Cough threshold in patients with chronic obstructive pulmonary disease

C H Wong, A H Morice

Abstract
Background—Cough is an important symptom of patients with chronic obstructive pulmonary disease (COPD). The cough threshold to citric acid and capsaicin in patients with COPD and in normal volunteers was measured, as well as bronchial hyperresponsiveness to methacholine.

Methods—Nineteen patients with COPD and 22 controls were recruited. Subjects underwent a methacholine bronchoprovocation test and a cough challenge to citric acid and capsaicin.

Results—The log citric acid cough threshold, D2 (concentration causing two coughs) was significantly lower in patients with COPD (mean 2.17 versus 2.56, mean difference (95% CI) 0.39 (0.04 to 0.74), p = 0.02) but not for capsaicin cough D2 (0.66 versus 0.8, p = 0.41). Sixteen patients with COPD had bronchial hyperresponsiveness which was correlated with baseline FEV1 (r = 0.6, p = 0.01, 95% CI 0.15 to 0.84).

Conclusions—Patients with COPD have a lower cough threshold to citric acid, possibly due to a differential effect of cigarette smoke on citric acid sensitive cough receptors.

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Keywords: chronic obstructive pulmonary disease; cough; bronchial hyperresponsiveness

Cough and breathlessness are common respiratory symptoms of patients with chronic obstructive pulmonary disease (COPD). The definition of chronic bronchitis—namely, daily cough with the production of phlegm for three months for at least two years—emphasises the importance of cough. However, the cough reflex has not been extensively studied in these patients.

Many patients with COPD have hyperreactive airways.1,3 Bronchial hyperresponsiveness in both smokers2 and patients with COPD3 is associated with a greater rate of annual decline in forced expiratory volume in one second (FEV1). This phenomenon may be explained by airway mechanics2 and the underlying pathology.7

It has become increasingly clear that the reflex responses of cough and bronchoconstriction, although closely related, are mediated by separate neural pathways. Evidence includes differential stimulation and inhibition of these reflexes by drugs.8,9 This study was performed to examine the relationship between the cough threshold and bronchial hyperresponsiveness in patients with COPD.

Methods
SUBJECTS
Patients with a documented diagnosis of COPD were recruited from the outpatient clinics. Inclusion criteria were a history of smoking, a reduced FEV1, or FEV1/FVC%, and less than 15% reversibility of baseline FEV1, 15 minutes after the inhalation of 5 mg nebulised terbutaline sulphate.

Control subjects were recruited by local advertisement and inclusion criteria were non-smokers, no history or family history of atopy, and normal spirometric values.

The study was approved by the local ethics committee and all subjects gave written informed consent.

COUGH CHALLENGE TEST
Cough challenge to inhaled citric acid and capsaicin was performed by a method previously described.10 Briefly, stock solutions of citric acid 1000 mM and capsaicin 1 µM were diluted with 0.9% saline to produce five log doubling doses of each (citric acid 10, 30, 100, 300, and 1000 mM; capsaicin 1, 3, 10, 30, and 100 µM). Citric acid was administered first and the doses were arranged in ascending order with two doses of saline randomly added in an attempt to preserve patient blinding. The solutions were delivered by a compressed air driven nebuliser controlled by a breath activated Mefar MB3 dosimeter (Mefar, Brescia, Italy). The output of the dosimeter was 0.1 ml/s. The subjects received four inhalations of each dose, each of one second duration, with a 10 second interval between each. The cough response during this interval was recorded. After a 10 minute interval the capsaicin was administered in a similar fashion. Log dose response curves were constructed for each test and the concentration causing two coughs, the cough threshold (D2), was calculated by linear interpolation. Subjects who did not achieve a cough threshold were assumed to have a D2 at the highest concentration of the stimulus.

SPIROMETRIC TESTS (Vitalograph, UK) were performed in all subjects before and after the cough challenge.

METHACHOLINE BRONCHOPROVOCATION TEST
Methacholine bronchoprovocation testing was performed using a method previously described.13 Methacholine was administered in doubling cumulative doses over the range 3.125–6400 µg via the Mefar MB3 dosimeter (Mefar, Brescia, Italy) and Vitalograph Spirotrack software version 2.03 (Vitalograph Ltd, Buckingham, UK). Airway responsiveness was expressed as the dose required to produce a 20% fall from baseline FEV1, (PD20).
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Data Analysis
The cough data were log transformed and compared using the Student’s unpaired t test. The number of subjects in both groups with bronchial hyperresponsiveness was compared using Fisher’s exact test. The correlation coefficient was used to examine the relationship between the FEV1 % predicted and PD20. Statistical significance was assumed at a p<0.05 level.

Results
Nineteen patients (13 men) of mean age 59 years (range 30–77 years) with COPD and 22 control subjects (16 men) of mean age 55 years (range 29–74) were recruited. The patients with COPD had a mean smoking history of 35 pack years (range 10–80) and had a 5% mean improvement of FEV1, with 5 mg nebulised terbutaline sulphate.

Patients with COPD had a mean (SD) FEV1, FEV1 % predicted, and FEV1/FEV% of 1.75 (0.59) litres, 59.8 (20.5)%, and 61.9 (11.2)%, respectively. Values for the control group were 3.43 (0.81) litres, 104.4 (12.6)%, and 80 (6.8)% , respectively.

Sixteen patients with COPD demonstrated bronchial hyperresponsiveness to methacholine (as defined by a fall of at least 20% in FEV1 to less than 6.4 mg methacholine) compared with two of the 22 control subjects (p<0.0001).

The mean (SD) log citric acid cough D2 was significantly decreased in patients with COPD compared with controls (2.17 (0.68) and 2.56 (0.42), respectively; mean difference (95% CI) 0.39 (0.04 to 0.74); p = 0.02). In contrast, the values for capsaicin were not significantly different (0.66 (0.57) and 0.8 (0.55) in patients with COPD and controls, respectively; p = 0.41; fig 1).

In the 16 patients with bronchial hyperresponsiveness there was a significant correlation between the baseline FEV1% and the level of bronchial hyperresponsiveness (r = 0.6, p = 0.01, 95% CI 0.15 to 0.84).

The relationship of the PD20 to methacholine was compared with both citric acid and capsaicin cough D2 in patients with COPD. No significant correlation was found in either group.

Discussion
Cough is a common symptom in patients with COPD. Cough challenge testing is used to examine many aspects of the cough reflex but few studies have applied this test in patients with COPD. In one of the earliest reports Taylor et al demonstrated a lower cough threshold to citric acid in those smokers who inhaled their cigarette more deeply.12 In a more recent study Auffarth et al found no difference in the citric acid cough threshold between asthmatic subjects and those with COPD, and there was no correlation between the cough threshold and non-specific bronchial responsiveness to histamine. Our study is the first to our knowledge to compare directly cough thresholds between patients with COPD and normal subjects. We found a significantly lower cough threshold to citric acid in patients with COPD but not to capsaicin. As part of a study of patients with chronic cough, Choudry et al included 11 patients with COPD; the cough threshold to capsaicin in these patients was not significantly different to controls.

We believe that citric acid and capsaicin stimulate cough through different mechanisms. Citric acid stimulates the rapidly adapting receptors (RARs or irritant receptors) located in the larynx and upper airways of the tracheo-bronchial tree to cause cough, whereas capsaicin may cause cough through stimulation of the C fibres via non-selective ion channels.16 The cough challenge results in this study support this hypothesis. In patients with COPD smoking may have a differential effect on citric acid sensitive receptors. One explanation may be the differential deposition of cigarette smoke in the airways. Larger particle aerosols at high inhalation flow rates tend to be deposited in central airways by inertial impaction.17 Cigarette smoke may be deposited on the more central airways where the citric acid sensitive cough receptors are more abundant.15 Laryngeal inflammation in COPD may play a part since we have observed a decrease in citric acid induced cough compared with capsaicin induced cough in patients who have had a laryngectomy.18

Cough and bronchoconstriction are now considered to be separate airway reflexes. In asthmatic subjects, cough but not bronchoconstriction, is caused by solutions of low chloride and non-isomolar solutions cause bronchoconstriction but not cough.19 Inhaled anaesthetics inhibit distilled water induced cough but not bronchoconstriction.5,9 Drugs such as atropine and sodium cromoglycate inhibit bronchoconstriction but not cough.9 The lack of correlation between cough threshold and bronchial hyperresponsiveness in asthmatic patients, those with COPD and normal subjects is further evidence. Our study confirms this relationship also.

Non-specific bronchial hyperresponsiveness is a characteristic feature of asthma but it is also seen in patients with COPD. The described incidence varies from 46% to 100%.2,5 In this study 84% of the COPD patients had bronchial hyperresponsiveness to methacholine. We observed an increased degree of bronchial
hyperresponsiveness as the predicted FEV\textsubscript{1} decreased, a relationship that has been well described.\textsuperscript{12}

In summary, we have found a lower citric acid cough threshold in patients with COPD which may be due to the effect of cigarette smoke on citric acid sensitive receptors in the larynx and upper airways.

3 Frew AJ, Kennedy SM, Chan-Yeung M. Methacholine reactivity, smoking and atopy as risk factors for accelerated FEV\textsubscript{1} decline in male working populations. \textit{Am Rev Respir Dis} 1992;146:878–83.
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