SEX DIFFERENCES AND PREDICTORS OF OBJECTIVE COUGH FREQUENCY IN CHRONIC COUGH

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ABSTRACT (250 words)

Background: Women are consistently over-represented in specialist cough clinics and known to have a more sensitive cough reflex than men. Whether female sex and other patient characteristics are associated with higher cough rates is not known. We aimed to determine the predictors of objective cough frequency in chronic cough patients presenting to a tertiary referral clinic.

Methods: 100 subjects [mean age 55.8yrs (SD±11.0), 65 female, median cough duration 4yrs (IQR 2.0-10.0yrs)] with unexplained chronic cough, completed flow-volume loops (FEV$_1$ 103% predicted (SD±15.2), FEF$_{50}$; 68.8% predicted, SD±24.1), methacholine challenge (42 % positive), citric acid cough reflex sensitivity [C5; 0.12M (IQR 0.06-0.50M)] and the Leicester Cough Questionnaire. 24-hour ambulatory cough monitoring was performed in 86 subjects; manually counted coughs were quantified as the number of explosive cough sounds per hour.

Results: Females coughed significantly more than males [geometric mean 16.6 coughs/hr (95%CI 13.1-21.0) versus 9.4coughs/hr (95% CI 6.4-13.9), p=0.01)]. The cough reflex was also more sensitive in females than males (median logC5 -0.9M versus -0.6M, p=0.002) but cough related quality of life was similar (females 12.0 (±3.6) versus males 12.2 (±3.2), p=0.76). Linear regression analysis showed 38.6% of the variation in cough rate was predicted by sex (p=0.01), logC5 (p= <0.001) and age (p=0.002) but not lung function or bronchial hyper-reactivity.

Conclusions: Ambulatory objective cough monitoring provides novel insights into factors modulating chronic cough. These findings suggest that effects of sex and age must be taken into account in the study of cough and when designing clinical trials testing novel anti-tussive agents.
INTRODUCTION

Cough is a common and troublesome symptom with chronic cough estimated to affect between 14 and 23% of the adult population. There is evidence that the prevalence of chronic cough may be greater in adult females than males. For example, a large international population survey found that reporting of nocturnal and non-productive cough was related to female sex and a UK survey suggested daily coughing was more commonly reported by women than men. Furthermore in specialist clinics caring for patients with chronic cough, female patients are consistently over-represented, particularly amongst those with idiopathic cough. This apparent female preponderance may be due to a true increased prevalence of chronic cough but it has been speculated that behavioural differences could account for the discrepancy, with females being more likely to access healthcare. Females may be driven to seek medical advice by more troublesome complications of coughing such as stress urinary incontinence and the associated impact on quality of life.

In addition to increased reporting of cough, the cough reflex is more sensitive to tussive agents in females. This effect is seen both in health and chronic cough subjects but the underlying mechanisms are not understood. More importantly, there is no data assessing whether women experience more severe coughing than men i.e. higher objective cough frequencies, in either health or those suffering from chronic coughing.

We tested the hypothesis that women with chronic cough have greater cough frequencies than men. We have studied patients with chronic cough attending a specialist cough clinic, to identify and quantify factors including sex which predict objective cough frequency determined by 24-hour ambulatory cough monitoring.
METHODS

Subjects
We studied consecutive patients complaining of chronic cough (>8 weeks duration) attending a tertiary specialist cough clinic (North West Lung Centre, University Hospital of South Manchester, UK). Current and ex-smokers of less than 6 months, patients taking ACE inhibitors and opiates, and patients with significant co-morbidities were excluded (e.g. diabetes, heart failure, chronic obstructive pulmonary disease). Ethical approval was granted by South Manchester Local Research Ethics Committee and written informed consent was completed by all subjects. The following tests were performed:

Cough Assessments

Ambulatory Cough Monitoring: 24-hour ambulatory cough sound recordings were performed using a custom built recording device with an air microphone and chest wall sensor (Vitalojak, Vitalograph, UK). Recordings were manually counted by a single trained observer and expressed as the number of explosive cough sounds per hour\(^2\). Subjects were encouraged to continue their normal routine throughout the recording period and noted the time of going to bed.

Cough Reflex Sensitivity: Citric acid challenge was used to assess cough reflex sensitivity\(^3\). Doubling doses (from 0.03M to 4.0M Citric Acid, Stockport Pharmaceuticals UK) were administered as single breath inhalations (KoKo dosimeter, Pds Instrumentation, USA) with three placebo inhalations of normal saline randomly interspersed in a double blind manner. Following each inhalation, the number of coughs in the subsequent minute was counted by an experienced observer and recorded. The challenge was terminated once the citric acid induced 5 or more coughs and the concentrations provoking 2 and 5 coughs were recorded (C2 and C5).
**Leicester Cough Questionnaire (LCQ)**: Cough related quality of life was measured using the LCQ; a validated questionnaire, comprising 19 questions in 3 domains (physical, psychological and social). Possible total scores range from 3-21 and domain scores from 1-7, with higher scores representing better quality of life.

**Pulmonary Function Tests**

*Flow Volume Loops*: Three technically acceptable and reproducible forced expiratory flow-volume loops manoeuvres were performed to ATS/ERS standards (Jaeger Masterscreen, Erich Jaeger, Germany). The highest values recorded were used for analysis.

*Bronchial Hyper-Reactivity Testing (BHR)*: BHR testing was performed using Methacholine Chloride solutions (Stockport Pharmaceuticals, UK) and the modified Yan method. Doubling doses (to a maximum of 5.96mg/ml) were delivered by dosimeter (KoKo dosimeter, Pds Instrumentation, USA) in order to achieve a provocative dose (PD_{20}); expressed as a 20% decrease in FEV\(_1\) from baseline.

**Diagnosis**

Final diagnoses were achieved based upon a combination of investigations and treatment trials as recommended by the British Thoracic Society Guidelines.

**Statistical Analysis**

Analyses were performed using SPSS version 13.0 (SPSS Inc, Chigago, Ill) and the standard 5% level was used for statistical significance throughout. Cough rates and cough reflex sensitivity data (C5) were log transformed to allow for parametric analysis where appropriate. Comparisons between male and female subjects were performed using unpaired t-test or Mann-Whitney U test. Relationships between objective cough frequency and continuous variables were assessed by correlation. To explore whether sex differences in objective cough frequency where a consequence of sex differences in other parameters (e.g. cough reflex sensitivity) linear regression analyses were performed. Variables found to significantly
influence cough frequency in the univariate analyses were included as the independent variables, and all models were adjusted for any effect of age.

Based on previous data in patients with chronic cough\textsuperscript{25} with a geometric mean 24-hour cough frequency of 12.9 coughs/hour (95\% CI 10.1-16.1), a sample size of 100 subjects (assuming ratio of males to females of 1:2) would have 90\% power to detect a 15\% difference in cough frequency between sexes.
RESULTS

Subjects

100 subjects [mean age 55.8 years (SD± 11.0), 65 female, and median cough duration 4.0 years (IQR 2.0-10.0)] with chronic cough were studied and of these, 86 subjects agreed to and completed 24-hour cough monitoring. Comparison of demographics and pulmonary physiology for male and female patients are shown in table 1. Male and female subjects had similar characteristics. All subjects achieved satisfactory FEV1 measurements, but 2 subjects were unable to complete full flow volume loops due to excess coughing. There was evidence of reduced FEF50 values in both females and males, which may represent increased airflow resistance in smaller airways. Positive methacholine challenges were found in 38 (44.2%) of patients and 23 (26.7%) had a previous diagnosis of asthma.

Table 1. Characteristics of male and female subjects with chronic cough undergoing ambulatory cough recording.

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=59</td>
<td>n=27</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55.3yrs ±10.9</td>
<td>58.3yrs ±9.4</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI</td>
<td>28.5 ±5.2</td>
<td>27.0 ±2.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Reported cough history</td>
<td>3 yrs (IQR 2-10)</td>
<td>3yrs (IQR 1.5-10)</td>
<td>0.68†</td>
</tr>
<tr>
<td>FEV1 percent predicted</td>
<td>103.3% ±15.3</td>
<td>103.4% ±16.5</td>
<td>0.99</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>76.9 ±7.8</td>
<td>74.1 ±6.9</td>
<td>0.11</td>
</tr>
<tr>
<td>FEF50 percent predicted</td>
<td>66.9% ±23.4</td>
<td>71.6% ±24.6</td>
<td>0.40</td>
</tr>
<tr>
<td>Bronchial hyper-reactivity (PD20 &lt;5.96mg/dl)</td>
<td>29/55 (49.2%)</td>
<td>9/27 (33%)</td>
<td>0.17*</td>
</tr>
</tbody>
</table>

Comparisons made by independent t-test except for those marked *Chi-squared test, †Mann-Whitney test.

Following collection of these data, subjects underwent further investigations and treatment trials to establish the underlying causes of their cough. A diagnosis was assigned if subjects
reported a partial or good response to specific treatment, diagnoses were gastro-oesophageal reflux disease (n=45), rhino-sinusitis (n=27), asthma (n=16), eosinophilic bronchitis (n=6), bronchiectasis (n=6) and idiopathic (n=25). Note some subjects had more than one diagnosis and in 25 subjects either the cough was resistant to treatment of identified conditions or no cause could be found.

**Ambulatory Cough Monitoring**

The geometric mean 24-hour cough rate was 13.9 coughs/hr (95%CI 11.3-17.0). Females coughed statistically significantly more than males, figure 1. Female cough frequency was not significantly higher during the daytime (at the 5% level, p=0.06), but was statistically significantly higher during the night when compared to males, figure 2 and table 2.

Patients with idiopathic cough [15 (60%) female, 10 (40%) male] had similar objective cough frequencies to patients with ‘explained’ cough (24-hour cough frequency p=0.75, day p=0.90, night p=0.57).

**Cough Reflex Sensitivity**

2 subjects coughed on inhalation of normal saline (placebo) and so C5 could not be measured. For the remaining 98 patients, the median C5 was 0.12M (IQR 0.06- 0.50) and C2 was 0.06M (IQR 0.03-0.06). Female subjects had a statistically significantly more sensitive cough reflex than males for C5, a difference of 1 doubling dose (figure 3 and table 2). For the C2 endpoint the difference did not reach significant at the 5% level.

**Leicester Cough Questionnaire (LCQ)**

The total LCQ score was 12.1(±3.4) and there were no statistically significant differences between cough related quality of life for females and males, (online supplement figure 5). Of the three domains of the scale, none showed a statistically significant sex difference (online
supplement figure 6). However the p value for the physical domain was low suggesting a possible effect with males tending to score more highly (better quality of life) than females.

Table 2 Measures of cough in female and male subjects

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cough Frequency (coughs/hr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=86</td>
<td>24-hour*</td>
<td>16.6 (95%CI 13.1-21.0)</td>
<td>9.4  (95% CI 6.4-13.9)</td>
</tr>
<tr>
<td></td>
<td>Day†</td>
<td>23.7 (IQR 12.4-37.5)</td>
<td>15.6 (IQR 11.1-24.3)</td>
</tr>
<tr>
<td></td>
<td>Night†</td>
<td>4.5 (IQR 2.1-12.9)</td>
<td>0.8 (IQR 0.1-4.5)</td>
</tr>
<tr>
<td></td>
<td>Log10C5†</td>
<td>-0.9M (IQR -1.2 to -0.6)</td>
<td>-0.6M (IQR -0.9 to 0.0)</td>
</tr>
<tr>
<td></td>
<td>Log10C2†</td>
<td>-1.12M (IQR -1.5 to -0.76)</td>
<td>-0.9M (IQR -1.22 to -0.6)</td>
</tr>
<tr>
<td><strong>Cough Reflex Sensitivity (Molar)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=98</td>
<td>Total‡</td>
<td>12.0 (±3.6)</td>
<td>12.2 (±3.2)</td>
</tr>
<tr>
<td></td>
<td>Physical‡</td>
<td>4.2(±1.1)</td>
<td>4.6(±1.0)</td>
</tr>
<tr>
<td></td>
<td>Social‡</td>
<td>3.9(±1.4)</td>
<td>3.8(±1.3)</td>
</tr>
<tr>
<td></td>
<td>Psychological‡</td>
<td>3.9(±1.5)</td>
<td>3.8(±1.2)</td>
</tr>
</tbody>
</table>

Data expressed as *geometric mean and 95% confidence intervals, †median and interquartile range, and ‡mean and standard deviation

**Predictors of Cough Frequency**

Cough rate negatively correlated with cough reflex sensitivity (logC5, r=-0.47, p<0.001; logC2, r=-0.23, p=0.05), figure 4. There was a weak positive correlation between age and cough frequency (r=0.20, p=0.07) which did not quite reach statistical significant, (online supplement figure 7). However, cough frequency was not related to the reported cough history (r=-0.03 p=0.78), lung function parameters (FEV₁ r=0.02 p=0.83, FEF₅₀ r=-0.12 p=0.29) or the level of BHR (PD₂₀ methacholine r=-0.22 p=0.19). Subjects with a positive rather than negative methacholine challenge did not cough more by day [median 18.4 (IQR 9.3-33.6) versus median 20.9 (IQR 12.7-34.5) p=0.49] or by night [median 4.4 (IQR 1.9-
10.4) versus 2.7 (IQR 0.3- 7.6), p=0.18] and ex-smokers did not cough more than non-smokers (p=0.54).

The interactions between predictors of objective cough frequency were assessed for 24 hour and night cough frequency, as significant sex differences were found for these parameters. Cough frequency (24-hour) was independently predicted by sex (p=0.01), age [(B= 0.01 (95%CI 0.004 to 0.018), p=0.002] and cough reflex sensitivity logC5 [B= -0.38 (95%CI -0.52 to -0.24), p<0.001]. These variables accounted for 38.6% of the variance in 24-hour cough frequency. Figure 4 shows how the relationships between cough reflex sensitivity and cough frequency differ between males and females. For the 24-hour monitoring period, in those subjects with the most sensitive cough reflexes, males and females have similar cough frequencies however in those subjects with least sensitive cough reflexes, females cough statistically significantly more than males (Figure 4A, note cough frequency is plotted on a logarithmic scale).

Night cough was statistically significantly predicted by sex (p<0.001), age [B=0.014 (95%CI 0.007 to 0.022), p=0.004] and logC5 [B=-0.22 (95%CI -0.37 to -0.07),p<0.001], explaining 36.4% of the variance. Overnight the slopes of the relationships between cough reflex sensitivity and cough frequency are very similar but for females the relationship is shifted towards greater cough frequencies for subjects with similar cough reflex sensitivities, regardless of the level (Figure 4B).
DISCUSSION

This study demonstrates for the first time, that female patients presenting to a specialist cough clinic have significantly higher objective cough rates than the male patients, particularly overnight. This observation along with the effect of age on cough frequency, need to be taken into account when studying cough frequency and designing clinical trials testing anti-tussive drugs. The greater cough rate experienced by women with chronic cough may explain their over-representation in specialist clinics, in addition to differences in behaviour or the impact of coughing on quality of life, although in this study using the LCQ, there were no sex differences in cough related quality of life.

The mechanisms underlying these and previous sex differences observed in chronic cough are uncertain. Consistent with previous reports, we have found cough reflex sensitivity to citric acid was heightened in women with chronic cough and moderately correlated with cough counts. Observational studies have suggested that sex hormones may modulate cough reflex sensitivity. The heightened cough reflex sensitivity in female adults compared to males has not been found in pre-pubertal children. Furthermore an additional enhancement of cough reflex sensitivity occurs in healthy post-menopausal women. In subjects who have developed a chronic cough, hormonal effects may be exaggerated and could operate via effects on airway inflammatory cells and/or directly on airway nerves. Sex differences in nociceptive transmission and neuronal sensitisation have been described in experimental pain studies, with evidence suggesting enhanced central sensitisation in females compared to males.

It could be argued that the sex differences in cough frequency observed in this study are simply a reflection of the differences in cough reflex sensitivity. To examine this possibility we performed linear regression analyses. Sex and cough reflex sensitivity independently predicted cough rates, suggesting that the degree of cough reflex hypersensitivity is not the
sole explanation for the greater rates of coughing in women. It can be clearly seen in figure 4B that overnight (where the main difference in cough frequency was apparent) women had consistently higher cough frequency than men for any given degree of cough reflex sensitivity.

Objective cough rates dramatically fall in a wide range of respiratory conditions overnight. It is generally believed that sleep inhibits coughing, with nocturnal cough occurring predominantly in periods of arousal but only one study in COPD has objectively demonstrated this. Although it is possible that females with chronic cough experience a greater number of arousals leading to greater nocturnal cough rates, this would be contrary to the objective data in healthy women who have better sleep quality than age-matched men. Perhaps the mechanisms responsible for cough inhibition overnight are less effective in females compared to males.

The finding that older subjects with chronic cough had higher cough frequency than younger subjects is counter intuitive. Though it might be expected that respiratory reflexes would deteriorate with age (leading to lower cough rates), previous studies have suggested that cough reflex sensitivity remains stable. However, the relationship between cough frequency and age was independent of the cough reflex sensitivity and also cough duration. We speculate that deficits in inhibitory mechanisms could also explain this phenomenon similar to the deterioration seen in endogenous inhibitory pain control mechanisms which starts in middle age.

In contrast to previous data generated using the Cough Quality of Life Questionnaire (CQLQ), with the LCQ we were unable to demonstrate a significantly poorer cough-related quality of life for females compared to males, despite almost double the objective cough frequency. This finding is surprising as across a wide range of chronic illness women tend to report worse quality of life compared to men. Whilst it is possible that women
complain less than men about the impact of cough for a given objective cough rate, differences between the items included in the LCQ and CQLQ may provide a more plausible explanation. On the CQLQ women scored more highly in the physical, extreme physical complaints and psychosocial domains. Many of the items describing physical consequences of coughing (e.g. retching, vomiting, headaches and dizziness) are not included in the LCQ, and in particular urinary incontinence which showed the greatest disparity between men and women, is omitted. The LCQ was chosen in this study because in our experience patients in the UK had some difficulty with the language used in some of the questions in the CQLQ. However this data suggests the CQLQ has a distinct advantage over the LCQ in it’s ability to capture sex differences in chronic cough.

Studies in cough will be facilitated by the introduction of automated cough monitors41. Current devices still require laborious manual counting, until improved cough detection algorithms are fully validated. In addition, no cough monitor yet allows any measure of cough intensity. Cough intensity may be as important as cough frequency in relating cough to quality of life and there may be sex differences yet to be explored.

In conclusion, ambulatory objective cough monitoring provides novel insights into the factors modulating chronic cough, forcing us to generate new hypotheses about the mechanisms which may underlie these observations. Furthermore these findings emphasise that effects of sex and age must be taken into account in the study of cough and when designing clinical trials testing novel anti-tussive agents.
COMPETING INTERESTS

KM, AW and JAS are inventors on a patent describing novel methods for cough detection and monitoring, filed by the University Hospital of South Manchester. KM, AW and JAS have an industrial collaboration and the University Hospital of South Manchester has a license agreement with Vitalograph Ltd to develop a commercial cough monitoring system (Vitalojak).

FUNDING

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FIGURE LEGENDS

Figure 1. The effect of sex on 24-hour cough frequency; note logarithmic scale, mean and 95% confidence interval shown

Figure 2. Day and night objective cough rates comparing females and males (median and interquartile ranges)

Figure 3. Box plot showing the effect of sex on cough reflex sensitivity (C5); error bars indicate range, median and 25th and 75th percentiles.

Figure 4 Relationships between cough reflex sensitivity (C5) and cough frequency in men and women for 24-hours and overnight. Regression lines represent the relationships for men and women. Note that over 24-hours the difference in cough rates occurs at higher cough reflex sensitivities whereas overnight women cough more than men for all levels of cough reflex sensitivity.
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ONLINE SUPPLEMENT
ONLINE SUPPLEMENT FIGURE LEGENDS

Figure 5 LCQ total scores for females and males; high score represents good quality of life

Figure 6 Physical sub-domain of LCQ scores for females and males; high score represents good quality of life

Figure 7 Correlation between age and cough frequency
Cough Frequency (coughs/h)

Day

- Female
- Male

\[ p=0.06 \]

Night

- Female
- Male

\[ p<0.001 \]
Log10 24-hour cough rate (explosive cough sounds/hr)

age

r=0.20 p=0.07