

Gastro-oesophageal reflux prevalence and relationship with bronchial reactivity in asthma

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Gastro-oesophageal reflux prevalence and relationship with bronchial reactivity in asthma. D. Vincent, A.M. Cohen-Jonathan, J. Leport, M. Merrouche, A. Geronimi, A. Pradaliere, J.C. Soulé. ©ERS Journals Ltd 1997.

ABSTRACT: The relationship between asthma and gastro-oesophageal reflux (GER) is controversial. In an allergy department, GER prevalence was evaluated in asthmatics, with a view to judging the potential influence of GER on asthma.

One hundred and five asthmatics were recruited and co-investigated for GER and lung function. Descriptive analysis was performed, patients with (GER+) and without (GER-) GER were then compared, and finally, stepwise regression analysis was used. GER prevalence was 32%.

Lung parameters did not differ between GER+ and GER- patients. When restricting analysis to GER+ patients, bronchial reactivity was closely correlated to the number of reflux episodes (NRE) ($r=0.983$; $p=0.001$). When comparing patients with more than 15 reflux episodes·day⁻¹ ($n=50$), with those having less ($n=43$), no differences were found in lung function and GER parameters. However, there was a positive correlation between the provocative dose of methacholine causing forced expiration volume to fall 20% from the baseline and NRE in patients with $NRE>15$ ($r=0.561$; $p=0.05$).

In conclusion, gastro-oesophageal reflux was observed in a third of the asthma patients studied. These data do not support a firm aetiological relationship between gastro-oesophageal reflux and asthma, but do suggest an association between the number of reflux episodes and bronchial hyperresponsiveness.

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Asthma is a bronchial disease characterized by an inflammatory process [1]. Gastro-oesophageal reflux (GER) has been suspected as a causal factor, but the relationship between GER and asthma remains controversial.

The physiopathological mechanisms involved in this potential relationship are still hypothetical [2–4], although two main mechanisms are usually accepted, reflex [5–7] or acid inhalation [8–10]. A possible relationship between the severity of GER and that of asthma has not been investigated previously.

GER prevalence is not precisely known in asthmatics; it has been estimated at levels of 20 to even 80% [11]. Finally, it is not known which groups of asthma patients in particular should be investigated for GER.

This controversy induced us to conduct a prospective assessment of GER prevalence in a population of 105 consecutively admitted asthmatic out-patients and to search for a relationship between the development of asthma and that of GER.

Materials and methods

Patients

One hundred and five consecutively admitted asthmatic out-patients were investigated. Asthma was diag-

nosed according to international consensus guidelines [12]. Besides clinical data, airway obstruction was measured and its reversibility was defined as a 20% improvement in forced expiratory volume in one second (FEV₁) after bronchodilator administration, or a 20% decrease in FEV₁ after methacholine bronchoprovocation. FEV₁ was measured with a pocket-sized spirometer (Spirobank®; Isotec, Saint-Quentin, France). Results were expressed in real values and as the percentage of standard values for age, gender and height [13]. Bronchoprovocation tests were performed in accordance with the American Thoracic Society guidelines [14]. Methacholine was provided by Allerbio (Varenes en Argonne, France) and administered with a breath-activated nebulizer (Pulmo-neb FDC 88; MSR, Rungis, France) and increasing doses in the range 0.02–43 µM. The provocation test was stopped when FEV₁ had fallen by 20% from the postsaline value. FEV₁, mean expiratory flow (MEF) at 25, 50, and 75% of vital capacity and provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀) were used for statistical analysis and thereby designated as lung function variables.

Asthma was considered to be nonallergic when clinical history, skin-prick tests and nasal allergic provocation were negative. It was considered as allergic when suggested in clinical history and when skin and/or nasal provocation tests were positive.

Asthma staging was taken from international consensus guidelines [12]: grade 1, FEV₁>80%; grade 2 and 3, FEV₁ 60–80%; grade 4, FEV₁<60%.

Asthma treatment was quantified when patients underwent lung function evaluation, and expressed as µg·day⁻¹ or mg·day⁻¹. β₂-agonists were self-administered; their use was quantitatively assessed as puffs·month⁻¹, then transformed into µg·month⁻¹, then µg·day⁻¹. Treatment was conducted in agreement with international consensus guidelines [12]. Every patient with grade 2, 3 or 4 severity (n=31) was treated with inhaled corticosteroids (ICS), with a mean daily dosage of 492±79 µg. Forty six patients used β₂-agonists when needed, with a mean daily dosage of 300±54 µg. Ten were receiving theophylline. Analysis according to asthma severity indicated that grade 1 patients (n=42) were using significantly less ICS than grade 2 and 3 patients (n=29) (370±96 versus 722±141 µg·day⁻¹, respectively, p=0.04). β₂-agonist dosage was higher in grade 2 and 3 than in grade 1 patients (517±104 versus 190±57 µg·day⁻¹ respectively). Allergy was diagnosed in 60 patients (57%). As expected, the main allergens were dust mites (60%) [15].

GER was evaluated through 24 h oesophageal pH monitoring, and defined as a drop in oesophageal pH below 4 lasting longer than 20 s. The diagnosis of GER was based on an acid exposure time (pH<4) exceeding 4.2% of the 24 h [16, 17]. The number of reflux episodes (NRE) was also monitored over the same period. Oesophageal manometry measuring mean lower oesophageal sphincter pressure (*P*_{oes,lsp}), and upper digestive endoscopy evaluating oesophageal mucosa, were also performed. Acid exposure time, expressed as a percentage of 24 h with oesophageal pH under 4, and NRE were used as GER criteria for statistical analysis. Oesophageal manometry and pH recording techniques are described in more detail elsewhere [18]. Hiatus hernia was diagnosed when gastric folds extended at least 2 cm above the diaphragmatic hiatus during quiet respiration. Oesophagitis was staged according to Savary's classification [19].

Statistics were computed with Statview 4.5 (Abacus Concepts Inc, Berkeley, CA, USA), on the whole group, and subsequently in the GER-positive patients only. Analysis was initially descriptive, then correlations were sought between lung spirometry data (FEV₁, MEF_{25%}, MEF_{50%}, MEF_{75%}, PD₂₀, and GER) criteria (percentage of 24 h with pH<4, NRE and *P*_{oes,lsp}). Adjustment was made for age, clinical symptoms of GER and asthma severity. Stepwise regression analysis was performed, using GER parameters and asthma treatment as predictive variables and lung spirometry values as dependent variables. Statistical significance was admitted when the p-value was less than 0.05.

This study was approved by a local Ethics Committee and every patient gave oral informed consent.

Results

Patients' characteristics

Demographic data. Of the 105 consecutive patients enrolled in the study, five declined to complete it, and six did not tolerate the 24 h pH monitoring, leaving 94 asthmatic patients for analysis. There were 41 women and 53 men with a mean age of 39.5±1.5 yrs.

Lung function and treatment. Mean FEV₁ was 84±4% whereas MEF_{25%} was 49±6%, MEF_{50%} 57±6%, MEF_{75%} 65±6% of normal values. Forty eight asthmatics were classified in grade 1, 29 patients in grade 2 and 3, and two in grade 4. No patients were treated with anti-reflux therapy.

GER. In the total asthmatic population studied, the mean percentage of 24 h with pH<4 was 5.7±1.4 (0–42%), the mean NRE was 28±2 per day (0–81), the mean *P*_{oes,lsp} was 2.0±0.1 (0.7–4.0) kPa (15.3±0.62 (5–30) mmHg).

GER was found in 30 patients, *i.e.* 32% of the total population studied. In these patients, the mean percentage of 24 h with pH<4 was 9.9±1.7 (4.2–42) %, the mean NRE for 24 h was 40±3 (2–81), and the mean *P*_{oes,lsp} was 2.0±0.2 (0.7–4.0) kPa (15.1±1.3 (5–30) mmHg). Fifteen of these 30 patients (50%) had no symptoms suggesting GER. Oesophagitis was present in eight patients, five grade 1, two grade 2 and one grade 4.

In GER-negative patients, the mean % of 24 h with pH<4 was 1.4±0.14, the mean NRE for 24 h was 20.7±2.1; mean *P*_{oes,lsp} (2.1±1.4 kPa (15.8±10.7 mmHg)) was not different from that in GER-positive patients.

Relationship between GER and lung function in the whole population

Comparison of asthmatics with and without GER showed no significant difference in spirometry parameters and drug intake (table 1). PD₂₀ was lower in GER-positive than in GER-negative patients, but this difference was not statistically significant (p=0.23). In the whole population studied, there was no correlation between spirometry results on the one hand, and GER parameters or *P*_{oes,lsp} on the other hand (table 2).

Table 1. – Patient characteristics in the presence or absence of gastro-oesophageal reflux (GER)

	GER+ (n=27)	GER- (n=46)	p-value
FEV ₁ % pred	79±3	85±3	0.19
MEF _{25%} % pred	43±4	52±4	0.16
MEF _{50%} % pred	50±4	61±4	0.07
MEF _{75%} % pred	60±5	72±4	0.07
β-agonist µg·day ⁻¹	353±87 (n=15)	246±74 (n=31)	0.38
ICS µg·day ⁻¹	452±126 (n=14)	512±104 (n=11)	0.73
PD ₂₀ µg	230±89 (n=6)	620±187 (n=14)	0.23

Values are mean±SEM. % pred: percentage of predicted values; PD₂₀: provocative dose of methacholine causing a 20% fall in FEV₁; FEV₁: forced expiratory volume in one second; MEF: mean expiratory flow of 25%, 50% and 75% of vital capacity; ICS: inhaled corticosteroids.

Table 2. – Correlation coefficients between spirometry parameters, asthmatic treatment and GER, NRE and *P*_{oes,lsp} in the whole population

	% of 24 h with pH<4	NRE	<i>P</i> _{oes,lsp}
FEV ₁ % pred	0.076	-0.44	0.006
MEF _{25%} % pred	0.098	0.122	0.052
MEF _{50%} % pred	0.093	0.085	0.035
MEF _{75%} % pred	0.005	-0.28	0.047
β-agonist (n=43)	-0.039	-0.23	-0.079
ICS (n=67)	-0.152	-0.87	0.062

*P*_{oes,lsp}: low oesophageal sphincter pressure; NRE: number of reflux episodes. For further definitions, see table 1.

There was no difference in the percentage of 24 h with pH<4 between patients classified according to asthma severity (5.8±2.3% in grade 1 patients and 5.3±1.5% in grade 2 and 3 patients; p=0.93). NRE was not different between these groups (25±2 in grade 1 patients; n=42; versus 30±3.6 in grade 2 and 3 patients; n=27; p=0.21). *P*_{oes,lsp} was also similar in all groups (2.0±0.1 kPa (15.3±0.7 mmHg) in grade 1, (2.2±0.2 kPa (16.6±1.3 mmHg) in grade 2 and 3 patients; p=0.17).

There was no correlation between the quantitative requirement of antiasthma medications, both in terms of dosage and type of drug, and oesophageal acid exposure or *P*_{oes,lsp} (table 2). Theophylline users were equally distributed between GER-positive (n=5) and GER-negative patients (n=5) (p>0.05).

Stepwise regression analysis did not point out any factor significantly determining lung function in the whole population (p>0.05) (table 3). Lung function parameters did not differ between patients with and without clinical signs of GER (table 4).

Finally, lung function parameters were compared between patients classified according to the NRE with a cut-off value of 15 episodes·day⁻¹. The mean percentage of 24 h with pH<4 was significantly different between the two groups (7.6±1.9 versus 1.1±0.26; p=0.04). No differences were found in GER and lung function parameters between the two groups (table 5). However, when taking into account patients with more than 15 reflux episodes·day⁻¹, a significant correlation was found between the NRE and bronchial reactivity, evaluated with methacholine PD20 (r=0.561; p=0.05; n=12).

Relationship between GER and lung function in the population of GER-positive asthma patients

In GER-positive patients, we found no correlation between FEV₁, MEF_{75%}, MEF_{50%}, MEF_{25%} and percentage of 24 h with pH<4, NRE and *P*_{oes,lsp}. There

Table 3. – Step 1 correlation coefficients for potential digestive determinants of lung function

	FEV ₁ % pred	MEF _{25%} % pred	MEF _{50%} % pred	MEF _{75%} % pred
% of 24 h with pH<4	0.1	0.1	0.1	0.02
<i>P</i> _{oes,lsp}	0.03	0.08	0.06	0.06

For definitions, see tables 1 and 2.

Table 4. – Comparative analysis of spirometric values and GER parameters between patients with and those without clinical signs of GER

	Presence of clinical signs of GER (n=43)	Absence of clinical signs of GER (n=40)	p-value
FEV ₁ % pred	82±3.4	82±2.7	0.98
MEF _{25%} % pred	49±4.5	48±3.9	0.83
MEF _{50%} % pred	58±4.5	56±3.8	0.85
MEF _{75%} % pred	71±4.7	66±4	0.40
PD20	242±137	726±215	0.07
β-agonist	339±64	238±96	0.37
NRE	28±3	28±2	0.94
<i>P</i> _{oes,lsp}	14±0.8	16±0.9	0.04
% of 24 h	7.1±2.5	4.0±0.7	0.26

Values are mean±SEM. % of 24 h: percentage of 24 h with pH<4. For further definitions, see tables 1 and 2.

Table 5. – Comparative analysis of spirometric values between patients with more and those with less than 15 reflux episodes per 24 h

	>15 episodes·day ⁻¹	<15 episodes·day ⁻¹	p-value
FEV ₁ % pred	82.2±2.7	84.4±4.2	0.66
MEF _{25%} % pred	51.9±3.9	43.6±4.6	0.23
MEF _{50%} % pred	60.3±3.9	51.9±4.2	0.22
MEF _{75%} % pred	70.2±4.1	64.5±5.8	0.44
β-agonists μg·day ⁻¹	296±61	266±179	0.84
ICS μg·day ⁻¹	480±100	568±159	0.63

Values are mean±SEM. For definitions, see tables 1 and 2.

Table 6. – Correlation coefficients between spirometry parameters, GER and *P*_{oes,lsp} in the GER-positive asthma population

	NRE	<i>P</i> _{oes,lsp}	% of 24 h with pH<4
FEV ₁	-0.18	-0.7	0.246
MEF _{75%}	-0.234	0.045	0.161
MEF _{50%}	-0.016	0.179	0.345
MEF _{25%}	0.133	0.401	0.341
PD20	0.983***	-0.317	0.338
ICS	-0.109	0.274	-0.276
Inhaled β-agonist	-0.33	0.1	-0.27

***: p<0.001. For definitions see tables 1 and 2.

was no correlation between β₂-agonist use on one hand, and *P*_{oes,lsp} (n=14; r=0.1; p=0.7), the NRE (n=15; r=-0.33; p=0.23), and the percentage of 24 h with pH<4 (n=15; r=-0.27; p=0.34) on the other.

However, there was a very strong correlation between PD20 and the NRE (n=6; r=0.983; p=0.001) (table 6).

There were no differences in GER parameters according to asthma severity in this group of GER-positive patients: percentage of 24 h with pH<4 was 17.3±7.9 in grade 1 and 8.9±2.4 in grades 2 and 3 (p=0.26); the number of reflux episodes were 33.5±5.5 in grade 1 and 40.8±3.5 in grade 2 and 3 (p=0.25); *P*_{oes,lsp} was 2.0±0.2 kPa (14.8±1.7 mmHg) in grade 1 and 2.2±0.3 kPa (16.8±2.0 mmHg) in grade 2 and 3 patients (p=0.46).

Stepwise regression analysis did not point out any relationship between lung function parameters and GER criteria in this group of patients.

Discussion

This study revealed a 32% prevalence of GER in a nonselected population of asthmatics attending our hospital out-patient clinic. In a subsample of the whole group, made up of patients with more than 15 reflux episodes·day⁻¹, a significant correlation between NRE and PD20 of methacholine was found. Moreover, a strong correlation was also shown in the group of GER-positive patients between NRE and PD20 of methacholine.

Other results were negative. No difference was observed in the lung function parameters of patients with and without clinical signs of GER, nor between GER-positive and GER-negative patients when GER was assessed on oesophageal pH monitoring data. Similar results were observed for antiasthmatic drugs, especially in the case of β₂-agonists. As recently observed and described by BOUSQUET *et al.* [20], mean dosage of ICS was lower than expected. There was no correlation between the

severity of asthma, evaluated on spirometry parameters, and severity of GER. No relationship was observed between drug consumption, especially β_2 -agonists, and GER or $P_{oes,isp}$. GER criteria (percentage of 24 h with oesophageal pH <4; NRE) were not different in patients with different asthma severity, *i.e.* asthma grade.

The design and methodology of this study were planned to avoid as much bias as possible. Asthma was well characterized and well documented. All asthmatics, except those with digestive complaints, who presented consecutively to our out-patient allergy clinic were recruited. This pattern of inclusion rules out bias in patient selection. All spirometry tests were performed by the same physician. Digestive investigations, particularly oesophageal 24 h pH monitoring, which is considered as the gold-standard assessment of GER, were performed in the same unit by the same two gastroenterologists. This allows the present study to define precisely the prevalence of GER in asthmatics, in comparison with other studies.

The absence of any relationship between lung function, drugs and GER parameters, except between NRE and bronchial hyperreactivity, minimizes the risk of missing any other relationship between asthma and GER in this study, even if interpretation of the results could be limited by the unknown real prevalence of GER in the general population.

The present study defined the prevalence of GER in asthmatics, in comparison with other studies. One hundred and ten healthy subjects were recently studied to define normal oesophageal pH values [17]. Results indicate that mean percentage of 24 h with oesophageal pH <4 is 1.1, varying from 0–8.6, but no frequency above normal limit is given. GER was influenced by gender and age in this study, in contrast with our results. SONTAG and co-workers [11, 21] compared GER parameters in 104 consecutive asthmatics and in 40 healthy controls and observed a decreased lower oesophageal pressure and greater oesophageal acid exposure time in asthmatics as compared to controls. They did not compare the respective prevalence in each population, and did not clearly define how they characterized GER.

The only prevalence of GER known in the general population is defined by questionnaires searching for clinical signs of GER. This is not useful in the interpretation of the results of this study, since we observed that 50% of patients with GER had no clinical sign of it [22].

The present data support the relationship between bronchial hyperresponsiveness and GER, as a very strong correlation between PD₂₀ of methacholine and NRE found. A relationship between GER and bronchial hyperresponsiveness was suggested by RAUSCHER *et al.* [23], who performed methacholine provocation before and after acid perfusion testing, and demonstrated a positive dose-dependent response between acid perfusion and bronchial hyperresponsiveness. These results were also supported by EKSTRÖM and TIBBLING [24], who measured bronchial hyperresponsiveness in parallel with FEV₁ modification after acid perfusion testing, during which they demonstrated a positive correlation between PD₂₀ of histamine and mean decrease in FEV₁.

The percentage of 24 h with oesophageal pH <4 is the most commonly used parameter for assessing GER.

This parameter is dependent both on the number of reflux episodes and their duration. It may have the same value with frequent reflux episodes of shorter duration and with scarcer episodes of longer duration. These data suggest that in asthmatics, the main determinant of the relationship between asthma and GER is the NRE.

Our results could be an explanation for the positive therapeutic results of HARDING *et al.* [25], who demonstrated the efficacy of acid suppressive therapy on asthma outcome.

In conclusion, gastro-oesophageal reflux was related neither to lung function nor to medical treatment in a nonselected population of asthmatics. The search for gastro-oesophageal reflux should then not be systematic in this population. A possible link between bronchial hyperresponsiveness and number of gastro-oesophageal reflux episodes is suggested.

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