

A comparison of objective and subjective measures of cough in asthma

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Background: Cough is widely recognized as a key symptom in the diagnosis and the monitoring of asthma, but little is known about how best to assess cough in asthma.

Objective: To determine how objective cough rates correlate with subjective measures of cough in asthma.

Methods: We studied 56 subjects, median age 42.0 years (range, 28.5-71), 34 (60.7%) female, with asthma. Subjects performed cough reflex sensitivity testing (concentration of citric acid causing 2 and 5 coughs [C2 and C5]), 24-hour fully ambulatory cough recordings, subjectively scored the severity of their cough (visual analog scales and 0-5 score) and completed a cough-related quality of life questionnaire (Leicester Cough Questionnaire). Ambulatory cough recordings were manually counted and reported in cough seconds per hour (cs/h).

Results: The median time spent coughing was 2.6 cs/h (range, 0.0-14.2), with subjects spending more time coughing by day (median, 3.9 cs/h [0.0-18.5]) than by night (median, 0.3 cs/h [0.0-8.7]; $P < .001$). A weak inverse relationship was seen between day cough rates and $\log_{10}$ C2 ($r = -0.39$; $P = .03$) but not $\log_{10}$ C5 ($r = -0.08$; $P = .65$). Objective time spent coughing was also weak-moderately associated with subjective cough scores and visual analog scales, and most strongly correlated with cough-related quality of life ($r = -0.54$; $P < .001$).

Conclusion: Subjective measures of cough and cough reflex sensitivity are poor surrogates for objective cough frequency in asthma. When designing studies to assess interventions for cough in asthma, we advocate a combination of both objective measures of cough and cough-related quality of life. (*J Allergy Clin Immunol* 2008;122:903-7.)

Key words: Cough, asthma, objective cough monitoring, quality of life

Abbreviations used

C2: Concentration of tussive agent causing 2 coughs
C5: Concentration of tussive agent causing 5 coughs
cs/h: Cough seconds per hour
feNO: Mean fraction of exhaled nitric oxide
ICS: Inhaled corticosteroid
LCQ: Leicester Cough Questionnaire
VAS: Visual analog scale

Cough is widely recognized as a key symptom in the diagnosis and monitoring of asthma,¹ but it is ill understood and underresearched. Although asthma is consistently cited as one of the most common conditions in adults presenting with chronic cough,² we know relatively little about the prevalence of cough in patients presenting with the classic asthma symptoms of wheeze and breathlessness. In the European Respiratory Health Survey, a diagnosis of asthma was a significant predictor of all types of cough (nocturnal, productive, and nonproductive),³ and a large population-based postal survey of asthma symptoms in Canada suggested nocturnal cough was more commonly reported than wheezing, especially in women.⁴ Furthermore, asthma therapies may not be very effective at reducing cough, because in a group of respiratory outpatients with moderately severe asthma, 61% complained of cough on most days, despite treatment in a tertiary referral center.⁵

Reported current asthma symptoms including cough correlate poorly with the degree of airflow obstruction,⁵ but there is evidence to suggest that the presence of cough in asthma may be longitudinally associated with asthma severity and poor prognosis. For example, in a 9-year study, worsening of cough had the highest predictive weight for severe asthma.⁶ Moreover, cough may be more troublesome to patients with asthma than is generally appreciated. A conjoint analysis of patient weighting of symptoms in chronic stable asthma showed that cough had the greatest impact for patients, and was of far greater importance than wheeze or sleep disturbance.⁷ A recent study examining cough-related quality of life in respiratory outpatients did not find significant differences between patients whether they presented with chronic cough, chronic obstructive pulmonary disease, bronchiectasis, or asthma.⁸

One of the main barriers to understanding the importance of cough in asthma has been the lack of well validated measures. The measurement of cough in both clinical practice and in clinical trials has generally been restricted to the use of subjective reports or scoring systems. In some small studies, cough reflex sensitivity to tussive agents such as capsaicin or citric acid has been used.^{9,10} However, we know little about how well these measures represent the actual amount of coughing or its impact on patients. In recent years, it has become feasible to make objective ambulatory

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measurements of cough using digital sound recording devices and manually counting cough events. In addition, validated cough specific quality of life measures have been developed to allow a better understanding of the impact of cough.¹¹⁻¹³

The aim of this study was to determine the relationships between objective and subjective measures of cough in patients with asthma—that is, objective cough monitoring, cough reflex sensitivity, subjective cough scores, cough VAS, and cough-related quality of life. Cough rates were also compared with those of a group of healthy volunteers, and the relationships between cough frequency and standard measures of asthma were explored.

METHODS

Subjects

To study a wide range of asthma severity, we recruited subjects from 2 sources at a regional respiratory unit (North West Lung Centre, Manchester, United Kingdom): a database of asthma volunteers and respiratory outpatient clinics (including a severe asthma clinic). Inclusion criteria were the diagnosis of asthma by a specialist pulmonologist and a positive methacholine challenge test (except in those with severe asthma). Healthy volunteers were also recruited to allow for comparisons of cough frequency with patients with asthma.

We excluded current and exsmokers of <1 year or >10 pack-year history; those taking opiates (including codeine), other antitussives, or angiotensin-converting enzyme inhibitors; and pregnant women. Subjects with a respiratory tract infection or taking part in any intervention/methodologic study in the preceding month were also excluded from the study. Ethical approval was obtained from the Local Research Ethics Committee, and subjects provided written consent.

A sample size of 60 subjects would have approximately 80% power to detect correlation coefficients of >0.35. In previous studies of patients with chronic obstructive pulmonary disease¹⁴ and chronic cough,¹⁵ the weakest correlation between objective and subjective cough measures was $r = 0.37$; hence, we powered this study to detect correlations of this order and above.

Assessment of asthma

Subjects performed spirometry (Jaeger Viasys Healthcare, Hoechberg, Germany) and underwent exhaled nitric oxide measurement at 50 L/s (NIOX; Aerocrine, Solna, Sweden). PD₂₀/PC₂₀ was estimated using the American Thoracic Society 5-breath dosimeter method,¹⁶ the modified Yan method,^{17,18} or the 2-minute tidal breathing method.¹⁶ Degree of bronchial hyperreactivity was calculated according to the method used. Severity of asthma was classified according to current medication as per British Thoracic Society guidelines.¹⁹

Objective measures of cough

Cough reflex sensitivity. Cough reflex sensitivity was measured by using a citric acid cough challenge test. Briefly, subjects inhaled doubling concentrations of citric acid (0.03–4 M) interspersed with 3 randomly assigned placebo doses (0.9% saline) blind to the subject and observer. A breath activated dosimeter (KoKo; Ferraris, Hertford, United Kingdom) with characterized nebulizer pots (Devillebliss 646, Sunrise Medical HHG Inc, Somerset, Pa) was calibrated to deliver 12 μ L per actuation. The number of coughs occurring in the minute after inhalation was counted to determine the concentration of citric acid to provoke 2 (C2) and 5 (C5) coughs.

Objective cough monitoring. Subjects underwent ambulatory cough sound recording as previously described^{14,20,21} while going about their normal daily activities. Recordings were stored on a 4-GB data card, downloaded onto a personal computer, and analyzed with an audio editing package (CoolEdit 2000; Syntrillium, Phoenix, Ariz). The number of seconds containing 1 or more explosive cough sounds (cough seconds) were manually counted as an estimate of the time spent coughing and calculated as a rate per hour (cs/h).²² There is no universally agreed method of quantifying cough, but

TABLE I. Numeric cough scoring system²⁵

Score	Day	Night
0	No cough during the day	No cough during the night
1	Cough for 1 short period	Cough on waking only
2	Cough for more than 2 short periods	Wake once or early due to cough
3	Frequent coughing which did not interfere with usual daytime activities	Frequent waking due to cough
4	Frequent coughing which did interfere with usual daytime activities	Frequent cough most of the night
5	Distressing cough most of the day	Distressing cough most of the night

we have recently demonstrated that cough seconds are extremely closely correlated with counting of explosive cough sounds, and hence the 2 measures are interchangeable.²³ This method is also highly reproducible between observers; the mean difference in cough seconds between 2 observers is 0.88 cough seconds (± 4.70).²⁴

Subjective measures of cough

Numeric cough score. On the day and evening of subjective cough recording, subjects were asked to complete a numeric cough score²⁵ (Table I).

Cough VAS. A subset of subjects marked a 100-mm linear VAS to indicate severity of their cough from “no cough” to “worst cough.”

Cough-related quality of life. The Leicester Cough Questionnaire (LCQ) was completed by each subject. This validated, repeatable questionnaire,¹¹ consists of 19 questions covering 3 subdomains: physical, social and psychological; the total score ranges from 3 to 21, with a higher score indicating better quality of life.

Statistical analysis

All data were analyzed by using SPSS Version 15.0 (SPSS Inc, Chicago, Ill). Appropriate parametric (mean [$\pm$ SD]) and nonparametric (median [range]) summary data are reported. Cough challenge endpoints (C2 and C5) were log-transformed before analysis. Spearman rank correlations were performed to compare measures of cough. Comparisons of paired and unpaired data were calculated by using the Wilcoxon signed-rank and Mann-Whitney *U* tests, respectively.

RESULTS

Subjects

We studied 56 subjects with asthma (median age, 42.0 years [range, 28.5–71], 34 [60.7%] female; Table II). Eleven (19.6%) subjects were exsmokers with a median smoking history of 1.5 pack-years (range, 0.3–6.0). Inhaled corticosteroids (ICSs) were taken by 32 (57.1%) subjects, and 3 (5.4%) were taking oral corticosteroids (median dose, 20 mg [7–30]). One subject was maintained with 8-weekly intramuscular triamcinolone injections. Bronchial hyperreactivity to methacholine was demonstrated in 49 subjects; in 7 subjects attending the regional severe asthma clinic, the test could not be performed (3 subjects had a low FEV₁; 3 subjects were on oral prednisolone, and 1 subject was treated with a continuous subcutaneous terbutaline infusion).

A group of 18 healthy volunteers also performed objective cough monitoring and were well matched with patients for age (median age, 42.0 years [range, 21–73]; $P = .77$) and proportion of

TABLE II. Subject characteristics

Characteristic	Value
Age (y)	41.5 (± 13.6)
Sex (% female)	34 (60.7%)
BMI (kg/m^2)	27.3 (20.5-49.1)
Asthma duration (y)	16.5 (2-58)
FEV ₁ (% predicted)	93.9% (27.9-126.5)
feNO (parts per billion)	28.6 (5.9-186.0)
Daily dose ICS (μg beclometasone dipropionate equivalent)	200 (0-4000)
British Thoracic Society treatment step	
1 Inhaled short-acting β_2 -agonist as required	23 (41.1%)
2 ICS 200-800 $\mu\text{g}/\text{d}$	18 (32.1%)
3 ICS plus inhaled long-acting β_2 -agonist	8 (14.3%)
4 ICS as much as 2000 $\mu\text{g}/\text{d}$ and/or addition of a fourth drug, eg, leukotriene receptor antagonist, slow release theophylline, β_2 -agonist tablet	3 (5.4%)
5 Systemic corticosteroids	4 (7.1%)

Data presented as means ($\pm$ SDs) or median (range).

females (11 females [61.1%]; $P = .42$) but had significantly better pulmonary function (mean FEV₁, 112.8% predicted [$\pm 15.1\%$]; $P < .001$).

Objective measures of cough

Cough monitoring. All 56 patients underwent both daytime and nighttime cough monitoring. Overall 24-hour cough rates were low (median, 2.6 cs/h [0.0-14.2]), with subjects spending more time coughing by day (median, 3.9 cs/h [0.0-18.5]) than by night (median, 0.3 cs/h [0.0-8.7]; $P < .001$; Fig 1). Day cough rates were moderately correlated with night cough rates ($r = 0.47$; $P < .001$). Twenty-four-hour cough rates in healthy volunteers were significantly lower than for the subjects with asthma (median, 0.4 cs/h [0.0-3.2]; $P < .001$); this was also true for the day cough rate (median, 0.7 [0.1-4.4]; $P < .001$) and night cough rate (median, 0.0 [0.0-1.1]; $P = .002$).

In patients with asthma, overall or daytime cough rates were not significantly different between female and male patients (overall: median, 3.2 cs/h [0-14.2] vs 2.9 cs/h [0-10.8], $P = .13$; and day: median, 5.1 cs/h [0.0-18.5] vs 2.7 cs/h [0.0-17.3], $P = .13$, respectively). Overnight, women spent more time coughing than men (0.6 cs/h [0-8.7] vs 0.1 cs/h [0-2.6]; $P = .03$). Cough rate had a weak but significant positive correlation with the subjects' ages ($r = 0.36$, $P = .006$ Spearman).

Cough reflex sensitivity. Thirty-five subjects underwent cough reflex sensitivity testing; 31 have C5 results, and 33 have C2 (2 subjects had a C2 > 4.0 mol; in addition, 3 subjects had a C5 > 4.0 mol, and 1 subject coughed > 5 times on placebo, causing termination of the test). Median C2 concentration was 0.12 mol/L (0.03-2.00), and median C5 was 0.25 M (0.03-4.00). Age and sex did not influence either logC2 ($r = -0.04$, $P = .84$, and $P = .90$, respectively) or logC5 ($r = 0.05$, $P = .79$, and $P = .13$, respectively).

Subjective measures of cough

Numeric cough scores. Median cough scores during the daytime were significantly higher than those at night (2 [0-4] vs 0 [0-3] respectively; $P < .001$).

Cough VAS. Median cough VAS scores were also significantly higher by day (19 mm [0-74]) than by night (7 mm [0-49]; $P < .001$).

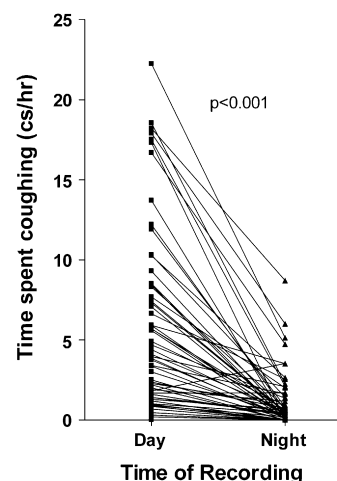


FIG 1. Time spent coughing during the day and night in patients with asthma.

Cough-related quality of life. The LCQ was completed by 53 subjects. Median total score was 17.8 (8.7-21.0); median scores for the subdomains were physical, 5.5 (2.6-7.0); psychological, 6.3 (3.1-7.0); and social, 6.5 (3.0-7.0). Sex did not significantly influence LCQ scores ($P = .49$), but there was a trend significant weak negative correlation between age and cough-related quality of life ($r = -0.36$; $P = .08$)—that is, worse quality of life with increasing age.

Relationships between measures of cough

Cough reflex sensitivity and objective cough counts. Cough reflex sensitivity to citric acid was weakly correlated with daytime cough rate for the logC2 endpoint ($r = -0.39$; $P = .03$), but not for logC5 ($r = -0.08$; $P = .65$; Fig 2).

Subjective cough measures and objective cough counts. The correlations between subjective measures of cough and objective cough counts were weak to moderate (Table III).

Cough-related quality of life and objective cough counts. There was a stronger correlation between time spent coughing and cough-related quality of life (Fig 3). The relationship remained significant when adjusted for age ($P < .001$) and explained 22.1% of the variance in LCQ (adjusted R^2). There were also moderate negative correlations between overall cough rates and the individual LCQ subdomains: physical ($r = -0.45$; $P = .001$), psychological ($r = -0.48$; $P < .001$), and social ($r = -0.55$; $P < .001$).

Relationships between objective cough and measures of asthma. There were no significant correlations between FEV₁ % predicted ($r = -0.06$; $P = .68$), mean fraction of exhaled nitric oxide (feNO; $r = -0.07$; $P = .63$), asthma duration ($r = -0.11$; $P = .43$), and overall time spent coughing. There was a weak statistically significant relationships between dose of ICS and cough frequency overnight ($r = 0.36$; $P = .008$) but not for day ($r = 0.17$; $P = .23$) or total cough rate ($r = 0.19$; $P = .18$). There were no significant correlations between dose response ratio to methacholine and cough rates overall ($r = -0.36$; $P = .81$), during the day ($r = -0.71$; $P = .63$), or during the night ($r = 0.13$; $P = .37$). Equally there were no significant correlations between feNO and cough rates overall ($r = -0.07$; $P = .63$), during the day ($r = -0.08$; $P = .59$), or during the night ($r = -0.20$; $P = .13$).

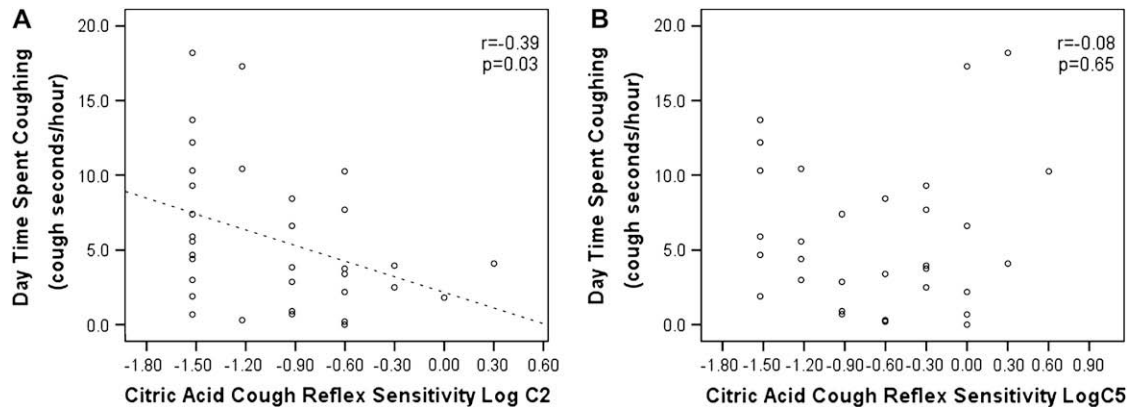


FIG 2. Correlations between cough reflex sensitivity during the day and day time spent coughing. **A**, LogC2 versus day cough rate. **B**, LogC5 versus day cough rate.

TABLE III. Relationships among objective cough counts, cough VAS, and cough scores

		Day cough rate	Night cough rate
Cough VAS	Day	$r = 0.45$ $P = .002$	—
	Night	—	$r = 0.43$ $P = .003$
Cough scores	Day	$r = 0.32$ $P = .02$	—
	Night	—	$r = 0.44$ $P = .001$

DISCUSSION

This study is the first to examine the relationships between objective and subjective measures of cough in subjects with classic asthma, not selected for the symptom of cough. The correlations between objective cough frequency and subjective measures of cough in asthma are at best moderate, and the relationship with citric acid cough reflex sensitivity is only weak for the less commonly used C2 endpoint. The best relationship with objective cough rates was seen for cough-related quality of life, implying validity of the LCQ in this patient group.

The poor relationships between objective cough frequency and subjective measures of cough may occur for a variety of reasons. Coughing occurs episodically, and when cough rates are low, as in this patient group, poor recall may be important. Measures of cough intensity are not yet available, but variation in intensity may account for some of the variability in scores. In addition, subjective measures may be modulated by the mood of the subject, attention paid to the symptom, and subjects' expectations. Similar factors are likely to influence cough quality-of-life scores, but these did correlate more strongly with objective counts. The correlations for each domain of the LCQ were similar, suggesting a general effect of cough on quality of life; therefore, a shorter questionnaire may capture cough-related quality of life in asthma.

Although cough reflex sensitivity has been used as a primary endpoint in studies testing the efficacy of drugs for cough in asthma,^{9,10,26} the relationship between objective cough reflex sensitivity and objective cough rate in this condition has not previously been studied. The finding that C2 rather than C5 related to cough rate in asthma is unexpected; in both chronic obstructive pulmonary disease¹⁴ and chronic cough,¹⁵ this was not the case.

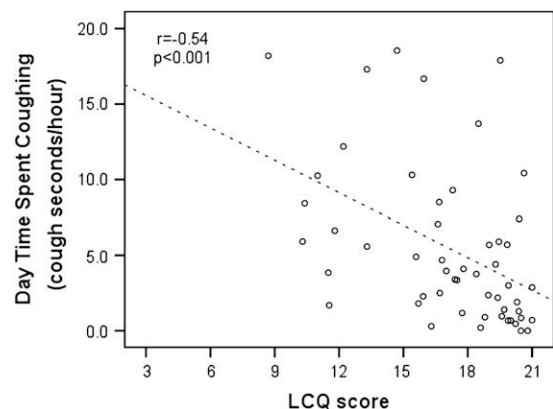


FIG 3. Correlation between LCQ total score and overall time spent coughing.

These different cough reflex thresholds may have different importance in different diseases; perhaps the eliciting stimulus for cough in asthma is lower than in other conditions in which C5 is more closely related to objective cough frequency.

The median objective cough rate in this group of patients with asthma was approximately a quarter of those we have reported in patients presenting with isolated chronic cough (median 24-h cough rate, 11.4 cs/h)¹⁵ and also less than in patients complaining of cough with chronic obstructive pulmonary disease (7.5 cs/h)¹⁴ and cystic fibrosis²⁰ (15.9 cs/h on admission with an exacerbation and 4.9 cs/h on discharge). Despite this, rates were still significantly greater than those in a small group of well matched healthy volunteers; the normal range for objective cough frequency has not yet been established. For the purpose of this and previous studies, we have quantified cough in terms of cough seconds per hour—that is, an estimate of the time spent coughing. We have recently demonstrated that this unit of cough is interchangeable with counting of explosive cough sounds and that both are similarly related to cough-related quality of life.²³

Although little specific information about how coughing changes quantitatively with age is available,²⁷ the positive correlation between objective cough frequency in asthma and patient age was surprising and counterintuitive. It might be expected that as patients' age increases, the acuity of the respiratory reflexes would reduce. Although this sample included patients from 18 to 71 years of age, this may have been an insufficient range to capture

age-related deterioration. However, this and the finding that females with asthma cough more than males at night replicate our data in patients with chronic cough (A.A. Kelsall, S.C. Decalmer, K. McGuinness, A.A. Woodcock, and J.A. Smith, unpublished data, June 2008). This suggests there may be underlying mechanisms influencing cough common to a variety of conditions.

Only limited conclusions can be drawn about the objective cough rates in asthma from this study because the sample was not population-based. Recruiting patients from both a database of volunteers for asthma studies and respiratory outpatient clinics (including a severe asthma clinic) did allow comparisons of measures of cough across a broad range of asthma severity. Previous studies measuring objective cough rates in asthma have used smaller patient groups and often subjects with asthma presenting with cough.^{25,28} This may explain why cough rates were higher than those reported here. Alternatively, the subjects in our study may have been less aware of the recording device because it is considerably less cumbersome than devices used in the past.

Finally, we also examined the relationships between standard measures of asthma and objective cough frequency; this was not the primary aim of this study, and hence these findings are entirely exploratory in nature. Objective cough frequency was not related to measures of pulmonary function, airway responsiveness, or FeNO as a surrogate measure of airway inflammation. There was an association between increasing cough frequency and dose of inhaled corticosteroid. It is possible that this reflects worse asthma control and greater treatment requirements in those with greater cough frequency, or alternatively, those patients with more cough are given additional asthma treatment in an unsuccessful attempt to control the cough.

Conclusion

These data show that in patients with asthma, subjective scores are poorly representative of objective cough rates and hence have limited value in the clinical evaluation of cough in this group. Objective cough rates also provide some insights into the mechanisms underlying cough in asthma, which were more influenced by age and sex than by standard measures of asthma. The finding that the lower threshold for citric acid cough reflex sensitivity (C2) relates to cough rate implies the relationship between these measures may vary between diseases and requires further investigation. Cough-related quality of life better reflected objective cough rates than subjective scores, suggesting that the LCQ is valid and that cough rates do have implications for quality of life in classic asthma. When designing studies to assess interventions for cough in asthma, we therefore advocate a combination of both objective measures of cough and cough-related quality of life.

We thank all of the subjects that took part in the study. We also thank Dr Surinder Birring for permission to use the LCQ.

Clinical implications: Patient reporting of cough frequency in asthma is poorly representative of objective cough rate, suggesting these measures are inadequate for the assessment of cough in clinical practice or clinical trials.

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