

Cough sensitivity in children with asthma, recurrent cough, and cystic fibrosis

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Abstract

In adults, cough sensitivity is influenced by gender and is heightened in those with non-productive cough. This study examined if cough sensitivity is (i) altered in children with asthma, recurrent cough, and cystic fibrosis and (ii) influenced by age, gender, or forced expiratory volume in one second (FEV₁).

Cough sensitivity to capsaicin and spirometry were performed on 209 children grouped by the diagnosis of asthma, recurrent dry cough, cystic fibrosis, and controls.

Cough sensitivity was increased in children with recurrent cough, and lower in children with cystic fibrosis when compared with children with asthma and controls. Age influenced cough sensitivity in the controls. In the asthmatics, FEV₁ (% predicted) correlated to cough sensitivity measures. There was no gender difference in cough sensitivity.

It is concluded that cough sensitivity is different among children with recurrent dry cough, asthma, and cystic fibrosis. In children, age, but not gender, influences cough sensitivity measures and when cough sensitivity is used in comparative studies, children should be matched for age and FEV₁.

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Cough in children is a common reason for parents to seek medical attention.¹ Although cough was under recognised as one of the symptoms of asthma,² it is now over treated,¹ and children with cough as their only symptom are increasingly diagnosed with asthma.³ The Tuscon longitudinal study showed that children with recurrent cough differ from those with asthma with, or without, cough.⁴ There is cross sectional epidemiological evidence that persistent nocturnal cough represents asthma in only a small number of children.⁵

Cough is a common symptom of respiratory disease. Using the capsaicin cough receptor sensitivity test, Choudry and Fuller concluded that cough occurs in association with either excess mucus production or increased sensitivity of the cough reflex.⁶ Capsaicin as a tussive agent has been established as a method of assessing cough sensitivity in children,⁷ and adults.^{6,8} The capsaicin cough sensitivity test has been shown to be a useful research tool in adults^{6,8} as it differentiates adults with produc-

tive and non-productive cough. Cough sensitivity decreases with successful treatment of persistent dry cough in adults.⁸ Gender is an additional factor affecting cough sensitivity in adults, women have increased sensitivity.⁹ Data on the difference in cough sensitivity in different pulmonology conditions and the influence of gender have not been shown in children. Cough is a very common problem in children, with a prevalence of 26.8%,¹⁰ and the pathology of cough in children is not necessarily the same as in adults. To identify the usefulness of the cough sensitivity test in children, it is important to know the relation between cough sensitivity and the various common pulmonary conditions as well as the relation of cough sensitivity to the common physiological influences in children. The aim of the study was to determine if cough sensitivity differs in children with asthma, recurrent cough, and cystic fibrosis. A secondary aim was to examine the relationship of cough sensitivity to age, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and gender. We hypothesised that, in children, cough sensitivity is (i) different in the various common respiratory problems, and that (ii) age but not gender influences cough sensitivity.

Subjects and methods

SUBJECTS

Children aged 6-18 years with the following conditions were recruited from the outpatients department; (a) recurrent cough (≥ 2 episodes of dry cough each lasting ≥ 2 weeks in the last 12 months). The exclusion criteria for this group were: the presence of a moist productive cough, bronchiectasis, whooping cough, immunodeficiency, a past history of cardiac or neonatal pulmonary problems, clinical gastro-oesophageal reflux, abnormal cardiopulmonary physical examination including the presence of wheeze or abnormal spirometry (FEV₁ or FVC $< 85\%$ predicted normal), or chest radiograph; (b) asthma (recurrent episodes of wheeze and tachypnoea that responded to salbutamol); (c) cystic fibrosis (increased sweat chloride); and (d) controls without a history of recurrent cough were recruited from classmates of the subjects or from a private school. In addition, a history of cigarette smoking and exposure to cigarette smoke at home was obtained. Formal consent was obtained from the parents and the study was approved by the hospital's ethics committee on human research.

STUDY DESIGN

Spirometry (Jaeger Spirometer, Germany, that meets American Thoracic Society require-

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Table 1 Characteristics of the children, FEV₁, FVC, and adjusted geometric means of cough sensitivity measures in the different groups

	Asthmatics (n=35)	Recurrent cough (n=47)	Cystic fibrosis (n=27)	Controls (n=100)
Age, median (range) years	10.3 (6–16)	9.0 (5–17)	11.9 (7–18)	10.7 (6–17)
Boy/girl	19/16	22/25	18/9	57/41
Exposure to smoke*	26	32	21	65
Mean (SE) FEV ₁ (% predicted)				
Before capsaicin	101.1 (2.5)	104.4 (2.8)	81.6 (3.9)	100.0 (1.3)
After capsaicin	101.2 (2.6)	104.7 (2.8)	82.2 (4.1)	97.5 (1.5)
Change (after–before)	0.2 (0.8)	0.3 (0.5)	0.6 (0.7)	-1.3 (1.1)
Mean (SE) before capsaicin	108.9 (2.3)	105.9 (2.4)	89.6 (2.9)	101.5 (1.1)
Geometric mean (95% CI) (μmol)				
Cth†	26.2 (17.1 to 40)	6.8 (4.7 to 9.9)	50.8 (30.3 to 85.1)	15.1 (11.5 to 19.8)
C5‡	125.9 (77 to 205.7)	19.5 (12.7 to 30)	98.8 (53.2 to 183.6)	64.2 (47.0 to 87.8)
Mean (95% CI) ratio of C5 to Cth‡	0.68 (0.47 to 0.89)	0.45 (0.29 to 0.62)	0.30 (0.18 to 0.42)	0.57 (0.47 to 0.67)

*Exposure to smoke = exposure to passive smoking, based on history obtained from parent(s).

†Cth, C5 = concentration of capsaicin that stimulated ≥ 2 coughs, and ≥ 5 coughs respectively.

‡Ratio of C5 to Cth = difference of log C5 and log Cth.

ments) was performed before and after the capsaicin cough sensitivity test, and the best of three tries was recorded. All the tests were performed in the afternoon (1300–1800 hours). In children with asthma and cystic fibrosis, the tests were performed during a non-acute phase (last exacerbation four weeks previously), and during a coughing period in children with recurrent cough, FEV₁, and FVC are expressed as percentage predicted values.¹¹

CAPSAICIN COUGH RECEPTOR SENSITIVITY TEST

We have previously described a method of performing the capsaicin cough sensitivity test in children, which has good repeatability.⁷ Briefly, capsaicin (Sigma-Aldrich, Australia) diluted in 20% alcohol was delivered through a nebuliser controlled by a dosimeter (MB3, MEFAR, Italy) in an arrangement that allowed regulation of the inspiratory flow. The dosimeter was set at 0.7 seconds inhalation time, and normal saline and diluent controls were given before doubling concentrations of capsaicin (1.23 μmol to 1250 μmol) were inhaled. The number of coughs in the subsequent 30 seconds were counted by an independent observer. Cough sensitivity measures were the lowest concentration of capsaicin required to stimulate two coughs (Cth) and five coughs (C5). In our laboratory, the single determination 95% range for repeatability¹² of this test in log₁₀ values is 0.33 and 0.31 for Cth and C5 respectively.⁷ Cough sensitivity is considered to be heightened or increased when Cth and C5 values are lower.

STATISTICAL ANALYSIS

Cth and C5 data were log₁₀ transformed to normalise the data. Analysis of covariance was performed to control for the possible influence of FEV₁, FVC, age, and gender on cough sensitivity variables among the groups. Multiple regression was used to examine the possible relation between the cough sensitivity with age, FEV₁, FVC, and gender. Pearson partial correlation controlling for sex, age, and FEV₁ was used to determine the strength of the relation between the variables. The 95% confidence interval (CI) for the correlation coefficient (*r*) was calculated after back transformation of the *z* value.¹³ Statistical software SPSS (version 6.0, SPSS Inc, Chicago, Illinois, USA) and

Stata (StataCorp, College Station, Texas, USA) were used for calculation of the statistics. For gender differences in cough sensitivity, sample size calculation was performed using the expected gender difference of threefold,⁹ and the larger of the standard deviation for C5 and Cth of the controls in this study. The required sample size for 90% power at the 0.05 level of significance was 32 per group.

Results

Table 1 shows the characteristics of the 209 children enrolled. None of the children smoked. In all groups, the cough sensitivity values of the children exposed to passive smoking were no different from those who were not exposed (data not shown). None of the groups had any significant change in FEV₁ after capsaicin inhalation. Among the children with cystic fibrosis, 14 (52%) had a daily productive cough and there was no difference in cough sensitivity in children with, or without, a daily productive cough. Controlling for age, sex, FVC, and FEV₁, the Cth and C5 of the children with recurrent cough were significantly lower (*p*<0.00001 for Cth and C5) than all other groups (fig 1). In addition, Cth, but not C5, was significantly higher in children with cystic fibrosis compared with controls and children with asthma. There was no significant difference in cough sensitivity among children with asthma and controls.

Using multiple regression there was neither a significant relation between cough sensitivity and FVC, nor between cough sensitivity and gender in any group. In the controls, only age had a significant relation to cough sensitivity (for C5, partial regression coefficient (B) was 0.064, (SE 0.02)); for Cth, B=0.059, (0.02)); and in the children with asthma only FEV₁ was significant (for C5, B=0.0366, (0.11)); for Cth, B=0.037, (0.01)). Table 2 shows partial correlation coefficients between cough sensitivity and age (controlling for FEV₁ and gender) and between cough sensitivity and FEV₁ (controlling for age and gender). Controlling for age, cough sensitivity correlated to FEV₁ in the asthma group only. In the controls, age was the only factor that correlated to cough sensitivity measures after controlling for other variables. In children with recurrent cough and cystic

Table 2 Pearson partial correlation coefficient (95% CI) between measures of cough sensitivity and age (controlling for FEV₁ and gender) and between cough sensitivity and FEV₁ (controlling for age and gender)

	Asthmatics	Recurrent cough	Cystic fibrosis	Controls
Cth				
Age	0.3475* (-0.0001 to 0.62)	-0.1389 (-0.42 to 0.16)	-0.2562 (-0.6 to 0.16)	0.3529† (0.16 to 0.52)
FEV ₁	0.4454† (0.11 to 0.69)	-0.0419 (-0.33 to 0.26)	-0.3599 (-0.67 to 0.05)	0.0307 (-0.17 to 0.23)
C5				
Age	0.3376 (-0.01 to 0.61)	0.0799 (-0.22 to 0.37)	-0.1836 (-0.55 to 0.24)	0.2898‡ (0.09 to 0.46)
FEV ₁	0.4632‡ (0.14 to 0.69)	-0.0451 (-0.34 to 0.26)	-0.1241 (-0.50 to 0.29)	0.0677 (-0.14 to 0.27)

*p=0.06; †p<0.002; ‡p=0.01.
Significant values are bold.

fibrosis, there was no correlation between cough sensitivity and any variable.

Discussion

In this study, we found that cough sensitivity to capsaicin in children with recurrent cough is significantly higher than controls and children with asthma or cystic fibrosis. Children with cystic fibrosis had increased threshold to cough when compared with controls. In controls, age influenced cough sensitivity outcome measures, and in children with asthma, FEV₁ (% predicted) was correlated to cough sensitivity. No gender difference was noted in any group.

The findings of this study detecting increased cough sensitivity in subjects with a recurrent non-productive cough, when compared with controls and subjects with productive cough (cystic fibrosis), is similar to that previously found in a predominantly adult study.⁶ Choudry and Fuller's study,⁶ which did not control for age, found that cough sensitivity is heightened in those with chronic dry cough when compared with normal controls and those with a productive cough from a variety of respiratory conditions. Our study, which controlled for age and FEV₁, found that children with cystic fibrosis not only had lower cough sensitivity when compared with those with a dry cough, but also had an increased threshold to cough (higher Cth values) in comparison with controls. However, the C5 values of children with cystic fibrosis were not different from controls, and consistent with the clinical impression that once these children

start coughing (cough threshold reached) they then cough multiple times in contrast with controls. We have no evidence, but suspect that altered airway mucus, chronic colonisation of airways with bacteria, or tachyphylaxis of cough receptors may account for insensitivity of cough receptors in children with cystic fibrosis.

This study supports epidemiological evidence that children with recurrent cough differ from those with asthma with, or without, cough.⁴ The development of increased cough sensitivity during a coughing phase may explain the difference in the children with recurrent cough. During a cough free phase, however, we have shown that the cough sensitivity in these children decreases to the levels of controls.¹⁴ Two conflicting studies of cough sensitivity in children are not comparable because of difference in the cough sensitivity test and the subject selection.^{15 16} Using nebulised (30 seconds) citric acid on a group of children who were questioned two years before the cough challenge test, Riordan *et al* found no relation between cough sensitivity and respiratory symptoms.¹⁵ In a small group of children and adults, no difference in cough threshold to acetic acid was found in children with productive cough and controls who were not matched.¹⁶

In the control group, it is not surprising that age influenced cough sensitivity measures as, irrespective of weight, the same dosage schedule and same inspiratory flow were used for all children, and the distribution of age in our study population is skewed towards the younger age group. As age has a significant influence on cough sensitivity measures, it is necessary to use controls matched for age in clinical studies comparing groups. Several previous studies that included children neither matched subjects nor corrected the data for age in the analysis of cough sensitivity values.^{6 16}

An unexpected finding is the small but significant influence of FEV₁ (predicted values) on cough sensitivity in children with asthma. While this correlation is significant for group data on children with asthma it is probably irrelevant to individual children. The relation between the change in FEV₁ and the corresponding change in cough sensitivity is not evaluated in this paper, and we suspect that for individuals there is no relation between these variables. Using paired analysis, several groups have shown the independence of cough receptor sensitivity and bronchomotor tone in the laboratory in children¹⁷ and adults.^{18 19} We have also found that in children with asthma recov-

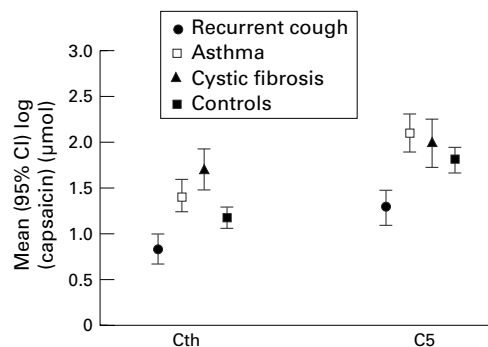


Figure 1 Cough sensitivity outcome measures in children with recurrent cough, asthma, cystic fibrosis, and controls. Means and CI were adjusted for ages, sex, and FEV₁. Cth (concentration of capsaicin that stimulated ≥ 2 coughs) and C5 (concentration of capsaicin that stimulated ≥ 5 coughs) of the children with recurrent cough were significantly lower ($p=0.00001$) when compared with all the groups. Cough sensitivity was similar in children with asthma and controls. In the children with cystic fibrosis, Cth, but not C5, was significantly higher than controls.

ering from an acute exacerbation, there is no relation between cough sensitivity and FEV₁.²⁰ A possible explanation of the positive correlation among Cth, C5, and FEV₁ (% predicted) values is related to the effect of airway calibre and deposition of the particles. Hansson *et al* have shown regional sensitivity of the airways to capsaicin using radio labelled aerosol.²¹ As the inspiratory flow in the capsaicin cough sensitivity test we used was kept constant for all children,⁷ different airway calibre may affect the site of deposition of the particles. However, in adults without asthma, cough sensitivity is also known to be influenced by FEV₁.⁹ We suggest that in the analysis of cough sensitivity data in children, it is important to correct the data for age and FEV₁.

Like Choudry and Fuller who also used the single breath method for capsaicin inhalation,⁶ we found no gender difference in cough sensitivity measures. Fujimura *et al*,⁹ using a technique that used a 15 second nebulisation of increasing doubling doses of capsaicin to measure cough sensitivity, found that adult women have three to five times increased sensitivity when compared with men. The difference in these studies may reflect the different delivery method of capsaicin and the subject selection. We studied children aged 6–18 years old who are not comparable with adults, as respiratory responses,²² among other physiological factors, are different in children. Epstein and Ciubotaru found that prior to extubation women had significantly lower tidal volume and higher respiratory rate when compared with men.²³ The pattern of breathing affects deposition of inhaled particles,²¹ and as the distribution of cough receptors is not evenly distributed throughout the airways,²⁴ it is possible that the gender difference in cough sensitivity described by Fujimura *et al*, which used the tidal breathing method, may simply reflect the gender difference in breathing pattern. The capsaicin cough sensitivity test used in our laboratory involved single breath inhalation of doubling doses of capsaicin and included the regulation of inspiratory flow, which has been shown by several groups to affect cough sensitivity outcome measures.^{7 21 25}

Children exposed to cigarette smoke at home are more likely to have respiratory symptoms especially cough.⁴ However, in all groups, we found no difference in cough sensitivity among children exposed to passive smoke and those not exposed. As urine cotinine levels were not measured and the exposure to cigarette smoke was based entirely on history, this finding is limited. We cannot exclude the small possibility that exposure to smoke may be a confounding factor.

We conclude that the cough threshold to capsaicin differentiates children with recurrent dry cough from children with cystic fibrosis and asthma. The cough sensitivity in children with non-acute asthma is similar to controls. This reflects the different pathophysiology of

cough in these conditions. In otherwise well children, age, but not gender, influences cough sensitivity to capsaicin measures and in children with asthma, FEV₁ affects cough sensitivity outcomes. Thus when using the capsaicin cough sensitivity test for comparative clinical studies it is important to match subjects for age and FEV₁.

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