Relation of perceived nasal and bronchial hyperresponsiveness to FEV$_1$, basophil counts, and methacholine response

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ABSTRACT Perceived nasal and bronchial hyperresponsiveness to tobacco smoke and cold air were assessed in 912 working men in the Paris area. Baseline lung function measurements and peripheral leucocyte counts with standard differential counts were performed. At least one perceived nasal or bronchial hyperresponsiveness symptom was reported by 15.7%. Current smoking was significantly less frequent among those with cough induced by tobacco smoke. Rhinitis induced by cold air was associated with lower FEV$_1$ (p < 0.01) and the association remained after adjustment for smoking, asthma, and wheezing (p = 0.06). Symptoms induced by cold air were related to circulating basophils. Neither perceived nasal nor perceived bronchial hyperresponsiveness was significantly related to the airway response to methacholine in a sample of the group (n = 324) surveyed again five years later. The results suggest that the symptom of rhinitis provoked by cold air is a possible “new” risk factor or marker for chronic airflow limitation.

In the 1960s allergy and bronchial hyperresponsiveness were considered in the Netherlands as major host risk factors for chronic airflow limitation. There is now a renewed interest in the “Dutch hypothesis.” Several studies have reported an association between bronchial hyperresponsiveness and decline in FEV$_1$. An association between lung function and serum IgE concentrations and eosinophilia have also been reported. Furthermore, mediators of the late nasal response to cold air have been shown to be produced by basophils. Thus immunological mechanisms related to IgE, eosinophils, and basophils might have a key role in the development of chronic airflow limitation. Perceived hyperresponsiveness to stimuli, although used in clinical practice, has rarely been considered in epidemiological studies and, in the absence of provocation tests, might provide information additional to that derived from the standard questions on asthma and wheezing.

We here describe the relationships of bronchial and nasal symptoms provoked by two non-specific stimuli, tobacco smoke and cold air, to FEV$_1$ and eosinophil and basophil counts, using data collected in 1980–1 in a cross sectional survey of a working population. The associations between perceived hyperresponsiveness symptoms and the airway response to inhaled methacholine response obtained five years later in a sample of the men are also reported.

Methods

FIRST SURVEY
The initial population studied in 1980–1 consisted of 912 men aged 22–55 years who were working in a large Parisian administration, mainly as policemen. The subjects were interviewed as part of an annual compulsory medical examination that used the BMRC–ECSC (British Medical Research Council–European Coal and Steel Community) questionnaire, and this included an evaluation of perceived hyperresponsiveness (table 1). Questions about wheezing were used to assess airway hyperresponsiveness and questions about fits of coughing and sneezing to assess irri-
and cold air is referred to as smoke induced and cold induced cough, and sneezing or runny nose as rhinitis induced by tobacco smoke or cold air. Wheezing induced by stimuli will not be considered further as only five subjects reported wheezing induced by tobacco smoke or cold air, three of whom reported a history of wheezing and asthma; one subject had wheezing but no cough or rhinitis with the same stimulus. Table 1 gives the prevalence of the four remaining perceived hyperresponsiveness symptoms. They have been analysed separately and also grouped by stimulus and by symptom. Questions concerning childhood eczema and hay fever were included as markers for an atopic diathesis.

Spirometric measurements were performed with a dry spirometer (Morgan) with the subject in a sitting position and wearing a nose clip. The best of three tracings was used for analysis. FEV₁, with tracings that satisfied ECSC criteria¹⁴ were available for 817 subjects. Values were converted to body temperature and pressure saturated with water. Regressions on age and height were calculated on the basis of data from the entire sample. Normalised residuals were used for analysis. In the presentation the normalised residuals were converted to values for subjects of mean age and height—that is, 37-0 years and 1-75 m. Success in producing a volume–time curve was less frequent for those who reported smoke induced cough (p = 0.05) and smoke induced rhinitis (p = 0.06).

Fasting blood samples were obtained from 886 men. Leucocyte counts and standard differential counts were estimated by a Coulter counter S (Coulter Electronics, Hialeah, USA) and microscopic examination of 100 cells. Eosinophil and basophil counts/mm³ were obtained by multiplying leucocyte counts by the percentage of eosinophils and basophils. Missing data for leucocyte counts were not associated with smoking habits, lung function values, or prevalence of symptoms.

We have shown previously in this population that low FEV₁ is associated with eosinophilia among never smokers, a history of bronchitis or pneumonia before the age of 2 years and the presence of a common cold on the day of examination among those with a history of wheezing.¹⁵ ¹⁶ This is taken into account in the analysis.

**SECOND SURVEY**

A second survey was performed in 1985–6 on a sample of the original population with good spirometric tracings in 1980. We planned to study 599 men, including all those with a history of asthma or wheezing, any perceived hyperresponsiveness symptoms, eczema, urticaria, bronchopneumonia before 2 years of age, or the PiMZ phenotype, and a similar number of control subjects. At the time of the second survey nine men had died, 18 refused to participate, 118 were lost to follow up, and 67 answered the postal questionnaire only. Thus 390 men came for the examination, with 324 men performing a methacholine test. The protocol included a questionnaire similar to that used in the 1980–1 survey and a methacholine provocation test (using the reservoir method⁹). The aerosol was generated by compressed
air through an Aerosolan Gauthier nebuliser (22 l/min) from a solution of 0.02 g/ml methacholine diluted in saline, and stored in a water sealed spirometer. The subject then inhaled from the bell four volumes from 1 litre to 10 litres. This corresponds to 200 μg methacholine per litre of aerosol according to the manufacturer, but weighing the nebulizer showed that the actual dose administered was 300 μg/l aerosol. The test was continued until a total administered dose of 6 mg had been given or a 20% fall in FEV₁ had occurred. Results were not obtained for 16 subjects for technical reasons, for the first 38 men because they were challenged with acetylcholine, and for 12 men for other reasons. The subjects who attended both surveys had significantly less rhinitis induced by cold air and a significantly lower FEV₁ at the first survey than those who failed to attend the second survey. Subjects with a 10% or greater fall in FEV₁ from the largest FEV₁ performed before and during challenge were defined as responders.

The associations of categorical variables were evaluated with the use of odds ratios (OR) and χ² tests. When adjustments were necessary the Mantel-Haenzel method was used. For continuous variables analysis of variance and multiple regression were used. Adjustment for smoking was carried out with a five class variable (never smokers; ex-smokers; and smokers of less than 10 g, 10–19 g, and 20 g or more of tobacco a day). Because of the skewness of the distribution of basophil and eosinophil counts, interquartile ranges are presented in tables and non-parametric tests were used to assess the significance of differences (SAS package).

Results

Of the 912 men examined in the first survey, 15.7% reported at least one perceived nasal or bronchial hyperresponsiveness symptom. Nasal symptoms were reported by 8.5%, bronchial symptoms by 5.3% and both by 1.9%.

All but one of the symptoms induced by either cold air or tobacco had an odds ratio of 1.9 at least for asthma and wheezing (table 1). Because of the small number of subjects in some cells, these odds ratios were often not significantly different from 1. The only odds ratio that was low was that for wheezing and smoke induced cough.

Smoke induced cough and cold induced cough were related (OR = 3.2; p = 0.07) as were smoke induced rhinitis and cold induced rhinitis (OR = 4.7; p = 0.05). Interestingly, the two more prevalent symptoms, smoke induced cough and cold induced rhinitis, were unrelated (OR = 1.0).

Wheezing was positively related to smoking habits (prevalence 2.3%, 4.4%, and 7.4% for never smokers, ex-smokers, and current smokers; p = 0.001), whereas smoke induced cough was negatively related to smoking habit (prevalence 11.1%, 9.8%, and 5.5% respectively; p = 0.05).

No association with lung function was observed for allergy, tobacco smoke induced symptoms, or cold induced cough, even after adjustment for smoking (table 2). Subjects with cold induced rhinitis had significantly lower FEV₁ levels than those without. This association remained (p = 0.06) after adjustment for all the factors previously shown to be related to FEV₁, level in this population (smoking habits, asthma, a common cold on the day of examination in those with a history of wheezing, eosinophilia among never smokers, and a history of bronchitis or pneumonia before 2 years of age).

The association of asthma, wheezing, and perceived hyperresponsiveness with eosinophil and basophil counts is shown in table 3. Eosinophil counts were related to asthma, as reported previously, and counts were higher in subjects with any perceived hyperresponsiveness symptom. The percentage of basophils among the total peripheral white cells was related to wheezing, to both cold induced symptoms, and, at borderline significance, to asthma. Similar results were observed for absolute basophil counts (except for cold induced rhinitis, where p = 0.06). Multiple regression analyses on ranks showed associations of basophils (as a percentage of total white cells) with wheezing (p = 0.01) and, of borderline significance, with cold induced rhinitis (p = 0.09). Absolute basophil counts were associated with wheezing (p = 0.007) and, of borderline significance, with cold induced cough (p = 0.08).

The relation of perceived hyperresponsiveness to a
relation of nasal and bronchial hyperresponsiveness to FEV₁, basophil counts, and methacholine response

Table 3  Relationships between eosinophil and basophil counts and perceived hyperresponsiveness to tobacco smoke and cold air, asthma and wheezing: initial survey (886 men with leucocyte counts)

<table>
<thead>
<tr>
<th></th>
<th>Eosinophils/mm³</th>
<th>Basophils/mm³*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>842</td>
<td>172</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>258**</td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>830</td>
<td>175</td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
<td>188</td>
</tr>
<tr>
<td>Perceived hyperresponsiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoke induced cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>806</td>
<td>175</td>
</tr>
<tr>
<td>Yes</td>
<td>74</td>
<td>195</td>
</tr>
<tr>
<td>Smoke induced rhinitis</td>
<td>No</td>
<td>860</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>214</td>
</tr>
<tr>
<td>Cold induced cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>857</td>
<td>175</td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>225†</td>
</tr>
<tr>
<td>Cold induced rhinitis</td>
<td>No</td>
<td>831</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>181</td>
</tr>
</tbody>
</table>

*Medians for basophils were always equal to zero. For basophil percentages p values (Wilcoxon rank test) were 0·07 for asthma, 0·004 for wheezing, 0·04 for cold induced cough and 0·05 for cold induced rhinitis.

**p < 0·01; tP < 0·10; †p < 0·05 (Wilcoxon rank test).

Q1—first quartile; Q3—third quartile.

Table 4  Relationships between asthma, wheezing and perceived hyperresponsiveness symptoms and methacholine response: second survey (324 men with methacholine challenge test—numbers for each item in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>PD₁₀ &lt; 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Asthma</td>
<td>34·2 (298)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>34·4 (274)</td>
</tr>
<tr>
<td>Perceived hyperresponsiveness</td>
<td></td>
</tr>
<tr>
<td>Smoke induced cough</td>
<td>36·7 (294)</td>
</tr>
<tr>
<td>Smoke induced rhinitis</td>
<td>36·4 (308)</td>
</tr>
<tr>
<td>Cold induced cough</td>
<td>37·6 (314)</td>
</tr>
<tr>
<td>Cold induced rhinitis</td>
<td>36·7 (270)</td>
</tr>
</tbody>
</table>

*p < 0·001; tP < 0·01.

PD₁₀—provocative dose of methacholine causing a fall in FEV₁, of 10% or more.

Discussion

In this working population rhinitis induced by cold air was related to lower FEV₁ values and symptoms induced by cold air were related to higher circulating basophil counts.

Symptoms of perceived hyperresponsiveness, although used in clinical practice and in some studies of work related symptoms, have rarely been used in epidemiological studies. We found a reasonable association between these symptoms and a history of asthma and wheezing. Wheezing induced by these stimuli, although specific, was too infrequent (five men) to be studied. The prevalence was much lower than the figures obtained by Mortagy et al. perhaps because of differences in the population studied or in the wording of the questions. Wheezing induced by cold air (0·9%) and by tobacco smoke (2·2%) was much less prevalent than cold induced or smoke induced cough, as in the study by Mortagy et al. Nasal hyperresponsiveness was not reported in that study. The questions we used have been further validated in the follow up of a sample from this population and their reproducibility was good. Questions on symptoms induced by a smoky atmosphere are relevant to any geographical location, but the meaning of symptoms induced by cold air depends on the climate of the region. In the Paris area the average winter temperature is around 5°C with an average minimum of —3°C.

We found no association between perceived hyperresponsiveness symptoms and response to methacholine challenge in the sample from the original study population investigated five years later. There was no association between methacholine response and rhinitis induced by cold air, though the greater loss to follow up of men with this symptom might explain the lack of association. Using the same questionnaire, Beziau et al. in a preliminary report describe a significant association between perceived hyperresponsiveness and the response to isocapnic ventilation with dry air in young smokers, and Mortagy et al. found that dyspnoea and wheezing induced by irritants were related to histamine responsiveness. Whether the discrepancies between the different studies are related to the different stimuli used or to the
sample studied is not clear. It would be interesting to
determine whether the lack of association between
rhinitis induced by cold air and the airway response
to meathacholine can be confirmed and to study the
relation of symptoms to results of nasal provocation
tests in a large population.

Our results suggest that subjects with cough induced
by tobacco smoke refrain from smoking and have, at
least at this stage, no reduction in FEV₁. The lack of
association with FEV₁ might be due to the self
selection against smoking or to the greater number of
poor spirometric tracings in those with smoke induced
cough.21 Selection bias in epidemiological studies of
factors related to hyperreactivity has been discussed.8

The influence of chronic symptoms on attitudes
towards smoking habits is well known.22-24 It is likely
that symptoms of hyperreactivity perceived as a
response to an identifiable stimulus may have even
more influence. In a case-control study, Lehrer et al
observed that perceived tobacco smoke sensitivity
(conjunctival, nasal, bronchial) was not related to
hypersensitivity to tobacco leaf or smoke antigen.25 It
would be interesting to know whether the increased
concentrations of IgE specific for Streptococcus
pneumoniae among smokers reported by Bloom et al26
vary according to perceived sensitivity to smoking.

Subjects who reported rhinitis induced by cold air
had a lower FEV₁ and, according to preliminary
results of a follow up study of a sample of these
subjects, a steeper reduction in FEV₁ with time.6 No
epidemiological study has considered nasal
hyperreactiveness as a risk factor for chronic airflow
limitation.

Both the symptoms induced by cold air were related
to higher values for basophils whether these were
expressed as total counts or as percentages of the total
white cell count. The method of counting basophils
was imprecise and large standard deviations were
observed, but this would tend to reduce any association
with other factors. The association of symptoms
with basophil counts has not been determined in
previous epidemiological studies. An increase in
basophils has been found before attacks of asthma and a
decrease after attacks, suggesting that basophil counts
could be used to predict a forthcoming attack.27
Higher basophil counts might be related to the
liberation of mediators of hyperreactiveness, and
our results fit well with the observations of Proud et al10
that mediators of the late nasal response to cold air
are produced by basophils or mast cells or both.
Potential confounding factors that might explain the
associations observed are not suggested by published
reports. In a study of 33 000 subjects basophils were
shown to increase during periods of cold weather
(temperature below 0°C) and there were variations
through the year with a maximum in July, possibly

Kauffmann, Neukirch, Annesi, Korobaeff, Doré, Lellouch
related to pollen.28 Preliminary results in our population
have shown that seasonal variations do not explain the association between cold induced
symptoms and basophil counts.29

Although rhinitis induced by cold air does not appear to be related to bronchial hyperreactiveness
to meathacholine the finding of perceived nasal hyperreactiveness to cold air as a potential "new"
risk factor or marker of chronic airflow limitation merits further study.

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