

Capsaicin cough sensitivity in bronchiectasis

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Abbreviations

C5 = concentration of capsaicin required to induce 5 coughs

FEV₁ = forced expiratory volume (litres) in 1 second

LCQ = Leicester Cough Questionnaire

SEM = standard error of the mean

Abstract

Bronchiectasis is a suppurative airway disease characterised by persistent cough and sputum production associated with bronchial dilatation. We determined whether cough sensitivity is increased in bronchiectatic patients.

We recruited 22 patients with bronchiectasis and 20 healthy non-smoking controls matched for age and gender and recorded quality of life using the Leicester cough score, total cough symptom score and extent of bronchiectasis from high resolution computed tomograms (HRCT). Cough sensitivity was assessed using incremental inhalation of capsaicin concentrations; the concentration at which 5 or more coughs occurred (C5) was recorded.

Patients with bronchiectasis demonstrated increased sensitivity to capsaicin compared to controls (mean \log_{10} C5 1.22 ± 0.20 vs. 1.89 ± 0.21 ; $p < 0.03$). Capsaicin sensitivity correlated positively with the Leicester Cough Questionnaire score ($r = 0.64$; $p = 0.005$), and inversely with total cough symptom score ($r = -0.58$; $p = 0.004$), but not with the extent of the disease. It also correlated with FEV₁ (L) ($r=0.58$; $p=0.005$), but not with FEV₁ (% predicted). Capsaicin sensitivity was not related to the presence of infected sputum or to corticosteroid or bronchodilator use.

A sensitive cough reflex is present in patients with bronchiectasis reflecting the severity of cough symptoms. A measure of cough severity could be part of health assessment for bronchiectasis.

Keywords

Bronchiectasis, Cough, Capsaicin

Introduction

Bronchiectasis is a chronic lung disorder characterised by irreversible dilatation of bronchi associated with the chronic daily production of mucopurulent sputum.¹ Many causes of bronchiectasis are recognised and these include cystic fibrosis, immunodeficiency, primary ciliary dyskinesia, chronic aspiration, rheumatic conditions and inflammatory bowel disease. A chronic productive cough is usually the predominant symptom of the disease. Patients suffering from a chronic cough due to a wide variety of causes usually have an increased cough sensitivity to inhaled capsaicin, as has been demonstrated in patients with asthma, chronic obstructive pulmonary disease (COPD)², pulmonary fibrosis³ and chronic idiopathic cough.⁴

The aim of this study was to determine capsaicin cough sensitivity in patients with bronchiectasis compared to healthy controls. Although cough in bronchiectasis is attributed to the need to clear excessive airway secretions and mucus, it is possible that there is also an increase in cough sensitivity that could contribute to the cough response in this condition. Such a possibility is supported by the presence of neutrophilic inflammation and epithelial damage that is observed in the airways of patients with bronchiectasis⁵. We also investigated the relationship between capsaicin cough sensitivity and spirometry, radiological extent of the disease, corticosteroid and bronchodilator use and the presence of infected sputum, and with cough symptom severity.

Methods

Twenty-two patients with bronchiectasis were recruited from The Royal Brompton Hospital clinics along with 20 healthy non-smoking controls matched for age and gender and were studied during a period of stability defined by no changes in symptoms for 4 weeks and no use of antibiotics for 12 weeks. We excluded patients whose bronchiectasis was associated with primary ciliary dyskinesia and allergic bronchopulmonary aspergillosis. None of the patients had a smoking history and all of them had a negative histamine challenge to exclude the diagnosis of asthma. All patients underwent capsaicin cough challenge, vitalographic measurements and symptom and quality of life questionnaires on the same day. The study was approved by the Ethics Committee of the Royal Brompton & Harefield Trust. Informed consent was obtained from each patient.

Capsaicin cough challenge was performed in all subjects by administration of incrementally doubling concentrations of capsaicin (0.98 μ M to 500 μ M) inhaled from a nebuliser connected to a breath-activated dosimeter (PK Morgan Ltd, Gillingham, UK). Two mls of solution were placed in the nebuliser that was driven at a pressure of 151 kPa for a period of one sec. Each puff delivered was 20 μ l, with a particle size of 4 μ m mass median aerodynamic diameter. Each dose was administered at one-minute intervals. Patients were instructed to inspire from functional residual capacity to total lung capacity at a flow rate to trigger the dosimeter. Patients were asked to cough freely and the number of coughs induced during the one-minute period after capsaicin administration was counted, although most of the coughs occurred within 10-15 seconds of inhalation. The end-point was the concentration of capsaicin required to induce 5 coughs (C5). Forced expiratory volume in one second (FEV₁) was measured in all subjects using a dry wedge spirometer (Vitalograph, Buckingham, UK).

An assessment of the impact on quality of life of chronic coughing in the patients with bronchiectasis was made using the Leicester Cough Questionnaire (LCQ).⁶ This consisted of 19 cough-related questions. A minimum total score of 19 indicates maximal impact on quality of life whereas a maximum total score of 133 indicates no impact on quality of life.

Severity of cough symptoms was also assessed using a previously-described cough symptom score.⁷ Severity of daytime and night-time cough symptoms were scored by the patients according to the following scales:

During the day: 0 = no cough during the day; 1 = cough for one short period; 2 = cough for two or more short periods; 3 = frequent coughing, not interfering with usual daytime activities; 4 = frequent coughing, interfering with usual daytime activities; 5 = distressing coughs for most of the day.

During the night: 0 = no cough during the night; 1 = cough on waking in the morning only; 2 = wake once or early due to cough; 3 = frequent waking due to coughs; 4 = frequent coughs most of the night; 5 = distressing coughs preventing any sleep.

Daytime and night-time scores were added together giving the total cough symptom score with a maximum possible score of 10.

High resolution computed tomography of the lungs was performed within 2 months of the capsaicin cough challenge. Radiological assessment of severity of bronchiectasis was performed using a modification described by Bhalla et al.⁸ One observer (DHC), a radiologist, scored high resolution computed tomographic images of each of the 6 lobes (the lingula was regarded as a separate lobe) according to the severity of bronchial dilatation, bronchial wall thickening, and mucus plugging.

Bronchial dilatation was scored relative to the diameter of adjacent pulmonary arteries: 0 = normal; 1 = 100–150% of arterial diameter; 2 = 150-200% arterial diameter; 3 = >200% arterial diameter. Bronchial wall thickening was also scored relative to adjacent pulmonary arteries: 0 = normal; 1 = <50% arterial diameter; 2 = 50-100% arterial diameter; 3 = >100% arterial diameter. Mucus plugging was scored as follows: 0 = absent; 1 = present; 2 = moderate; 3 = marked.

Use of inhaled corticosteroids and bronchodilators by the patients was recorded and samples of sputum were sent for bacteriological assessment when the patients were recruited into the study. In case sputum samples were not provided on the day (as in 6 subjects), the patient was asked to provide a sputum specimen within the week. None of the patients were on oral corticosteroids.

All statistical analyses were performed using GraphPad Prism version 3.03. Unpaired t test was used to analyse differences in quantitative data (age, C5, FEV₁) between groups and the chi-squared test was used to analyse dichotomous data. All correlation coefficients were calculated using the Pearson's test. A p value < 0.05 was considered statistically significant. Data are expressed as mean (SEM).

Results

Baseline demographic data are shown in Table 1.

Table 1. Characteristics of patients with bronchiectasis and healthy controls

	Bronchiectasis	Controls
Number	22	20
Age [years] (SD)	59 (3)	49 (3)
Gender [Female (%)]	18 (82%)	16 (80%)
FEV ₁ [% predicted] (SD)	82.9 (6.3)	99.9 (1.9)
Inhaled corticosteroid use	13 (59%)	0
Inhaled bronchodilator use	13 (59%)	0

SD: Standard deviation

The groups were matched for age and gender. Bronchiectatic patients demonstrated a significantly lower mean FEV₁ (% predicted) when compared to controls (82.9 (6.3) vs 99.9 (0.9); $p < 0.02$). Thirteen (59%) of the bronchiectatic patients were taking regular inhaled steroids and 13 (59%) were taking inhaled bronchodilators. Of the 22 bronchiectatic patients, 10 had culture positive sputum with the following organisms: *Haemophilus influenzae* (HI), *Pseudomonas aeruginosa* (PA), *Streptococcus pneumoniae* (SP) and *Moraxella catarrhalis* (MC). One patient had 3 organisms growing in their sputum (HI + MC + SP). Five patients had a combination of 2 organisms (2 with HI + PA, 2 with HI + MC, and 1 with HI + SP).

Capsaicin data was normalised by using logarithms of C5 values. The bronchiectatic patients had a significantly lower mean log C5 compared with controls (1.22 (0.20) vs 1.89 (0.21); $p < 0.03$; Fig 1), indicating heightened cough sensitivity. In 9 of the 22 patients, capsaicin cough sensitivity was repeated 1-2 years later. Analysis of these 9 responses for repeatability according to the Bland and Altman method shows that the mean difference between the two log C5 measurements was 0.02, and the limits of agreement within which 95% of the repeat measurements are estimated to lie were -0.98 and 1.38.

The mean Leicester Cough Questionnaire score and the mean cough symptom score among the patients were 97 (6) and 2.3 (0.3), respectively. There was a strong negative correlation between LCQ score and cough symptom score ($r = -0.9$; $p < 0.0001$; Fig 2). The mean CT scan score for these patients was 14.3 (1.2).

Capsaicin sensitivity (\log_{10} C5) in the bronchiectatic patients was positively correlated with FEV₁ (L) ($r = 0.58$; $p = 0.005$; Fig 3A), and with LCQ score ($r = 0.64$; $p = 0.005$; Fig 3B). However, FEV₁ expressed as % predicted did not correlate with capsaicin sensitivity or with LCQ scores. There was a negative correlation between log C5 and the total simple cough score ($r = -0.58$; $p = 0.004$; Fig 3C). There was no correlation between log C5 and the radiological assessment (bronchial dilatation, bronchial wall thickening, mucus plugging and air trapping). The presence of infected sputum and the organism grown from the sputum did not correlate with capsaicin sensitivity. Finally, the dose and use of bronchodilators or of inhaled corticosteroids did not relate to capsaicin sensitivity.

Discussion

Bronchiectasis is primarily the result of airway injury and remodelling secondary to chronic inflammation and recurrent airway infections characterized by chronic cough and sputum production. We found that there was a significant increase in cough reflex as measured with inhaled capsaicin of the order of a four-fold increase in sensitivity in a cohort of moderate to severe bronchiectasis. This degree of capsaicin cough sensitivity was correlated with FEV₁, the severity of cough symptoms and with the impairment of quality of life as measured by the Leicester Cough Questionnaire. These data indicate that the degree of capsaicin sensitivity may be a good clinical marker to complement the severity of bronchiectasis evaluation.

In a previous report, the capsaicin cough sensitivity of 7 patients with bronchiectasis that was grouped amongst patients with a chronic productive cough was reported. As a whole, this group had a similar capsaicin cough sensitivity as control subjects who do not cough but when the 7 bronchiectatic patients were compared to the control group, they were found to have a smaller capsaicin C5 value⁹. The severity of the bronchiectatic disease was not reported but they were reported to have infected sputum. Our study does not link the presence of infected sputum at the time of capsaicin measurement to the degree of capsaicin sensitivity, although it is likely that our study may have lacked the power to show such a relationship. We did not note the purulence of the sputum at the time, and our definition of infected sputum was the presence of significant bacterial growth from the sputum collected. It would be interesting to determine whether the purulence was related to capsaicin cough sensitivity. This larger study of patients with extensive bronchiectasis indicates that this chronic pulmonary condition most often presenting with chronic cough demonstrates capsaicin hypersensitivity, similar to other chronic lung diseases such as chronic obstructive pulmonary disease, asthma and pulmonary fibrosis.^{2,3}

The factors involved in cough induction in bronchiectasis include the continuous presence of sputum and airway secretions, often containing bacteria, as in the majority of our patients studied. The mucus stasis is also compounded by damage to mucociliary clearance which represents damage to the epithelium¹⁰.

We did not include patients with primary ciliary dyskinesia in our cohort because the cause of the bronchiectasis in this condition is primarily due to ciliary dysfunction which is different from abnormalities usually observed in the patients with 'idiopathic' bronchiectasis that we studied. In addition, the occurrence of concomitant diseases such as rhinosinusitis or gastrooesophageal reflux may contribute to or exacerbate cough. We now demonstrate that one additional factor that favours cough in bronchiectasis is the enhanced cough reflex. Underlying this could be the presence of the chronic neutrophilic inflammation and damage that could lead to cough sensitisation. Thus, in bronchoalveolar lavage fluid obtained from stable bronchiectatic patients, there are neutrophils and neutrophil products such as neutrophil elastase and myeloperoxidase, and the proinflammatory cytokines TNF α , IL-6 and IL-8¹¹. Release of inflammatory prostaglandins and bradykinin could lead to sensitisation of the cough reflex. In addition, the presence of bacterial infection is usually associated with more severe inflammation¹². Apart from the presence of mucus, an enhanced cough reflex may be related to neuroplasticity of both central and peripheral cough pathway, such as overexpression of substance P in the brain stem nuclei¹³. In the periphery, there may be changes in the cough receptor caused by the neutrophilic inflammation such as an overexpression of transient receptor potential vanilloid-1 (TRPV-1), the receptor for capsaicin. Aspects of neuroplasticity of the

cough afferent pathways are also likely to contribute to the heightened reflex associated with chronic cough¹⁴.

The severity of cough has not really been well-studied in bronchiectasis. Although the St George's Respiratory Questionnaire (SGRQ) contains some specific questions on cough, how much the presence of a chronic cough specially contributes to the overall impact on quality of life has not been reported¹⁵. SGRQ scores have been shown to correlate well with measures of wheeze or breathlessness in bronchiectasis. It may be important to add more specific questions relating to the severity of cough since in bronchiectasis, this seems to contribute significantly to the overall impairment of life quality. The Leicester Cough Questionnaire, on the other hand, is a newly-devised health status measure specifically focusing on cough; the patients with bronchiectasis scored a range of 50-133, of a maximum score of 133, indicating moderate impairment of quality of life resulting from chronic cough. In addition, this score correlated closely with a simpler cough symptom score that only recorded the degree of coughing, and also with the precise single measure of the capsaicin cough sensitivity. The capsaicin cough sensitivity may contribute to the clinical severity of bronchiectasis.

Cough can be a nuisance in bronchiectasis and contributes to deterioration in quality of life. However, cough should not be totally suppressed in bronchiectasis since it provides the only effective mechanism whereby excessive secretions are removed from the large airways.

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Competing interest

All authors declare that they have no competing interests with respect to this work.

Figure Legends

Figure 1. Comparison of capsaicin sensitivity (\log_{10} C5) between patients with bronchiectasis and controls. Horizontal bars indicate mean.

+ $p < 0.03$ compared to patients with bronchiectasis.

Figure 2. Relationship between Leicester Cough Questionnaire scores and cough symptom score in patients with bronchiectasis.

Figure 3. Relationship between capsaicin sensitivity (\log C5) and FEV₁ (A), Leicester Cough Questionnaire (LCQ) score (B), and cough symptom score (C) in patients with bronchiectasis.

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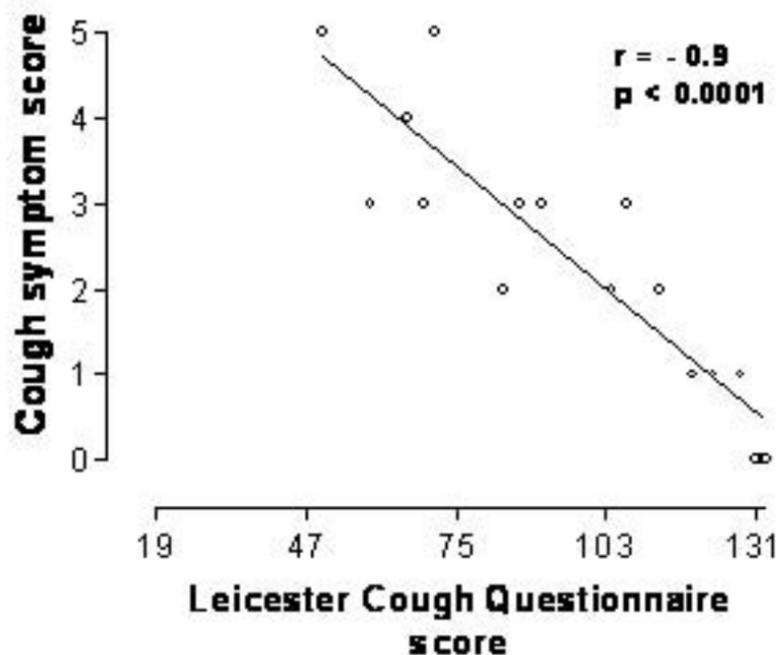


Fig 2

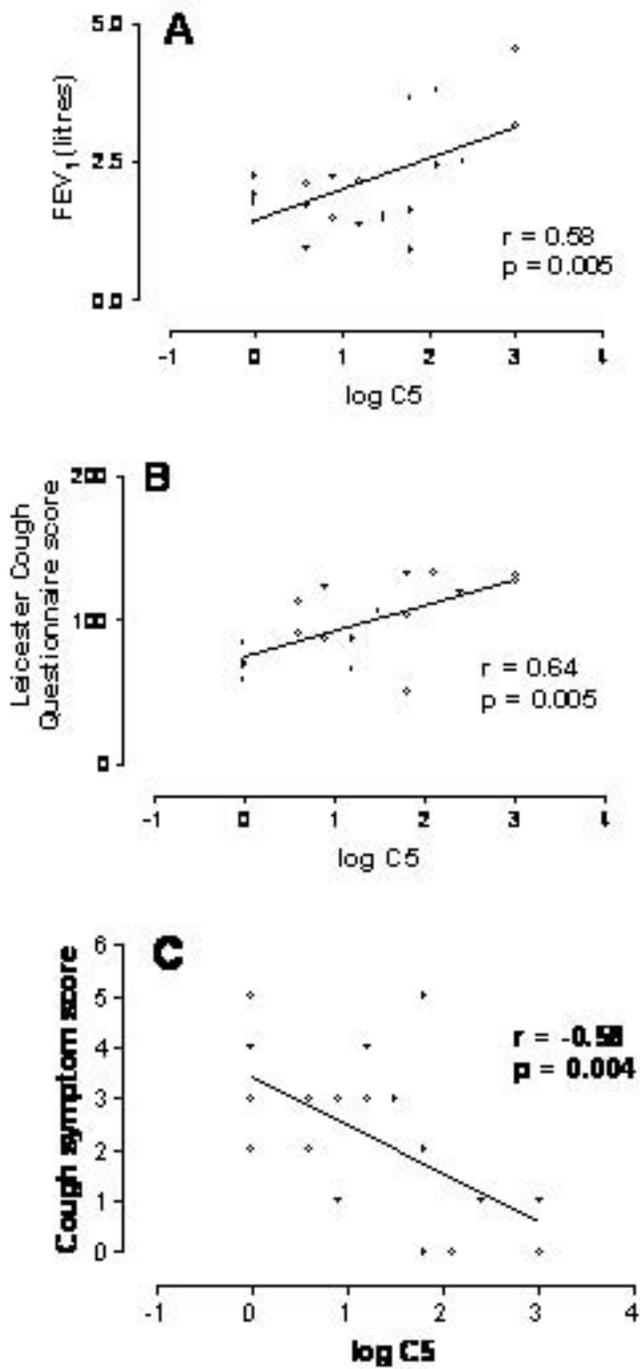


Fig 3