

Relation between measurements of cough severity

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Arch Dis Child 2003;88:57-60

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Accepted 14 August 2002

Background: In asthma, measurements of airway inflammation correlate poorly with clinical markers and airway hyperresponsiveness. While the relation between determinants of asthma severity is known, that for cough is unknown. We hypothesised that cough sensitivity changes relate to changes in cough scores and objectively measured cough frequency.

Aims: To examine the relation between commonly used outcome measurements of cough severity in children.

Methods: The concentration of capsaicin causing two and five or more coughs (C2 and C5 respectively), cough frequency objectively measured using an ambulatory cough meter, and parent and child recorded subjective cough scores were determined in 40 children with recurrent cough on two occasions.

Results: On occasion one, log cough frequency significantly correlated with parent and child recorded log cough score ($r_s = 0.32$, $p = 0.05$; and $r_s = 0.32$, $p = 0.046$ respectively) and significantly negatively correlated with log C2 ($r_s = -0.5$, $p = 0.005$). Subjective cough scores did not relate to either C2 or C5. On occasion two, the relation between cough frequency and C2 and C5 measures was lost, but C2 had a weak but significant relation to parent recorded cough score ($r_s = -0.38$, $p = 0.047$). When the changes in the log values were determined, C5 but not C2 significantly related to cough frequency.

Conclusion: In children, measures of cough sensitivity have a weak relation with cough frequency. Subjective cough scores have a stronger and consistent relation with cough frequency. These cough severity indices measure different aspects of cough. The choice of indices depends on the reason for performing the measurement.

Appropriate outcome measurements in clinical medicine are essential. Although cough is the commonest symptom of respiratory disease, unlike asthma severity, measurements for cough severity are not well established.¹ Furthermore, the relation between the available measurements is largely unknown. The study of cough has inherent limitations as isolated cough is generally poorly reproducible,² nocturnal cough is unreliably reported,³ and cough is subjected to the period effect (spontaneous resolution of cough when studied)⁴ and to psychological influences.⁵ Only relatively recently has a cough diary system been validated.⁶

Outcome determinants of asthma severity include assessment of clinical symptoms, pulmonary function indices (peak expiratory flow, FEV₁, or its variability), degree of airway hyperresponsiveness, quality of life, and airway, serum, and urine inflammatory markers. Those for cough severity include cough receptor sensitivity thresholds (for example, capsaicin, citric acid, acetic acid),⁷ cough frequency (day or night), diary cards (parent or child reported), and cough amplitude.⁸ Cough receptor sensitivity (CRS) has been shown to be a useful research tool⁹ and can be reliably measured in children when the inhalation method, including inspiratory flow is controlled.¹⁰ Increased CRS (indicating a hyperresponsive state) occurs in some disease processes where cough is problematic, both in adults^{9 11} and children.^{12 13} CRS decreases when the aetiology of the cough is treated⁷ and when the cough resolves.¹⁴ Thus CRS may be a useful outcome measure for evaluating antitussives. Log cough frequency significantly relates to diary scores of cough severity,⁶ but it is unknown how cough receptor sensitivity relates to cough frequency or to cough scores. Understanding the relation between these variables would promote better evaluation of cough and better understanding of these measures for cough severity. The absence of data on the predictability of the capsaicin cough response and the relation of the response to objective markers

were recently highlighted.¹ The objective of this paper was to examine the relation between these commonly used measurements of cough severity in children. CRS, objectively measured cough frequency, and cough scores were examined in children with recurrent cough on two occasions. We hypothesised that CRS changes relate to changes in cough scores and objectively measured cough frequency.

METHODS

Children (6-17 years) with recurrent cough (two or more episodes of cough, each lasting at least two weeks in the past 12 months) were recruited from the Royal Children's Hospital outpatient department during a coughing episode. The children were assigned to one arm of a double blind placebo randomised controlled trial (inhaled salbutamol) as previously reported.¹⁵ On days 1 and 7, the children performed the capsaicin CRS test, and wore an ambulatory cough meter for a 24 hour period.¹⁶ Parents and children also completed separate colour coded cough diary cards.⁶ Formal consent was obtained and the study was approved by the hospital's Ethics Committee on Human Research.

A reliable method of performing the capsaicin CRS test in children was utilised.¹⁰ Briefly, capsaicin (Sigma-Aldrich, Australia) diluted in 20% alcohol, was delivered through a nebuliser, controlled by a dosimeter (MB3, MEFAR, Italy) in a configuration that allowed regulation of the inspiratory flow and pattern. The dosimeter was set at 0.7 s inhalation time; 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

Abbreviations: CRS, cough receptor sensitivity; EMG, electromyogram; FEV, forced expiratory volume; VAS, visual analogue scale

Table 1 Correlation between the different markers of cough severity on days 1 and 7

	Spearman correlation (95% CI)			
	Log cough score (child recorded) (n=40)	Log cough score (parent recorded)	Log C2	Log C5
<i>Day 1</i>				
Log cough score (parent recorded) (n=40)	0.81 (p=0.00001) (0.67 to 0.90)			
Log C2 (n=29)	-0.23 (0.56 to 0.15)	-0.35 (-0.64 to 0.02)		
Log C5 (n= 40)	-0.08 (-0.38 to 0.23)	-0.18 (-0.47 to 0.14)	0.62 (p=0.00001) (0.32 to 0.81)	
Log cough frequency per 24 hours (n=40)	0.32 (p=0.05) (0.01 to 0.57)	0.32 (p=0.046) (0.01 to 0.58)	-0.5 (p=0.005) (-0.74 to -0.18)	-0.12 (-0.42 to 0.20)
<i>Day 7</i>				
Log cough score (parent recorded) (n=37)	0.79 (p=0.00001) (0.63 to 0.89)			
Log C2 (n=23)	-0.301 (-0.6 to 0.07)	-0.38 (p=0.047) (-0.66 to -0.01)		
Log C5 (n=37)	-0.14 (-0.44 to 0.20)	-0.223 (-0.51 to 0.11)	0.87 (p=0.00001) (0.74 to 0.94)	
Log cough frequency per 24 hours (n=37)	0.44 (p=0.01) (0.13 to 0.67)	0.42 (p=0.02) (0.11 to 0.65)	-0.26 (-0.56 to 0.11)	0.3 (-0.03 to 0.57)

C2, concentration of capsaicin that produced 2–4 coughs; C5, concentration of capsaicin that produced 5 or more coughs.

was counted by an independent observer. CRS measures were the lowest concentration of capsaicin required to stimulate 2–4 coughs (C2) and ≥ 5 coughs (C5). The cough meter used was a validated ambulatory cough meter¹⁶ that continuously records simultaneous electromyogram (EMG) and acoustic signals for 24 hours.

The parent(s) and child were given a colour coded chart and were asked to separately rate the severity of the child's cough using a visual analogue scale (VAS). The VAS is a vertical scale from 1 to 10, with 10 representing the presence of the most severe cough and 1 representing the absence of cough.

Analysis

Cough frequency, C2, and C5 were \log_{10} transformed. Spearman rank correlation (r_s) was used to assess the association between variables, and 95% CI were calculated with z transformation and back transformed.¹⁷ SPSS (Illinois, USA) statistical software package was utilised; a two tailed p value of ≤ 0.05 was considered significant.

RESULTS

Forty three children enrolled in the study. The cough meter analysis was unsatisfactory in three children: microphone dislodged in one; and cough meter removed because of intolerable itch in two. Data from these children were omitted from the analysis. The median age of the remaining 40 children (23 girls, 17 boys) was 9.4 years (range 6.2–17). Of these children, three pulled out of the trial and day 7 data were therefore incomplete.

The median number of coughs/24 hours was 75 for day 1 (range 9–719) and 44 for day 7 (0–500). On day 1, median value of child recorded VAS was identical to parent recorded VAS (median 4, range 1–10) and that for day 7 was 2 (range 1–10) and 3 (range 1–10) respectively. Not all children obtained a C2 value as their first outcome measure in the CRS test resulted in five or more coughs. Mean log C2 was 0.80 (geometric mean 6.37, 95% CI 0.6 to 1.01) and that for C5 was 1.31 (geometric mean 20.6, 95% CI 12.02 to 34.67) on day 1. C2 and C5 values both increased (representing reduced cough

Table 2 Correlation between differences (change) of day 7 and day 1 of the different markers of cough severity

	Spearman correlation (95% CI)			
	Change in log cough score (child recorded)	Change in log cough score (parent recorded)	Change in log C2*	Change in log C5†
<i>Day 1</i>				
Change in log cough score (parent recorded) (n=37)	0.65 (p=0.00001) (0.40 to 0.80)			
Change in log C2 (n=23)	-0.12 (-0.51 to 0.30)	-0.38 (-0.68 to 0.04)		
Change in log C5 (n=37)	-0.05 (-0.37 to 0.28)	-0.38 (p=0.024) (-0.63 to -0.07)	0.63 (p=0.00001) (0.28 to 0.83)	
Change in log cough frequency per 24 hours (n=37)	0.38 (p=0.03) (0.04 to 0.64)	0.36 (p=0.047) (0.01 to 0.63)	-0.40 (p=0.06) (-0.70 to 0.02)	-0.38 (p=0.03) (-0.63 to -0.07)

C2, concentration of capsaicin that produced 2–4 coughs; C5, concentration of capsaicin that produced 5 or more coughs. All differences refer to value of day 7 – value of day 1.

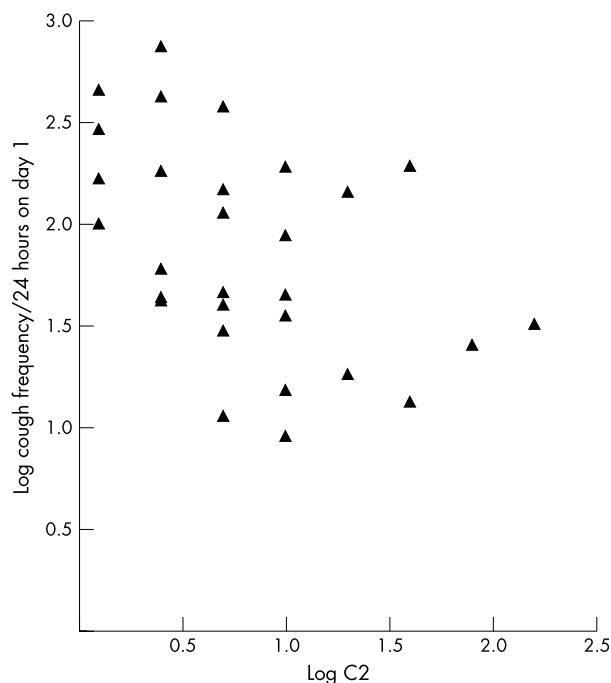


Figure 1 Log cough frequency measured using an ambulatory cough meter significantly correlated with log C2 (concentration of capsaicin required to stimulate 2–4 coughs); $r_s = -0.5$ (95% CI -0.74 to -0.18), $p = 0.005$.

sensitivity) on day 7. The respective values for day 7 were 0.90 (geometric mean 8.0, 95% CI 4.66 to 13.8) for C2 and 1.5 (geometric mean 31.8, 95% CI 18.62 to 53.7) for C5.

On day 1, log cough frequency significantly correlated with parent and child recorded cough score and significantly negatively correlated with C2 (fig 1) but not C5 (table 1). Neither CRS outcome measure related to the subjective cough score (parent or child). On day 7, the relation between cough

frequency and CRS measures was lost, although C2 had a weak but significant relation to parent recorded cough score ($r_s = -0.38$, $p = 0.047$). When the differences (changes) of the log values were taken (table 2), C5 related significantly to cough frequency, and the relation with C2 was just outside statistical significance ($p = 0.06$) as shown in fig 2. While 37 data points were available for C5, only 23 were available for C2.

DISCUSSION

This study shows that objectively measured cough frequency related to both subjective cough scores and CRS. The change in log cough frequency also related to the changes between cough scores and CRS. However, the relations between these commonly used indices of cough were modest and complex, and CRS measures related poorly to cough scores.

In a recent international symposium on cough, the lack of knowledge of the predictability of the capsaicin response and the relation of the response to objective markers were highlighted.¹ To date, there are no published data on the relation between CRS and objectively measured cough frequency or that between CRS and cough scores. This study shows that CRS related to cough frequency inconsistently and in a complex manner. The change in log values of cough frequency was significantly related to the change in log C5 value. This confirms the complex relation between cough frequency and CRS measurements. In contrast, the relation between cough frequency and cough scores was consistently significant. However, the relation was also not simple, reflected both in single time measurements and changes between measurements. We have previously shown a much stronger relation between cough scores and log cough frequency ($r_s = 0.6$ to 0.69),⁶ and the smaller correlation coefficient values in this study may reflect the smaller sample size (75 in previous study versus 40 in this study).

While objective measurements of cough frequency and subjective cough scores are easy to conceptualise, that of CRS is not as straightforward. CRS measures the ease of cough receptor stimulation by the tussive agent¹⁰ and hypersensitive (hyperresponsive) states have been documented in adults

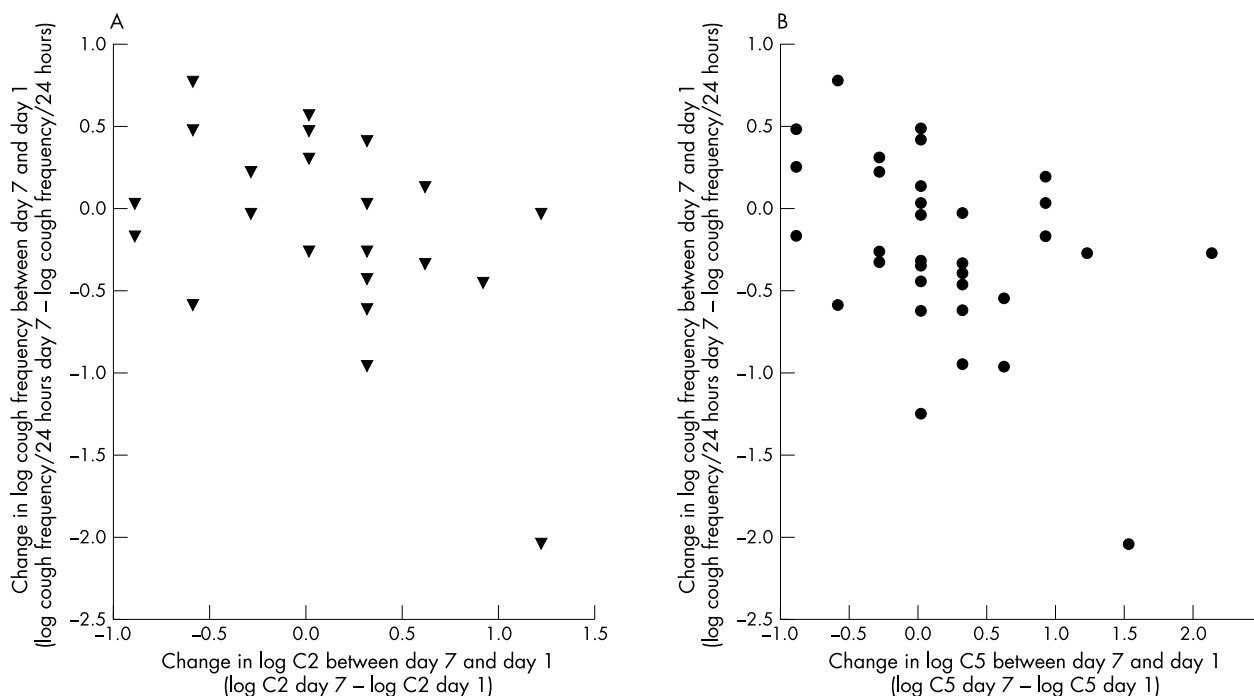


Figure 2 The change in measurements of the two occasions the tests were undertaken. (A) The correlation between the change in log cough frequency with change in log C2 was just outside statistical significance, $r_s = -0.4$ (95% CI -0.7 to 0.02), $p = 0.06$. (B) Change in log cough frequency significantly correlated with change in log C5, $r_s = -0.38$ (95% CI -0.63 to -0.07), $p = 0.03$.

with idiopathic chronic cough, gastro-oesophageal reflux, rhinitis, viral respiratory tract infections,^{7 11 18} and children with recurrent cough and cough dominant asthma.^{13 14} There are different classes of cough receptors in any species type and interspecies differences are significant.^{19 20} In humans, capsaicin stimulates vallinoid sensitive neurones.²¹ Changes in CRS have no relation to airway calibre changes.^{14 22} Although measures of CRS have been shown to be useful in research for more than a decade, its relation to the different types of airway inflammation in the human airway is largely unknown. In children with cough and asthma, eosinophilic inflammation markers have no relation with CRS measures.²³ Neurogenic inflammation is closely linked to cough²⁴ and it is likely that markers of neurogenic (rather than neutrophilic or eosinophilic) inflammation have the closest relation to cough sensitivity.²⁵ Understanding these factors would be beneficial in the development of a cough suppressant agent that diminishes the hypersensitive response while preserving the cough expiratory reflex. This would be clinically useful in some conditions.¹

While CRS and subjective cough scores related in some manner with objective cough frequency, the relation between CRS and subjective cough scores was poor. It is likely that these different outcome indices measure different aspects of cough, although it is difficult to explain this further. The most clinically relevant index is thus, yet to be defined. At this stage, as with asthma airway hyperresponsiveness,²⁶ the most relevant outcome measure for cough will depend, at least in part, on the reason for performing the measurement. We conclude that in children, CRS has a modest relation with objectively measured cough frequency, and that subjective cough score has stronger and consistent relation to cough frequency. These cough severity indices measure different aspects of cough that are not interchangeable. The choice of which determinant to use thus depends on the reason for performing the measurement.

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