

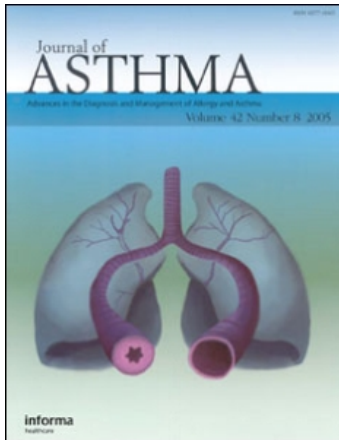
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ORIGINAL ARTICLE

A MCh Test Pre-post Esophageal Acidification in Detecting GER-related Asthma

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The direct effect of gastro-esophageal reflux (GER) on lung function is still debated. *Objective.* To investigate the role of esophageal acidification in affecting airway response to MCh in GER-related versus atopic asthmatics and to assess specificity and sensitivity of events. *Subjects.* A total of 56 never-smoking, mild asthmatics: 27 non-atopic asthmatics and acid GER (GER+ve) and 29 atopic asthmatics without any GER (GER-ve). *Methods.* Each subject performed an MCh challenge in baseline (MCh_b), and 30 minutes after an acid drink (125 mL at pH = 2; MCh_{ac}), one day apart. PD₂₀FEV₁ MCh_b and MCh_{ac} were compared by estimating the area under the ROC curve (AU-ROC). Results. GER+ve and GER-ve subjects (well matched in baseline) had a different duration of esophageal acid contact (24-hour monitoring; pH-24h AU₄), and PD₂₀FEV₁ MCh_{ac} (both $p < 0.001$). AU-ROC was 86.3% (76% to 97%, 95%CI). Sensitivity and specificity of changes were 82.8% (72.9% to 92.7%, 95%CI) and 85.2% (75.9% to 94.5%, 95%CI), respectively. The difference in MCh threshold that maximized both the sensitivity and specificity level was 100 μ g. *Conclusions.* The esophageal acidification identified GER-related asthma with a good level of both sensitivity and specificity by enhancing the MCh response only in the presence of acid GER. Data are supporting the effectiveness of this procedure for clinical purposes.

Keywords gastro-oesophageal reflux, bronchial asthma, bronchial hyperreactivity, lung function, GER-related asthma, oesophageal acidification

INTRODUCTION

The esophagus and the airways can mutually interact through several mechanisms (1) through their anatomical proximity and common embryology.

Acid Gastroesophageal Reflux (GER) represents a digestive dysfunction that can frequently occur also in normal people at a some extent, but it is not surprising that GER occurrence frequently combines with the onset of one or more respiratory symptoms of different severity and relevant clinical impact (2–6). In these circumstances, cough and wheezing represent the most frequent respiratory complaints, which are usually related spontaneously to GER occurrence in the patient.

The prevalence of respiratory manifestations of GER often remains undefined because the cause-effect relationship between the occurrence of GER events and the onset of respiratory-related symptoms proves really difficult to assess, and frequently the patient's history still remains the unique feature of some clinical value in these cases (7). Unfortunately, usual indices of lung function (namely, PEFr measurements, spirometrical lung volumes and flows, airway resistance) prove too poor sensitivity and specificity in assessing respiratory dysfunctions related to acid GER (8), and GER-induced respiratory troubles can actually occur although pulmonary function is normal (6, 9).

Moreover, the usual measure of bronchial hyperreactivity (BHR) to non-specific stimuli (namely, histamine or metha-

choline) showed a poor diagnostic power in the presence of GER (10–13).

In 1986, Herve et al. proved that the repeated stimulation of esophageal acid-sensitive receptors can interact with the bronchomotor tone and for the first time suggested that the presence of an hyperacidic esophageal environment can enhance bronchial hyperresponsiveness to non-specific stimuli (14).

The aim of the present study was to investigate non-invasively the effects of a standardized acid esophageal challenge on the bronchial response to MCh in asthma patients with and without acid GER to assess both the specificity and the sensitivity of respiratory changes observed and to calculate the potential diagnostic role of this procedure in identifying patients suspected for acid GER-related asthma.

MATERIALS AND METHODS

Fifty-six never-smoking mild asthmatics (basal FEV₁ \geq 80% predicted) in stable conditions were recruited after their informed written consent: 27 subjects (7 males) were non-atopic asthmatics with a symptomatic and pathologic acid GER, which was first suspected by the recurrence of specific clinical signs (namely, acid regurgitation and retrosternal burning \geq 3 days/week) and then confirmed by a 24-hour gastro-esophageal pH monitoring, while the remaining 29 subjects (5 males) were atopic asthmatics without any clinical sign of acid GER occurrence, being the presence of GER excluded by means of the pH monitoring procedure.

The atopic condition had been confirmed or excluded on the basis of patients' clinical history, their total IgE level measured in blood; their prick test (to a panel of the 21 most

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frequent allergen classes), and the measurement of corresponding specific IgE (RAST).

All subjects were regularly taking only inhaled steroids for at least 24 weeks: their daily doses ranged from 400 to 500 μg BDP (or equivalent), and their compliance to treatment was good ($\geq 75\%$ prescribed dose). Short-acting β_2 agonists were the only rescue medication permitted during the study. Exclusion criteria were basal $\text{FEV}_1 < 80\%$ predicted; unstable bronchial obstruction (PEFR variability $> 30\%$); frequent use of short-acting β_2 agonists in the last 4 weeks; regular use of high doses of ICS; use of PPIs and/or anti H_2 compounds ≥ 2 days/week in the last 4 weeks; pregnant or lactating women; systemic concomitant diseases; neoplasms; mental limitations.

Lung function was basally assessed by a spirometric test (Masterscreen; Vyasis-Jaeger; Hoechberg; Germany); FEV_1 was expressed as an absolute value (L) and as % predicted (CECA 1993, in the range 18–70 years) (15). The bronchial response to MCh was first assessed in baseline, and results were expressed in micrograms MCh needed for a 20% decrease of FEV_1 from its basal value ($\text{PD}_{20} \text{FEV}_1$). The bronchial challenge was performed by doubling MCh doses (ranging 50 to 3,150 μg) via APS System (Vyasis-Jaeger; Hoechberg; Germany) up to the $\text{PD}_{20} \text{FEV}_1$ (16).

After a 24-hour interval, and at an average of 3 hours before lunch, each subject repeated the MCh challenge 30' following the esophageal acidification (namely, after drinking 125 mL of a standardized acid solution at a controlled $\text{pH} = 2$) and the corresponding bronchial response was compared with that assessed in baseline, before the acid challenge.

In all subjects, the presence of a pathologic acid GER had been previously (in the previous 12 weeks) detected (e.g., confirmed or excluded) by means of a 24-hour gastro-esophageal pH monitoring: A combined monocrystalline antimony catheter was used with a pressure sensor to locate the LES (Digrapper MKIII; Synectics Med., Stockholm, Sweden), and the diagnostic DeMeester's criteria were assumed (17). In the present study, the result of the 24-hour pH monitoring was synthetically expressed as "AU under pH 4" (AU_4 — area under the curve of $\text{pH} < 4$), such as the parameter that indicates the extent of the acid contact at a $\text{pH} < 4$ into the esophagus (17).

The overall patients' sample was then divided into two subgroups: the patients in whom presence of a pathologic acid GER was documented (GER +ve; $n = 27$) and those without any significant registration of GER events (GER -ve; $n = 29$).

Statistics

The two subgroups of patients were compared for age; basal weight; height; BMI; pH 24-hour AU_4 ; absolute FEV_1 value; basal $\text{PD}_{20} \text{FEV}_1$ to MCh in baseline (MCh_b), and $\text{PD}_{20} \text{FEV}_1$ to MCh after the acid drink (MCh_{ac}); Student's t test was used to compare corresponding means \pm SD, and $p < 0.05$ was assumed as the minimal level for statistical significance.

As ROC (Receiver Operating Characteristic) curves have been widely accepted as the standard method for describing and comparing the accuracy of diagnostic medical procedures (18), the accuracy of a diagnostic test based on the absolute difference between $\text{PD}_{20} \text{MCh}_b$ and $\text{PD}_{20} \text{MCh}_{ac}$ as assessed in the two subgroups of subjects was checked by the

TABLE 1.—Demographics, mean basal FEV_1 ; $\text{PD}_{20} \text{FEV}_1 \text{MCh}_b$; $\text{PD}_{20} \text{FEV}_1 \text{MCh}_{ac}$; pH-24h $\text{AU}_4 \pm$ sd, and the corresponding t test p values.

	GER +ve	GER -ve	p
n	27	29	
Sex (n and % males)	7 (25.9%)	5 (17.2%)	0.429†
Age (y)	41.7 \pm 13.8	41.6 \pm 14.9	ns
Weight (kg)	63.5 \pm 14.4	61.2 \pm 10.0	ns
Height (cm)	162.7 \pm 7.5	163.4 \pm 6.8	ns
BMI	24.1 \pm 5.9	23.0 \pm 3.8	ns
FEV_1 (l)	2.8 \pm 0.7	3.0 \pm 0.6	ns
$\text{PD}_{20} \text{MCh}_b$ (μg)	1607.5 \pm 882.3	1965.0 \pm 610.4	ns
$\text{PD}_{20} \text{MCh}_{ac}$ (μg)	787.8 \pm 751.1	2197.1 \pm 685.4	<0.001
pH-24-hour AU_4	114.1 \pm 94.7	10.8 \pm 7.4	<0.001

† = Pearson's chi-square test.

estimate of the area under the ROC curve (AU ROC), with a 95% confidence interval.

In the present paper, the area under the ROC curve was expressed in percentage of the total area, and the estimator's standard error was also indicated. Analyses were undertaken by using Stata 8.0 (19).

RESULTS

Descriptive statistics (means \pm SD) of all variables observed in the two subgroups of subjects are reported in Table 1, together with the corresponding significance (p value) for statistical comparisons.

GER +ve and GER -ve subjects were well matched for sex, age, weight, height, and body mass index (BMI). They also were comparable in terms of their basal lung function (namely FEV_1 , and basal bronchial response to MCh - MCh_b) (Table 1).

Nevertheless, the subgroups were different in terms of pH-24h AU_4 (the extent of esophageal acid contact at $\text{pH} < 4$ during the 24-hour monitoring) and of their response to MCh after the acid esophageal challenge (MCh_{ac}) (both $p < 0.001$) (Table 1).

The area under the ROC curve was = 0.863 (0.055 estimator's standard error); or, 86.3% of the total area available under the ROC, being 76% to 97% of the corresponding 95% CI (Figure 1).

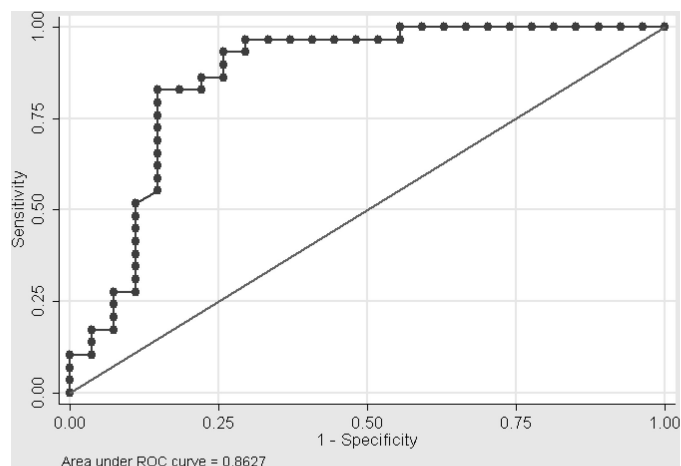


FIGURE 1.—The area under the ROC curve for the diagnostic procedure. The AUC estimation of the ROC curve for the diagnostic procedure is (0.86 CI 95% [0.76–0.97]).

TABLE 2.—Classification data corresponding to the maximized values for both sensitivity and specificity of the procedure; absolute decrease in PD₂₀ FEV₁ MCh before and after the acid esophageal challenge was = 100 μg MCh.

Diagnostic test	Groups				
	GER+	GER-			
pos.	23	5			
neg.	4	24			
Total	27	29			
True D defined as group ~ = 1			[95% CI]		
Sensitivity	Pr(+ D)	82.76%	72.87%	92.65%	
Specificity	Pr(- ~D)	85.19%	75.88%	94.49%	
Positive predictive value	Pr(D +)	85.71%	76.55%	94.88%	
Negative predictive value	Pr(~D -)	82.14%	72.11%	92.17%	

Values calculated for both sensitivity and specificity of measures were 82.8% (72.9–92.7%, 95% CI) and 85.2% (75.9–94.5%, 95% CI), respectively. Moreover, values for both sensitivity and specificity proved to change according to the extent of the absolute difference between the PD₂₀ MCh_b and the PD₂₀ MCh_{ac} threshold observed (such as the values for PD₂₀ FEV₁ MCh calculated before and after the acid esophageal challenge). The corresponding curvilinear trends were obtained and then compared.

The decrease in PD₂₀ FEV₁ MCh that enabled to maximize both the sensitivity and the specificity levels of the diagnostic procedure was = 100 μg from baseline (Table 2). Figure 2 shows sensitivity and specificity curves for all absolute differences in PD₂₀FEV₁ MCh_b and PD₂₀FEV₁ MCh_{ac} as calculated in the two different subgroups of subjects. In agreement with data reported in Table 2, it is clearly shown that the two curves intercept in correspondence of a 100-μg MCh difference between the basal and the post-acid MCh condition.

All patients performed the two MCh challenges without any discomfort.

DISCUSSION

The occurrence of respiratory symptoms in asthma patients with digestive disorders (namely, acid GER) is a frequent

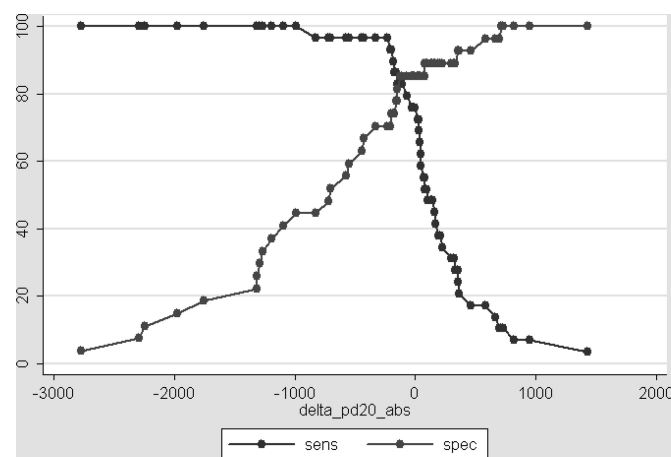


FIGURE 2.—Sensitivity and specificity curves for all absolute differences in PD₂₀ FEV₁ MCh calculated in the two different subgroups of subjects.

occurrence, although the limits of this relationship are still debated, as well as the direct and causative role of esophageal acidification in inducing significant and specific changes in lung function (12, 13). Actually, while new technologies contributed substantially in providing some reliable methods for investigating upper digestive tract dysfunctions more specifically in the last decade (and the 24-hour pH monitoring was regarded as the golden standard), usual pulmonary lung function tests did not contribute as effectively in discriminating patients with respiratory disorders when they were related to the presence of acid gastro-esophageal reflux (10–13).

In previous studies, the esophageal acid perfusion was shown to cause only a 0.2L decrease in vital capacity (20), while peak expiratory flow rate (PEFR) was found to decrease in asthmatics with or without GER (21). Conversely, a significant reduction in PEFR was observed only when both the esophageal and the tracheal acidification were performed, with the effects on PEFR of the sole esophageal acidification clinically negligible (22, 23).

From a general point of view, although episodic experiences (in both experimental and clinical studies) proved the effective role of esophageal acidification in inducing a transient airway obstruction (10, 11, 24), the assessment of the direct and causative role of esophageal acidification (spontaneous or induced) in determining a measurable airway involvement (such as narrowing) still represents a true diagnostic challenge.

When the diagnostic role of the measure of airway response to MCh also was investigated from this point of view in asthma subjects with gastroesophageal reflux, MCh-induced airway narrowing was shown to coexist with longer lasting periods of reflux as compared with the baseline condition (25), although the sole basal assessment of non-specific BHR did not consent any precise identification of a specific and reliable GER-induced pattern of lung function response in these cases (26, 28).

Data of the present paper are in good agreement with this vision as both the basal spirometrical measurements and the basal value for MCh threshold proved not specific enough to discriminate acid GER +ve asthma subjects from controls.

Conversely, the enhancement of the original bronchial response to non-specific stimuli by triggering esophageal acid-sensitive receptors according to the Herve's hypothesis (14) can now be regarded as interesting scientific evidence suggesting the true diagnostic value of the assessment of respiratory effects due to induced esophageal acidification in asthma patients with acid GER.

A few years ago, preliminary data from a controlled study carried out in a selected sample of very mild, non-atopic asthmatics with acid GER, originally unresponsive to MCh, showed that their basal bronchial response to MCh was systematically and substantially affected (such as enhanced) when the non-specific bronchial challenge had been repeated after the esophageal stimulation with an acid drink at a pH = 2, which proved to act as an effective trigger *per se* (29). These pivotal data were strictly fitting with the Herve's hypothesis and also confirmed the results obtained in a previous similar study in which airway reactivity to histamine was assessed in asthma subjects with GER according to a double blind controlled design (30).

Although this pattern of respiratory response to esophageal acid stimulation was confirmed in different sequential sets of subjects with comparable characteristics (personal data on file), the rigorous assessment of both sensitivity and specificity of parametrical changes achievable following esophageal acidification was needed, and a strict statistical design was required to check the potential diagnostic role of this investigational procedure.

Data of the present study are providing the first evidence to our knowledge of the high discrimination power of measurements of bronchial response to MCh when performed and compared before and after a standardized esophageal acid challenge, with the AU ROC calculated for differences higher than 86%.

Actually, a diagnostic procedure should be regarded as characterized by a good discrimination power only when the corresponding AU ROC is greater than 80%, the "discrimination power" reached in the present investigational procedure. Based on the PD₂₀ MCh_{ac}- MCh_b comparison, it is highly probable that the misclassification found by that diagnostic test performed in a randomly selected patient from one of the two subsets of subjects (namely from GER+ve subjects) is lower than that observed in the subjects of the other group.

In other words, as the pattern of lung function that is obtained in response to the esophageal acid challenge (and the corresponding extent of non-specific BHR) confirms as quite peculiar in GER+ve asthma subjects only, it would be suggested that the effective presence of acid in lower esophagus, which was induced by the acid drink in our model, can directly affect airway reactivity substantially. This demonstrates that this kind of measurement can be of true and effective diagnostic value when performed according to a strict protocol of investigation.

Present data provide the first contribution to our knowledge aimed to the standardization of a non-invasive diagnostic procedure oriented to the detection and assessment in a clinical setting of changes in lung function specifically due to esophageal acidification in asthma patients suspected of the presence of acid GER. Actually, the method proves promising because it is effective enough in clinical terms, easy to perform, of low cost, and without any significant discomfort for the patients.

Finally, although the MCh challenge repeated after esophageal acidification is suggested as a sensitive and specific procedure for detecting and discriminating GER-related asthma, further studies are needed to confirm results of the present methodological approach. These studies will be aimed at investigating the pattern (peculiar indeed) of acid-induced hyperreactive response of airways in subjects with acid GER-related asthma.

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