

Increased sensitivity of the cough reflex in progressive systemic sclerosis patients with interstitial lung disease

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Increased sensitivity of the cough reflex in progressive systemic sclerosis patients with interstitial lung disease. U.G. Laloo, S. Lim, R. DuBois, P.J. Barnes, K.F. Chung. ©ERS Journals Ltd 1998.

ABSTRACT: Cough is a common presenting symptom of interstitial lung disease (ILD). The aim of this study was to examine the cough reflex in patients with progressive systemic sclerosis (PSS), with and without associated ILD.

The cough reflex to inhalation of chloride deficient solutions and capsaicin was determined in patients with PSS with associated ILD (n=12), compared to patients with PSS without ILD (n=12). In addition, patients with a chronic dry cough (n=12) and healthy subjects (n=10) without cough were studied. Cough responses to inhalation of isotonic solutions containing 150, 75, 37.5 and 0 mM Cl⁻ ions and of capsaicin (0.9–500 mM) were measured.

PSS patients with ILD reported a significantly higher cough score than PSS patients without ILD (p<0.03). ILD patients coughed more than those without ILD to Cl⁻ of 37.5 and 0 mM (19.1±5.0 vs 6.2±1.9 coughs·min⁻¹ (p<0.03), and 29.2±5.0 vs 14.1±4.1 coughs·min⁻¹ (p<0.04), respectively). The log concentration of capsaicin causing two or five coughs was lower in PSS with ILD compared to PSS without ILD (0.74±0.15 mM vs 2.12±0.26 mM; p<0.002). Patients with chronic dry cough had a similar degree of response to low-chloride and capsaicin solutions as patients with PSS and ILD, whilst healthy controls had a similar degrees of response to PSS patients.

There is an increased cough reflex in patients with interstitial lung disease, which may represent sensitization of airway sensory nerves. This may be the basis for the chronic dry cough in patients with interstitial lung disease.

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In addition to breathlessness, a chronic dry cough is often a troublesome symptom of interstitial lung disease (ILD) [1]. The basis for the chronic cough in ILD is not known. Although some patients may report small amounts of mucoid sputum, most patients complain of a dry cough. Based on our current understanding of chronic dry cough, an increased cough reflex has been described in such patients, whose cough may be associated with viral upper respiratory tract infections, postnasal drip or gastro-oesophageal reflux, or without obvious cause [2, 3]. Increased cough reflex usually represents a reflex of enhanced cough sensitivity present in the proximal upper airways, where cough receptors are usually located [4]. However, it is not known whether there is enhanced cough reflex in ILD. We therefore examined the cough response to inhaled capsaicin and low-chloride content solutions of patients suffering from ILD in association with progressive systemic sclerosis (PSS). ILD associated with systemic sclerosis is histologically identical to that observed in lone chronic fibrosing alveolitis [5]. We investigated patients with systemic sclerosis, those with and without ILD, and also patients with a chronic dry cough.

Materials and methods

Patients

A total of 24 consecutive PSS patients (12 with ILD and 12 without ILD) were recruited. The diagnosis of ILD was made on the basis of an abnormal chest radiograph, showing irregular shadowing and reduction in lung volume, and an abnormal computed tomographic (CT) scan, with evidence of interstitial fibrosis and/or inflammation [6]. Patients with a productive cough or who gave a history of gastro-oesophageal reflux were excluded. As positive controls, 12 patients with a chronic dry cough without clinical, radiographic and high-resolution computed tomographic (HRCT) evidence of lung disease were studied. The causes of chronic dry cough in this group were: asthma (n=2); post upper respiratory viral infections (n=1); gastro-oesophageal reflux (n=2); postnasal drip (n=1); and idiopathic (n=6). Ten healthy subjects with no history of cough were used as negative controls. All subjects were nonsmokers and none of the patients were on any medication. All subjects gave informed consent for participation

in this study, which was approved by the Royal Brompton Hospital Ethics Committee.

Cough challenges

Patients attended the laboratory between 08:00 and 11:00 h, following abstinence from caffeine-containing drinks for at least 6 h, and fasted for at least 2 h prior to attendance. Before undergoing cough challenge, all subjects were asked to assess any symptom of cough on a visual analogue scale of 0 to 10, with 0 representing no cough and 10 representing cough occurring at an incapacitating frequency and intensity. Cough challenges were then performed first with chloride-deficient solutions, followed by capsaicin solutions after an interval of 15 min, as described previously [7].

Chloride-deficient solutions. Patients breathed tidally for 1 min through the mouthpiece of an ultrasonic nebulizer (De Vilbiss Ultraneb 2000; Somerset, PA, USA; mass median particle diameter 5 μm ; output 4 $\text{mL}\cdot\text{min}^{-1}$) containing 15 mL of solution. Subjects were instructed to cough through the mouthpiece, and the coughs during and 1 min following nebulization were counted by the same experienced technician. Four iso-osmolar solutions (300 MOsm) were made by serially diluting 0.15 M saline (150 mM sodium, 150 mM chloride) with 1.26% sodium bicarbonate (150 mM sodium, 150 mM bicarbonate) to produce four solutions containing 150, 75, 37.5 and 0 mM chloride, respectively. The cough challenge was commenced with the 0.15 M saline solution followed by solutions, with decreasing chloride content.

Capsaicin challenge. Capsaicin challenges were administered as single-breath inhalations from a dosimeter (P.K. Morgan Ltd, Gillingham, UK) set at a driving pressure of 151 kPa (22 $\text{lb}\cdot\text{in}^{-2}$) and a dosing period of 1 s. Two millilitres of solution were placed in the nebulizer, which delivered 20 μL solution (particle size 4 μm mass median aerodynamic diameter). Noseclips were worn and subjects were instructed not to hold their breath after inhalation to maximum inspiration. Coughs were counted for 1 min after the inhalation by direct observation. Capsaicin was administered in 10 concentration increments from 0.98 to 500 mM at 1 min intervals, and the challenge was terminated once the subjects coughed five or more times. The concentrations of capsaicin causing two or more coughs and then five or more coughs were denoted the C2 and the C5, respectively. If five or more coughs were not achieved, then the C5 was denoted as the maximum concentration of capsaicin for analysis.

Data analysis

Cough counts are presented as mean \pm SEM. Mann-Whitney U-test was used to compare cough numbers between groups. Unpaired Student's t-test was used to compare other variables between groups. A p-value of less than 0.05 was taken as significant.

Results

As expected, the patients with ILD had significantly lower values of forced expiratory volume in one second

(FEV₁), whilst those without ILD had normal FEV₁ (table 1). Patients with ILD reported higher cough scores compared with those without ILD (3.1 \pm 0.5 vs 1.7 \pm 0.4; $p < 0.03$), and the patients with a chronic dry cough reported the highest scores (7.8 \pm 0.4).

Table 1. – Characteristics of controls and patients

Group	Healthy controls	Chronic cough	PSS	PSS + ILD
Subjects n	10	12	12	12
Age yrs	51 \pm 4	50 \pm 4	48 \pm 2	53 \pm 3
Gender M/F	4/6	0/12	4/8	4/8
FEV ₁ % pred	107 \pm 5	94 \pm 12	89 \pm 4	64 \pm 4 ⁺
Cough score	-	7.8 \pm 0.4	1.7 \pm 0.4	3.1 \pm 0.5 [#]

Data are presented as absolute number or mean \pm SEM. PSS: progressive systemic sclerosis; ILD: interstitial lung diseases; M: male; F: female; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value. ⁺: $p < 0.001$; [#]: $p < 0.03$ for PSS compared to PSS + ILD.

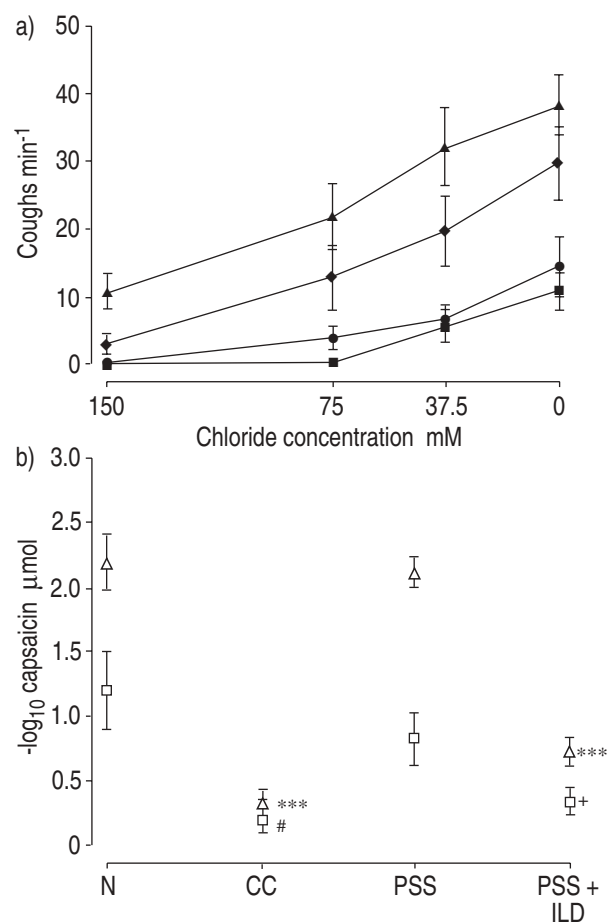


Fig. 1. – Mean cough counts in response to inhalation of: a) low-chloride content solutions; and b) capsaicin solutions, in healthy normal subjects (N), patients with a chronic dry cough (CC), patients with progressive systemic sclerosis with interstitial lung disease (PSS + ILD), and patients with progressive systemic sclerosis alone (PSS). Panel a shows responses to solutions with decreasing chloride content, with higher cough responses in patients with chronic dry cough and in patients with PSS and ILD when compared to the healthy controls. \blacktriangle : chronic dry cough; \blacklozenge : PSS + ILD; \bullet : PSS alone; \blacksquare : healthy normals. Panel b shows the C2 (\square) and C5 (Δ) concentrations, which are the concentrations of capsaicin causing more than two or five coughs. There were a significantly lower C2 and C5 concentrations in the patients with chronic cough and in patients with PSS and ILD. Data are presented as mean \pm SEM. ⁺: $p < 0.02$; [#]: $p < 0.005$; ^{***}: $p < 0.001$, versus healthy normal subjects.

Low chloride cough challenge

Two patients with PSS and ILD and six patients in the chronic dry cough group only managed to inhale down to the 37.5 mM chloride concentration. In these cases, the response to zero chloride was assumed to be similar to their responses to 37.5 mM concentration. Five patients with PSS with ILD also coughed to the 150 mM chloride solutions. They had a higher cough response to all concentrations of chloride when compared to responses of patients with PSS without ILD, but this was significant only for 37.5 and 0 mM chloride (fig. 1a). However, the response of patients with a chronic cough was significantly higher than that of patients with PSS without ILD and higher, although not significantly so, than those with PSS with ILD.

Capsaicin challenge

The capsaicin C2 and C5 values were significantly lower in patients with PSS and ILD and in patients with a chronic dry cough, when compared to the responses of normal volunteers. However, patients with PSS without ILD had C2 and C5 values that were not different from normal subjects (fig. 1b).

Discussion

We have demonstrated that patients with PSS and ILD without a productive cough had a sensitized cough reflex of a similar intensity to that seen in patients with a chronic dry cough without ILD. The group of PSS patients without ILD did not have a sensitized cough reflex, indicating that ILD *per se* was related to the increased cough reflex. Interestingly, all of the 12 consecutive patients with PSS and ILD studied reported that they had a dry cough, of an intensity less than that reported by patients with a chronic dry cough.

The sensitization of the cough reflex was observed with the inhalation both of capsaicin and chloride deficient solutions in patients with PSS and ILD, and in patients with chronic dry cough. Sensitization of the cough reflex may involve both the nonmyelinated C-fibres and the rapidly adapting irritant, myelinated A δ -fibres. Based on studies in guinea-pig airways, solutions deficient in chloride ions stimulate the myelinated A δ -fibres and nonmyelinated C-fibre sensory nerves by inducing a loss of intracellular chloride ions, leading to their depolarization [8]. The solutions with low chloride content that were used in the present study had an alkaline pH (150 mM chloride = pH 5.89; 75 mM chloride = pH 9.19; 37.5 mM chloride = pH 9.22; and 0 mM chloride = pH 9.04), but it is unlikely that alkalinity was the major stimulus of the cough because the pHs were similar and yet there was an increase in the cough numbers with diminishing chloride content. The effects of alkalinity on A δ - and C-fibre activity are not known. Although capsaicin is a selective stimulant of the nonmyelinated bronchial C-fibres *in vitro* [9, 10], stimulation both of A δ - and C-fibres has also been reported *in vivo* [11, 12]. Capsaicin acts by the opening of a relatively nonselective cation channel on the C-fibre and subsequent activation of an inward depolarizing current.

Both types of sensory fibres associated with cough are predominant in the proximal airways. The capsaicin-sensitive cough receptors appear to be more plentiful in the airways below the larynx, as the sensitivity of capsaicin-induced cough in humans is enhanced when capsaicin is delivered as an aerosol of smaller particle size with enhanced deposition in the lower airways [13]. It is unlikely that there is any preferential deposition in the distal airways or alveolar regions, particularly in the patients with ILD who demonstrated some degree of airways obstruction. In addition, there appear to be few or no cough receptors in intrapulmonary airways [14]. Much of the response to low-chloride content solutions appears to be initiated by receptors situated mainly in the larynx [15]. Our data would indicate that the enhanced cough reflex was initiated by stimulation of cough receptors in the upper proximal airways.

The mechanisms causing sensitization of the proximal cough receptors in ILD that affects the parenchyma and bronchioles are unknown. It is possible that sensitization of the cough reflex could occur through inflammation of the proximal airways. Increased recovery of neutrophils and eosinophils in bronchoalveolar lavage fluid has been observed in ILD of systemic sclerosis [6, 16], but there have been no histological studies of the proximal airways in this condition. An alternative possibility is that inflammatory processes in the lung parenchyma may damage pulmonary C-fibres, which has been shown to inhibit the cough reflex [17], thus leading to an enhanced cough reflex operating at a central level.

The present study shows that a dry cough is not uncommon in patients with ILD. Because the patients studied also had progressive systemic sclerosis, the possibility of gastro-oesophageal reflux underlying this has to be considered. None of the patients gave a history of gastro-oesophageal reflux, and by matching patients with ILD and without ILD on the basis of age, sex and duration of systemic sclerosis, the possibility of any occult oesophageal reflux would be balanced between the two groups. It is of note that even those patients with systemic sclerosis without ILD recorded a low level of cough symptoms, but much lower than for the patients with ILD. However, these patients showed no increase in cough reflex.

Our studies, therefore, indicate that patients with interstitial lung disease demonstrate an enhanced cough reflex similar to that observed previously in patients with a chronic dry cough, without evidence of interstitial lung disease. This is likely to be the basis for their chronic dry cough which often goes unreported in this condition.

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