Thorax 1988;43:456–461

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.[1] There is now a renewed interest in the "Dutch hypothesis."[2–4] Several studies have reported an association between bronchial hyperresponsiveness and decline in FEV_1.[5,6] An association between lung function and serum IgE[7] concentrations and eosinophilia[8,9] have also been reported. Furthermore, mediators of the late nasal response to cold air have been shown to be produced by basophils.[10] 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[11,12] 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.

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Accepted 17 March 1988

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,[13] 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 irritative responses. Hyperresponsiveness of secretory mechanisms was considered for nasal secretions but not for bronchial secretions as this is difficult to assess by questionnaire. The stimuli that were asked about were tobacco smoke and cold air. Cough induced by smoke

Table 1 *Relationships between asthma, wheezing, allergy, and perceived hyperresponsiveness to tobacco smoke and cold air: initial survey (912 working men)*

		Associations with			
	Prevalence (%)	*Asthma (OR)*	*Wheezing (OR)*	*Hay fever (OR)*	*Eczema (OR)*
Asthma (Have you ever had asthma?)	3·9				
Wheezing (Have you ever had wheezing?)	4·9	5·9*			
Allergy					
Hay fever (Have you ever had hay fever—that is, attacks of sneezing with stuffy or runny nose and watering eyes?)	24·0	2·8†	2·6†		
Eczema (Did you ever have eczema in childhood?)	7·7	2·6‡	3·0§	1·7	
Perceived hyperresponsiveness					
Smoke induced cough (When you enter a smoky room, does it usually induce a fit of coughing?)	8·3	1·9	1·1	1·8§	1·3
Smoke induced rhinitis (When you enter a smoky room, does it usually induce sneezes or a runny nose?)	2·3	4·6‡	3·5	2·1‡	3·0
Cold induced cough (When you are in contact with cold air, does it usually induce a fit of coughing?)	2·6	2·4	7·6*	7·6*	1·3
Cold induced rhinitis (When you are in contact with cold air, does it usually induce sneezes or a runny nose?)	5·4	2·4	3·0‡	0·7	1·4

*$p \leq 0{\cdot}001$; †$p \leq 0{\cdot}01$; ‡$p \leq 0{\cdot}10$; §$p \leq 0{\cdot}05$ by χ^2 test or Fisher's exact test when expected numbers were lower than 5.
OR—odds ratio.

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. FEV_1 with tracings that satisfied ECSC criteria[14] 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 ($p = 0{\cdot}05$) and smoke induced rhinitis ($p = 0{\cdot}06$).

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/mm^3 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 FEV_1 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.[9 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 method[6]). The aerosol was generated by compressed

air through an Aerosolan Gauthier nebuliser (22 l/mn) 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 nebuliser 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 FEV_1 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 FEV_1 at the first survey than those who failed to attend the second survey. Subjects with a 10% or greater fall in FEV_1 from the largest FEV_1 performed before and during challenge were defined as responders.

The associations of categorical variables were evaluated with the use of odds ratios (OR) and χ^2 tests. When adjustments were necessary the Mantel-Haenzel method was used. For continuous variables analysis of variance and multiple regression were used.[17] 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; $p \leqslant 0{\cdot}001$), whereas smoke induced cough was negatively related to smoking habit (prevalence 11·1%, 9·8%, and 5·5% respectively; $p \leqslant 0{\cdot}05$).

Table 2 *Relationships between mean FEV_1 and perceived hyperresponsiveness to tobacco smoke and cold air, asthma and wheezing: initial survey (817 working men with good spirometric tracings)*

	FEV_1 (l) (mean (SD))	
	No	*Yes*
Asthma	4·18* (0·49) (780)	3·65 (0·77)† (30)
Wheezing	4·18 (0·49) (765)	3·87 (0·67)† (41)
Perceived hyperresponsiveness		
Smoke induced cough	4·16 (0·51) (750)	4·19 (0·50) (63)
Smoke induced rhinitis	4·16 (0·51) (797)	4·12 (0·60) (16)
Cold induced cough	4·16 (0·51) (792)	4·07 (0·55) (21)
Cold induced rhinitis	4·17 (0·51) (768)	3·97 (0·52)‡ (44)

*Values were adjusted for age and height on the basis of the regression on the whole sample, and presented for a "mean" subject of 37·0 y and 1·75 m tall. Numbers of subjects are shown in the second parentheses. Slight variations in the total number of subjects are due to missing values.
†$p \leqslant 0{\cdot}001$; ‡$p \leqslant 0{\cdot}01$.

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 FEV_1 levels than those without. This association remained (p = 0·06) after adjustment for all the factors previously shown to be related to FEV_1 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

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)*

		Eosinophils/mm³			*Basophils/mm³**	
	n	*Mean*	*Median*	*Q1–Q3*	*Mean*	*Q1–Q3*
Asthma No	842	172	133	61–236	18	0–0
Yes	35	258**	177	120–332	29†	0–60
Wheezing No	830	175	134	62–240	18	0–0
Yes	44	188	174	75–281	40**	0–68
Perceived hyperresponsiveness						
Smoke induced cough No	806	175	134	62–240	18	0–0
Yes	74	195	161	78–236	22	0–45
Smoke induced rhinitis No	860	176	135	63–240	19	0–0
Yes	20	214	142	66–198	24	0–56
Cold induced cough No	857	175	134	63–236	18	0–0
Yes	23	225†	243	81–366	48‡	0–86
Cold induced rhinitis No	831	176	138	65–240	18	0–0
Yes	48	181	104	0–257	30†	0–56

*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.
**$p \leqslant 0{\cdot}01$; †$p \leqslant 0{\cdot}10$; ‡ $\leqslant 0{\cdot}05$ (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)*

	$PD_{10} \leqslant 6$ mg	
	No	*Yes*
Asthma	34·2 (298)	68·0* (25)
Wheezing	34·4 (274)	54·8† (40)
Perceived hyperresponsiveness		
Smoke induced cough	36·7 (294)	40·0 (30)
Smoke induced rhinitis	36·4 (308)	53·3 (15)
Cold induced cough	37·6 (314)	20·0 (10)
Cold induced rhinitis	36·7 (270)	38·9 (54)

*$p \leqslant 0{\cdot}001$; †$p \leqslant 0{\cdot}01$.
PD_{10}—provocative dose of methacholine causing a fall in FEV_1 of 10% or more.

positive response in the bronchial provocation test for the 324 men undergoing methacholine challenge is shown in table 4. Only asthma and wheezing reported in 1985 were associated with a positive response to methacholine.

Discussion

In this working population rhinitis induced by cold air was related to lower FEV_1 values and symptoms induced by cold air were related to higher circulating basophil counts.

Symptoms of perceived hyperresponsiveness, although used in clinical practice[18] and in some studies of work related symptoms,[11] have rarely been used in epidemiological studies.[12] 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*,[12] 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.[19] 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*[20] 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*[12] 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 methacholine 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 FEV_1. The lack of association with FEV_1 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 al*[26] vary according to perceived sensitivity to smoking.

Subjects who reported rhinitis induced by cold air had a lower FEV_1 and, according to preliminary results of a follow up study of a sample of these subjects, a steeper reduction in FEV_1 with time.[6] No epidemiological study has considered nasal hyperresponsiveness 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 hyperresponsiveness, and our results fit well with the observations of Proud *et al*[10] 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 related to pollens.[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 hyperresponsiveness to methacholine the finding of perceived nasal hyperresponsiveness to cold air as a potential "new" risk factor or marker of chronic airflow limitation merits further study.

We thank D Charpin, S Perdrizet, Q T Pham, and J F. Tessier, who participated in the writing of the questions on perceived hyperresponsiveness symptoms in an ad hoc working group, as part of the activities of the Commission of Epidemiology of the French Society of Respiratory Diseases (coordinator the late R Bollinelli). We also thank M J Marne for help with the collection of data, M H Verdier Taillefer for help with data processing, M P Oryszczyn for the second survey, the men who participated in the study, and the referees for their suggestions. This work was supported by INSERM grant 810124, by a grant from Caisse Nationale d'Assurance Maladie, and by special funds (84-B/4) from the Comités Départements Contre les Maladies Respiratoires et la Tuberculose.

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