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ORIGINAL ARTICLE

Gastro-oesophageal reflux, eosinophilic airway inflammation and chronic cough

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ABSTRACT

Background and objective: **Patients with eosinophilic airway inflammation (EAI) often show a therapeutic response to corticosteroids. Non-invasive methods of diagnosing EAI are potentially useful in guiding therapy, particularly in conditions such as chronic cough, for which corticosteroids may not be the first-line treatment.**
Methods: **The value of exhaled nitric oxide (ENO) in the diagnosis of EAI was prospectively investigated in a cohort of 116 patients with chronic cough of varying aetiology. An optimum cut-off value was derived for differentiating between EAI and non-EAI causes of chronic cough. As the diagnosis was gastro-oesophageal reflux in 70 patients (60.3% of the total), the possible relationship between ENO and EAI in the presence or absence of reflux was subsequently investigated.**
Results: **The optimum value of ENO for differentiating EAI (32% of patients) from non-EAI causes of cough was 33 parts per billion (sensitivity 60.5%, specificity 84.6%). In the subgroup of patients with reflux, ENO was highly specific for the diagnosis of EAI (sensitivity 66%, specificity 100%). Conversely, in the patients without reflux, ENO did not discriminate between cough due to EAI or other causes (sensitivity 100%, specificity 28.9%).**
Conclusions: **These results suggest that the presence or absence of reflux should be taken into consideration when interpreting ENO measurements in the diagnosis of chronic cough associated with EAI.**

Key words: asthma, cough, eosinophil, gastro-oesophageal reflux.

SUMMARY AT A GLANCE

This study provided support for an association between gastro-oesophageal reflux and EAI and raised the possibility that when exhaled nitric oxide levels are high, concurrent treatment of both entities, rather than corticosteroid therapy for EAI alone, may be required to achieve satisfactory responses to treatment in patients with chronic cough.

INTRODUCTION

It is important to assess the presence of eosinophilic airway inflammation (EAI) in patients with chronic cough because of their excellent response to corticosteroid therapy.[1] Among those patients presenting with chronic cough, only a proportion show demonstrable eosinophilic inflammation. It is difficult to differentiate these patients from other chronic cough patients because of their similar clinical histories.

Exhaled nitric oxide (ENO) has frequently been shown to be elevated in patients with classical asthma, and more recently evidence has accumulated that it is also a marker of eosinophilic inflammation in patients with chronic cough.[2,3]

Gastro-oesophageal reflux (GOR) is recognized as a common cause of chronic cough,[4] and recent findings correlate the release of neuropeptides in patients with asthmatic cough to coexistent acid reflux,[5] suggesting that reflux may be a stimulus for the development of Th2-mediated airway inflammation.

The influence of reflux on the sensitivity and specificity of ENO measurements may have important consequences for the accurate diagnosis of EAI.

METHODS

Patients

A cohort of 116 consecutive patients with chronic cough lasting more than 2 months underwent

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complementary studies at the tertiary Cough Unit of Hospital Ramon y Cajal. Smokers or patients with COPD were not included as they were managed using established therapies for the relevant condition.

A modified protocol derived from the European Respiratory Society (ERS) guidelines on the management of cough in adults,[4] with the additional inclusion of baseline measurements of ENO, was applied to every patient. Features of reflux as an aggravating factor for cough were also specifically assessed.

The clinical features of various cough-related phenotypes were systematically assessed in all patients and sequential therapeutic trials were performed as recommended in the guidelines. A final diagnosis was confirmed when patients reported that the symptoms of cough had resolved completely, either spontaneously or as a result of therapeutic intervention, after 6 months of follow up. Patients were then grouped into those with EAI- (asthma and eosinophilic bronchitis) and non-EAI-associated causes of cough, and ENO measurements were compared between the groups.

Diagnostic criteria for cough phenotypes

Asthmatic cough

Asthmatic cough was diagnosed if the patient had reversible airflow obstruction and a history of episodic wheeze or breathlessness with a positive bronchodilator response or methacholine challenge. Treatment for asthma included inhaled corticosteroids (≥800 μg/day budesonide or equivalent).

Eosinophilic bronchitis

Eosinophilic bronchitis was diagnosed if the patient had sputum eosinophilia of >2% or >4% eosinophils in BAL, with a negative methacholine challenge. Treatment for eosinophilic bronchitis included inhaled corticosteroids (≥800 μg/day budesonide or equivalent).

Gastro-oesophageal reflux

The diagnosis of GOR was made on the basis of several criteria. These included a clinical history compatible with oesophageal and extra-oesophageal manifestations of reflux[6] in addition to either a positive barium swallow that demonstrated reflux or a hiatus hernia, or an improvement in cough after 1 month of anti-reflux therapy. Symptoms included heartburn, dysphagia or regurgitation, an association between cough and hoarseness, excess mucus or clearing of the throat, globus or dysphonia. Three or more symptoms were considered suggestive of GOR.

Alternatively, patients were considered to have oesophageal disease on the basis of positive physiological studies. Positive findings were a pH < 4 for >4% of the total 24-h period of ambulatory pH monitoring, or manometric abnormalities including the number of non-conducted contractions being >30% of the total number of swallows; low amplitude peristaltic contractions of <15 cm of H_2O; lower oesophageal sphincter pressure of <10 cm of H_2O; and the presence of double-peaked, triple-peaked, simultaneous or tertiary contractions.[7]

In all cases, the diagnosis of GOR was supported if the patient recognized that their cough had resolved completely after a 3-month trial of anti-reflux treatment. This included proton pump inhibitors (omeprazole 20 or 40 mg bd) and advice about diet and posture, with the addition of cinitapride or metoclopramide as stimulants of oesophageal motility in patients showing poor responses after 1 month of treatment with omeprazole.

Upper airway cough syndrome

A high probability of rhinosinusitis was suggested by symptoms of frequent throat clearing, post-nasal drip, nasal discharge, nasal obstruction or sneezing, plus CT showing changes in the sinuses.

Postviral cough

Postviral cough was considered highly probable when the onset of cough showed a clear temporal relationship with an episode of upper respiratory tract infection and this episode resolved within 2 months.

Angiotensin converting enzyme inhibitor induced cough

This diagnosis was made if the cough symptoms resolved after cessation of the use of angiotensin converting enzyme (ACE) inhibitors.

Other pulmonary diseases

Bronchiectasis was confirmed by high-resolution CT. COPD was defined as airflow obstruction without bronchodilator reversibility.

Idiopathic and psychogenic cough

Cough was categorized as being idiopathic only when trials of treatment for asthma, reflux and upper airway cough syndrome (UACS) were all unsuccessful. When there was a suspicion of a psychogenic cause, patients were referred for cognitive therapy.

Investigative procedures

Measurement of exhaled nitric oxide

The recently developed handheld sensor device (NIOX MINO) that is suitable for routine clinical

practice, and gives highly reproducible measurements, was used.[8] ENO measurements were performed once in the morning at least 2 h after breakfast.

Spirometry and reversibility

Spirometry was performed using a Jaeger compact spirometer and reversibility was defined as an increase in FEV_1 of >15% from baseline and >200 mL.

Airway responsiveness

Methacholine bronchoprovocation was performed according to the ERS recommendations.[9] Testing was performed using the tidal breathing method.

The study was performed according to the Good Clinical Practice guidelines and approval was obtained from the Ethics Committee of Hospital Ramón y Cajal to use patient records with patient consent.

Statistical analysis

Categorical variables are presented as absolute and relative frequencies and continuous variables as means and SD or, if not normally distributed, as medians and 25–75th percentiles. Hypothesis testing of differences between groups was performed using the Mann–Whitney *U*-test with a level of significance of $P < 0.05$. ENO levels in the presence or absence of EAI are depicted by box plots. Receiver operating characteristic (ROC) curves were used to determine the optimum cut-off point for distinguishing between patients with or without EAI according to ENO levels and the presence of reflux. The optimum cut-off point was identified as the point at which the sum of the sensitivity and specificity was a maximum on the ROC curve. A retrospective sample size calculation was performed to estimate the power of the analysis. With an area under the ROC curve of 0.811, a null hypothesis of 0.5, a type I error of 0.05 and 56 patients, the power of the study was 99% (type II error = 0.01).

RESULTS

Of the 116 patients with chronic cough (70.7% women; mean age of 62.3 years (range 29–91)), 83 (71.5%) showed complete resolution of symptoms after 6 months of treatment.

The diagnosis of eosinophilic inflammation was made in 38 patients (33 asthma, 5 eosinophilic bronchitis) and the diagnosis was non-eosinophilic inflammation in 78 patients (GOR in 70 patients (60.3% of the total); ACE-induced cough in seven; UACS in five; idiopathic in two). The demographic details of the study population and the patients with or without EAI are shown in Table 1. In 30 patients the diagnosis of GOR was made on clinical grounds. The remaining 40 patients showed poor responses to anti-acid treatment and oesophageal studies were performed to confirm the diagnosis, with 24 h ambulatory pH monitoring being positive in 14 patients and manometry being abnormal in 26 patients.

Table 1 Characteristics of the chronic cough patients with or without eosinophilic airway inflammation

	Eosinophilic airway inflammation	
	Yes ($n = 38$)	No ($n = 78$)
Women[†]	33 (86.8)	51 (66.2)
Age, years[‡]	67 (55, 73)	61 (53, 70)
Initial ENO, parts per billion[‡]	37.5 (23, 62)	21 (15, 26)
Asthma[†]	33 (86.8)	0 (0)
GOR[†]	30 (78.9)	40 (51.3)
Eosinophilic bronchitis[†]	5 (13.2)	0 (0)
ACE inhibitor cough[†]	2 (5.3)	7 (9)
UACS[†]	9 (23.7)	13 (16.7)
Idiopathic cough[†]	0 (0)	2 (2.5)

[†] Data are number (%) of patients.
[‡] Data are medians (25th percentile, 75th percentile).
ACE, angiotensin converting enzyme; ENO, exhaled nitric oxide; GOR, gastro-oesophageal reflux; UACS, upper airway cough syndrome.

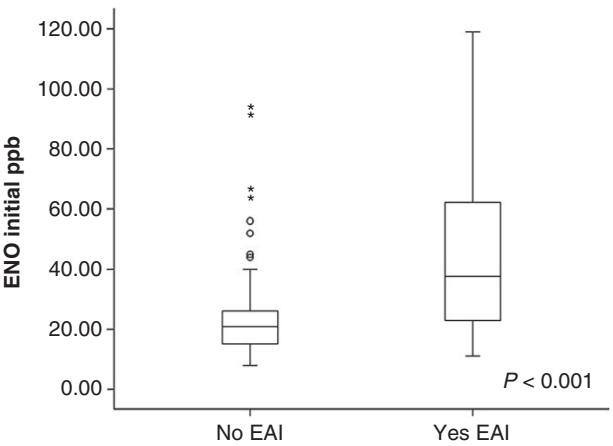

Figure 1 Initial measurements of exhaled nitric oxide (ENO) in chronic cough patients with or without eosinophilic airway inflammation (EAI). ppb, parts per billion.

Initial measurements of ENO in the whole study population were normally distributed. The mean ENO concentration was 24.8 parts per billion (ppb) (SD 16) in the non-EAI group, whereas it was 45.1 ppb (SD 28.3) in the EAI group. Comparison of ENO concentrations between the two groups showed a statistically significant difference ($P < 0.001$) (Fig. 1).

The cut-off point on the ENO ROC curve for differentiating chronic cough patients with or without EAI was 33 ppb. This value of ENO showed a sensitivity of 60.5% and a specificity of 84.6% (positive predictive value 65.7%; negative predictive value 81.4%) (Fig. 2).

In the group of patients with reflux and EAI the median ENO concentration was 40.5 ppb (25–75th

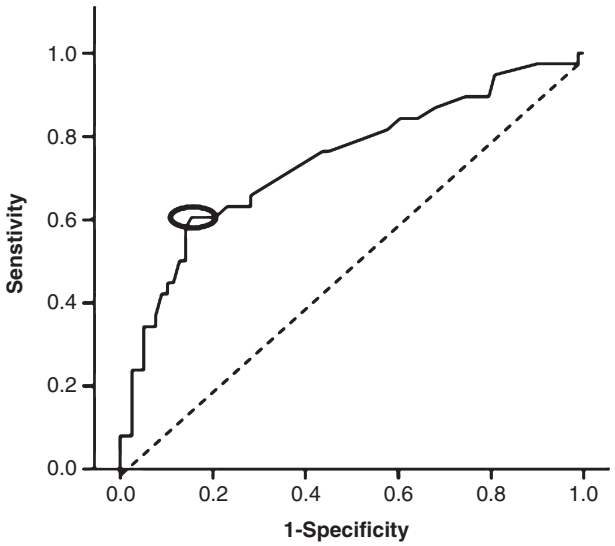

Figure 2 Receiver operating characteristic (ROC) curve for determining the cut-off point for exhaled nitric oxide for differentiating chronic cough patients with or without eosinophilic airway inflammation. The area under the ROC curve was 0.74 (95% CI: 0.638–0.842, $P < 0.001$).

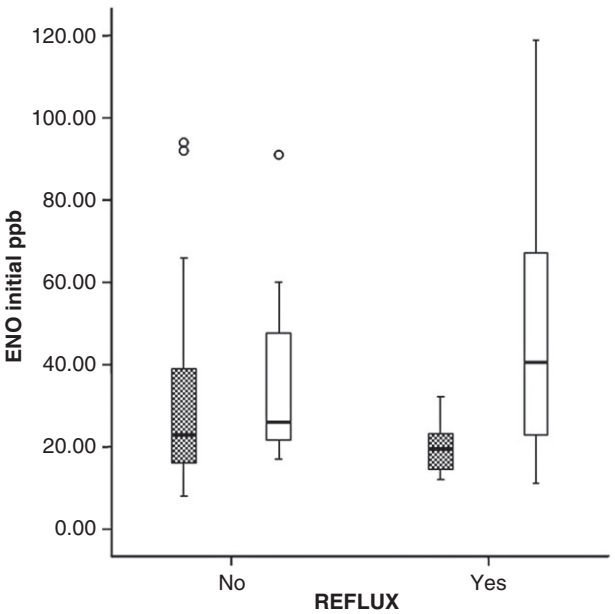

Figure 3 Box and whisker plots showing exhaled nitric oxide (ENO) concentrations in chronic cough patients with or without gastro-oesophageal reflux and with or without eosinophilic airway inflammation. ppb, parts per billion. Eosinophilic inflammation (▩) No; (□) Yes.

percentile, 23–67), compared with 19.5 ppb (14.5–23) in those without EAI ($P < 0.001$). Conversely, in the group without reflux, the median ENO concentration was 26 ppb (21.5–47.5) for patients with EAI compared with 23 ppb (16–39) for those without EAI ($P = 0.34$) (Fig. 3).

Assessment of the discriminative value of an ENO concentration of 33 ppb for diagnosis of EAI in patients with reflux showed that a specificity of 100% was achieved using this value (Fig. 4). However, the specificity of ENO concentration for the diagnosis of EAI in patients without reflux was only 28% (Fig. 5).

DISCUSSION

Chronic cough associated with EAI (asthma or eosinophilic bronchitis) can be successfully treated with corticosteroids. Studies have shown that ENO is a useful marker that may discriminate between chronic cough due to EAI or other causes.[2,3] Although different cut-off values for ENO were used in these studies (38 ppb and 30 ppb), the specificities (87% and 85%) were similar to that determined in the present study (84.6%). In addition, the presence of reflux improved the specificity of ENO for diagnosing EAI (100%) but the specificity of ENO was poor in the absence of reflux (28.9%). A previous study investigating the relationship between GOR and ENO in cough and asthma showed a modest, non-significant correlation between the number of episodes of acid reflux and ENO[10]. However, the limitations of using conventional oesophageal physiology for the diagnosis of reflux cough[11] may mean that the prevalence of gaseous and non-acid reflux was underestimated.[12,13]

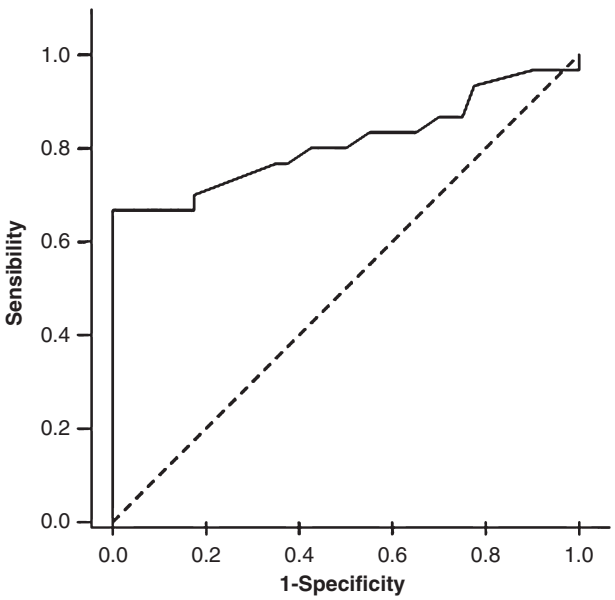

Figure 4 Receiver operating characteristic (ROC) curve using an exhaled nitric oxide (ENO) concentration of ≥33 parts per billion for the diagnosis of eosinophilic airway inflammation in patients with gastro-oesophageal reflux. The area under the ROC curve was 0.811 (95% CI: 0.696–0.927, $P < 0.001$).

The diagnosis of reflux associated chronic cough has been the subject of much debate. The high but variable prevalence of classic GOR with dyspepsia in chronic cough (60.3% in our experience) may be the

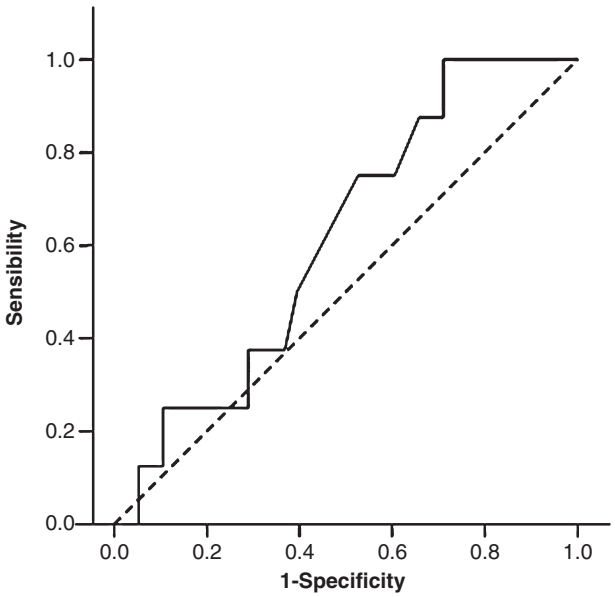

Figure 5 Receiver operating characteristic (ROC) curve using an exhaled nitric oxide (ENO) concentration of ≥33 parts per billion for the diagnosis of eosinophilic airway inflammation in patients without gastro-oesophageal reflux. The area under the ROC curve was 0.613 (95% CI: 0.426–0.801, $P < 0.317$).

result of using differing diagnostic criteria. The incidence of non-acid reflux in chronic cough is unknown due to the lack of reliable diagnostic tools.

The relationships among reflux, asthma and cough are also a controversial subject. Asthmatic patients show a high frequency of reflux, although it is not known whether this relationship is causal. Recent investigations called attention to two theories for the coexistence of cough-asthma and GOR: the reflex theory and the reflux theory. The former may explain the increased tachykinin levels in induced sputum of cough-asthma patients with acid reflux, which may represent an oesophago-bronchial reflex[5] and the observation that distal oesophageal acidification increases the frequency, duration and intensity of cough.[14] The reflux theory suggests that altered laryngopharyngeal sensitivity and microaspiration of gastric contents may lead to the development of a Th2-mediated reaction in the airways.[14]

The absence of a response in some chronic cough patients (28.5%) in the present study could have several explanations. The complete resolution of cough was assessed after 6 months of follow up. This differentiates the present study from another series[15] in which patients were only assessed in the short term, and were labelled responders even if there was a partial resolution of cough. Because the patients in the present study were only treated for 3 months, there might not have been sufficient time for resolution of cough in patients with cough and laryngopharyngeal reflux.[15] Finally, the authors of the earlier report failed to recognize the role of non-acid, proton pump inhibitor resistant reflux as a cause of chronic cough.

The present study population consisted predominantly of women, which is consistent with the chronic cough population seen in clinical practice.[16] ENO was used as a surrogate marker of EAI based on studies showing that these two parameters are strongly correlated.[17,18] The mean age of the population was higher than would be expected, and patients were not specifically characterized in terms of their atopic status; however, previous work suggests that ENO levels are correlated with sputum eosinophilia regardless of gender, age, atopic status and lung function.[19] Smoking status does affect the relationship but current smokers were actively excluded from the present study.

The findings described here also provide support for an association between reflux and EAI and raise the possibility that concurrent treatment is required for both entities. Overall, the data support the need for further investigations into the relationships among reflux, EAI and ENO. The influence of reflux disease on chronic cough, asthma and eosinophilic bronchitis also needs to be characterized in greater detail.

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