Changes in bronchial responsiveness to inhaled histamine over four years in middle aged male smokers and ex-smokers

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ABSTRACT Bronchial hyperresponsiveness to inhaled histamine in smokers is associated with an accelerated annual decline in FEV_1 and low baseline FEV_1 values. The evolution of bronchial hyperresponsiveness and whether it precedes or follows the accelerated decline in FEV_1 and reduction in FEV_1 is unknown. Measurements of the provocative concentration of inhaled histamine required to reduce FEV_1 by 20% (PC_{20}) were repeated after a four year interval in 27 male smokers (mean age 59 years, smoking on average 27 cigarettes a day in 1986) and 16 men who were ex-smokers in 1982 and who remained non-smokers until 1986 (mean age 53 years in 1986). These men were originally recruited to a prospective study in 1974 and had their first PC_{20} measurement in 1982. PC_{20} was positively related to baseline FEV_1 in both smokers and ex-smokers in both 1982 and 1986 (r ranging from 0.56 to 0.76, $p < 0.01$). In smokers mean FEV_1 fell from 83% to 77% predicted ($p < 0.001$) and geometric mean PC_{20} from 7.11 to 3.27 mg/ml ($p < 0.001$) between 1982 and 1986. The change in PC_{20} in individual smokers over the four years was related to change in FEV_1 ($p = 0.012$). In ex-smokers mean FEV_1 was 93% predicted both in 1982 and in 1986 and there was no significant difference in geometric mean PC_{20} between 1982 (6.68 mg/ml) and 1986 (5.98 mg/ml). Thus in smokers there was an accelerated annual decline in FEV_1 and an increase in bronchial hyperresponsiveness as FEV_1 fell. The ex-smokers had comparable levels of bronchial hyperresponsiveness in 1982. Mean PC_{20} values were unchanged in 1986 in these men, who showed a normal age related decline in FEV_1 . These longitudinal results emphasise the importance of baseline airway geometry in influencing bronchial hyperresponsiveness to histamine in middle aged smokers and ex-smokers.

Introduction

Longitudinal studies have shown that only a minority of cigarette smokers develop progressive deterioration of lung function sufficient to lead to appreciable disability.¹ More than 20 years ago Dutch workers proposed that susceptible smokers might be those individuals who showed non-specific bronchial hyperresponsiveness,² and subsequent studies have shown that smokers with an accelerated decline in lung function show bronchial hyperresponsiveness to methacholine³ and histamine.^{4,5} Although these findings are consistent with the "Dutch hypothesis," they do not distinguish between this hypothesis and

the possibility that the increased responsiveness is a consequence of accelerated decline in lung function. The natural history of established bronchial hyperresponsiveness in smokers and ex-smokers is unknown. In this paper we describe changes in FEV_1 and bronchial response to inhaled histamine between 1982 and 1986 in 27 men who continued to smoke and in 16 male ex-smokers who continued not to smoke.

Methods

SUBJECTS

The men studied were originally recruited to a prospective study of lung function in 1974⁶ and at that time any who gave a history of asthma were excluded. In 1982 the bronchial response to inhaled histamine was assessed for the first time.⁴ Of 223 men tested in 1982, 42 cigarette smokers and 23 ex-smokers had a provocative concentration of histamine that

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reduced FEV₁ by 20% (PC₂₀) of less than 32 mg/ml. In 1986 we restudied baseline FEV₁ and bronchial response to histamine in all the available men who had had a PC₂₀ below 32 mg/ml in 1982 and who had maintained consistent smoking habits in the interval—a total of 27 continuing cigarette smokers and 16 ex-smokers who had already stopped smoking in 1982 and had not resumed smoking in the years before our repeat study in 1986. Of the 15 smokers studied in 1982 who were not restudied in 1986, two had died of bronchogenic carcinoma, five had stopped smoking or switched to cigars or pipes, and eight refused to be restudied. Four men who had stopped smoking in 1982 had resumed in 1986 and three ex-smokers in 1982 declined to be restudied. Reported smoking habits were confirmed by several measurements of the fractional concentration of carbon monoxide in mixed expired gas and plasma cotinine concentrations. Subjects were not studied within six weeks of an upper or lower respiratory tract infection. None of the men was receiving bronchodilator treatment.

MEASUREMENTS

The men were studied between 09 00 and 12 00 hours, after first responding to a questionnaire regarding smoking habits and respiratory symptoms. Venous blood was drawn for measurement of total white blood cell counts, eosinophil counts, and total IgE levels. Skin reactivity to extracts from nine commonly inhaled antigens (grass pollen, cat and dog dander, mixed feathers, *Alternaria* sp, *Cladosporium* sp, *Aspergillus fumigatus*, house dust, and *Dermatophagoides pteronyssinus*) was assessed by prick tests in forearm skin. The response to the test was recorded as positive when the mean weal diameter was over 2 mm. Technical details of these measurements have been described.⁷

Forced expiratory volume in one second (FEV₁) was measured in the standing position with a dry bellows spirometer,⁸ which was calibrated daily. The highest FEV₁ from three technically satisfactory forced expirations expressed at BTPS was taken as the baseline and compared with reference values.⁹ The PC₂₀ histamine was then determined with the same equipment and technique as was used in the 1982 study.^{4,10} Subjects wore a noseclip and inhaled a solution of 0.9% saline followed by doubling concentrations of histamine phosphate (0.5–32 mg/ml) generated by a compressed air driven Wright nebuliser at a flow rate of 7.5 l/min through a mouthpiece during tidal breathing for two minutes. The output of the nebuliser, which was checked regularly, was 0.14 ml/min. FEV₁ was recorded at 60 and 90 seconds and then at two minute intervals to determine the lowest value after each inhalation. The

challenge was terminated when FEV₁ fell below 20% of the lowest post-saline value or the 32 mg/ml concentration of histamine was reached. The PC₂₀ histamine was obtained by linear interpolation from log dose-response curve.

ANALYSIS

The annual decline in height corrected FEV₁ (ml/m³/yr) between the two measurements of histamine response was calculated by subtracting the highest baseline value recorded in 1986 from the highest value in 1982 and dividing by the cube of the height in metres. Because four year estimates of change in FEV₁ have a relatively low signal to noise ratio, we also calculated the annual change in FEV₁ between 1974 and 1986 using the highest baseline value obtained in 1974. All PC₂₀ and IgE values were logarithmically transformed before analysis, and geometric mean values were derived. Student's *t* test was used to compare group mean values and to determine differences in paired observations between and within groups. The change in PC₂₀ (Δ PC₂₀) in an individual was regressed on the change in FEV₁ to obtain the relationship between trends in the two measurements over the four years. *P* values below 0.05 were considered statistically significant.

Results

In 1986 the mean (SEM) reported cigarette consumption for smokers was 27 (2.5) per day. The ex-smokers who had stopped smoking for a mean period of 11 (2.6) years and a minimum of 5 years, were younger and had significantly more features suggestive of atopy with a larger number of positive skin test responses and higher total serum IgE levels (table 1). Nevertheless there was no significant correlation between PC₂₀ values and either skin test scores or IgE levels and no significant difference in either FEV₁ or PC₂₀ values between men with two or more positive skin prick responses and those with less than two positive responses. Current smokers had significantly higher total white cell counts than ex-smokers, although the absolute eosinophil counts were not different.

Baseline FEV₁ was significantly related to PC₂₀ in both smokers and ex-smokers in 1982 (*r* = 0.69 and 0.67, *p* < 0.01 for both) and in 1986 (*r* < 0.56 and 0.76, *p* < 0.001) (fig 1). Similar relationships were found when FEV₁ was expressed as a percentage of the predicted value. Though ex-smokers had larger baseline FEV₁ values (both absolute values and % predicted) than continuing smokers in 1986, the response to histamine did not differ significantly between smokers and ex-smokers (table 1). Indeed histamine responsiveness at a given FEV₁ % predicted value appeared to be slightly greater in our ex-smokers.

Table 1 Baseline data (mean (SEM) values) for smokers and ex-smokers in 1982 and 1986

	Ex-smokers (n = 16)	Smokers (n = 27)	p
Measurements in 1986			
Age (y)	53 (2.7)	59 (1.2)	0.02
Height (m)	1.76 (0.01)	1.73 (0.01)	0.096
No of positive skin responses	1.6 (0.4)	0.3 (0.1)	0.01
WBC ($\times 10^9/l$)	6.75 (0.3)	8.81 (0.5)	0.002
Eos ($\times 10^9/l$)	0.25 (0.02)	0.26 (0.02)	0.79
IgE (U/ml)			
log ₁₀	2.12 (0.09)	1.64 (0.11)	0.01
geometric mean	131.0	43.7	
PC ₂₀ (mg/ml)			
1982 log ₁₀	0.825 (0.09)	0.852 (0.09)	0.83
geometric mean	6.68	7.11	
1986 log ₁₀	0.777 (0.12)	0.515 (0.10)	0.10
geometric mean	5.98	3.27	
FEV ₁ (l)			
1982	3.27 (0.16)	2.66 (0.11)	0.004
1986	3.15 (0.18)	2.38 (0.11)	0.001
FEV ₁ (% pred)			
1982	93.0 (4.0)	83.0 (4.0)	0.057
1986	93.0 (4.0)	77.0 (4.0)	0.0056

WBC—total white blood cell count in peripheral blood; Eos—total blood eosinophil count; IgE—total serum IgE; PC₂₀—provocative concentration of histamine causing a 20% fall in FEV₁.

FEV₁(l) CURRENT SMOKERS FEV₁(l) EX-SMOKERS

Fig 1 Relation between baseline FEV₁ and histamine responsiveness (expressed as the provocative concentration causing a 20% fall in FEV₁, PC₂₀) in 27 smokers (left panel) and 16 continuing ex-smokers (right panel). Measurements in 1982 (○) and 1986 (●) in each subject are joined by solid lines. Correlation coefficients (r) are shown for the relation between FEV₁ and PC₂₀ in 1982 and 1986.

Table 2 Mean (SEM) changes with time in FEV₁ and histamine responsiveness (PC₂₀) in smokers (S) and ex-smokers (XS)*

	Ex-smokers (n = 16)	Smokers (n = 27)	p (XS v S)
1982-6			
Annual Δ FEV ₁ /ht ³ (ml/m ³ /y)	5.9 (2.3)	13.9 (2.2)	0.02
Δ PC ₂₀ (mg/ml)			
Δ log ₁₀	0.0492 (0.053)	0.336 (0.061)	0.0007
Δ geometric mean†	1.12*	2.17	
1974-6			
Annual Δ FEV ₁ /ht ³ (ml/m ³ /y)	8.3 (1.1)	13.4 (1.1)	0.03

*Changes in all measurements over time were significant (paired *t* test), *p* < 0.001, except change in PC₂₀ in ex-smokers (*, *p* = 0.37).

†Ratio of geometric mean PC₂₀ 1982 to geometric mean PC₂₀ 1986.

than in the continuing smokers (fig 2).

There was a good correlation between values of PC₂₀ measured in 1982 and in 1986 in individual smokers and ex-smokers (fig 1). Between 1982 and 1986 mean values of FEV₁ (in litres and as % pred) and PC₂₀ declined significantly in smokers (mean decline 70 ml/year) but only absolute FEV₁ declined significantly in ex-smokers (table 2) (fig 2). Indeed, FEV₁ when expressed as % pred was identical in 1982 and 1986 in ex-smokers.

In individual smokers the change in PC₂₀ over four years (1982-6) was positively related to the decline in FEV₁ (expressed as ml.m⁻³.y⁻¹) (*r* = 0.463, *p* = 0.012). The regression of Δ log PC₂₀ on Δ FEV₁ had a slope of 12.23 (SEM 4.55) in smokers. For ex-

smokers the slope was 9.22 (5.46), which did not differ significantly from zero or from the slope obtained for smokers (difference in slopes 3.01, 95% confidence interval -13.06 to 19.08).

The mean annual decline in FEV₁ in smokers over the 12 years 1974-86 was similar to that observed from 1982 to 1986 (table 2). The 12 year decline in FEV₁ was correlated negatively with 1986 values of baseline FEV₁ (*r* = -0.480, *p* < 0.02) and PC₂₀ (*r* = -0.481, *p* < 0.02). In ex-smokers the annual decline in FEV₁ over 12 years was somewhat greater than the decline during 1982-6. This was expected as in the early years of follow up some individuals were smoking.

Discussion

Since the first descriptions in the 1960s^{2,12} many studies have confirmed that smokers with some degree of airflow obstruction but without evidence of atopy show bronchial hyperresponsiveness to inhaled histamine and methacholine. Moreover, smokers with bronchial hyperresponsiveness are known to have had a faster annual decline in FEV₁ than smokers without hyperresponsiveness.³⁻⁵ A reduced FEV₁, however, is an important association of a low PC₂₀ in smokers^{4,13-15} and it is also commonly associated with a preceding accelerated decline of FEV₁ ("horseracing effect").¹ Because of these close interrelations between baseline FEV₁, bronchial hyperresponsiveness, and rate of decline in FEV₁, it is uncertain whether hyperresponsiveness is important in the pathogenesis of progressive airflow obstruction in smokers or merely a consequence of its development, analogous to the development of increased vascular reactivity in hypertension.¹⁷

In this study we have shown that smokers and ex-smokers who had bronchial hyperresponsiveness in 1982 still had it in 1986. Over the four years there was an association between accelerated decline in FEV₁ and reduction in PC₂₀ in smokers, whereas in ex-smokers there was only the predicted age related decline in FEV₁ and no change in mean PC₂₀. A

Fig 2 Comparison of geometric mean and SEM PC₂₀ values and baseline FEV₁ % pred between smokers and ex-smokers in 1982 and 1986. The open symbols represent measurements in 1982 and the closed symbols the 1986 values. The asterisks indicate a significant fall in both FEV₁ % pred and PC₂₀ in smokers over this period according to paired *t* tests. (Reproduced from Pride et al¹¹ by courtesy of the Bulletin Européen de Physiopathologie Respiratoire.)

expected from our earlier analysis of the larger group that contained these men in 1982,⁴ baseline FEV₁ was correlated with PC₂₀, in both smokers and ex-smokers. Similar correlations were found in the 1986 results. These results confirm those of many other investigators who have studied patients with "chronic obstructive pulmonary disease" or middle aged smokers^{4,5,13-16}; this relation is much less consistent in asthma.¹⁸

Our new finding is that as a group smokers showed a significant decline in PC₂₀ over the four years' follow up and that in individual smokers the extent of decline in PC₂₀ was related to the rate of annual decline in FEV₁. Because we first measured bronchial responsiveness in these men when they had already smoked for many years and often had some degree of airflow obstruction, we cannot conclude that bronchial hyperresponsiveness followed rather than preceded the development of airflow obstruction in 1982, but our follow up results strongly indicate that airway geometry plays an important part in determining hyperresponsiveness. We believe that the results in ex-smokers also support this conclusion. In the ex-smokers, although on average FEV₁ in 1982 was slightly below expected values, over the following four years there was only the predicted age related further decline, so that the mean FEV₁ value was 93% of the predicted value in both 1982 and 1986. Despite this normal rate of decline in FEV₁, on average there was no attenuation of bronchial hyperresponsiveness. Because inflammatory changes, as indicated by white blood cell counts,⁷ cell counts from bronchoalveolar lavage fluid,¹⁹ and sputum volume,²⁰ are usually reduced after stopping smoking, we interpret the overall lack of change in PC₂₀ in ex-smokers as emphasising the role of geometric rather than inflammatory changes in determining PC₂₀ in smokers. In the only other follow up studies of bronchial hyperresponsiveness in smokers we have identified, Simonsson and Rolf²¹ also found no attenuation of bronchoconstrictor responsiveness in two mildly responsive men in the first year after stopping smoking, while Buckzo *et al*²² found no change in methacholine responsiveness in 17 smokers 99 days on average after they reported stopping smoking.

When our longitudinal study started in 1974 we excluded men who gave a history of asthma or were receiving bronchodilator treatment.⁶ Subsequently we have analysed the significance of atopic factors (positive skin test responses to common inhalant allergens, a family history of asthma or rhinitis, raised total blood IgE and peripheral blood eosinophil counts) in the recruited men^{4,7} and found an increased prevalence of positive skin responses in ex-smokers. This, together with a higher mean value for total blood IgE, was also found in the present subgroup of ex-smokers (table 1). Thus an alternative interpretation

of our results in ex-smokers is that some of them had a subclinical form of asthma: in these men bronchial hyperresponsiveness might have been "endogenous," predating the onset of smoking, and stopping smoking might have been preferentially induced by symptoms related to the hyperresponsiveness. Against this alternative explanation, these men had averaged 29.7 pack years of smoking before stopping and we found no relation between PC₂₀ and either IgE levels or skin test reactivity in the present subgroup with bronchial hyperresponsiveness, or in the larger group of ex-smokers with and without bronchial hyperresponsiveness from whom these men were drawn.⁴

Previous studies have shown that bronchial hyperresponsiveness is associated with preceding accelerated annual decline in FEV₁ in smokers; in the present study we have been able to show this prospectively, smokers showing a considerably greater rate of decline in FEV₁ than ex-smokers studied concurrently or than never smokers and a less selected group of smokers studied earlier in our laboratory.⁴ Although the follow up period of four years is relatively brief for establishing the annual rate of decline in FEV₁, this is less of a problem in studying smokers with accelerated decline and similar rates were obtained when decline was calculated over a 12 year period (eight years before and four years after the first measurement of bronchial responsiveness). Further studies of the relation between PC₂₀ in 1982 and the subsequent course of lung function are planned.

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