Cough frequency, cough sensitivity and health status in patients with chronic cough

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Summary
Background: Little is known about the frequency of cough in health and in patients with chronic cough.
Methods: We measured cough frequency and its relationship with other markers of cough severity in 20 patients with chronic cough and 9 healthy subjects using the Leicester Cough Monitor (LCM), which is an automated ambulatory digital cough monitor that records sound only. All subjects had a 6-h recording and recordings were manually counted. A subgroup of 6 normals and 6 patients with a stable chronic cough had repeat measurements up to 6 months apart.
Results: Mean (SEM) cough counts/hour were 43(8) in patients with chronic cough and 2(1) in normals (mean difference 41; 95% confidence interval 24–59; P < 0.001). The cough counts were repeatable (within subject standard deviation: 23 coughs/hour; intraclass correlation coefficient 0.8). Cough counts correlated significantly with physical (r = −0.6, P = 0.03), social (r = −0.7, P = 0.01) and total Leicester Cough Questionnaire (LCQ) health status scores (r = −0.6, P = 0.03) and cough sensitivity (concentration of capsaicin causing 5 coughs: r = 0.9, P = 0.008).
Conclusion: We have shown that there are marked differences in cough frequency between patients with chronic cough and healthy subjects, that these measurements are repeatable, and that they correlate with cough-specific health status.

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Introduction

Cough is one of the commonest causes of presentation to general practice. Most cases are acute and self-limiting although a significant minority are referred for a specialist opinion with an isolated persistent chronic cough. The assessment of patients with chronic cough is commonly based on the anatomical, diagnostic protocol which is a systematic evaluation based on the understanding that most cases are due to disease of the upper respiratory tract where cough receptors are most plentiful. Treatment trials form an important part of the assessment of patients with chronic cough. However, there are few well-validated outcome measures to assess treatment efficacy.

Cough visual analogue scores, cough specific health status questionnaires, cough reflex sensitivity measurement and cough monitors have been proposed as potential tools to assess cough. The subjective nature of symptom scores and health status questionnaires and the poor specificity of cough reflex sensitivity measurement to identify patients with chronic cough has led to a renewed interest in the development of automated ambulatory cough monitors. Current cough monitors are limited by expense and size, reliance on combined sound and electromyographic signals and are poorly validated in the chronic cough setting. As a result, little is known about cough frequency in healthy adults and patients with chronic cough and there is no information on repeatability, and the relationship between cough frequency to other parameters of cough severity such as cough sensitivity and health status. These factors are important determinants of the clinical usefulness of cough frequency measurement and the pursual of automated cough monitors. We have utilised recent advances in digital recording technology to develop the Leicester Cough Monitor (LCM), an ambulatory cough monitor that records sound only. The aim of this preliminary validation study was to assess cough frequency and its repeatability in healthy adults and patients with chronic cough and assess the relationship between cough frequency, cough sensitivity and cough specific health status in patients with chronic cough.

Methods

Subjects

Twenty consecutive patients with an isolated chronic cough (>3 weeks duration) were recruited from a specialised cough clinic. The causes of cough in patients with chronic cough were: cough variant asthma (n = 5), eosinophilic bronchitis (n = 3), gastro-oesophageal reflux (n = 3), idiopathic (n = 3), post-viral (n = 2), bronchiectasis (n = 2), chronic bronchitis (n = 1) and chronic obstructive pulmonary disease (n = 1). The clinic receives referrals from primary and secondary care largely confined to a population of 970,000 within Leicestershire. Nine normal controls were recruited from healthy volunteers responding to local advertising. Investigations were carried out according to a standardised algorithm. The protocol for investigation and treatment, and criteria for accepting diagnosis were as previously described. Normal subjects were asymptomatic, non-smokers and had normal spirometry and a methacholine PC20 FEV1 > 16 mg/mL. No subjects had received corticosteroids or other specific treatment for the condition causing cough for at least six weeks prior to the study. Six healthy subjects and 6 patients with a stable chronic cough (3 with cough variant asthma, 1 with gastro-oesophageal reflux associated cough, 1 with bronchiectasis and 1 with idiopathic chronic cough) participated in cough frequency repeatability studies. A randomly selected subgroup of 8 healthy subjects and 7 patients with chronic cough also had cough reflex sensitivity measurement. All subjects gave full informed consent to participate. The protocol for this study was approved by the Leicestershire Research Ethics Committee.

Cough monitor

The LCM is a digital ambulatory cough monitor (personal stereo size) that records sound from a free field microphone attached to the anterior chest wall. Data stored on the recorder is downloaded onto a computer when the recording is complete where it is analysed by a cough detection algorithm. The current data was generated by manual counting since the cough detection algorithm is currently under development and is not fully validated. For each subject, the entire recording was analysed by an experienced observer and each cough was identified separately whether occurring singly or in a cluster or ‘epoch’ of coughs.

Protocol and clinical measurement

The cough monitor was attached at 9 am in all subjects and returned 6 h later. Subjects were told that the LCM was a new investigative tool being developed to assess the nature of the cough and
were encouraged to resume their normal activity in their usual environment. Cough sensitivity was assessed after the cough recording with capsaicin cough challenge test using a dosimeter method standardised to limit inspiratory flow to 0.5 L/s.5 Cough specific health status was assessed in patients with chronic cough with the Leicester Cough Questionnaire (LCQ)3 which is a 19 item, self-completed, well validated cough-specific health status questionnaire that has 3 domains (physical, psychological and social). The range for total LCQ score is 3–21 where a higher score indicates a better health status and the range for domains scores is 1–7. To assess repeatability, subjects with a stable chronic cough had a second cough frequency measurement three to six months after the first, at the same time of day in order to avoid possible bias from diurnal variations.

**Analysis**

Subject characteristics were described using descriptive statistics and expressed as means (standard error). The concentration of capsaicin that causes 2 and 5 coughs (C2 and C5µmol/L) were calculated by linear interpolation of the log-dose–response curves and described as geometric mean (log-SEM). Cough frequency was expressed as individual coughs per hour for the duration of the recording. Comparisons of cough frequency, health status and cough sensitivity were undertaken using unpaired \( t \)-tests. Correlations between variables were analysed using Pearson’s correlation coefficient (\( r \)). Repeatability data was assessed as the intraclass correlation coefficients.

**Results**

The subject characteristics are as shown (Table 1). Mean (SEM) cough counts/hour were 43(8) in patients with chronic cough and 2(1) in normals (mean difference 41; 95% confidence interval of difference 24–59; \( P < 0.001 \); Fig. 1). There were no significant differences in cough frequency between diagnostic groups or gender in patients with chronic cough. Cough frequency decreased with increasing time of recording in patients with chronic cough but not normals (Fig. 2).

The mean (SEM) LCQ cough specific health status scores in patients with chronic cough were total: 13.1 (1.0), physical: 4.3 (0.3), psychological: 4.5 (0.4) and social: 4.3 (0.3). Patients with a chronic cough had heightened cough reflex sensitivity compared with the control group for both geometric mean C2 (3.3 vs. 12.5 µmol/L; mean difference 1.9 doubling doses (DD); 95% confidence interval of difference 0.4–3.4 DD; \( P = 0.017 \)) and C5 (33.7 vs. 266.7 µmol/L; mean difference 3.0 DD; 95% CI of difference 0.3–5.7 DD; \( P = 0.035 \)). Cough counts per hour in patients with chronic cough correlated significantly with physical (\( r = -0.6, P = 0.03 \)) but not psychological scores (\( r = -0.5, P = 0.08 \); Table 2). There was no correlation between cough counts per hour

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject characteristics.</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Number (male)</td>
<td>9 (0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 (3)</td>
</tr>
<tr>
<td>Cough duration (years)</td>
<td>—</td>
</tr>
<tr>
<td>FEV1%predicted</td>
<td>92 (4)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>80 (1)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SEM); FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.
in normal subjects and cough sensitivity ($C_2$: $r = 0.2$, $P = 0.7$ and $C_5$: $r = 0.2$, $P = 0.6$). There was a significant correlation between cough frequency and cough sensitivity in patients with chronic cough ($C_2$: $r = 0.8$, $P < 0.05$; $C_5$: $r = 0.9$, $P < 0.01$; Fig. 3). There were no significant correlations between LCQ scores and cough sensitivity in patients with chronic cough.

The cough counts were repeatable in the 12 subjects that underwent repeatability testing (within subject SD: 23 coughs/hour; intraclass correlation coefficient 0.8) and the tendency for cough frequency to decrease with time was also evident in the second recording in patients with chronic cough but not healthy subjects.

**Discussion**

This is the first study to investigate the relationship between cough frequency, cough reflex sensitivity and cough specific health status in adult patients with chronic cough. We found large differences in cough frequency between patients with chronic cough and healthy controls and we have shown that this measure was repeatable. Cough frequency was related to cough reflex sensitivity and cough specific health status in patients with chronic cough but not in healthy controls. Our findings suggest that daytime cough frequency measurement is potentially useful in the assessment of patients with chronic cough.

We found that cough was present in healthy subjects but that it was significantly more frequent in patients with chronic cough, consistent with cough frequency data from combined electromyo- and graphic and sound signals reported by others. 

Pavesi et al. have developed a computerised cough monitor that has been evaluated in subjects with acute cough in a confined setting but has not been assessed or validated in patients with chronic cough. We used manual cough counts from the entire recording to measure cough frequency since they are considered the gold standard and are free from the false positives seen with automated recordings due to incorrect categorisation of other sounds such as sneezing, throat clearing and speech. The manual counting process is very time consuming and not practical for clinical practice, so there is a need for automated cough detection algorithms. The data from this study provides a strong basis to pursue the development of automated cough monitors. There was a tendency for cough counts to decrease with time in patients with chronic cough suggesting that there is diurnal
variation in cough frequency as reported by others.\textsuperscript{6,14} The alternative possibility that cough counts decreased as subjects adjusted to the cough monitor seems unlikely as the same pattern was seen in repeat recordings of patients with chronic cough. Furthermore, healthy subjects did not have a reduction in cough frequency with time. Patients with chronic cough, cough very little at night\textsuperscript{6} so we doubt that confining our recordings to daytime affected the validity of our measure. However, when advances in battery life allow, further work is required to investigate the relationship between 6 and 24-h recordings.

We did not find differences in cough frequency between different diagnostic groups or gender in patients with chronic cough. The numbers involved in this study were small and it was not our aim to study disease specific cough frequency so it is possible that differences could have been missed due to lack of power. This was a preliminary study to investigate the range and repeatability of cough frequency measurement and assess its relationship with other markers of chronic cough. The results of this study indicate that cough frequency measurement shows promise as a method of validating the presence of chronic cough and monitoring the response to treatment and should encourage the further development of this technique.

Unexpectedly, our findings suggest a positive relationship between cough frequency and cough reflex sensitivity. This may have been a chance finding and larger studies are required. However, the relationship between these parameters is likely to be complex since a heightened cough reflex sensitivity is not always associated with chronic cough and many patients with chronic cough have normal cough sensitivity.\textsuperscript{5} More work is required since the cough frequency in healthy subjects with heightened cough reflex sensitivity is not known.

There are several potential uses for cough monitors such as the LCM. It can be used to validate the presence of cough, assess its frequency and identify patients with an altered perception of cough rather than increased frequency. It can be used to assess the response to treatment trials which form an integral part of the anatomical, diagnostic protocol widely used to investigate patients. Since cough can be a prominent feature of airway diseases such as asthma and COPD, cough monitors may be used to assess a wider range of disorders. Finally, cough monitors may have a role in monitoring paediatric asthma where other objective recordings such as peak expiratory flow may not be possible.

In conclusion, we have shown large differences in cough frequency between patients with chronic cough and healthy subjects and that daytime cough frequency relates to health status. Our preliminary findings should stimulate the development of more practical, automated detection systems and the use of cough monitoring in validation and monitoring of chronic cough in clinical practice.

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References