold and 11-fold, respectively, the frequency of prolonged reflux episodes during the nonpostprandial period, but there was no difference between the two groups of asthmatics. Bars indicate mean ± SE. There were no differences in any parameters (P = NS) between asthmatics on pulmonary medications and asthmatics on no pulmonary medications.

GER (19), and GER has been implicated as an etiologic factor in nocturnal wheezing (31). In a clinical trial of 18 patients with asthma and symptomatic GER, nighttime asthma scores improved significantly in the group receiving cimetidine (32), suggesting that acid reflux has a role in nocturnal wheezing. Our results strongly support a role for nocturnal reflux in asthma. Although nocturnal reflux was similar in asthmatics who required bronchodilators and those who did not, when compared to controls they had more than four times the acid reflux and 19 times the frequency of prolonged reflux episodes. Thus, with or without bronchodilator therapy, asthmatics have significantly more acid reflux when asleep than do nonasthmatics.

Postprandial Reflux. We did not measure the effect on acid reflux of lying down immediately after eating, since our patients were specifically instructed not to go to sleep for at least 3 hr after supper. Since esophageal acid clearance time is increased in the supine position 3 hr after eating (13), lying down immediately after a meal might be

expected to result in even greater GER. Indeed, even during the upright period, the greatest acid reflux occurs after eating (33) in both refluxers and controls. Of interest is the GER that continued to occur in our asthmatics after the immediate 3-hr postprandial period when the stomach should have been empty. This continued reflux suggests that asthmatics may have delayed gastric emptying that is independent of bronchodilator therapy. Thus, a large meal at supper time in an individual with delayed emptying might be expected to remain in the stomach after bedtime, promote nocturnal GER, and contribute to nighttime bronchoconstriction. It still is unknown whether the bronchoconstriction is due to a vagal reflex or direct aspiration.

More than 50 years ago, Bray observed in some of his patients that dietary indiscretion could lead to asthmatic attacks (20). He believed that gastric distension from late-evening overeating could cause a vagally mediated reflex bronchoconstriction. More recently, Mansfield et al demonstrated in dogs a significant fall in respiratory conductance and functional residual capacity after distension of the esophagus and intraesophageal hydrochloric acid infusion (34).

Could our results have been influenced by selection bias? To ensure that the asthmatic population studied was representative of the general asthmatic population and was not skewed in favor of those with gastrointestinal symptoms, we studied consecutive asthmatics based on whether or not they had asthma. This was accomplished by actively soliciting from the pulmonary and nongastroenterology outpatient clinics every available patient with the diagnosis of asthma, regardless of whether gastrointestinal symptoms were present. In addition, patients were selected by three of the investigators who work in the general walk-in clinic, which is a primary clinic for all new patients and those without appointments. All asthmatics whose primary symptoms were asthma were asked to participate in the study. Thus, patients who were not specifically endoscoped because of our asthma/GER prevalence study were not included in the results. Finally, 56 patients were referred for endoscopy from the gastroenterology clinic or because of gastrointestinal symptoms who were then discovered to have asthma. The results from these patients are not considered as prevalence data and are not a part of this report. Therefore, we studied a population of asthmatics that represents, as much as possible, the overall asthmatic population.

We conclude that regardless of the use of bronchodilator therapy, asthmatics, when compared to controls, have significant GER when asleep and after meals that continues beyond the postprandial period to the next meal.

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