

Effect of salbutamol on gastroesophageal reflux in healthy volunteers and patients with asthma

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The aim of this work was to establish whether β -adrenergic agonists promote or increase gastroesophageal reflux in patients with asthma. Ten healthy individuals and eight patients with asthma were studied on 2 different days. One day they received a placebo, and the other day they received 4 mg of salbutamol by mouth. Complete measurements of esophageal manometry were performed before and every 30 minutes for 210 minutes after the administration of the drugs. Esophageal pH was measured continuously for the duration of the experiment. The results demonstrate that (1) salbutamol had no effect on the lower esophageal sphincter pressure gradient, the peak esophageal contraction pressure, or the number and duration of reflux episodes in patients with asthma and normal individuals, and (2) patients with asthma have a resting lower esophageal sphincter pressure higher than healthy subjects. We conclude that the administration of salbutamol does not affect esophageal function. (J ALLERGY CLIN IMMUNOL 1991;87:762-7.)

A relationship between asthma and gastroesophageal reflux has been reported for years, and it is currently believed by many clinicians that the treatment of esophageal reflux, either medically or surgically, will improve or even cure many patients of their asthma.¹ Several mechanisms have been invoked to explain the relationship between reflux and asthma: macro- or microaspiration of gastric contents or a vagal reflex triggered by the distention or the irritation of the esophagus.^{2,3} It has also been suggested that it is not reflux that causes asthma but rather asthma that predisposes to increased gastroesophageal reflux because of the mechanical changes in the chest wall and abdomen consequent to the bronchoconstriction.³ Although numerous studies have been conducted to test

Abbreviation used

LES: Lower esophageal sphincter

these hypotheses, the results have not conclusively proven any of the hypotheses.

Another factor that could promote or increase gastroesophageal reflux in patients with asthma is antiasthma medication. Although this factor is often mentioned,² there are few detailed studies on the short- or long-term effects of β -adrenergic agonists and xanthines on gastroesophageal reflux in patients with asthma. The aim of the present work was thus to study the effect of salbutamol administration on esophageal motility and gastroesophageal reflux in normal individuals and in patients with asthma.

METHODS AND TECHNIQUES

Subjects

Ten healthy volunteers (five male and five female subjects), aged 17 to 42 years, participated in the study. None had a history of respiratory or gastrointestinal disease.

Eight patients with a diagnosis of asthma according to the criteria of the American Thoracic Society⁴ also took part in the study. There were three women and five men, 23 to 44 years of age. Six of the patients needed medication daily to control their asthma. The two remaining subjects took

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TABLE I

Subjects	Sex	Age (yr)	Duration of asthma (yr)	FEV ₁ % predicted		Medication
				P	S	
1	M	37	8	66	79	BA, T
2*	F	44	17	—	—	—
3	M	25	15	75	—	CS, T
4	M	29	28	83	86	BA, T
5	F	26	7	71	78	BA*
6	M	23	22	68	65	BA, B
7	F	29	2	100	100	BA, T*
8†	M	37	12	51	68	BA, T, P,* BE

P, Placebo; S, salbutamol; BA, β -adrenergic daily; *p.r.n.*, as needed; BA*, β -adrenergic *p.r.n.*; T, theophyllin daily; T*, theophyllin *p.r.n.*; CS, cromoglycate sodium *p.r.n.*; B, budesonide daily; P*, dexamethasone *p.r.n.*; BE, beclomethasone daily.

*Unable to perform a correct FEV₁ maneuver.

†Symptoms of reflux.

medication only occasionally. Only one of the subjects with asthma had symptoms of gastroesophageal reflux. The subjects' characteristics and the medication administered are presented in Table I. The study was approved by the human investigation committee of Hôtel-Dieu Hospital and each participant gave informed consent.

Esophageal manometry

Measurements were obtained with a triple lumen polyvinyl manometric assembly ending in a silicon rubber sleeve sensor, 6 cm long and 0.7 cm wide (Dentsleeve, Adelaide, South Australia). The sleeve, which measures LES pressure, is built on a silicon rubber assembly 5.5 mm in diameter that contains five silicon rubber catheters. The lumina of the rubber catheters are joined to the distal ends of the polyvinyl catheters with 6 mm long stainless steel tubes used as stints. The sleeve is perfused via the lumen of an underlying silicon rubber catheter connected to its proximal margin. This system elicits accurate, continuous recordings of LES pressures despite oral-aboral motions of the sphincter along the sleeve.⁵ Three ports oriented 120° from each other and located on separate polyvinyl tubes, 1, 5, and 10 cm above the sleeve, measured esophageal contraction pressures and peristalsis. A fourth port located distal to the sleeve recorded intragastric pressure. Each catheter was continuously perfused with water at a rate of 0.5 ml/min via a constant pressure pump (Maui, Toronto, Ontario, Canada). Pressure signals were measured with Hewlett-Packard (Cupertino, Calif.) 128DB pressure transducers and recorded on an 8-channel pen-heated recorder (Hewlett-Packard). All measurements were made with the subject in a recumbent position. A 30-minute adaptation period was allowed before any recording. The recording of control values and all subsequent values were made after 10 voluntary swallows with a 5 ml water bolus introduced into the mouth by a syringe. One minute of rest was allowed between each voluntary swallow. Interpretation criteria of the LES pressure levels

were the absolute resting pressure (measured at midrespiratory cycle), the contraction pressure (closing pressure of the LES), and the end relaxation pressure (i.e., pressure at which the sphincter relaxes on swallowing). The LES pressure gradient was calculated by subtracting intragastric pressure from LES resting pressure. In the esophageal body, the resting pressure and the peak contraction pressure were recorded at all three ports. The incidence of propulsive waves in response to swallowing was obtained for each period of recording. Spontaneous, secondary, and tertiary contractions were also measured and interpreted separately.

Esophageal pH measurement

The pH was recorded continuously with a Sandhill RMS (Sandhill Corp., Denver, Colo.) system. The pH electrode was positioned 5 cm above the LES. The pH electrode is an antimony electrode and is calibrated with buffer solutions at pH 4 and 7 before and after each experiment. Esophageal pH was recorded via a data logger, and the complete recording was transmitted to an NEC-APC (Sandhill Corp.) computer for interpretation. Complete analysis of the wave shapes elicited the number of reflux episodes and their duration during the recording period.

Salbutamol serum concentrations

Salbutamol was assayed according to the method of Loo et al.⁶ with minor modifications. Methyl tertiary butyl ether and tetrahydrofuran were high-performance liquid chromatography grade, whereas all other reagents were reagent grade. The dextran-coated charcoal suspension was prepared by mixing 1 gm of Norit A (Serva, Fisher Scientific, Toronto, Canada) charcoal, 100 mg of dextran, 280 mg of gamma globulin (bovine Cohn fraction II) in phosphate buffer, pH 7.4. Tritiated salbutamol (specific activity, 17.1 Ci/mmol, nonspecific labeled) was purchased from Nuclear Research Center, Negev, Israel. Antiserum at a titer of 1/2000 was used in the study.⁷ One milliliter of plasma was

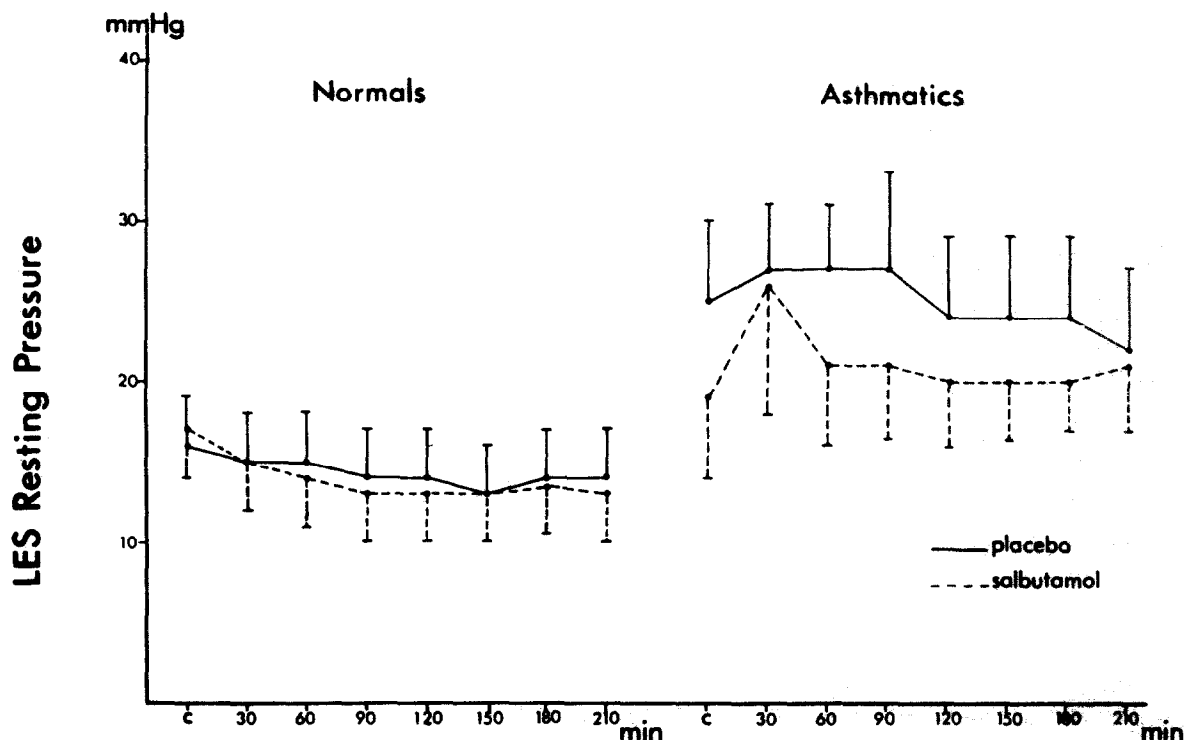


FIG. 1. Measurements of LES pressures in normal subjects and subjects with asthma.

extracted with 10 ml of methyl acetate in a screw cap tube, and 9.5 ml of the organic phase was dried (45°C N_2). The residue was partitioned between 1 ml of tetrahydrofuran methyl tertiary butyl ether (50:50) and 2.5 ml of 0.01 N of ammonium hydroxide. The aqueous phase was dried in a Speed Vac concentrator (Savant Instruments, Inc., Farmingdale, N.J.). The residue was immediately reconstituted with 0.25 ml of buffer (0.2 mol/L), pH 7.4. The radioimmunoassay was conducted with 50 μl of blank plasma, 100 μl of antiserum, and 100 μl of tritiated salbutamol. After 8 hours of incubation at 4°C , the free and bound fractions were separated with 500 μl of charcoal-dextran after 15 minutes of incubation and centrifuged for 15 minutes at 4°C . The radioactivity in the bound fraction was measured by adding 10 ml of Scintiverse (Fisher Scientific, Toronto, Canada) and counted in a beta Wallac gamma counter (LKB Instruments, Bromma, Sweden). The stock solution of salbutamol was prepared in distilled water at a concentration of 0.64 mg/ml (as base); it was used to prepare the plasma standards containing 0.2, 0.4, 0.8, 1.6, 3.2, and 6.4 ng/ml of salbutamol. The parameters that characterized the standard curve ($n = 10$) were specific binding, 31%; nonspecific binding, 0.75%; slope factor, 1.06 ± 0.20 ; effective dose of 3440 ± 89 pg/ml and an r^2 , 0.9944.

Protocol

Each subject was studied twice, at least 72 hours apart. One day, the subject received 4 mg of salbutamol by mouth, and the other day, placebo. The order of administration was randomized, and the study was conducted in a double-blind

fashion. Women were studied during the first part of their menstrual cycle since LES pressure is decreased during the second half of the cycle because of progesterone secretion.⁸ Each study started at 9 AM after the subjects had fasted for 12 hours preceding the study. Patients with asthma refrained from taking their medication after midnight. Their FEV₁ was measured on arrival at the laboratory. Shortly after arrival, the esophageal catheter, the pH electrode, and an intravenous line were installed. The subjects rested quietly in the supine position. Measurements of esophageal manometry and salbutamol serum levels were made at 30-minute intervals beginning 30 minutes before and ending 210 minutes after the administration of the drug (placebo or salbutamol); pH was continuously recorded. Two sets of esophageal manometry measurements were taken at 30-minute intervals, one during resting conditions and the other measurement after the subjects had breathed for 15 minutes through an inspiratory resistance (inspiratory muscle trainer, DHD Medical Products, Canastota, N.Y.) designed to increase the pleural pressure to -30 cmH₂O. This latter maneuver was included to allow us to evaluate the effect of changing intrathoracic mechanics on esophageal function.

Data analysis

Data were analyzed with analysis of variance for repeated measures. Three factors were taken into account: one *group* factor to represent the group distinction (normal versus patients with asthma) and two other factors to test the differences between placebo and salbutamol conditions (factor *medication*) and the evolution of the parameters between

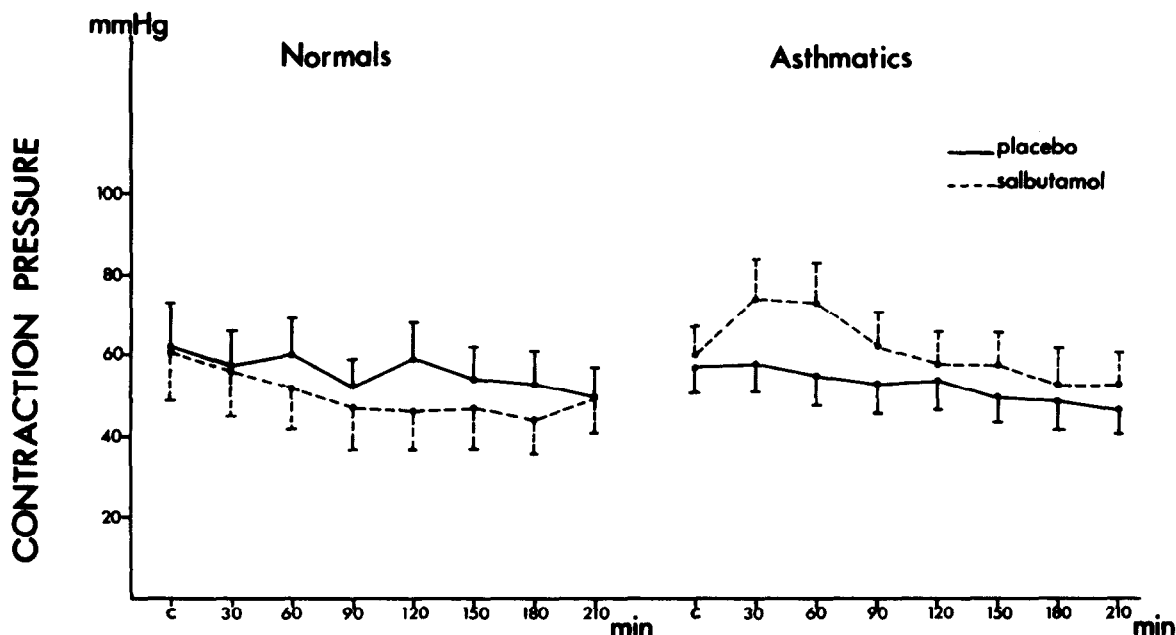


FIG. 2. Measurements of contraction pressure in normal subjects and subjects with asthma.

the eight measures taken during the experiment (factor *time*). The analysis therefore included one between-subject and two within-subjects factors. Simple main effects were calculated whenever significant interactions were found and multiple comparison procedures (Tukey, *B*) were applied when an effect involving the *time* factor reached significance level. The α -level was set to 0.05 for all the analysis.

RESULTS

Esophageal manometry

Because breathing with an added inspiratory resistance did not affect measurements of the LES resting pressure, the LES gradient, or the contraction pressure of the distal esophagus, the measurements made after breathing with the inspiratory resistance were pooled with measurements taken after the resting period for each 30-minute interval. In Fig. 1, measurements of the LES resting pressure are illustrated for the healthy volunteers and for the patients with asthma. The resting pressure was higher in the patients with asthma than in the normal volunteers on both days of the experiment ($0.05 \leq p \leq 0.069$). In neither group did salbutamol treatment significantly affect the LES pressure. In Fig. 2, measurements of the contraction pressure of the distal esophagus are illustrated for both groups of subjects. Again, salbutamol had no effect on the force of contraction in either normal subjects or patients with asthma. Reflux duration is illustrated in Fig. 3. The high value during the control period and the subsequent 30 minutes in the patients with asthma is due to a single subject (No. 1) who had 16

minutes of reflux during the control period and 11 minutes during the first 30 minutes after drug administration.

Salbutamol plasma concentrations

In the group of healthy subjects, after a 4 mg oral dose of salbutamol, plasma concentrations rose gradually to a peak of 13.9 ng/ml at 150 minutes to decrease slowly afterward (Fig. 4). Plasma concentrations of salbutamol in patients demonstrated a very similar pattern and reached identical concentrations. The area under the curve of salbutamol concentrations, from 0 to 210 minutes, was similar in both groups of subjects, suggesting that the exposure to the drug was also the same.

The statistical analysis demonstrated that all parameters of esophageal manometry decreased slightly but significantly over time for both groups of subjects.

DISCUSSION

An association between gastroesophageal reflux and various respiratory diseases, such as asthma, bronchitis, recurrent pneumonia, and pulmonary fibrosis, has been reported for years.¹ In subjects with asthma, estimates of the incidence of gastroesophageal reflux vary from 30% to 89%.² Several mechanisms have been proposed to explain this association; however, despite numerous studies, it is still not known whether reflux enhances asthma, whether asthma enhances reflux, or whether both mechanisms could be operating.

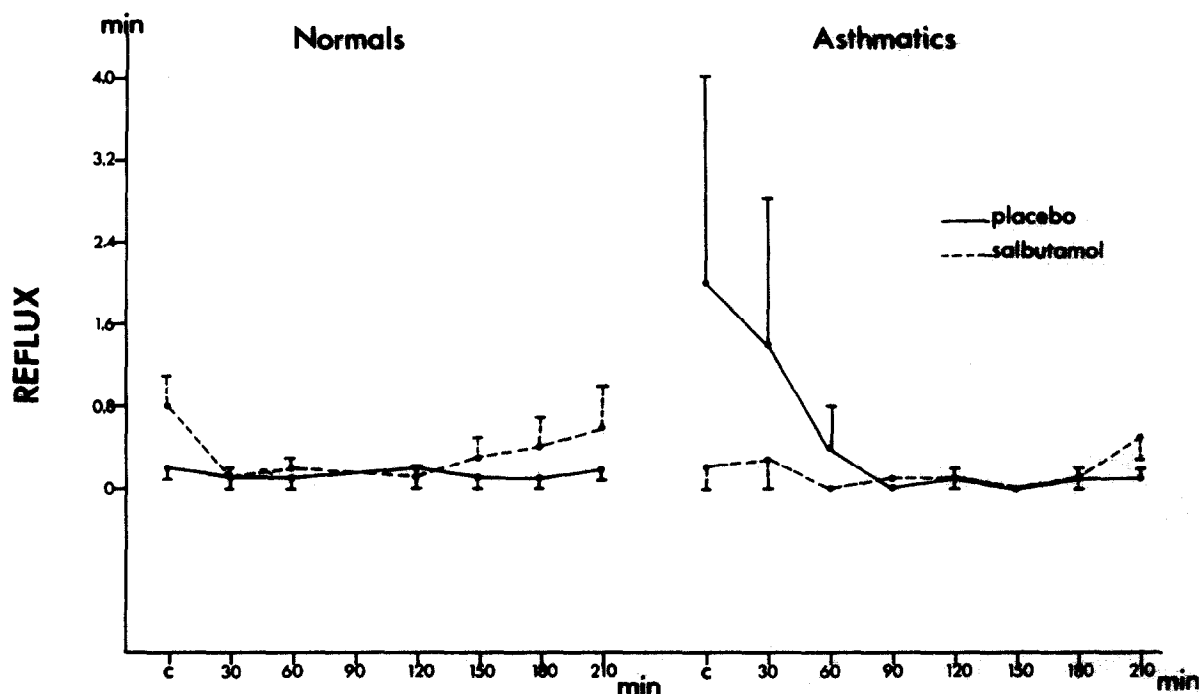


FIG. 3. Reflux duration in normal subjects and subjects with asthma.

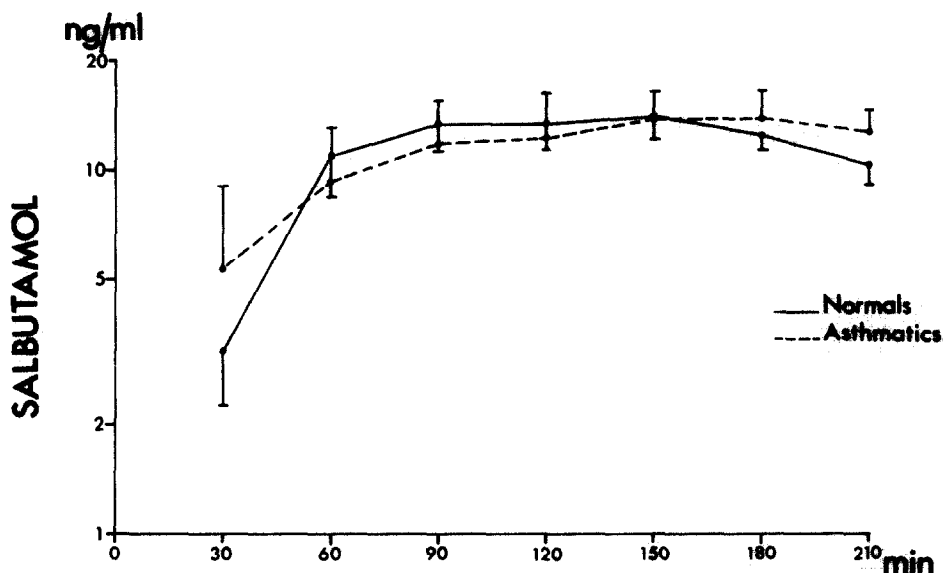


FIG. 4. Plasma salbutamol concentrations in normal subjects and subjects with asthma.

One factor that could promote or increase esophageal reflux in subjects with asthma is the drugs most often used for the treatment of the disease, particularly β_2 -adrenergic agonists and theophylline. Although it has been reported that β_2 -adrenergic agonists can reduce LES pressure in healthy individuals,⁹ the effect of these drugs on esophageal motility and gastroesophageal reflux in subjects with asthma has received

little attention. Thus, the aim of our study was to observe and compare the effects of salbutamol on gastroesophageal function in normal individuals and in subjects with asthma. The results demonstrate that salbutamol plasma concentrations, in healthy volunteers as well as in patients with asthma, were similar to results usually reported in patients receiving salbutamol chronically.^{10, 11} At these concentrations, sal-

butamol had no immediate effect on gastroesophageal motility. It did not reduce either the peak peristaltic pressure, the resting LES pressure, or the pressure gradient across the LES; nor did it increase the number or duration of reflux episodes. These data are consistent with data of Schindlbeck et al.¹² who measured the effect of inhaled albuterol on gastroesophageal reflux in healthy volunteers and reported no change in esophageal motility or reflux. Zfass et al.,⁹ in contrast, observed a significant decrease in LES pressure after the intravenous infusion of isoproterenol in healthy volunteers. A likely explanation for the difference between their data and our data is the dose of β_2 -adrenergic agonist administered. Zfass et al.⁹ infused a dose of isoproterenol large enough to induce tachycardia ($0.03 \mu\text{g/kg/min}$). In a more recent study, DiMarino and Cohen¹³ also observed a decrease in LES pressure after the oral administration of carbutoleol in normal individuals. However, interpretation of the results of this study is hampered by the fact that they did not compare the effect of carbutoleol to the effect of a placebo. Thus, we believe that the decrease in LES pressure that these authors measured 90 minutes after the ingestion of carbutoleol reflects the same phenomenon that we observed in our study, namely, the decrease of esophageal motility parameters over time rather than a true effect of the β_2 -adrenergic agonist. This explanation is reinforced by the fact that they did not document a dose effect on the decrease in LES pressure.

Some authors have suggested that asthma itself predisposes to gastroesophageal reflux.^{3, 14} The hypothesis in this situation is that the increased transdiaphragmatic pressure produced by airflow obstruction could pump gastric content back into the esophagus. In our study, we attempted to recreate the mechanical conditions existing inside the thorax during an asthma attack by asking the subjects to breathe through an added inspiratory resistance designed to increase inspiratory pressure to $-30 \text{ cmH}_2\text{O}$. This maneuver did not produce or increase gastroesophageal reflux in any of our patients. In addition, there was no gastroesophageal reflux in patient No. 8 who had a fair degree of bronchial obstruction on the placebo-treatment day of the experiment.

An interesting observation emerging from our results is that the LES resting pressure and the pressure gradient across the LES were consistently higher in the patients with asthma than in the normal subjects. A similar observation has been reported by Griffith et al.¹⁵ in four patients. A higher LES resting pressure would suggest that the smooth muscle tone of the esophagus, like the tone of the airways, is increased in individuals with asthma. This increase in tone could

be due either to an increase in smooth muscle reactivity or to mechanical changes produced by an increased negative intrathoracic pressure. In any case, additional studies on a larger number of patients will be needed to confirm our observation.

In summary, our results demonstrate that the administration of a single dose of β_2 -adrenergic agonist has no immediate effect on esophageal motility and esophageal reflux in healthy subjects and in individuals with asthma.

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