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Respiratory symptoms relate to physiological changes and inflammatory markers reflecting central but not peripheral airways. A study in 60-year-old 'healthy' smokers and never-smokers

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The aim of this study was to evaluate the relationship between respiratory symptoms, lung function and inflammatory markers in 'healthy' smokers.

The study population was recruited from an epidemiological study with subjects of the same age, 60 years. Only smokers who considered themselves healthy ($n=58$) and a random sample of never-smokers ($n=34$) were investigated. All subjects underwent lung function tests—spirometry, carbon monoxide transfer (DLco) and the single-breath N₂ method (N₂ test)—together with high-resolution computed tomography (HRCT). A flexible bronchoscopy with a bronchoalveolar lavage (BAL) was performed in 30 smokers and 18 never-smokers. Bronchial biopsies were also taken.

Smokers who reported non-specific respiratory problems, chronic bronchitis and wheezing in a symptom questionnaire had a lower forced expiratory volume in 1 sec (FEV₁), FEV₁% and specific airway conductance (sGaw), lung function tests supposed to reflect the more central airways, than smokers without respiratory symptoms. A limited number of smokers with occasional non-specific respiratory problems also had more cytotoxic T cells (CD8) in bronchial biopsies. No differences were found in DLco and the N₂ test, lung function tests supposed to reflect the more peripheral airways including the alveoli, HRCT-diagnosed emphysema or inflammatory markers in blood and BAL between smokers with and without respiratory symptoms.

It is concluded that even when smokers consider themselves 'healthy' they have mild symptoms that are related more to physiological changes and inflammatory markers that may reflect events in the central airways than to changes that may reflect events in the peripheral airways.

Key words: respiratory symptoms; lung function; inflammatory markers; bronchial biopsies.

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Introduction

Many smokers develop chronic bronchitis, and at least 15% will develop chronic obstructive pulmonary disease (COPD) (1,2). It would be desirable to diagnose COPD early, before the patient has become seriously handicapped. Chronic obstructive pulmonary disease is an insidious disease in its early phases, however, and it is difficult to identify persons at risk of developing severe COPD. The

importance of symptoms in early phases of the disease has not been well documented.

Many investigators have tried to identify which pulmonary function test is the most sensitive for predicting the future development of COPD. Burrows *et al.* found that a decreased forced expiratory volume in 1 sec/forced vital capacity (FEV₁/FVC) ratio in male smokers was almost uniformly associated with a high rate of decline in FEV₁ (3). Carbon monoxide transfer (DLco) below 85% of predicted level was found to be a significant predictor of the all-cause mortality rate in the U.S. population (4). It has not yet been shown whether a low DLco is a risk factor for developing, or dying from, COPD. Some evidence suggests that a reduced DLco predicts a future decline in FEV₁ (5). The single-breath N₂ test (N₂ test) has been found to be sensitive for detecting small-airways disease in smokers and for predicting the rate of decline in FEV₁ (6–8).

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Smoking is the most important risk factor in COPD (9). Smokers have a greater number of respiratory symptoms, such as cough, increased sputum production, wheezing and dyspnoea compared with non-smokers (1,10,11). Many years ago, Fletcher *et al.* stated that a diagnosis of chronic bronchitis was not a risk factor for developing COPD (12). More recent studies have shown that chronic hypersecretion is independently related to decreased lung function and to death from obstructive lung disease (13–15).

Smokers have a neutrophil inflammation in the bronchii, as reflected in bronchoalveolar lavage (BAL) (16–18). This inflammation is more exaggerated in smokers with decreased lung function (17,19,20). ‘Healthy’ smokers also have a neutrophil inflammation in the bronchii that is related to a fall in DLco but not to a fall in FEV₁ (21). In about 40% of these smokers, high-resolution computed tomography (HRCT) shows emphysematous lesions related to a fall in transfer factor (DLco/VA) (22) and to an increase in the neutrophil-specific inflammatory marker HNL in BAL (21,23).

Several studies show a possible involvement of lymphocytes in COPD (24–27). This lymphocytic inflammation in the bronchial mucosa is characterized by a predominance of CD8 + T lymphocytes related to a decrease in FEV₁ (27,28). ‘Healthy’ smokers had a similar correlation in the bronchial mucosa related to a small fall in FEV₁ (29).

The aim of this study was to evaluate whether there is any respiratory symptom in smokers with preclinical disease (subjects who regard themselves as ‘healthy’) and lung function changes, high-resolution computed tomography (HRCT) findings or inflammatory markers believed to indicate the presence of COPD/emphysema. This was done by comparing respiratory symptoms with lung function, emphysema score and inflammatory markers. All subjects underwent both lung function tests aimed at reflecting the more central airways [FEV₁, specific airway conductance (sGaw)] and lung-function tests aimed at reflecting the more peripheral airways including the alveoli (DLco and N₂-test), together with HRCT to diagnose emphysema. About 60% of the subjects accepted undergoing a flexible bronchoscopy, where we obtained bronchial biopsies and performed bronchoalveolar lavage (BAL).

Material and methods

SUBJECTS

The subjects were recruited from the population study ‘Men born 1933 in Göteborg’ (Fig. 1), a random half of all men born in 1933 and residing in Göteborg in 1983 ($n=1016$) (30). Eight hundred and seventy-nine men in the original cohort who were still alive and living in Göteborg were recruited for a second examination in 1993. Of the 602 participating men, 532 were evaluated by spirometry. Of these, 112 were smokers, 198 were never-smokers and 222 were former smokers who had not smoked for at least 1 month. All smokers and a random sample of 60 lifelong never-smokers were offered a lung examination. Fifty-eight smokers and 34 never-smokers consented to further

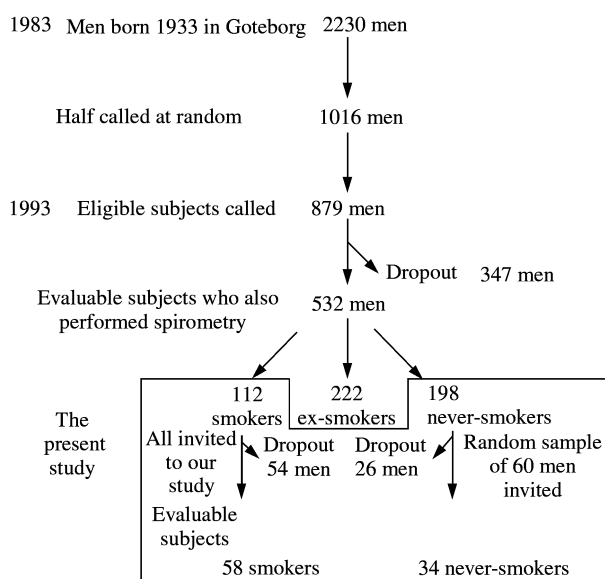


FIG. 1. Subject recruitment for the present study from the WHO study ‘Men born in 1933 in Göteborg’.

investigations and, of these, 30 smoking and 18 never-smoking men accepted undergoing a bronchoscopy.

Among those originally included in the study, subjects were excluded if they had any airway disease for which they had sought medical attention ($n=11$), had a history of congestive heart failure or unstable angina pectoris ($n=4$) or had any other severe disease ($n=5$). Subjects would also have been excluded if they had scoliosis or other diseases with thorax deformation, any kind of infection during the 4 weeks preceding the examination or had received corticosteroids, N-Acetylcysteine (NAC) or acetylsalicylic acid (ASA) treatment less than 4 weeks prior to blood tests or bronchoscopy. No subject was excluded for any of these reasons. Acetyl salicylic acid treatment was allowed in subjects with prior myocardial infarction ($n=8$). Four smokers had quit smoking before they came to the follow-up and were therefore excluded. The rest of the dropouts were not willing to participate in the study for various reasons ($n=56$). The dropout frequency was equally distributed among smokers and never-smokers.

Thirty-three out of 58 (57%) were current heavy smokers (≥ 15 cigarettes per day) and 25 out of 58 (43%) were current light smokers (< 15 cigarettes per day). The median number of pack-years was 35 (9–79) years.

Lung function, biopsy findings, lymphocyte sub populations in BAL and blood, the cytokine pattern in blood and BAL and emphysematous changes have been described in earlier papers (21,22,29).

The study was approved by the local Ethics Committee at Sahlgrenska University Hospital, Göteborg, Sweden.

QUESTIONNAIRE

The questionnaire was a modified version of the European Community Respiratory Health Survey (31). It was divided

into three principal parts. The first section, symptoms, contained items concerned with the level of symptomatology, including wheezing, dyspnoea, cough, sputum production and one non-specific question, 'Do you ever have trouble with your breathing?' if the answer to this last question was yes, the subject was asked to indicate whether this was continuously/repeatedly/only rarely. The subjects were to deny having asthma. The second section contained items concerned with smoking habits. In the third section, the subjects were asked about other diseases and concomitant medication. The subjects answered the questionnaire before any lung function test, bronchoscopy or HRCT was done. All subjects answered the questionnaire except for one smoker and one never-smoker.

LUNG-FUNCTION TESTS

Lung volumes and sGaw were obtained by a flow-displacement body plethysmograph (SensorMedics 2200, Bilthoven, The Netherlands). Forced expired volume in 1 sec and vital capacity (VC) were obtained on a water-sealed, regularly calibrated bell spirometer. Carbon monoxide transfer was assessed by the single breath method with standard equipment (SensorMedics 2200, Bilthoven, The Netherlands). The slope of phase III was obtained by the single breath N₂ method (32). For lung volumes and spirometry the European Coal and Steel Community (ECSC) reference values were used (33) and for DL_{co} and DL_{co}/VA the reference values according to Salorinne were used (34). For single breath N₂-test the authors' own data, from earlier studies were used (35).

FIBRE-OPTIC BRONCHOSCOPY AND SAMPLE COLLECTIONS

Pre-medication was given with diazepam 5 mg orally followed by 0.5 ml morphine-scopolamine intramuscularly. If the person had a history of kidney or gall bladder disease, petidine 75 mg intramuscularly and atropine 0.5 mg subcutaneously were given instead of morphine-scopolamine. Additional diazepam (2.5–5 mg) was given intravenously during the bronchoscopic procedure in some cases. All individuals were given terbutalin 0.25 mg/dose 2 × 3 in nebulizer to avoid unexpected bronchoconstriction during the procedure. Local anaesthesia was given initially with 1% tetracaine-spray in the mouth and laryngeal tract. Additional anaesthesia was applied through the bronchoscope channel for the lower respiratory tract. The bronchoscopy was performed transorally with an Olympus flexible fibre-optic bronchoscope (Tokyo, Japan). The subjects were examined in a supine position by one experienced bronchoscopist. Oxygen saturation was measured with an Ohmeda Pulse Oximeter (Louisville, U.S.A.) during the bronchoscopy and supplemental oxygen was given at a rate of 2–3 l min⁻¹ through a nasal catheter when needed.

All bronchoscopies were made between 08.00 hours and 10.00 hours. Bronchial biopsies (3–4 biopsies/subject) were taken with an alligator forceps from subsegmental septa in

the lower left lobe. The biopsies were gently removed from the forceps, immediately placed in a sterile moistened chamber and transported to the laboratory for further processing. Fourteen out of 30 biopsies from the smokers and 10 out of 18 biopsies from the never-smokers were evaluable. In five out of 30 smokers and in one out of 18 never-smokers, no biopsy material was obtainable. In 11 out of the remaining 25 smokers and seven out of the remaining 17 never-smokers, the biopsy samples were not histologically evaluable. These subjects, not analysed with immunohistochemistry, did not differ in sex, age or lung function, except for DL_{co} (% pred.) in never-smokers, compared with those evaluated (29). For detailed description of the immunohistochemistry method used, the authors refer to an earlier paper (29).

Bronchoalveolar lavage was performed as follows; with the bronchoscope in a wedged position 3 × 50 ml of phosphate buffered saline (PBS) were instilled into the middle lobe and after each portion of PBS, suction was done into siliconized bottles placed on ice. The samples were immediately transported to the laboratory for analysis. On the basis of earlier results (29), T lymphocytes (CD3+), T helper/inducer (T_H) lymphocytes (CD3+4+), T cytotoxic/suppressor (T_C) lymphocytes (CD3+8+), and T lymphocyte activation markers CD28+, CD3+57+ and CD3+69+, together with the marker for Natural killer (NK) cells (CD3-56+16+) both in BAL and in blood were chosen for analysis. Bronchoalveolar lavage was performed during all bronchoscopies. In 11 out of 30 smokers and in one out of 18 never-smokers, the BAL FACScan analysis was impossible to interpret due to debris and dead cells. For a detailed description of the flow cytometry method and the analysis of inflammatory markers (HNL, MPO, IL-8, IL-1β, lysozyme, CC-16), earlier papers are referred to (21,29).

HIGH-RESOLUTION TOMOGRAPHY

The examination was performed with a Picker PQ 2000. The subjects were examined in a supine position and at full inspiration. The entire thorax was scanned with a slice thickness of 1.5 mm and 3 mm inter-slice distance. Exposure data were 130 kV and 200 mA. The images were reconstructed with the sharp algorithm of Picker and six images were copied to each 14" × 17" film. Window width was set at 1499 HU and the level at -400 HU.

The images were analysed from the hard copies by two experienced chest radiologists independently, without knowledge of whether the subject was a smoker or not. The radiologists analysed each slice in each lung. The diagnosis of emphysematous changes was based on findings of areas of low attenuation and/or the presence of stretched, narrowed vessels. The degree of emphysema was scored as 0=no emphysema, 1=1–25% of the parenchymal area was involved, 2=26–50% involvement, 3=51–75% involvement and 4=more than 75%. The scores for each slice and lung were added and the sum divided by the number of slices. In this way a score of total lung involvement could be calculated and the individual observer's evaluations compared. To evaluate

the interobserver agreement in the interpretation, a weighted kappa-analysis was used, which was 0.78 (36).

STATISTICAL METHODS

The distribution of values for T lymphocytes and lymphocyte subsets in blood and BAL, as well as soluble inflammatory markers in the same compartments, are presented with their mean and range. The distribution for T cells in the bronchial mucosa are presented with median and range. For lung-function variables, mean and standard deviation (SD) are presented. The χ^2 -test or Fischers' exact test, were used for the comparison of the proportions of different symptoms in the groups of smokers and never-smokers. The Mann-Whitney *U*-test was used for the comparison of different inflammatory markers in smokers with and without different symptoms. All tests were two-sided and *P*-values lower than 0.05 were regarded as significant. Abacus Concepts, Stat View 4.5[®] (Abacus Concepts, Inc., Berkely, CA, U.S.A.) was used as a statistical package. A professional statistician was also consulted.

Results

PREVALENCE OF RESPIRATORY SYMPTOMS

Although the smokers considered themselves healthy, both the diagnosis of chronic bronchitis and the respiratory symptoms of wheezing and non-specific trouble with breathing ('Do you ever have trouble with your breathing?') were common. Twenty-one of the 57 smokers (37%) gave a positive answer to this question, compared with nine of 33 never-smokers (27%) (*P*=0.23). Among these smokers, none had this symptom always, 3/21 had it repeatedly and 18/21 had it occasionally. Among the never-smokers that stated they had this symptom, most had it occasionally (5/9).

Fourteen of 57 smokers were classified as having chronic bronchitis (25%). Respiratory symptoms were classified as chronic bronchitis by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration, present on most days for a minimum of 3 months a year, for at least 2 successive years (37). Never-smokers with symptoms classified as chronic bronchitis (*n*=3) were excluded before the start of the study.

Wheezing was present in 22 of 57 (39%) of the smokers and in four of 33 (12%) of the never-smokers (*P*=0.0001).

Questions about dyspnoea 'sometimes at rest', 'sometimes at exercise', 'sometimes at night', resulted in very few positive answers and did not show significant differences between smokers and never-smokers.

As this study was aimed at evaluating the relationship between respiratory symptoms in smokers with a decrease in lung function, emphysema or inflammatory markers, only the data in smokers was chosen to be presented here.

Furthermore, the positive observations in never-smokers were too few for statistical analysis.

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND PACK-YEARS

Smokers that answered yes to 'Do you ever have trouble with your breathing?' and those who had chronic bronchitis, did not differ in pack-years as compared with smokers without these symptoms. Smokers with wheezing had significantly more pack-years as compared with smokers without this symptom [mean 38 (range 12–79) vs. 31 (9–56), *P*<0.001].

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND LUNG-FUNCTION TESTS

Smokers that answered yes to 'Do you ever have trouble with your breathing?' had significantly lower FEV₁ and VC than smokers that denied having this symptom (Table 1). Smokers with chronic bronchitis also had significantly lower FEV₁, FEV% and SGaw than smokers without this symptom (Table 1). Smokers with wheezing had significantly lower FEV₁, FEV% and SGaw than smokers without this symptom (Table 1). There was no significant relation between respiratory symptoms and DLco or the N₂ test.

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND BIOPSY FINDINGS

Smokers that answered yes to 'Do you ever have trouble with your breathing?' had significantly more CD8+T cells than those who denied this symptom (Table 2). There were no other relations between other respiratory symptoms and T cells or T cell sub-populations in bronchial biopsies.

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND LYMPHOCYTE SUB-POPULATIONS IN BLOOD AND BAL

Smokers that answered yes to 'Do you ever have trouble with your breathing?' had a significantly higher expression of the T cell activation marker CD69+ in blood as compared to smokers without this symptom— [0.12 (0–0.85) vs. 0.02 (0–0.09) × 10⁹/l, *P*=0.004. There was no difference in any other lymphocyte sub-population [CD3+, CD3+4+, CD3+8+, CD3+28+, CD3+57+, CD3+69+ (in BAL), CD3-56+16+] between the two groups in blood or BAL.

Smokers with chronic bronchitis (CB) had a significantly lower expression of the T cell activation marker, CD28+ [38% (31–54%), vs. 61% (24–87%), *P*=0.045] in BAL, as compared with smokers without CB. There was no difference in any other lymphocyte sub-population [CD3+, CD3+4+, CD3+8+, CD3+28+ (in blood), CD3+57+69, CD3–56+16+] between the two groups in blood or BAL.

TABLE 1. Symptoms and lung-function tests in smokers

	'Ever have problems with your breathing?'			Chronic bronchitis			Wheezing		
	Yes (n=21)	No (n=35)	P	Yes (n=14)	No (n=44)	P	Yes (n=22)	No (n=36)	P
TLC (% pred.)	94 ± 12	99 ± 14	n.s.	98 ± 12	97 ± 13	n.s.	98 ± 14	95 ± 12	n.s.
RV (% pred.)	120 ± 30	114 ± 34	n.s.	128 ± 36	112 ± 30	n.s.	124 ± 32	102 ± 24	0.02
VC (% pred.)	82 ± 10	92 ± 14	0.01	83 ± 10	90 ± 14	n.s.	86 ± 12	90 ± 14	n.s.
FEV ₁ (% pred.)	85 ± 13	100 ± 17	0.001	85 ± 11	97 ± 17	0.01	90 ± 16	99 ± 15	0.03
FEV%	71 ± 8	75 ± 7	n.s. (P=0.05)	70 ± 7	75 ± 7	0.04	72 ± 8	76 ± 6	0.03
sGaw	2.0 ± 1.2	2.5 ± 1.4	n.s.	1.6 ± 0.8	1.6 ± 0.8	0.01	1.8 ± 1.1	2.9 ± 1.5	0.004
N ₂ test (% pred.)	200 ± 90	183 ± 83	n.s.	206 ± 78	183 ± 86	n.s.	184 ± 50	172 ± 78	n.s.
DLCO (% pred.)	84 ± 14	82 ± 16	n.s.	83 ± 14	82 ± 16	n.s.	83 ± 12	83 ± 17	n.s.
DLCO/VA (% pred.)	85 ± 18	79 ± 15	n.s.	81 ± 86	82 ± 16	n.s.	82 ± 16	83 ± 17	n.s.

Data are presented as mean and standard deviation, *P*-value according to Mann-Whitney's *U*-test

TABLE 2. Respiratory symptoms in relation to biopsy findings in smokers

	'Ever have problems with your breathing?'			
	Yes [n=6 (22)]	No [n=7 (35)]	P	
Lymphocyte markers				
T lymphocytes	CD3 Epithelium	451 (206–593)	411 (84–911)	n.s.
	CD3 Lamina propria	408 (43–744)	184 (0–659)	n.s.
T helper	CD4 Epithelium	158 (0–365)	139 (0–384)	n.s.
	CD4 Lamina propria	161 (19–518)	41 (0–336)	n.s.
T cytotoxic	CD8 Epithelium	362 (295–700)	284 (121–625)	n.s.
	CD8 Lamina propria	272 (169–417)	98 (13–312)	0.02
Activation marker	CD69 Epithelium	172 (0–307)	62 (0–396)	n.s.
	CD69 Lamina propria	120 (0–222)	10 (0–194)	n.s.

Data are presented as median and range, *P*-value according to Mann-Whitney's *U*-test

Smokers with wheezing did not differ in any lymphocyte sub-population (CD3+, CD3+4+, CD3+8+, CD3+28+, CD3+57+, CD3+69+, CD3-56+16+), compared with smokers without wheezing.

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND SOLUBLE INFLAMMATORY MARKERS IN BLOOD AND BAL

Smokers that answered yes to 'Do you ever have trouble with your breathing?' did not differ in any soluble inflammatory marker measured in serum or BAL compared with smokers without this symptom.

Smokers with chronic bronchitis had higher HNL [200 (140–320) vs. 160 (80–301), *P*=0.02] and lysozyme [1570 (920–2120) vs. 1360 (790–2660), *P*=0.03] in serum as

compared with smokers without CB. There was no difference in BAL between the groups.

Smokers with wheezing also had higher HNL [180 (100–320) vs. 150 (80–220), *P*=0.03] and lysozyme [1640 (1040–2660) vs. 1250 (790–1770), *P*=0.004] in addition to myeloperoxidase (MPO) [280 (170–490) vs. 220 (120–310), *P*=0.04] in serum, compared with smokers without this symptom. There was no difference in BAL between the groups.

RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND EMPHYSEMA SCORE

Smokers with different respiratory symptoms such as occasional non-specific respiratory problems, chronic bronchitis and wheezing, did not differ in their emphysema score compared with smokers without these symptoms.

RELATIONSHIPS BETWEEN RESPIRATORY SYMPTOMS, BIOPSY FINDINGS AND LUNG FUNCTION

Smokers with decreased FEV₁ had a related increase in CD8+ T cells in the lamina propria compartment, as previously published (29). Smokers with both decreased FEV₁ and increased CD8+ cells answered positively to the question 'Do you ever have trouble with your breathing?' more often than smokers with normal lung function and CD8+ levels (Fig. 2).

Discussion

To the authors knowledge, no other study has investigated respiratory symptoms in smoking subjects chosen on the basis of being 'healthy', i.e. they have not sought medical attention due to any bronchial or pulmonary disease. As previously reported, these individuals had both decreased lung function, expressed as decreased FEV₁ and DLCO, as well as an increased N₂ test, and 44% also had emphysematous lesions on HRCT (21,22). Despite feeling healthy, they reported symptoms which they obviously considered to be part of their 'normal' condition. Smokers with occasional non-specific respiratory problems, chronic bronchitis symptoms and wheezing had decreased lung-function tests, e.g. FEV₁, FEV% and sGaw supposed to mainly reflect the central parts of the airways. Smokers with occasional non-specific respiratory problems also had more CD8+ cells in bronchial biopsies. No important differences were found between smokers with and without respiratory symptoms in other tests, such as DLCO and the N₂ test—supposed to mainly reflect the more peripheral parts of the airways (including the alveoli)—in HRCT-diagnosed emphysema or inflammatory markers in BAL.

In contrast to what the authors had expected, no difference in neutrophil-associated soluble inflammatory markers in BAL was found between smokers with and without respiratory symptoms (17,18,38,39). This may be

because BAL is thought to mainly reflect events in the peripheral parts of the airways including the alveoli, while respiratory symptoms belonging to chronic bronchitis and wheezing might reflect events in the more central airways. However, in the present study, smokers with chronic bronchitis or wheezing had increased serum levels of HNL and lysozyme and, for wheezing, increased serum levels of MPO. These soluble inflammatory markers in serum may reflect events in the more central airways or may be a marker of smoking (21). In BAL and blood, small differences in a few T cell activation markers were found between smokers with and without respiratory symptoms although these were of questionable biological significance. Thus, it seems that respiratory symptoms in 'healthy' smokers reflects inflammation in central airways but not in peripheral airways.

Several studies have demonstrated a relationship between a decrease in FEV₁ and an increase in CD8+ T cells in bronchial biopsies from the subsegmental airways of smokers, i.e. relatively central airways. This relationship has been seen in both 'healthy' smokers and smokers with known chronic bronchitis and/or COPD (27–29). In this study in smokers with only mild symptoms, it was found that these mild symptoms were more prevalent in subjects with decreased FEV₁ and increased CD8+ T cells. Even though the number of subjects was small, it underscores the importance of the relationship between FEV₁ and CD8+ cells and gives a clinical correlate. It further indicates that the increase in CD8+ cells could be an early finding in smokers' airway disease.

No relationship between respiratory symptoms and emphysema score was found. It is known from earlier studies that mild emphysema, a peripheral event, may affect lung parenchyma without subjects having respiratory symptoms (22,40,41). Non-specific respiratory symptoms are probably not signs of mild emphysema.

The present findings are consistent with a hypothesis that smokers' airway disease includes two separate processes, a more centrally localized bronchitis and a more peripheral alveolar destructive process. The more centrally localized bronchitis is mainly the result of a lymphocytic inflammation (28). It seems to give respiratory symptoms early in the process, in accordance with the present data where symptomatic subjects seemed to have more lymphocytic inflammation. The alveolar destructive process is the result of a more peripheral neutrophil-dominated inflammation (21,42) and causes fewer respiratory symptoms early in the process, as neutrophilic changes locally were less related to symptoms. These findings may explain why some patients have only mild respiratory symptoms despite severely impaired lung function and emphysema. It may be possible to develop severe emphysema without any obvious respiratory symptoms, in the absence of more centrally localized bronchitis.

In conclusion, mild respiratory symptoms are observed in smokers that consider themselves 'healthy'. These symptoms are related to an impaired FEV₁ and increased levels of CD8+ cells in bronchial biopsies and probably reflect a more centrally localized bronchitis. In contrast, early emphysematous changes and signs of peripheral airways

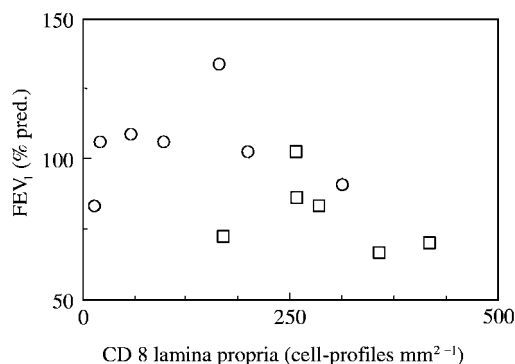


FIG. 2. The relationship between the respiratory symptom 'Do you ever have trouble with your breathing — rarely?' (□:yes; ○:no), biopsy findings (CD8+ cell/profiles mm²⁻¹) and lung function [FEV₁ (% pred.)].

disease, reduced DLCO and an increased N₂ test, seem not to be reflected in respiratory symptoms.

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