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Sensitivity of the cough reflex in patients with chronic cough

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ABSTRACT: Cough may occur in association with excess bronchial secretions and may, therefore, be productive. However, in a proportion of patients the cough is non-productive and a possible association with an enhanced response of the cough reflex has been postulated.

Using the irritant capsaicin, the sensitivity of the cough reflex was measured in 363 individuals. A questionnaire was used to divide subjects into three groups: Group A) non-coughing controls; Group B) subjects with non-productive cough; and Group C) subjects with productive cough. The group means (±99% confidence interval (CI)) of the log capsaicin concentration causing two or more coughs (C_2) for groups A, B, C were 0.98 (±0.08), 0.64 (±0.09) and 1.04 (±0.23), respectively. The log capsaicin concentration causing five or more coughs (C_5) for groups A, B, C were 1.78 (±0.1), 1.16 (±0.12) and 1.54 (±0.25), respectively. Group B was significantly more sensitive to inhaled capsaicin than the other groups ($p<0.01$). No significant difference was observed between groups A and C. Some differences were found when subgroups were examined within groups B and C. In group B, patients with post-nasal drip were found to have a normal sensitivity of the cough reflex and were, therefore, different from the remainder of patients with non-productive cough. In group C, patients with bronchiectasis and current infection showed an increase in the sensitivity of their cough reflex.

It is concluded that cough can occur in association with either excess mucus production leading to productive cough or an increase in the sensitivity of the cough reflex, possibly leading to non-productive cough.

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Cough is the most common symptom in respiratory disease. The prevalence of cough in the population is modified by factors such as cigarette smoking and other environmental pollutants. Surveys of various populations have reported the prevalence to be within the range of 5–40% [1–3]. Sales of antitussives have been estimated to be in excess of £38 million in the UK [4] and over $500 million in the USA [5]. Antitussives comprise the largest category of "over the counter" drug sales. This is highlighted by the number of self-prescriptions of antitussives, which has been estimated to be 75 million doses per annum in the UK [6].

Cough is a basic defence mechanism of the respiratory tract and its function is to remove unwanted particles and tracheobronchial mucus and other secretions from the airways. Indeed, productive cough probably arises from mucus stimulating the mechanoreceptors [7]. Many patients, however, have a non-productive cough which is not associated with the clearance of mucus and may, therefore, be stimulated through a different mechanism. There are data from patients with viral infection and angiotensin converting enzyme inhibitor cough to suggest that non-productive cough may be due to an abnormal increase in the sensitivity of the cough reflex [8, 9]. Clearly, if cough in some patients is due to the presence of an abnormal cough reflex without excess mucus production then the priorities for investigation and treatment would be altered. Ideally, therapies may become available which would selectively decrease either the sensitivity of the cough reflex or mucus production.

We present data on the sensitivity of the cough reflex in patients with either productive or non-productive cough attending a chest clinic and selected control groups. The patients were assessed by questionnaire to determine their frequency of sputum production and divided into those with and those without sputum production. Other diagnostic labels were given by the treating physician according to standard clinical criteria. In this study, the object was to relate sensitivity of the cough reflex to sputum production and airway responsiveness, as assessed by histamine challenge, and no attempt was made to assess the effect of therapy on the result.

Methods

Subjects

The study was carried out on 363 individuals with or without the symptom of cough including normal volunteers and patients attending the chest clinic (table 1). The respiratory diagnosis was given by the referring consultant pulmonary physician using standard clinical criteria. Patients were diagnosed as having asthma on the basis of positive history, clinical symptoms and a positive histamine test as described by YAN *et al.* [10]. Patients were grouped into non-productive and productive cough on the basis of the questionnaire described below.

Table 1. – The groups of patients and controls used in the study

Group	n	Sex	Mean age (range)	Smoking history			
				NS	EX	S	NK
Group A - no cough							
Normals	90	37F	29 (19–56)	57	6	15	13
ACE-I no cough	35	19F	57 (25–73)	26	2	5	0
Hypertension	15	10F	55 (43–68)	10	1	3	1
Asthma no cough	18	12F	34 (5–76)	10	0	2	6
Group B - unproductive cough							
Idiopathic	65	46F	45 (5–80)	33	9	4	19
Post-nasal drip	13	8F	49 (23–74)	5	1	1	6
Post-viral cough	5	3F	46 (14–73)	2	0	2	1
Asthma + cough	23	13F	41 (7–71)	15	2	6	0
ACE-I + cough	43	30F	56 (32–79)	24	5	4	10
Oesophageal reflux	14	7F	53 (31–79)	14	0	0	0
Group C - productive cough							
Bronchietasis	12	6F	46 (19–73)	5	1	6	0
Bronchiectasis with no infection	7	4F	46 (19–64)	3	4	0	0
COAD	11	5F	65 (48–76)	4	2	5	0
ILD	12	4F	51 (32–85)	4	2	6	0

NS: nonsmoking; EX: ex-smoker; S: smoker; NK: not known; ACE-I: angiotensin converting enzyme inhibitor; COAD: chronic obstructive airway disease; ILD: interstitial lung disease.

Questionnaire

The respiratory symptoms questionnaire was modified from that devised by GULSVIK [11], which was originally used in a population of nonsmokers in Oslo. The questionnaire included background information including age and sex. The subjects were asked if they had a regular cough and if so how often. If the answer was "yes", then the subjects were also asked whether they produced phlegm and how often. All patients were then asked if they suffered from shortness of breath or chest pain. Detailed information regarding smoking habits was obtained. This included the number of cigarettes smoked per day, time over which the subject was a regular smoker and, for former smokers, for how long a period they had smoked before ceasing. Subjects were also asked about their disease and current treatment, and for any other medical history. From the questionnaire the patients were divided into three groups: those without cough (group A); those who had cough which was never or rarely associated with phlegm production, *i.e.* non-productive cough (group B); and those who mostly or always produced phlegm when coughing, *i.e.* productive cough (group C).

Cough challenge

Cough challenges were performed using our single-breath inhaled capsaicin method [9]. Capsaicin is a sensory nerve stimulant and when inhaled produces a concentration dependent cough [12]. Subjects inhaled either single breaths (0.008 ml) of vehicle or capsaicin solution (1.95–500 μM) given from a breath-activated nebulizer controlled by a dosimeter (P.K. Morgan Ltd, Gillingham, Kent, UK). The concentrations in this study were given in ascending order and inhalations of saline were interspersed randomly during the challenge as a blinding procedure. Inhalation was given at one minute intervals and the number of coughs during that minute were counted. The challenge was terminated when the subject coughed five or more times.

Bronchial challenge

To measure bronchoconstrictor responsiveness an identical method to that described by YAN *et al.* [10] was used, with the exception that the histamine doses delivered were: 0.04, 0.12, 0.27, 0.58, 2.4 and 4.9 μmol. The normal cut-off value used was a 20% fall in forced expiratory volume in one second (FEV_1) at <1.5 μmol.

Protocol

Patients first answered the questionnaire, then had a cough challenge followed if practicable by a bronchial challenge. The diagnostic labels (group assignment) were therefore assigned to patients before the challenges were performed. Any drugs that the patients were taking were withdrawn from the night before study, with the exception of inhaled glucocorticosteroids in the asthmatics.

Statistical analysis

The results are expressed as the log of the capsaicin concentration causing two or more coughs (C_2) and five or more coughs (C_5). Mean and 99% confidence intervals were calculated for each group. The data for the control population were normally distributed. However, for the patient groups this was not the case. Data were therefore analysed by non-parametric analysis of variance and Mann-Whitney U-test. In view of the multiple comparisons, a value of $p<0.01$ was considered to be significant.

Results

Group A consisted of normal controls and clinic patients with no cough including asthmatic patients with no current cough, patients taking angiotensin converting enzyme (ACE) inhibitor therapy who have not developed cough and patients on hypertensive therapy other than with an ACE inhibitor. Group B were patients with a non-productive cough associated with ACE inhibitor therapy, asthma, post-viral cough, post-nasal drip, oesophageal reflux and those without diagnosis (idiopathic). The patients without diagnosis had no clear history of previous viral infections, asthma, post-nasal drip or oesophageal reflux and/or had failed to respond to adequate therapy for the latter two diseases and had a negative histamine test. Group C consists of patients with productive cough including those with chronic obstructive airway disease (COAD), bronchiectasis and interstitial lung disease (ILD) consisting of eight patients with sarcoid and four with fibrosing alveolitis.

Bronchial challenges with histamine were found to be positive in all asthmatics tested. Fifty two of the 65 patients in the idiopathic group were tested and all responded with either no fall in FEV_1 or a >20% fall at above 1.5 μmol. Within the normal and control patient group (group A), no difference in the sensitivity of the C_2 and C_5 between the sexes was seen. The log mean (±99% CI) C_2 and C_5 for the females was 1.05 (±0.17) and 1.80 (±0.22) μM, respectively, and for the males was 1.02 (±0.14) and 1.81 (±0.14) μM, respectively. There was no difference between the patients in the subgroups in group A. Also, within group A no difference was seen in the sensitivity of the C_2 and C_5 between nonsmokers, smokers and ex-smokers. The log mean (±99% CI) C_2 for the nonsmokers, smokers, ex-smokers and unknown was 0.962 (±0.08), 1.00 (±0.16), 0.99 (±0.20) and 1.01 (±0.21) μM, respectively. The log mean (99% CI) C_5 for the nonsmokers, smokers, ex-smokers and unknowns was 1.69 (±0.10), 1.90 (±0.18), 2.06 (±0.20) and 1.84 (±0.27) μM, respectively.

Table 2. – The mean log of the capsaicin concentration causing two or more coughs (C_2) and 5 or more coughs (C_5) with 99% confidence intervals (CI) in groups A, B and C

Group	log C_2 μM (CI)	log C_5 μM (CI)	Histamine challenge		
			+ve	-ve	NK
Group A - no cough					
Normals	1.04 (0.02)	1.81 (0.14)	ND	ND	-
ACE-I no cough	0.94 (0.18)	1.8 (0.19)	ND	ND	-
Hypertension	0.91 (0.27)	1.77 (0.36)	ND	ND	-
Asthma no cough	0.87 (0.22)	1.49 (0.37)	18	0	0
Group B - unproductive cough					
Idiopathic	0.6 (0.12)	1.08 (0.19)	0	52	13
Post-nasal drip	1.3 (0.49)	1.93 (0.3)	2	9	2
Post-viral cough	0.59 (0.35)	1.14 (0.62)	ND	ND	-
Asthma + cough	0.65 (0.25)	1.06 (0.41)	23	0	0
ACE-I + cough	0.53 (0.18)	1.13 (0.25)	1	25	18
Oesophgeal reflux	0.54 (0.07)	0.8 (0.12)	1	6	7
Group C - productive cough					
Bronchiectasis	1.25 (0.41)	1.94 (0.38)	ND	ND	-
Bronchiectasis with infection	0.5 (0.22)	1.11 (0.58)	ND	ND	-
COAD	0.92 (0.43)	1.44 (0.52)	ND	ND	-
ILD	1.29 (0.53)	1.50 (0.51)	ND	ND	-

ND: not done; NK: not known. For further abbreviations see legend to table 1.

The results for the three groups are shown in table 2 and in figure 1. There was no significant difference between groups A and C. Within group C, all patients had a similar sensitivity except those with bronchiectasis and acute infective exacerbations in whom the sensitivity of the cough reflex was increased ($p<0.01$) compared to those without infection and the normal control group. The means for group B were significantly ($p<0.0001$) different from those of the other groups. In group B, although most patients had an increase in the sensitivity of the cough reflex this was not the case with the group who had post-nasal drip. The post-nasal drip subset of non-productive cough in group B had significantly higher C_2 and C_5 values ($p<0.01$) compared to the remainder of group B.

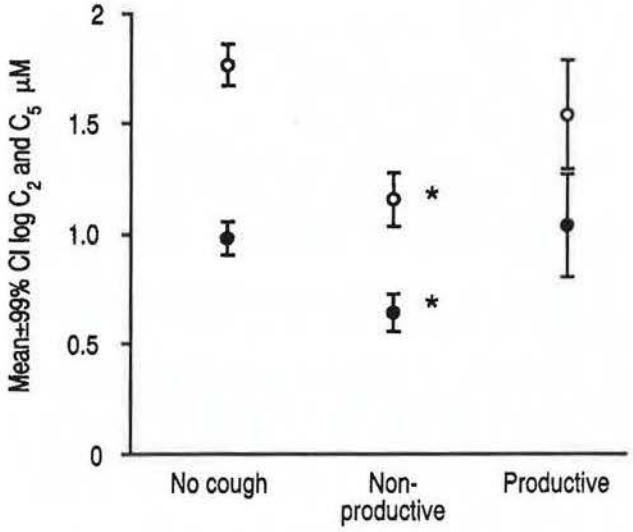

Fig. 1. – Mean log of the capsaicin concentration causing two or more coughs (C_2) (closed symbols) and five or more coughs (C_5) (open symbols) with 99% confidence intervals (CI) for 158 subjects with no cough, 163 subjects with a non-productive cough and 42 subjects with a productive cough.

In the two patient groups lung function data were available for some of the patients. The mean (±99% CI) FEV_1 % predicted for 48 patients from the non-productive group B was 90.1 (±8.5)% (including 8 asthmatics) and for 16 patients from the productive cough group C was 54.1 (±12.9)%. FEV_1 for the productive group was significantly lower than for the non-productive cough ($p<0.01$). The value for the eight asthmatics 66.1 (±27.5)% was also lower than the value for the other patients with non-productive cough 94.9 (±8.0)%, $p<0.05$.

Discussion

Patients with a non-productive cough (group B) have a heightened sensitivity of the cough reflex, when compared to non-coughing subjects (group A) and to patients with stable productive cough (group C). There were two unexpected inclusions in the subgroups as patients with post-nasal drip reported a non-productive cough and those with interstitial lung disease a productive cough. Those with interstitial lung disease had a similar normal cough sensitivity to the other patients with a reported productive cough, however, those with post-nasal drip had a different response from patients with non-productive cough as their reflex was normal. The other exception was patients with bronchiectasis with active infection, who had an increased sensitivity of the reflex compared to other patients with productive cough. These observations support the hypothesis that cough can be associated with either increased mucus production, leading to productive cough, and/or an increased sensitivity of the cough reflex. These results are, therefore, consistent with previous reports of increased cough responses [8, 9] in volunteers with viral infections and in patients who had the symptom of cough whilst taking an ACE inhibitor.

In a number of patient groups it is possible to ascertain the cause of the cough and/or the abnormal cough reflex. Obviously, in those patients with productive cough no other explanation is required for the coughing. However, in patients with a non-productive cough the cause of the cough is less certain. The patients reported here with non-productive cough, except those with post-nasal drip, had an associated abnormal cough reflex. Whether this abnormality is the cause or just an association in the majority of the patients is a matter for speculation, as in this study systematic measurements on the patients while coughing and in remission was not possible. It is known that in volunteers with a virally induced increase in the sensitivity of their cough reflex, this recovered with time [8]. Such temporal association was also reported by us in association with ACE inhibitor cough as we showed that the abnormal reflex only occurs in patients with cough and that the reflex becomes normal as the cough resolves [9]. Whether the abnormal reflex is the cause of coughing will require further study.

Since several diseases result in chronic non-productive cough and an abnormal cough reflex, there is probably more than one mechanism involved. The presence of mediators in the airways or bronchial wall may cause hyperalgesia of the sensory nerves. Such an increase in inflammatory mediators may well occur in patients with asthma and ACE inhibitor cough. Such an increase in the cough reflex occurs with the inhalation of prostaglandins E_2 and $F_{2\alpha}$ [13, 14], and in ACE inhibitor cough, a cyclooxygenase inhibitor, sulindac, reduced the sensitivity of the reflex and cough [15].

Gastro-oesophageal reflux and post-nasal drip are both important causes of chronic cough [16, 17] and in this study the former was associated with an abnormal cough reflex and the latter not. It is possible that in our patients the abnormality of the cough reflex was due to the chronic reflux and further study in this group is being performed.

Patients with post-nasal drip have secretions which originate in the nasal pharynx and drain down to the posterior pharynx where they are thought to provoke cough [16], as the cough can be treated with appropriate nasal therapy [17]. This would be consistent with our finding of a normal cough reflex in this group, which suggests that the cough follows mechanical stimulation of the larynx. It is surprising, if this is the case, that the cough is not perceived as being productive by these patients.

The association between asthma and cough is well-established [18] and in this study a non-productive cough associated with an increase in capsaicin sensitivity was found in 23 of 41 asthmatics. Abnormal capsaicin sensitivity and a history of non-productive cough were closely related since the non-coughing asthmatics had capsaicin sensitivities which were not significantly different from normal. Therefore, asthma *per se* does not cause an abnormal cough response. It is possible, that airway inflammation in more severe asthma leads to sensitization of the cough receptors [19], since an increase in the responsiveness of cough receptors has been found in other patients with bronchial asthma [20].

Although asthma is clearly the cause of an abnormal cough response in asthmatics, as the majority of patients with the abnormality did not have asthma, then other explanations are required. Differences in lung function could have contributed to the difference in the cough reflex, as the distribution of capsaicin may be affected by airflow. Indeed, it is possible that the results in those patients with productive cough may be artificially increased by this mechanism. However, it should be noted that the asthmatics, despite having a reduced FEV_1 % predicted, also had an abnormally increased response to capsaicin. The FEV_1 % predicted data cannot, therefore, explain the increased cough response in the non-productive group, as in this group the FEV_1 was within normal limits.

It has been reported that females may have a difference in the sensitivity of the cough reflex compared to males. We compared the response between the sexes and found no difference in either the non-coughing or the coughing group. Smoking has also been suggested to have an influence on the cough reflex, however, in our control group there was no difference between the smokers and nonsmokers. Finally, non-asthmatic inflammation has been reported to cause cough [21] and inflammation may indeed explain the abnormal cough response in the infected bronchiectatics.

We can conclude that cough can occur in association with either: a) excess bronchial secretions leading to a productive cough; or b) an increase in the sensitivity of the cough reflex, possibly leading to non-productive cough. Clinically it may be possible to use cough reflex testing in the investigation of cough and also to direct therapy to normalize the abnormal cough reflex, should this abnormality be shown to be causative in coughing.

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