

Relationship between gastro esophageal reflux and airway response to acid infusion test in asthmatic children

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SUMMARY

Gastro esophageal reflux (GER) was investigated in 15 children with asthma by esophageal pH monitoring and manometry. Bronchial response to Acid Infusion Test (AIT) was also evaluated by comparing specific baseline airway resistance (sRAW) and carbachol bronchial responsiveness before and after AIT. The response of the children in this study to AIT was considerably less than that reported in adults. AIT did not change baseline sRAW or bronchial sensitivity to carbachol ($p = \text{NS}$), but did significantly increase the bronchial reactivity ($p < 0.05$) to carbachol. Weak but significant correlations were found between bronchial reactivity and patterns of GER ($p < 0.05$) and lower esophageal pressure ($p < 0.01$). These results show that in children the relationship between GER and asthma is not constant.

RÉSUMÉ

Relation entre le reflux gastro-œsophagien et la réponse aux tests de perfusion acide chez l'enfant asthmatique. – Le reflux gastro-œsophagien (RGO) a été mis en cause comme facteur aggravant le bronchospasme chez l'asthmatique. Différentes hypothèses non confirmées ont été proposées pour expliquer ce phénomène : mécanisme neurogène via le vague ou aspiration trachéale de liquide gastrique (syndrome de Mendelsohn). Le but de ce travail est d'étudier l'effet sur les bronches d'une perfusion intra-œsophagienne d'HCl chez des enfants asthmatiques et de lier cet effet aux caractéristiques du RGO. L'étude a porté sur 15 enfants asthmatiques âgés de 5 à 13 ans. Sept nécessitaient un traitement bronchodilatateur permanent et huit intermittent. Chez tous, le RGO, diagnostiqué par le TOGD, était traité médicalement. Cependant, lors de l'étude, aucun n'avait de symptomatologie digestive. Il n'y avait aucune

prise médicamenteuse durant les 12 heures précédant l'examen. Le RGO a été apprécié par une pH-métrie de 7 heures (4 heures à jeun et 3 heures post-prandiales). Un reflux était défini par une variation soudaine du pH de durée supérieure à 10 secondes. Les paramètres mesurés ont été : la valeur du pH basal, la durée des reflux, le pourcentage de temps de $\text{pH} < 4$ et la constante de temps des reflux. La manométrie œsophagienne, par sonde à ballonnets, permettait l'appréciation de la pression gastrique, cardiaque et de la motricité 5 et 10 cm au-dessus de ce point. La capacité résiduelle fonctionnelle et la résistance bronchique spécifique pléthysmographique ont été mesurées. Après obtention de la fonction basale, un test de provocation bronchique au Carbachol a été réalisée [21], le seuil de réponse étant déterminé par la chute de 40 % de la conductance spécifique initiale (PD40S Gaw). Les résultats sont exprimés en terme de sensibilité et de réactivité : pente de réponse aux doses successives. Ces mesures étaient réalisées avant et après un test de perfusion acide (150 ml/h d'HCl 0,1 N durant 20 minutes). L'analyse statistique a été réalisée par des tests non paramétriques usuels. Le test de perfusion acide ne modifie ni la résistance basale ni la sensibilité bronchique ($p = \text{NS}$, fig. 1). Par contre, la réactivité augmente significativement ($p < 0,05$, fig. 2) et d'autant plus que la réactivité basale était plus élevée ($p < 0,01$, fig. 3). Les résultats de l'exploration digestive montrent la fréquence du RGO dans une population asymptomatique d'asthmatiques. La réactivité bronchique est significativement mais faiblement corrélée au pourcentage de temps de $\text{pH} < 4$ ($p < 0,05$) et à la constante de temps des reflux ($p < 0,05$). Parmi les nombreuses études consacrées à la relation entre asthme et RGO [4, 5, 7, 8, 9], seul Davis [9] a réussi à mettre en évidence un bronchospasme franc induit par la perfusion acide dans les conditions particulières du sommeil paradoxal. Notre étude montre que le test de perfusion acide simulant un RGO, augmente la réactivité bronchique chez les enfants asthmatiques. Ces résultats peuvent donc expliquer l'aggravation des symptômes, couramment observée en clinique, en présence d'un reflux gastro-œsophagien.

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Aspiration of gastric juices into the lungs has long been known to induce an acute asthma-like reaction (Mendelsohn syndrome) [28], and intratracheal infusion of acid evokes rapid reflex bronchoconstriction in animals [24]. However, in humans, pulmonary aspiration of gastric contents is not always observed in asthmatic subjects [30]. Andersen et al [2] measured pH in the upper third of the esophagus during distal acid infusion test (AIT), which induces bronchoconstriction, and did not observe any retrograde movement of acid. In contrast, Ducolone et al [10] did detect pulmonary aspiration of gastric juices by scintiscanning in 27 % of asthmatics with gastro esophageal reflux (GER).

Several authors reported that intraesophageal instillation of 0.1 N hydrochloric acid in asthmatic children with GER triggered bronchospasm or increased bronchial responsiveness and triggered a positive response to the Bernstein test (defined as thoracic pain after instillation of hydrochloric acid into the esophagus) [2-17]. Some authors have proposed that GER might worsen bronchospasm in asthmatics via a vagally mediated reflex [8-17], as would be suggested by the direct bronchoconstrictor effect of AIT [2, 17, 25] and its prevention by atropine [2, 25]. Moreover, it is difficult to explain a delayed response (from 20 to 90 minutes after the stimulus) as a result of a simple neurological reflex.

These previous studies assessed bronchial response induced by esophageal AIT in asthmatic children with normal or abnormal pHmetry. However, the effects of lower esophageal sphincter perfusion with 0.1 N HCl on bronchial responsiveness to cholinergic agents has not been previously reported in asthmatic children. It is well established that GER is a normal occurrence, but the frontier between normal and pathological GER is uncertain and depends on age, food, sleep state and posture [27].

In the present study, we examined the direct bronchial effects of a distal esophageal acid perfusion test in asthmatic children and the responsiveness to cholinergic agents. In addition, we report here the first study of the relationship between the bronchial response to AIT and quantitative patterns of GER in terms of frequency and duration.

SUBJECTS

Fifteen children (ten boys and five girls) from 5 to 13 years of age (mean $\pm$ SD: 8 ± 4 years) were studied. All had established asthma on the basis of the diagnostic criteria of the American Thoracic Society [1]. All were atopic on the basis of family and/or personal history. Positive

immediate skin tests to common allergens correlated with history [32, 34]. Seven of the subjects required permanent bronchodilator drugs (>1 year) combined in two cases with inhaled beclomethasone dipropionate (>6 months). The other eight required intermittent treatment for acute asthmatic attacks or for prevention of asthma induced by exercise. All the children had a GER diagnosed by pathological barium esophagram [26, 36] without spilling into the pharynx and received medical treatment for their GER. None presented digestive symptoms suggestive of GER at the time of the study. Informed consent was obtained from the parents and/or the children. For obvious ethical reasons, it was not feasible to have a control group without GER.

METHODS

Studies of GER and lung function were performed during the same week on each subject.

GER study [6]

We systematically performed prolonged esophageal manometry (45-60 min) and monitored esophageal pH for seven hours. All medication was stopped 24 hours prior to manometry and pH monitoring, and patients fasted overnight before testing, which started at 8.30 a.m.

Two monopolar electrodes were used to record intraesophageal pH. The measuring electrode (MI 506 Ref) was passed through the nose inside a feeding probe (ORX 391.10) and positioned 5 cm above the eleventh dorsal vertebra. The position was radiologically verified. The reference electrode (MI 402) was placed on a leg or on the abdominal wall. Both electrodes were connected to an amplifier (BHN 81 Tacussel Electronique) and their output was recorded on a graphic recorder at 5 cm/min. During the test, each child adopted a standard position: on his bed in a Fowler position (i.e. semidecubitus).

Before and after each measurement, the electrodes were calibrated against pH buffer at 4.1 and 7.41 (Buffer 4.100 and 7.410 Intrumentation Laboratory). Studies extended over a 7-hour period: 4 hours before and 3 hours after ingestion of a test meal (custard tart) containing 6.7 % proteins, 6.3 % lipids and 25 % glucose (184 Kcal per 100 g).

A reflux was defined as a sudden decrease of pH below pH = 4 lasting more than 10 seconds. The baseline value of pH, the number of refluxes per hour of recording (h^{-1}), the duration of reflux (%), the duration of pH < 4 (%) and the time constant (min^{-1}) defined as the time to decrease to 50 % of the minimal pH value of the longest reflux, were measured before and after the test meal.

Esophageal motility [6]

Esophageal motility was tested on a different day than that of pH measurements. A four balloon probe for recording esophageal pressure, lower esophageal sphincter (LES) pressure and gastric pressure was used. Each balloon and its tube were filled with water and connected via a pressure transducer (PM6 Statham) to an amplifier and a recorder (Gould Brush). The low pass filter of the assembly was 20 Hz.

From the chart recording, we took four direct measurements : resting pressure 10 cm and 5 cm over LES, LES and gastric pressure. Four other values were calculated from chart data : percentage of peristalsis 10 and 5 cm over LES, and percentage of tertiary waves 10 and 5 cm over LES.

Documentation of lung function and of bronchial responsiveness.

All medication was stopped 12 hours prior to testing. Measurement of the parameters in this study did not require active cooperation from the children. Specific airway resistance (S Raw) was determined with a Fenyves body plethysmograph [3]. The coefficient of variation of S Raw is usually 20 % due to the variable degree of glottis closure. To reduce this source of error in our measurements, we asked the patients to increase their respiratory frequency and tidal volume, giving a more regular breathing pattern. This gave a coefficient of variation, calculated from 6 to 10 successive breaths in each basal and post provocative measurement, of 10 % [14, 34]. After baseline S Raw was measured, bronchial provocation was realized by carbachol inhalation tests according to Orehek's and al. procedure [29]. S Raw was converted to specific conductance (S Gaw) in $\text{sec}^{-1} \text{cmH}_2\text{O}^{-1}$. The children inhaled a volume of 1.5 liter corresponding to 0.3 mg of Carbachol in each dose, and S Raw was assessed 1 minute after each dose. Successive inhalations of equivalent volume-dose (cumulative dose) were repeated until at least a 300 per cent increase in initial S Raw, corresponding to a 76 % decrease in S Gaw, was observed, or at most a total dose of 2.7 mg (9 successive doses) was given. This dose was chosen as a maximum, because the asthmatic children tested in our laboratory were responders below 2.4 mg of Carbachol (results not shown).

The results were expressed in terms of sensitivity and reactivity.

– *Sensitivity* : the threshold was a decrease of 40 % compared to initial S Gaw (PD 40S Gaw) calculated by linear interpolation from the two points obtained below and beyond a 40 % S Gaw change.

– *Reactivity* : The dose response curves were obtained using the successive dose-response points from the first point deviating by 20 % from baseline [11]. The slope was calculated by the linear regression equation ($\log y = a + bx$) where b is the slope, y the S Gaw and x the dose. At least, 3 points were required for the curve to be considered in the data (range : 3 to 6 points).

Experimental protocol : bronchial response to AIT

Baseline lung function and bronchial provocation Carbachol test (BPT) before AIT were performed at 9 AM. One hour after the end of BPT, S Raw was again measured every 15 minutes until the initial pre-BPT value was reached. Thereafter, AIT was performed : 0.1 N HCl at room temperature (20 to 22°C) was perfused into the esophagus at a rate of 150 ml. h^{-1} during 20 minutes via a naso-esophageal tube (French gauge n° 6) terminating in the distal third of the oesophagus [37] in the sitting position. Immediately after removing the catheter, bronchial response to acid perfusion was assessed by measurement of S Raw, followed by a second BPT (test after AIT).

No thoracic pain was provoked by hydrochloric acid instillation into the esophagus in any children studied.

STATISTICAL ANALYSIS

Because of the size of the groups, non parametric tests were used : Spearman correlation coefficient for the study of correlation between variables, Wilcoxon paired test for the comparison of two distributions [35].

RESULTS

Bronchial responses.

During esophageal AIT, no children complained of digestive (heartburn, regurgitation of acid into the mouth) or respiratory (cough, dyspnea) symptoms.

Table I indicates the values of baseline S Raw and the bronchial response to esophageal perfusion. HCl infusion did not change resting S Raw when compared with baseline values in any subject. Comparison by the Wilcoxon paired test showed no change in sensitivity (Fig. 1) but did show a significant increase in reactivity after AIT ($p < 0.05$) (Fig. 2). The study of Spearman's coefficient showed significant correlations bet-

TABLE I. - Respiratory parameters and results of acid infusion test (AIT) on respiratory function ($M \pm SEM$ and range) (N = 15) Sensitivity is expressed in μg of carbachol (See text for more explanation)

	Before AIT	After AIT
S Raw	5 ± 1.6 (1.5-8)	5.3 ± 1.5 (3.8-9.1)
Sensitivity	606 ± 156 (155-2003)	649 ± 100 (234-1491)
Reactivity	0.60 ± 0.11 (0.08-1.40)	0.81 ± 0.15 (0.15-2.28)

ween the reactivity before and after AIT ($p < 0.01$) (Fig. 3), i.e. the higher the reactivity before AIT, the higher the reactivity after AIT.

Digestive results

During pHmetry, we observed no asthma-like symptoms (wheezing, shortness of breath...). Table II indicates values measured by pHmetry and table 3 gives values measured by esophageal manometry. These results showed that GER may be present even in asthmatic children without digestive symptoms.

TABLE II. - Results of pH metry ($M \pm SEM$ and range) (N = 15)

	Before AIT	After AIT
Resting pH (pH units)	6.4 ± 0.1 (5.8-7)	6.2 ± 0.1 (5.7-7.1)
Percentage of time of pH < 4 (%)	2.3 ± 0.7 (0-9)	14.4 ± 6.1 (0-94)
Number of refluxes per Hour (H^{-1})	0.6 ± 0.2 (0-2.7)	1.7 ± 0.4 (0-3.3)
Time constant of the longest reflux (mn^{-1})	1.7 ± 0.4 (0-5.5)	8.3 ± 2.6 (0-38)
Percentage of time of reflux (%)	3.7 ± 1.1 (0-12)	16.4 ± 3.9 (0-54)

TABLE III. - Results of esophageal manometry ($M \pm SEM$ and range) (N = 15)

	5 cm over LES	10 cm over LES
LES Pressure (cm H20)	17.8 ± 2.0 (8.4-39)	
Gastric pressure (cm H20)	14.7 ± 1.9 (3.6-33)	
Resting pressure (cm H20)	18.1 ± 2.5 (3.6-36)	15.1 ± 1.8 (3.5-27)
Percentage of peristalsis (%)	15.0 ± 1.8 (2.8-26.8)	12.6 ± 1.4 (2.9-20.4)
Percentage of tertiary waves (%)	4.9 ± 1.5 (0-15)	2.4 ± 1.4 (0-15)

LES = Lower esophageal sphincter.

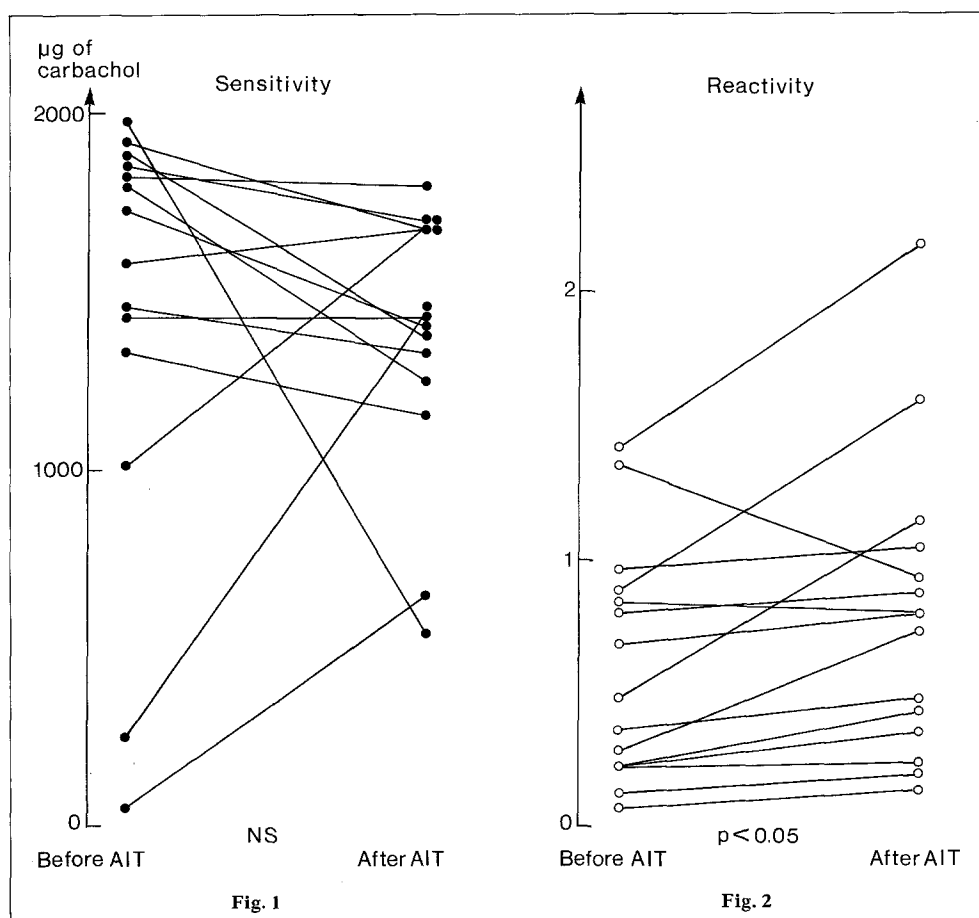


Fig. 1. - Comparison of the sensitivity (expressed in μg of carbachol) before and after Acid Infusion Test (AIT).

Fig. 2. - Comparison of the reactivity (determined as the slope b of the linear regression $\text{Log } S_{\text{Gaw}} = a + b \cdot \text{Dose}$) before and after Acid Infusion Test (AIT).

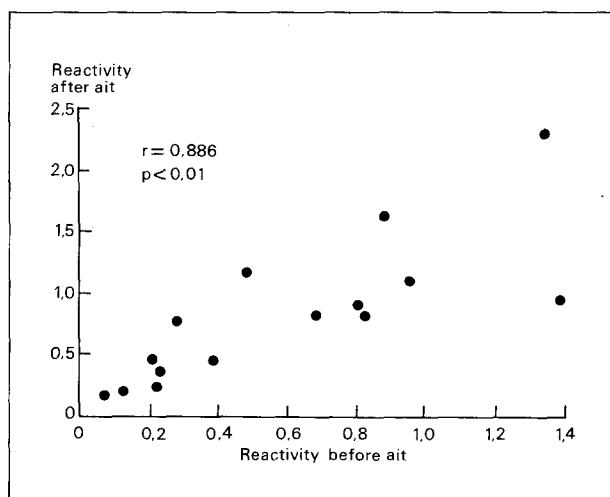


Fig. 3. – Relationship between reactivity before and after Acid Infusion Test (AIT).

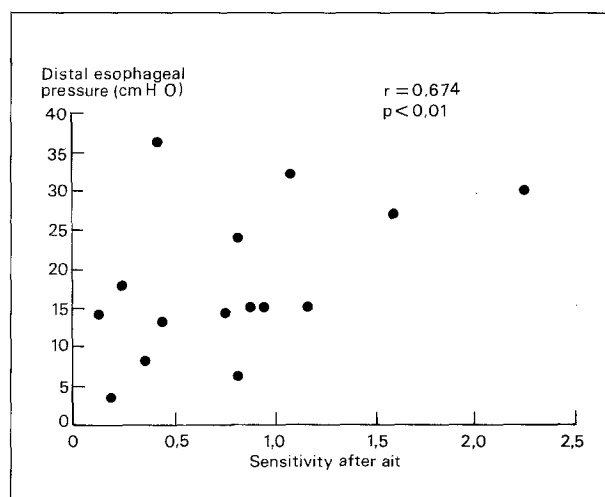


Fig. 4. – Relationship between distal esophageal pressure (expressed in cm H₂O) and sensitivity (expressed in μ g of carbachol) after Acid Infusion Test (AIT).

Correlation between respiratory and digestive results

pHmetry: the time during which pH was inferior to 4 after the test meal was correlated with the reactivity before AIT ($p < 0.05$). The time constant of the longest reflux after the test meal was also correlated with the reactivity before ($p < 0.05$) or after AIT ($p < 0.05$). But these correlations are very weak, with an r^2 approaching 25 %, i.e. 75 % of the variance of the respiratory variable is not explained by the relationship with the digestive parameters.

Manometry: distal esophageal pressure was correlated with the sensitivity after AIT ($p < 0.01$) (Fig. 4).

DISCUSSION

Unlike previous studies, no change in lung function following AIT was seen in any subject in this study. AIT did not induce bronchospasm in our asthmatic children when measured 25 minutes after the onset of AIT, in agreement with Wilson's data [41]. In contrast, some degree of bronchospasm was detected in certain other studies [2, 8, 10, 25], but in most of these cases the bronchial change was delayed from 20 to 90 minutes after the onset of acid instillation. The delay was always modest [2, 25, 40] and was present only in some of the asthmatic patients with GER. Moreover, there were some conflicting results according to the functional test used to detect bronchospasm [10, 25]. Only one clinical study [8] clearly showed that acid infusion induced bronchospasm with audible wheezing, but it was done during REM sleep (at 4-5 AM).

As pointed out by Johnson et Rajacopal [9], GER can trigger asthma symptoms more easily at night time, especially during REM sleep, partly due to a prolonged acid contact and partly due to the nocturnal increase of basal obstruction tied to the circadian rhythms.

The degree of bronchial responsiveness may be used as a sensitive index of the deleterious effect of GER in asthma. Bronchial responsiveness may be analysed in terms of sensitivity or in terms of reactivity. Several reports have shown very good reproducibility for the level of sensitivity [7, 16, 22, 33], especially when the interval between the 2 tests was less than 24 hours [26]. S Raw may be questionable because its variation coefficient is greater than with FEV1, but it has been shown that there was no significant difference between Histamine and Metacholine PD35 S Gaw and PD20 FEV1 [22]. The reproducibility of reactivity with this technique was demonstrated previously in our laboratory [32]. On the basis of the reactivity coefficient, acid esophageal instillation increased bronchial responsiveness.

The calculation of the dose-response curve is controversial. Some authors used linear/linear plots [29], other used semi-logarithmic regression on the straight part of the "dose-response" curve [11]. This second method was used for the present study and gave sensitivity and reactivity coefficients. The importance of a change in bronchial reactivity in the absence of significant change in bronchial sensitivity has to be questioned. This could have occurred because the bronchial reactivity was determined by the "best-fit" line. The variability of the resistance was minimized by increasing the respiratory frequency and tidal volume and gave a coeffi-

cient of variation of 10 %. The use of the same method of calculation for the reactivity coefficients for the two tests (before and after AIT), the significant difference between the reactivity before AIT and after AIT (Fig. 2), and the correlation ($p < 0.01$) between these two coefficients (Fig. 3) minimized possible errors due to the calculation of the best-fit dose-response line. The degree of bronchial reactivity reflected the bronchial aptitude for strong bronchospasm. In our study, the positive change of reactivity was not accompanied by a change of sensitivity but means that an identical trigger induces a stronger bronchospasm; nevertheless, the change of reactivity was weak in terms of absolute variation (0.60 ± 0.11 vs 0.81 ± 0.015). Although statistically significant, this change was minimal, despite the fact that esophageal acidification was probably more prolonged and intense than occurs spontaneously. In studies with adult patients, airway response to AIT was often found [10, 25, 40, 41]. Perhaps children do not develop esophagitis so readily, in which case, their response to AIT is then minor.

Esophageal manometry and pH monitoring have found increased use in recent years for diagnosing reflux in childhood [21]. While pH monitoring gives a direct indication of GER, esophageal manometry is used to study physiological aspects of reflux prevention [9].

The relationship between distal esophageal pressure on one hand and sensitivity and reactivity after AIT on the other hand might be explained by physiological mechanisms: the esophagus is a soft muscular tube and, as such, intraluminal pressure increases as a function of applied extrinsic environmental pressure and intrinsic myogenic tone [9]. Distal esophageal pressure is an indirect indication not only of thoracic pressure but also of esophageal muscular tone. We have not found a relationship

between the LES pressure and reactivity or sensitivity either before or after AIT. Pressure of the LES was lower in patients with symptoms of GER than in normal subjects [12, 15]. Despite this statistical correlation, it was often found that the severity of the symptoms correlated poorly with the competence of the lower esophageal sphincter in adults [38] or in children [23]. The peristaltic activity of the esophagus did not participate in the response to AIT in the children studied.

Intra esophageal pH monitoring is the sensitive and specific test for GER [31]. Many authors have proposed scoring procedures to evaluate pathological reflux [5, 13, 18, 20]. However, no relationship has been found between the severity of esophageal or pulmonary symptoms and patterns of GER [23]. By the same token, pulmonary aspiration, either clinically diagnosed or radiologically suspected, has not been shown to be correlated with GER documented by pH monitoring [23]. Despite the high incidence of pathological GER in asthmatic children, the relationship between GER and asthma has most often been studied by qualitative indices (presence or absence of pathological GER) [3, 10, 27], instead of quantitative measurements.

CONCLUSION

This study shows that in asthmatic children bronchial reactivity is related to the time constant of the longest reflux and to the percentage of time the pH is inferior to 4. The acid infusion test stimulated GER and slightly increased bronchial reactivity in these children. These results show that GER, whether moderate or severe, can aggravate unconstantly asthma, though an explanation of the mechanism must await further studies.

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