Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis

J A Smith, E C Owen, A M Jones, M E Dodd, A K Webb, A Woodcock


Pulmonary exacerbations are frequently used as an outcome measure in clinical trials of cystic fibrosis (CF). Exacerbations are defined based upon clinical criteria, usually an acute worsening in respiratory function and symptoms (such as a change in sputum production and an increased cough) which resolve with intensive treatment. Because of the difficulties in measuring cough, little is known about cough frequency in adults with cystic fibrosis (CF). This study aimed to determine (1) daytime and overnight cough rates in patients with CF at the beginning and end of a course of antibiotics for treatment of an exacerbation; (2) the relationship between cough frequencies and standard clinical measures of disease; and (3) the relationship between objective cough rates and the subjective assessment of cough.

Methods: Nineteen adult patients admitted with a pulmonary exacerbation performed daytime and overnight sound recordings on admission; 13 had repeat recordings prior to discharge. Coughs were manually quantified in cough seconds (time spent coughing). Patients subjectively scored their cough using a visual analogue scale (VAS) and numerical score. Lung function, C-reactive protein (CRP) levels, and sputum weights were recorded.

Results: Cough rates fell substantially with treatment; median fall in cough rate was 51.3% (IQR 32.3–77.5) (p<0.001) for daytime and 72.2% (28.6–90.1) (p = 0.049) for overnight. Multivariate regression analyses showed that forced expiratory volume in 1 second and CRP levels predicted overnight cough rates on admission. On discharge, sputum volume predicted daytime cough rates. Only the change in overnight VAS correlated with the change in objective cough rates.

Conclusions: The cough rate significantly decreases with treatment of a pulmonary exacerbation in adults with CF. Lung function, sputum volume, and CRP influences the cough rate, with the effects differing from day to night and between admission and discharge. Subjective reporting of a nocturnal cough may indicate a pulmonary exacerbation of CF in adults.
and low amplitude sounds) and to assist manual counting of the time spent coughing. Time spent coughing was defined as the numbers of seconds per hour that contained at least one explosive cough sound. Coughing induced by physiotherapy was excluded from the analyses. Each recording takes approximately 2.5–3 hours to process. We have previously validated this methodology by comparing coughs counted from digital sound recordings with those counted from video recordings and found excellent agreement between the two methods. To check reliability of the manual counting, 10 randomly selected tracks were recounted by a second trained observer. To examine the relationships between time spent coughing (cough seconds, cs) and cough epochs, the first 3 hours of each daytime recording was recounted in cough epochs. Cough epochs are defined as a period of coughing with less than 2 seconds interruption.

Sputum was collected during the day and night and weighed at the end of each recording period. Clinical assessment routinely includes sputum collection, spirometric tests, and measurement of CRP levels (normal <5 mg/l).

Patients were asked to score the severity of their cough subjectively by day and by night. Two methods of subjective assessment were used; a visual analogue scale (100 mm line marked “no cough” to “worst cough”) and a cough score chart with a range of scores from 0 to 5 (table 1).

### Statistical analysis

A power calculation to determine sample size could not be performed due to the lack of existing data on time spent coughing in CF; after consultation with a statistician it was decided to recruit 20 subjects. Both day and night cough data were positively skewed. For clarity, the median and interquartile ranges are reported for day and night, on admission and discharge. However, for the primary outcome (the comparison of time spent coughing before and after treatment) the log 10 transforms were used and means compared using a paired t-test (two sided).

For the secondary hypotheses, multivariate linear regression analyses were performed to examine the influence of FEV1, CRP, and sputum weight on cough frequency. Again data were log transformed for these analyses. Subjective measures of cough were also skewed but could not be improved by transformation and hence Spearman’s correlations were used to examine the relationships between subjective and objective measures of cough.

Statistical analysis was performed using SPSS Version 11.0 (SPSS Inc, Chicago, IL, USA) and Prism 4.0 (Graphpad Software Inc, San Diego, CA, USA).

### RESULTS

Twenty patients with CF and an exacerbation of their chest disease entered the study. The median age was 23 years (interquartile range (IQR) 19–30), nine were men, and the median body mass index was 19.6 kg/m² (IQR 18.2–22.3). After the study was completed, one patient was found to be a current smoker and so was excluded. Of the remaining 19 subjects, one patient performed recordings only on admission and withdrew from further study for personal reasons. Of the 74 recordings performed, five were technically faulty; hence, cough recording data were available for 19 subjects on admission and for 13 subjects prior to discharge. Each analysis was performed on the fullest data set available. The mean (SD) time between admission and discharge recordings was 8.0 (3.0) days. Agreement between manual cough counts for two trained observers was excellent with a mean difference of 0.25 cs between observers (95% limits of agreement –2.17 and 2.67).

#### Table 1 Cough symptom scores for daytime and night time

<table>
<thead>
<tr>
<th>Score</th>
<th>Daytime</th>
<th>Night time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No cough during the day</td>
<td>No cough during the night</td>
</tr>
<tr>
<td>1</td>
<td>Cough for one short period</td>
<td>Cough on waking only</td>
</tr>
<tr>
<td>2</td>
<td>Cough for more than two short periods</td>
<td>Wake once or early due to cough</td>
</tr>
<tr>
<td>3</td>
<td>Frequent coughing which did not interfere with usual daytime activities</td>
<td>Frequent waking due to coughs</td>
</tr>
<tr>
<td>4</td>
<td>Frequent coughing which did interfere with usual daytime activities</td>
<td>Frequent coughs most of the night</td>
</tr>
<tr>
<td>5</td>
<td>Distressing cough most of the day</td>
<td>Distressing cough most of the night</td>
</tr>
</tbody>
</table>

### Daytime and overnight cough during and after exacerbation

After treatment there was a significant fall in time spent coughing for both day and night recording periods, with a median fall in cough rate of 51.3% (IQR 32.3–77.5) for...
daytime and 72.2% (IQR 28.6–90.1) for overnight (fig 1, table 2). A paired t test of the log transformed cough rates showed the fall in cough rate to be statistically significant for daytime (p<0.001, mean difference 2.29-fold (95% CI 2.29 to 3.26)) and night time (p = 0.049, mean difference 2.51-fold (95% CI 1.02 to 6.31)). Two patients had an increase in the daytime cough rate and four had an increase in the nocturnal cough rate; however, the total cough rates (cumulative day and night) fell in all patients. These patients did not have a different clinical outcome to the remainder of the group.

Patients had a wide range of cough rates and there was a significant diurnal variation in cough rate on both study days (p<0.001 admission, p = 0.002 discharge; table 2).

The temporal change in cough seconds over each recording period is shown in fig 2. The median cough rate at each time point is higher and more variable on admission than at discharge during the day. Coughing virtually stops overnight. When log10 cough epochs are compared with log 10 cough seconds, there are significant linear relationships (admission r = 0.92, p<0.001; discharge r = 0.92, p<0.001). However, the length of cough epochs (to the nearest second) significantly reduced with treatment (median (IQR) 2 seconds (1–2) on admission; 1 second (1–1) on discharge, p = 0.009).

Statistical analysis (linear regression) did not find a significant difference between the relationships between cough seconds and cough epochs over the short period analysed.

### Relationships between coughs and clinical measures

There were improvements in lung function, a decrease in daytime sputum weight, and a decrease in CRP levels with treatment of the infective exacerbation (table 2). Multivariate regression analyses were performed to examine the predictive

#### Table 2 Median (IQR) cough frequencies and clinical parameters on admission and discharge

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Admission</th>
<th>Discharge</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% predicted)</td>
<td>41.8 (32–67.8)</td>
<td>56.1 (40.2–76.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>60.5 (54.2–73.6)</td>
<td>65.0 (58.2–75.3)</td>
<td>0.213</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>16 (1–31)</td>
<td>5 (1–13)</td>
<td>0.050</td>
</tr>
<tr>
<td>Cough rate (cs/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>21.2 (14.0–34.9)</td>
<td>9.0 (5.8–12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Night</td>
<td>4.8 (1.0–6.8)</td>
<td>1.5 (0.8–5.0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Sputum (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>7.1 (3.8–21.8)</td>
<td>2.8 (0.0–4.5)</td>
<td>0.041</td>
</tr>
<tr>
<td>Night</td>
<td>2.2 (0.0–5.3)</td>
<td>0.0 (0.0–4.5)</td>
<td>0.959</td>
</tr>
<tr>
<td>Cough score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>3.0 (2.0–3.0)</td>
<td>1.5 (1.0–2.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Night</td>
<td>1.0 (0.0–2.0)</td>
<td>1.0 (0.0–1.0)</td>
<td>0.216</td>
</tr>
<tr>
<td>Visual analogue scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>60 (43–73)</td>
<td>18 (12–53)</td>
<td>0.005</td>
</tr>
<tr>
<td>Night</td>
<td>20 (3–46)</td>
<td>7 (2–27)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CRP, C-reactive protein.

#### Table 3 Correlations between changes in subjective estimates of cough frequency (cough scores and visual analogue scale, VAS) and time spent coughing during the day and night

<table>
<thead>
<tr>
<th>Change in day cough rate</th>
<th>Change in night cough rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in cough score</td>
<td>r=0.34, p=0.204</td>
</tr>
<tr>
<td>Change in VAS</td>
<td>r=0.19, p=0.510</td>
</tr>
</tbody>
</table>

Figure 2 Temporal distribution of coughs during daytime and overnight on admission and before discharge (median time spent coughing per 30 minute period).
value of FEV$_1$, sputum weight, and CRP for time spent coughing during the day and night on admission and on discharge. Variables were again log$_{10}$ transformed for analysis to allow the use of parametric statistics. FEV$_1$ (B = −0.321 (95% CI −0.459 to −0.184), p < 0.001) and CRP (B = 0.006 (95% CI 0.001 to 0.012), p = 0.026) were significant predictors of overnight cough frequency on admission. Together they accounted for 74.4% of the variance significant predictors of overnight cough frequency on admission. The only significant correlation for subjective measures in this study occurred between changes in time spent coughing and, in addition, was limited to daytime cough rate. A similar effect would be difficult to identify overnight as the majority of overnight sputum volumes fell to zero after treatment.

Although adults with CF cough much more during the day than at night, they are poor at subjectively estimating the severity of their daytime cough. Subjects may become so accustomed to high daytime cough rates that they do not perceive coughing as interfering with their daily activities and are not able to estimate changes well. It is also possible that, when scoring cough severity, subjects take into account other factors not measured in this study such as intensity of the cough. Visual analogue scales are clearly superior to cough scores for subjective estimation of changes in cough frequency in adults with CF.

Discrepancies between subjective and objective assessments of cough frequency have been reported in other conditions where cough is a predominant symptom. In a group of adults with cough variant asthma there was no relationship between objective and subjective measures. Poor agreement for reporting of nocturnal cough compared with tape recordings was also found in a group of children with asthma. However, adults with seasonal allergic rhinitis had a significant moderate correlation between objective and subjective cough frequency. In children with chronic recurrent cough there was an excellent correlation between objective cough frequency and diary card visual analogue scales scored by the children and their parents. The usefulness of subjective measures of cough seems to vary with subject groups and the tools employed.

The only significant correlation for subjective measures in this study occurred between changes in time spent coughing overnight and visual analogue scales overnight. We speculate that sleep disruption may be the explanation for this. As subjects are most aware of overnight coughing, clinicians should pay particular attention to reporting of worsening overnight coughing as an indicator of an exacerbation.

Our findings of a substantial fall in the cough rate in adults treated for an exacerbation of CF are in contrast to a similar study in children with CF. In that study the cough was identified from sound and EMG signals and cough epochs (that is, bursts of coughing) were counted. In children with CF cough and sputum production may be less responsive to treatment. We found that the length of cough epochs significantly shortened from admission to discharge. A device counting only epochs could not appreciate this change and hence cough epochs may be an inferior method for quantifying cough. Measuring epoch frequency may underestimate the reduction in coughing with treatment in CF. However, we could not demonstrate a significant difference between the measures analysed over a 3 hour period.

The main limitation of this study is that available digital recording equipment does not currently allow continuous 24 hour sound recordings of adequate quality. Rapid improvements in storage capacity and battery life should make this possible soon. Manual counting to quantify cough
is time consuming and hence studies are restricted to relatively small numbers of subjects; however, algorithms to identify cough automatically are showing promise.

In conclusion, we have used an accurate although labour intensive method for objectively quantifying cough in adults with CF. We were able to quantify the change in cough frequency associated with treatment of an acute exacerbation. Cough rates during an exacerbation may be more influenced by airway inflammation and FEV₁ than sputum volume but the relationships may be reversed after treatment. An accurate 24 hour automated cough monitor would greatly improve the evaluation of the burden of cough in all respiratory diseases.

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Authors’ affiliations

J A Smith, E C Owen, A Woodcock, North West Lung Centre, South Manchester University Hospitals Trust, Manchester, UK
A M Jones, M E Dodd, A K Webb, Manchester Adult Cystic Fibrosis Centre, South Manchester University Hospitals Trust, Manchester, UK
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