Respiratory symptoms and peripheral airways disease in a cross-sectional study on a random population sample

Jan Yngve Olofson, Birgitta Houltz, Maria Nilsson Tengelin, Björn Bake

ABSTRACT

Objectives: Respiratory symptoms are associated with spirometry results but more strongly with smoking history, suggesting that alterations in the lung other than those revealed by spirometry contribute to cause symptoms. Smoking may cause obstruction of peripheral airways that is poorly detected by spirometry. The slope of phase III of the single-breath nitrogen (N₂) test detects smoking-induced alterations in smokers before spirometry is impaired. The aim of the present investigation was to study the association between respiratory symptoms and the slope of phase III adjusting for spirometry results and smoking history.

Design: Single-centre retrospective cross-sectional study.

Setting: University hospital in Gothenburg, Sweden.

Participants: A random population sample of 430 elderly men.

Methods: The presence of seven different respiratory symptoms were analysed by a multiple logistic regression model in relation to spirometry results, smoking history (pack-years) and the slope of phase III in a population sample of 430 elderly men, age span 50–67 years. Furthermore, smoking normalised values of the slope of phase III were calculated and differences between subjects reporting/not reporting symptoms were tested.

Results: The presence of some cough symptoms was significantly associated with a steep slope of phase III also when adjusting for spirometry results and smoking history. Furthermore, smoking normalised slope of phase III was significantly steeper among subjects with cough symptoms compared to those without cough symptoms.

Conclusions: Cough symptoms may be an effect of abnormalities in peripheral airways at least among elderly men.

INTRODUCTION

The ability of respiratory symptoms to predict chronic obstructive pulmonary disease (COPD), that is, spirometric airflow limitation, has been found to vary greatly both in random and in non-random population studies, as exemplified by various reported sensitivities (54–92%), specificities (19–89%), positive predictive values (30–92%) and negative predictive values (75–96%). The general impression is, however, that respiratory symptoms are rather poor predictors of airflow limitation/COPD. Thus, respiratory symptoms appear to be only weakly related to low spirometric results.

Smoking history has been shown to be a stronger predictor of COPD than respiratory symptoms, suggesting that smoking-induced airway alterations cause respiratory symptoms without detectable airway obstruction by spirometry. The pathological processes in smokers and COPD begin in the peripheral airways and spirometry is insensitive in detecting early obstruction in the peripheral airways. Therefore, it appears conceivable that the obstruction of peripheral airways contributes to the origination of respiratory symptoms.
Respiratory symptoms and peripheral airways disease

The slope of phase III of the single-breath nitrogen (N₂) test (slope of phase III) is more sensitive than spirometry in detecting obstruction of peripheral airways in smokers. Respiratory symptoms in smokers may therefore be associated with an abnormal slope of phase III also when spirometry is within normal limits. Viegi et al. found that the slope of phase III was significantly steeper among male smokers with respiratory symptoms than among those without symptoms. However, cigarette-smoking-associated large airway obstruction and possible effects of smoking other than small airway obstruction were not adjusted for.

The aim of the present analysis was to challenge the hypothesis that obstruction of peripheral airways is related to respiratory symptoms independently of spirometric results and smoking history. This was tested by analysing the relationship between reported respiratory symptoms and the slope of phase III when spirometry results and smoking history are adjusted for.

MATERIAL AND METHODS

The present analysis is based on materials obtained from population studies performed in 1973 and 1980. The study sample in 1973 consisted of 387 men born in 1913 and 220 men born in 1923, living in Gothenburg, Sweden. They were randomly selected from the national register comprising all residents of Sweden. In 1980, 305 of the men born in 1913 and 157 of the men born in 1923 attended for reinvestigation. On both occasions the examinations were performed during the same season of the year. Subjects lacking data on FEV₁ (forced expiratory volume in 1 s), VC (vital capacities), slope of phase III and smoking habits at both occasions were excluded from the study sample. Information on respiratory symptoms on both occasions of at least 10/12 questions should be available at both occasions otherwise the subjects were excluded. No subjects were excluded due to known disease. Accordingly, 30 subjects were excluded and a total of 430 men with data on respiratory symptoms (12 symptoms, see table 2), smoking habits, spirometry and the slope of phase III of the single-breath N₂ test in both investigations, constitute the present material.

All lung function measurements were performed by well-trained technicians and with the subjects in the sitting position and a nose clip applied. Spirometry was performed with a servospirometer (Model 150A, Med-Science Electronics, Ohio, USA) connected to a rapid UV-light recorder (Ultralette, ABEM, 5651, Stockholm, Sweden). Volumes and flows were corrected to body temperature pressure saturated (BTPS) condition. Calibrations of the equipment were performed regularly. Two satisfactory slow VC, one inspired and one expired, and three satisfactory forced VC measurements were performed by each subject. The largest VC and FEV₁ were used in the analyses and FEV₁/VC was calculated. VC and FEV₁ were expressed in per cent of predicted normal (%pred) using reference values according to Hedenström et al.

The single-breath N₂ test was performed as described by Oxhøj et al. At least two tests with satisfactory tracings were attempted for each subject with an interval between the tests of a minimum of 5 min. Tests with a difference of more than 10% between inspired and expired VC, were excluded. All tracings were coded and examined by one investigator, unaware of the identification and characteristics of the subjects. The slope of phase III was calculated as the increase of the nitrogen concentration from the point where 825 ml (BTPS) had been expired from total lung capacity until the beginning of phase IV (closing point), divided by the corresponding expired volume. The slope of phase III was calculated as per cent nitrogen per litre (BTPS) and expressed in %pred, using the reference values according to Sixt et al. All lung function data, that is, the slope of phase III, VC, FEV₁ and FEV₁/VC are presented as the calculated mean value of the values obtained from the two investigations.

Respiratory symptoms were assessed using a translation of the questionnaire approved by the British Medical Research Council Committee on the aetiology of chronic bronchitis. A total of 12 questions on the symptoms: cough without or with expectoration, wheeze or squeaks and dyspnoea were evaluated (table 2). For each of the 12 symptoms, only subjects with the presence of that specific symptom on both investigations, or the absence of that symptom at both occasions, were included in the analysis and evaluated in relation to smoking habits, the slope of phase III of the single-breath N₂ test and spirometry.

Smoking habits are estimated according to the classification reported in the second investigation. The subjects are characterised as follows: as non-smokers if they were never-smokers or had smoked less than 1 g tobacco a day for 6 months, exsmokers if they had stopped smoking 6 months or more before the second investigation, and considered smokers if they were smokers on the second occasion, had smoked at least 1 g tobacco a day for more than 6 months or had stopped smoking within the last 6 months. In the original database, the amount of tobacco consumed was registered in grams (g) per day (d) within given ranges, for example, 1–4 g/d, 5–15 g/d, etc. In the present estimation, we simplified the tobacco consumption accordingly; 1–4 g/d=3 g/d, 5–14 g/d=10 g/d, 15–24 g/d=20 g/d and ≥25 g/d=25 g/d. One gram of tobacco is considered equivalent to one cigarette. On the basis of these approximations, the tobacco consumption was calculated in terms of pack-years. The mean consumption between the two investigations is used in the present analysis.

Data analysis

Statistica 7.0 (Statsoft, Inc, Tulsa, OK, USA) was used for the statistical analyses and a p value ≤0.05 was considered statistically significant in all analyses performed.
In a multivariate logistic regression model of presence/absence of a given symptom, we included as independent variables the slope of phase III (%pred), FEV₁ (%pred), FEV₁/VC and pack-years. As the slope of phase III is highly right-skewed log-transformed values were used.

To further challenge the association between symptoms and the slope of phase III, smoking normalised values were calculated. Thus, the slope of phase III expressed in per cent of predicted normal values were regressed against smoking category and pack-years in the present material (n=430) and smoking normalised predicted values were calculated. Observed values were then expressed as a percentage of the smoking normalised predicted values. The resulting average smoking normalised values were close to 100% for smokers as well as for non-smokers.

The ability of symptoms to predict an abnormal slope of phase III was also tested. Only smokers ≥20 pack-years were included as there were relatively few subjects among light smokers and exsmokers with symptoms (see below). The limit 20 pack-years lie in between the median and the mean of tobacco consumption among smokers and exsmokers in the present material. Diagnostic characteristics of the relevant symptoms were calculated in terms of sensitivity, specificity, positive and negative predictive values and the likelihood ratio, and based on cut-offs defined by the 95th or 5th percentile of the predicted normal values among non-smokers without symptoms in the present material. The corresponding prediction of an abnormal FEV₁/VC was included for comparison.

**RESULTS**

General characteristics of the study population are presented in table 1. Lung function deteriorates with smoking as expected, and the slope of phase III of the single-breath N₂ test is increased in smokers as well as in smoking as expected, and the slope of phase III was also tested. Only smokers ≥20 pack-years were included as there were relatively few subjects among light smokers and exsmokers with symptoms (see below). The limit 20 pack-years lie in between the median and the mean of tobacco consumption among smokers and exsmokers in the present material. Diagnostic characteristics of the relevant symptoms were calculated in terms of sensitivity, specificity, positive and negative predictive values and the likelihood ratio, and based on cut-offs defined by the 95th or 5th percentile of the predicted normal values among non-smokers without symptoms in the present material. The corresponding prediction of an abnormal FEV₁/VC was included for comparison.

Diagnostic characteristics are presented in table 5. Pack-years were strongly associated with all the symptoms. The slope of phase III was significantly related to two of the cough symptoms whereas FEV₁ was associated with the wheeze and dyspnoea symptoms and FEV₁/VC to one cough symptom.

Table 4 gives smoking normalised values of the slope of phase III in relation to the cough symptoms being associated with the slope of phase III among exsmokers and smokers. The slope of phase III is significantly steeper among subjects reporting symptoms also after adjusting for smoking history. Diagnostic characteristics are presented in table 5. Cut-off values for the slope of phase III and the FEV₁/VC ratio were 147% predicted normal and 0.65,
Table 2  Number of subjects, and the corresponding percentage, in relation to the presence of symptoms

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers</th>
<th></th>
<th>Ex-smokers</th>
<th></th>
<th>Smokers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No symptoms</td>
<td>Symptoms</td>
<td>Missing</td>
<td>Percentage with symptoms</td>
<td>No symptoms</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Cough usually in the morning during winter</td>
<td>85</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>149</td>
<td>9</td>
</tr>
<tr>
<td>Cough usually day or night during winter</td>
<td>88</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>145</td>
<td>4</td>
</tr>
<tr>
<td>Cough most days at least 3 months a year or more during winter</td>
<td>88</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>147</td>
<td>6</td>
</tr>
<tr>
<td>Cough and expectoration usually in the morning</td>
<td>85</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>136</td>
<td>11</td>
</tr>
<tr>
<td>Cough and expectoration usually day or night in winter</td>
<td>88</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>143</td>
<td>3</td>
</tr>
<tr>
<td>Cough and expectoration most days 3 months a year or more</td>
<td>90</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>148</td>
<td>8</td>
</tr>
<tr>
<td>Wheeze or squeaks anytime</td>
<td>71</td>
<td>9</td>
<td>16</td>
<td>11</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>Wheeze or squeaks anytime connected with a common cold</td>
<td>80</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>127</td>
<td>17</td>
</tr>
<tr>
<td>Wheeze or squeaks anytime unconnected with a common cold</td>
<td>92</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>147</td>
<td>6</td>
</tr>
<tr>
<td>Wheeze or squeaks most days a year</td>
<td>94</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>170</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnoea when walking fast on the level or walking up an incline</td>
<td>82</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>118</td>
<td>15</td>
</tr>
<tr>
<td>Dyspnoea when walking on the level at ordinary pace</td>
<td>92</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>164</td>
<td>4</td>
</tr>
</tbody>
</table>

Subjects with missing data are excluded from the percentage calculation.
respectively. The sensitivities of the cough symptoms were low but the specificities were relatively high to identify an abnormal/normal slope of phase III. However, ‘cough usually in the morning during winter’ predicts an abnormal slope of phase III with 92% probability among smokers ≥20 pack-years and it is about 5 times more likely that someone reporting this symptom has an abnormal slope of phase III compared to someone not reporting this symptom.

Regarding identification of an abnormal FEV₁/VC ratio the sensitivities were rather similar to that of an abnormal slope of phase III but the specificities and resulting probabilities and likelihood ratios were lower.

**DISCUSSION**

The present study shows that: (1) some cough symptoms are significantly associated with the slope of phase III also after allowing for spirometry results and smoking (pack-years); (2) wheeze and dyspnoea are similarly significantly associated with FEV₁; (3) smoking normalised slope of phase III is significantly steeper among men reporting respiratory symptoms; (4) some cough symptoms predict an abnormal slope of phase III with 79–92% probability among smokers (≥20 pack-years).

The present material was obtained during 1973 and 1980 in a random population study in Gothenburg, Sweden, of men born in 1913 and 1923. The respiratory symptoms were, however, not analysed at the time. Although the material is between 32 and 39 years old there is no apparent reason to question the contemporaneity, as the measurements of lung function would meet modern standards and the questions would be phrased similarly today. Only consistent reports of symptoms and mean values of lung function results from both occasions were considered in the present analysis. This strategy was chosen in order to obtain as reliable data as possible for the statistical analysis. A limitation of this strategy is that missing data are somewhat high (table 2). However, when analysing subjects with missing data for some of the symptoms there were no essential differences compared to subjects who reported symptoms. Some subjects with lung disease are included in the analysis, a quality of a random population sample. For example, 10 subjects reported chronic bronchitis or asthma on both occasions in the present study but information on other diseases is lacking. The definition of smoking habits presented some considerations. Mean values appeared to be impossible to calculate why smoking habits reported 1980 were accepted: Furthermore, if a subject was reported as a smoker in 1973 but non-smoker in 1980 he was considered an ex-smoker in 1980. The lack of detailed daily cigarette consumption and the resulting approximation of the calculation of pack-years may furthermore be a limitation.

The prevalence of cough symptoms and dyspnoea among non-smokers, exsmokers and smokers in the present study was lower whereas wheeze was similar.
compared with the study by Medbø et al., whereas compared to Sherman et al. cough prevalence was similar, while wheeze and dyspnoea were more common among smokers. Differences in questionnaires, definitions of symptoms and population samples presumably explain these differences.

Viegi et al. showed that the slope of phase III of the single-breath N2 test was significantly more abnormal in male smokers with the symptoms cough, phlegm, wheeze and dyspnoea compared to asymptomatic male smokers based on a random population sample drawn from northern Italy. These results are in line with the findings in the present study, and we confirm that the results regarding some cough symptoms are valid also after adjusting for the amount of smoking and spirometric results.

The interpretation of the logistic regression models is complicated by correlations between the slope of phase III, FEV1 and FEV1/VC. These variables are also biologically interrelated but reflect to a certain extent different parts of the airways and lungs. In a model where pack-years and only one of the lung function variables are included, this lung function variable is significantly related to all the symptoms, illustrating the common information carried by the three lung function variables. Anyhow, cough symptoms may to some extent be an effect of obstruction in peripheral airways whereas wheezes and dyspnoea may to some extent be an effect of obstruction of larger airways, at least among elderly men. This is in line also with the clinical experience that early symptoms in smokers are usually cough with or without expectoration, while wheeze and dyspnoea seem to reflect later stages of more severe respiratory airway and lung damage. Furthermore, when the slope of phase III is normalised for smoking it is still significantly steeper among subjects with cough symptoms compare to those without cough symptoms also (table 4), thus confirming the association between cough symptoms and the slope of phase III.

The ability of respiratory symptoms to predict an abnormal slope of phase III has, to our knowledge, not been reported previously. In the present study ‘cough usually in the morning during winter’, ‘cough most days at least 3 months a year or more during winter’ and ‘cough and expectoration usually in the morning’ could predict an abnormal slope of phase III with a probability of 79–92% among smokers ≥20 pack-years. The sensitivities were low, however, as only 39–45% of

### Table 4 Effects of cough symptoms on the slope of phase III

<table>
<thead>
<tr>
<th></th>
<th>Exsmokers and smokers</th>
<th>Phase III (% pred)*</th>
<th>Phase III (% expected, smoking normalised)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No symptoms</td>
<td>Symptoms</td>
<td>p Value</td>
</tr>
<tr>
<td>Cough usually in the morning during winter</td>
<td>140</td>
<td>245</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough most days at least 3 months a year or more during winter</td>
<td>137</td>
<td>238</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p Values refer to difference between no-symptom and symptom; Mann-Whitney U test. *Phase III=slope of phase III of the single-breath nitrogen (N2) test.

### Table 5 Diagnostic characteristics of three cough symptoms to detect a normal/abnormal slope of phase III and FEV1/VC ratio in male smokers with a history of ≥20 pack-years

<table>
<thead>
<tr>
<th></th>
<th>Cough usually in the morning during winter (n=78)</th>
<th>Cough most days at least 3 months a year or more during winter (n=77)</th>
<th>Cough and expectoration usually in the morning (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase III &gt;147% FEV1/VC &lt;0.65</td>
<td>Phase III &gt;147% FEV1/VC &lt;0.65</td>
<td>Phase III &gt;147% FEV1/VC &lt;0.65</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.42</td>
<td>0.44</td>
<td>0.39</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.92</td>
<td>0.76</td>
<td>0.85</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.92</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.44</td>
<td>0.72</td>
<td>0.41</td>
</tr>
<tr>
<td>Pretest probability</td>
<td>0.67</td>
<td>0.35</td>
<td>0.66</td>
</tr>
<tr>
<td>Post-test probability</td>
<td>0.92</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>5.3</td>
<td>1.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Phase III=slope of phase III of the single-breath nitrogen (N2) test. FEV1, forced expiratory volume in 1 s; VC, vital capacities.
subjects with an abnormal slope of phase III had one of the cough symptoms. Cough receptors in the peripheral airways which seem to be more sensitive in, for example, COPD could to some extent explain the association between cough and peripheral airway obstruction as found in the present study.

The knowledge that cough symptoms may indicate smoking-induced peripheral airway obstruction and probably an increased risk of developing COPD may provide a useful argument for smoking cessation and when applicable also an argument regarding avoidance of occupational exposure. A clinical follow-up could be worthwhile to consider.

We conclude that, some cough symptoms may be an effect of obstruction in peripheral airways and a predictor of peripheral airways disease at least among male middle-aged smokers. Cough—a sound from the silent zone?

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Contributors JD designed and performed the study, analysed data, wrote the paper, MNT designed the study, wrote the paper, BH designed and performed the study, analysed data and wrote the paper.

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Competing interests None.

Ethics approval This work was performed at the Institution of Medicine at Sahlgrenska Academy, University of Gothenburg, Sweden. The study in 1973 and 1980 was approved by the Committee for Medical Research Ethics at the University of Gothenburg.

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