Capsaicin induced cough in cryptogenic fibrosing alveolitis

M J Doherty, R Mister, M G Pearson, P M A Calverley

Abstract

Background—Cough is a common and troublesome symptom in cryptogenic fibrosing alveolitis (CFA) but the mechanisms responsible are not known. The cough threshold to inhaled capsaicin is increased in asthma and chronic obstructive pulmonary disease (COPD) where lung volumes are increased, but the relationship between cough response and symptom intensity has not been studied in CFA where lung volumes are reduced.

Methods—Capsaicin challenge tests were performed on 15 subjects with proven CFA and 96 healthy controls. Symptoms, as assessed by daily diary card cough score and by visual analogue scale (VAS), were related to the capsaicin sensitivity (C5) and compared with lung volumes. Volume restriction was produced in a group of 12 normal healthy subjects by a plastic shell tightly strapped to the chest wall. Capsaicin challenge tests were performed in these subjects, both strapped and unstrapped, to determine whether volume restriction altered the cough reflex.

Results—The median C5 response in normal subjects was more than 500 µM compared with 15.6 µM in those with CFA (p<0.001). The C5 response of the CFA patients was not related to symptoms of cough (whether measured by diary card or by VAS), nor was it related to percentage predicted total lung capacity (TLC) or forced vital capacity (FVC). Volume restriction of normal subjects with chest strapping successfully restricted lung volumes to levels similar to that of the CFA patients but did not change the sensitivity to capsaicin.

Conclusions—The cough reflex measured using capsaicin is markedly increased in patients with CFA. This increase is not the result of alterations in the deposition of inhaled particles of capsaicin brought about by volume restriction. It could be related to reduced lung compliance leading to sensitisation of rapidly adapting receptors, other mechanical changes, or to destruction of pulmonary C fibres secondary to interstitial inflammation. The capsaicin test may be a useful method of objectively monitoring cough propensity in CFA.

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Keywords: cryptogenic fibrosing alveolitis; cough threshold; capsaicin; volume restriction

Cryptogenic fibrosing alveolitis (CFA) is characterised by a mixture of inflammation and fibrosis of the pulmonary interstitium and air spaces and has a prevalence of up to six per 100 000 population. Patients with CFA usually have reduced lung volumes, a reduced transfer factor, and relatively preserved forced expiratory volume in one second (FEV1), but this is not always present. Although breathlessness is the best recognised symptom, cough is reported by 86% of patients with CFA.

Capsaicin (trans-8-methyl-N-vanillyl-6-noneamide) is the pungent extract of red pepper which, when inhaled, induces cough reproducibly without tachyphylaxis. Inhalation of increasing doses of capsaicin is a sensitive way of assessing the cough reflex in a variety of disease states.

Although cough is often reported by patients with CFA, the underlying mechanisms are not clear. Sputum production is infrequent and airway inflammation is not a prominent feature, unlike asthma and chronic obstructive pulmonary disease (COPD) where capsaicin sensitivity is increased. Cough receptors are thought to be present in proximal airways whereas the damage in CFA affects small airways and alveoli. At present the available data are conflicting and limited. In one study of 12 patients (four with CFA, eight with sarcoidosis) no abnormality in the cough response was found, although little information about the physiological and radiographic severity was included. In contrast, a larger study of patients with progressive systemic sclerosis (PSS) reported an increased cough response to capsaicin, and noted self-reported cough only in those patients with evidence of lung fibrosis.

We hypothesised that capsaicin responsiveness might be increased in CFA for similar reasons to the patients with PSS, and that there should be a relationship between this increase and the severity of the restrictive disorder. Such changes might be a consequence of increased central airways deposition or loss of pulmonary stretch receptor inhibition of the cough reflex. To test this possibility we studied capsaicin responsiveness in a group of healthy volunteers before and during chest wall restriction sufficient to mimic the lung volumes experienced by patients with fibrosing alveolitis.

Methods

COMPARISON OF PATIENTS WITH CFA AND HEALTHY CONTROLS

We studied 15 patients with CFA currently attending our outpatient clinics and 96 healthy individuals recruited from hospital staff and...
### Table 1 Comparison of mean (SD) demographic factors in normal subjects, in the 14 oldest normal subjects, and in patients with cryptogenic fibrosing alveolitis (CFA)

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n=96)</th>
<th>Older normal subjects (n=14)</th>
<th>CFA (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 (12)</td>
<td>57 (4)</td>
<td>65 (6)</td>
</tr>
<tr>
<td>% Male</td>
<td>34 (29)</td>
<td>73 (73)</td>
<td></td>
</tr>
<tr>
<td>% predicted FEV₁</td>
<td>107 (14)</td>
<td>99 (13)</td>
<td>82 (11)</td>
</tr>
<tr>
<td>% predicted FVC</td>
<td>100 (13)</td>
<td>90 (9)</td>
<td>75 (14)</td>
</tr>
<tr>
<td>TLCO</td>
<td>–</td>
<td>–</td>
<td>57 (20)</td>
</tr>
<tr>
<td>VAS cough</td>
<td>–</td>
<td>–</td>
<td>3.0 (1.9)</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; TLCO = carbon monoxide transfer factor; VAS = visual analogue score.

Most patients with CFA reported symptoms of cough (mean (SD) VAS 3.0 (1.9) cm and average daily cough score 2.6 (0.9)). However, the severity of cough measured by these reproducible C5 was found. The dosimeter had an in-built 0.25 second time delay and an inhalation time of two seconds, and during this time it delivered 0.009 ml of nebulised solution. The mass median diameter (MMD) of the particles produced was 5.2 µm.

**Pulmonary function**

Spirometric parameters (FEV₁ and forced vital capacity (FVC)) were recorded before capsaicin testing using a bellows spirometer and the best values from three technically acceptable attempts were used.

Static lung volumes including functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC) were measured using the helium dilution technique. Gas transfer factor (TLCO) was measured using a single breath method.

**PROCEDURES**

**Symptom scores**

Symptomatic cough was measured in two ways in subjects with CFA: (1) Diary card: this was completed at home over the two weeks before the capsaicin test. The subjects recorded cough severity on a scale from 1= no cough to 5= distressing cough most of the day. This score was used to calculate the average daily diary cough score for each subject. The diary card data were accepted if it had been completed for at least 10 of the 14 days. (2) Visual analogue scale (VAS): each subject recorded the severity of their cough at their first attendance before any other testing using a 10 cm VAS ranging from no cough to worst cough imaginable.

**Capsaicin challenge test**

Each subject inhaled a single breath of solution via an Acorn nebuliser controlled by a custom made breath activated dosimeter. Saline was given first followed by doubling concentrations of capsaicin between 1.95 and 500 µM. The concentrations were given in ascending order and the subjects were not aware of the concentration they were inhaling. Each concentration was given at 30 second intervals and the number of coughs induced in this time was counted. The concentration that induced five or more coughs was denoted as the maximum concentration of capsaicin for the purposes of analysis. Given the differences in distribution of the ages of our normal population and the patients with CFA, a separate analysis of the older normal subjects is also presented for comparison.

**DATA ANALYSIS**

Data are expressed as mean (SD). Cough symptom data were analysed non-parametrically throughout. C5 data are expressed as concentration steps and, when correlated with other data, the Spearman rank test was used as the distribution of the response in the patients with CFA was not normal. The Mann-Whitney U test was used to compare changes in lung volume and changes in C5 in healthy subjects during the strapping experiments. If five or more coughs were not achieved during the capsaicin challenge the C5 was denoted as the maximum concentration of capsaicin for the purposes of analysis. Given the differences in distribution of the ages of our normal population and the patients with CFA, a separate analysis of the older normal subjects is also presented for comparison.

**RESULTS**

Demographic and spirometric data for the study populations are presented in table 1. Patients with CFA were significantly older and more likely to be male than the healthy control group. To aid comparisons data are also presented on the 14 oldest members of the control population. Patients with CFA had a restrictive pattern of lung volumes with a significant reduction in TLCO in both comparisons. More CFA patients than controls were current or ex-smokers (73% vs 27%).

Most patients with CFA had symptoms of cough (mean (SD) VAS 3.0 (1.9) cm and average daily cough score 2.6 (0.9)). However, the severity of cough measured by these...
Table 2  Mean (SD) lung volumes and C5 responses of normal subjects, both strapped and unstrapped, compared with patients with CFA.

<table>
<thead>
<tr>
<th></th>
<th>Unstrapped (n=9)</th>
<th>Strapped (n=9)</th>
<th>CFA (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC % predicted</td>
<td>111 (14)</td>
<td>63 (14)</td>
<td>75 (14)</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>123 (15)</td>
<td>71 (15)</td>
<td>82 (11)</td>
</tr>
<tr>
<td>RV % predicted</td>
<td>100 (24)</td>
<td>75 (30)</td>
<td>75 (30)</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>101 (16)</td>
<td>67 (15)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>FRC (l)</td>
<td>3.2 (1.0)</td>
<td>2.2 (0.8)</td>
<td>2.5 (0.9)</td>
</tr>
<tr>
<td>IC (l)</td>
<td>3.5 (0.8)</td>
<td>2.0 (0.6)</td>
<td>1.9 (0.4)</td>
</tr>
</tbody>
</table>

FVC = forced vital capacity; FEV1 = forced expiratory volume in one second; RV = residual volume; TLC = total lung capacity; FRC = functional residual capacity; IC = inspiratory capacity.

Figure 1  Cumulative frequency of the proportion with a positive capsaicin sensitivity (C5) response at each concentration of capsaicin for normal healthy controls, older healthy controls, and patients with cryptogenic fibrosing alveolitis (CFA).

Figure 2  Comparison between the cough responses of patients with cryptogenic fibrosing alveolitis (CFA) and normal subjects with and without chest strapping.

Discussion

Cryptogenic fibrosing alveolitis is a disabling form of interstitial pulmonary fibrosis which appears to be becoming more frequent as the population ages. Although breathlessness is the dominant clinical symptom, chronic cough is frequently present as seen from our symptomatic assessment. Our data show a markedly enhanced cough responsiveness to capsaicin in patients with CFA which we hypothesise as being likely to reflect the presence of pulmonary fibrosis, although the precise mechanisms involved remain to be determined.

In patients with obstructive airways disease cough is well recognised and an increased C5 cough response to citric acid and capsaicin has been reported. The median cough threshold to capsaicin was 2–3 doubling dilutions less than normal in patients with COPD but was six doubling dilutions less in our patients with CFA. This marked increase is difficult to explain. One possibility could be a change in the distribution of the capsaicin aerosol. This might be a factor in the obstructed patients but is not likely to occur in restrictive disorders like CFA. The particles we used had an MMD of 5.2 µm and should be deposited throughout the airways with a limited proportion reaching the alveoli. Previously we have conducted a radiolabelled deposition study using the same dosimeter in patients before and after chest strapping to a similar degree to that reported here, and we found no difference in the pattern of aerosol deposition (D Spence and D Pavia, personal communication), nor did we see any relationship between FVC, TLC, or the C5 response in our patients as might have been expected if altered structure leading to altered deposition were to explain the changes. Thus, while differences in the pattern of inhaled capsaicin deposition between normal subjects and those with disease might explain the increased sensitivity to capsaicin in obstructive airway disease, it seems unlikely to be an explanation in CFA.

To date, there is only limited information about cough symptoms and the response to tussive agents in interstitial lung disease. The VAS cough score in our patients was very similar to that in the PSS patients with fibrosis studied by Laloo et al, but significantly less than that reported in patients with chronic unexplained cough. The capsaicin challenge we used was similar to that reported previously and we adapted the method of previous studies in assigning an arbitrary value to the peak concentration administered. We did not report the concentration provoking two coughs (C2) as we found it less reproducible and it produced a less clear distinction between health and disease. The mean C5 value in the normal sub-
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VAS cough score and the FEV1/FVC ratio

ing spells.

cough threshold to cause symptomatic cough-
tivity is only one factor responsible for sympto-
processes but it is clear that cough reflex sensi-
association with C5 may reflect these adaptive

al

receptors which some,13 but not all,20 believe

are important in capsaicin induced cough.

Two further alternatives are worth consider-
ing. Although most pathological studies focus
on the intense inflammation and fibrosis around
the alveolar structures in patients with CFA, one
report has commented on the presence of
inflammation in the airways.4 However, the
normal C5 data from patients with sarcoidosis,
where airway inflammation is common, argue
against inflammation alone being important.

More plausible is a role for pulmonary fibrosis in
causing destruction of the pulmonary C fibres.3

Stimulation of pulmonary rather than bronchial
C fibres inhibits the cough response in animal
studies.21 Moreover our patients were selected
for the presence of histological and/or CT
evidence of fibrosis. The distribution of these
changes in CFA is identical to that in PSS22
where fibrosis was also associated with a reduced
C5 value, in contrast to sarcoidosis where
preserved capsaicin responses were found.6 It

will be difficult to distinguish these effects in
humans from those caused by rapidly adapting
receptor damage, but it might be possible using
careful CT staging of the pattern of parenchy-
mal damage.23 However, technical differences
between the diagnostic scans precluded this
assessment in our patients.

Our study provides further evidence that
cough is a common symptom in CFA and sug-
gest that reflex regulation of cough is markedly
altered in this disease. Whether these findings
are due to mechanical disruption or to specific
disease processes is unknown. Similarly, whether
they have prognostic importance remains to be
determined. The high frequency with which an
abnormal capsaicin sensitivity is found in these
patients makes this non-invasive test a poten-
tially useful way of monitoring the effects of
treatment on this distressing symptom.

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Conflicts of interest: none.

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