

The importance of serum IgE for level and longitudinal change in airways hyperresponsiveness in COPD

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Summary

Background Airways hyperresponsiveness (AHR) is an important feature of patients with chronic obstructive pulmonary disease (COPD). Little is known about factors that modulate AHR in COPD.

Objective To study these factors, we performed a long-term, double-blind, parallel intervention study in 58 male, non-allergic patients with COPD.

Methods During a period of 2 years, patients were treated with inhaled budesonide (1600 µg/day), inhaled budesonide (1600 µg/day) plus oral prednisolone (5 mg/day), or placebo. PC₂₀ histamine was measured at 4-monthly intervals. The influence of treatment, smoking, age, level of lung function, initial serum IgE level and peripheral blood eosinophils on level and longitudinal change of PC₂₀ histamine was analysed.

Results During follow-up, PC₂₀ decreased in our group, and this decrease was not influenced by treatment. PC₂₀ tended to decrease faster in current smokers than in ex-smokers. PC₂₀ was significantly associated with pre-challenge FEV₁ at each time point. Level nor decline of PC₂₀ were significantly related to age. A higher initial serum IgE level was independently associated with a lower PC₂₀. Moreover, a higher initial serum IgE level was associated with a slower annual decline of PC₂₀, regardless of treatment, pre-challenge FEV₁, and other modulating factors. No significant associations were found between initial blood eosinophils and level or decline of PC₂₀.

Conclusion We conclude that AHR increases over time in non-allergic patients with COPD. Treatment with an inhaled corticosteroid alone or in combination with oral prednisolone does not change this increase. Our study suggests an important role for IgE in the course of the disease, since a higher initial serum IgE level predicts a more favourable course with regard to annual decline of PC₂₀ histamine.

Keywords: chronic obstructive pulmonary disease, airways hyperresponsiveness, corticosteroids, IgE

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Introduction

Airways hyperresponsiveness (AHR) is a characteristic feature of patients with obstructive airway disease, both asthma and chronic obstructive pulmonary disease (COPD) [1]. It is thought to result from inflammatory processes in the airways, although the type, location, and intensity of inflammation may differ between the two disease entities

[2]. AHR is an important phenomenon, not only because of the presumed role as risk factor for the development of asthma and COPD [3–5], but also because of the relation with the prognosis of both disease entities [6,7].

AHR may be regarded as the expression of complex relationships between genetically determined factors and environmental factors such as atopy and smoking [8]. An extensive overview of determinants of AHR has been provided by O'Connor *et al.* a few years ago [9]. In asthma, the main determinant of hyperresponsiveness is

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allergy, the presence of which is usually demonstrated by positive skin tests, elevated levels of specific or total serum IgE, and blood eosinophilia. An effect of level of lung function on AHR has been demonstrated in asthmatics [10], although less consistently than in patients with COPD. In COPD, factors modulating AHR are less clear [7]. The repeatedly observed correlation between hyperresponsiveness and pre-challenge level of lung function in COPD points to the importance of airway diameter as a determinant of hyperresponsiveness in these patients. More often than in asthma, evidence of allergy is absent. Yet epidemiological studies in older men have found an association between IgE and AHR [11] and between eosinophilia and AHR [12], independently of skin-test reactivity, a diagnosis of asthma, and smoking status. Although smoking is generally regarded as the most important risk factor for development of COPD and the most important cause of subsequent ongoing accelerated decline in lung function, the effect of smoking on AHR has not been elucidated. Data from epidemiological studies suggest that smoking may cause increased AHR, at least in subjects with a large number of pack years. Older age is associated with accelerated decline in lung function in patients with COPD. In cross-sectional studies an age-related increase of AHR has been observed, at least after 40 years of age. It is unclear, however, whether this increase is caused by an age effect itself or by an age-related change in level of pulmonary function [9]. Even less is known about the longitudinal change of AHR in COPD and its relation with lung function, smoking, and atopic parameters.

Based on the hypothesis that inflammation plays a key role in the expression of AHR, corticosteroids have been advocated for the treatment of patients with obstructive airway disease. These drugs have been shown to successfully reduce AHR in asthma in both short- and long-term studies [13]. Short-term studies in COPD do not show any benefit, whereas long-term studies are scarce [14]. In addition, their interpretation is often hampered by patient selection, for instance because of inclusion of allergic individuals [15] or patients with rapidly deteriorating lung function [16].

The aim of our study was to investigate the influence of long-term treatment with corticosteroids and modulating factors, such as age, level of lung function, smoking, total serum IgE, and peripheral blood eosinophils, on airways hyperresponsiveness in a group of non-allergic patients with COPD.

Patients and methods

Patients

Fifty-eight male patients were selected from the pulmonary outpatient clinic according to the following selection criteria:

- clinical diagnosis of COPD based on history (persistent

dyspnoea, mainly on exertion, without sudden attacks of dyspnoea);

- forced expiratory volume in one second (FEV₁) < 80% of the predicted value;
- residual volume (RV) > 100% of the predicted value;
- specific compliance expressed as a percentage of the predicted value (C_{sp} percentage predicted) > 100% after bronchodilation; when, however, air trapping (calculated as thoracic gas volume measured by body plethysmography minus functional residual capacity measured with an indicator gas) [17] was greater than 1.5 L, specific compliance was allowed to be < 100% of predicted;
- no signs of allergy (negative skin tests, total serum IgE < 200 IU/mL, eosinophils in peripheral blood < $250 \times 10^3/\text{mL}$);
- stable phase of the disease;
- age ≤ 70 years.

Excluded were patients on continuous corticosteroid therapy and patients with severe concomitant disease, likely to interfere with the purpose of the study.

Smokers as well as ex-smokers were included. All ex-smokers had stopped smoking at least 1 year before entering the study, except one patient who stopped 4 months before entry. Smoking history was expressed as pack years (estimated average number of packs of 25 cigarettes smoked per day $\times$ number of years of smoking).

Study design

The study was designed as a randomized, double-blind, placebo-controlled trial with three parallel treatment arms. Prior to the study, all patients received a short course of oral prednisolone (40 mg/day, during 8 days) in order to assess corticosteroid responsiveness. After a run-in period of at least 3 months without any corticosteroid medication baseline measurements were carried out and patients were allocated blindly (by computerized randomization stratified for smoking) to one of the following 2-year treatment regimens:

- inhaled budesonide 800 μg b.i.d. plus placebo tablet once daily;
- inhaled budesonide 800 μg b.i.d. plus oral prednisolone 5 mg once daily;
- placebo inhalations b.i.d. plus placebo tablet once daily.

Budesonide (or placebo inhalation) was inhaled from a metered dose inhaler (m.d.i.) through a 750 mL spacer (Nebuhaler^R, Astra/Draco, Sweden). At each visit, the inhalation technique was checked.

During the study, PC₂₀ histamine was measured 6 times at 4-monthly intervals. The measurements were only done during clinically stable periods and they were always carried out on the same time of day, after the patients had refrained from bronchodilators for at least 8 h.

Throughout the study, patients were maintained on their usual bronchodilator medication, consisting of anti-cholinergics, β -agonists, theophylline, or a combination of these drugs. Theophylline serum levels were checked regularly (therapeutic range: 8–15 mg/L). Exacerbations were treated in a standardized way with a short course of oral prednisolone (35 mg/day decreasing by 5 mg/day to 0 mg in 7 days), which was combined with an antibiotic (amoxicillin or doxycycline) in case of a microbial infection; meanwhile all other medication was continued.

Patients were free to withdraw from the study at any time. Patients were withdrawn by the investigators in case of: (1) three or more exacerbations within 3 consecutive months (2) severe, progressive deterioration of lung function without infectious origin and failing to react to a short course of oral prednisolone.

Informed consent was obtained from all participants. The study protocol was approved by the medical ethics committee of the hospital.

Methods

Airways hyperresponsiveness was measured with serial inhalations of histamine diphosphate solutions in doubling concentrations ranging from 0.5 to 32 mg/mL [18]. The solutions were nebulized with a 'Wiesbadener Doppelspray' (Wiesbadener Inhalatoren-Vertrieb, Wiesbaden, Germany) with an airflow of 8 L/min. Nebulizer output was 0.12 mL/min, and particle size was less than 5 μ m [19]. The aerosols were inhaled for 30 s during tidal breathing in a semi-closed system, until a fall in FEV₁ of $\geq 20\%$ as compared with baseline, or until the highest concentration was reached. The provocation concentration of histamine required to produce a fall in FEV₁ of 20% (PC₂₀ value) was calculated from the log dose–response curve. A PC₂₀ of 32 mg/mL by this method is roughly equivalent to a PC₂₀ of 8 mg/mL by the method of Cockcroft *et al.* [20].

Slow inspiratory VC, FEV₁ and FIV₁ were measured with a water-sealed spirometer (Lode BV, Groningen, The Netherlands). Reversibility of airways obstruction was tested with terbutaline (2 puffs of 250 μ g per m.d.i.). RV and TLC were determined by the closed-circuit helium dilution method. All volumes are expressed as ATPS. Static compliance was calculated from the volume-pressure diagram of the lung, obtained by means of an intra-esophageal balloon. Predicted values for lung volumes and lung mechanics were those of Quanjer *et al.* [21].

Total serum IgE concentrations were quantified using the enzyme immuno-assay procedure (Pharmacia Diagnostics BV, Uppsala, Sweden). Blood eosinophil numbers were counted in a Bürker chamber after staining with eosine.

Drug intake was expressed as percentage of the prescribed intake by weighing of canisters and counting of tablets.

Statistical analysis

Statistical analysis was performed on a personal computer, using SPSS/PC + [22] and BMDP [23] programs. The distribution of data was examined with the Kolmogorov–Smirnov test for normal distributions [22]. To normalize the distributions, serum IgE and blood eosinophil numbers were transformed to the base-10 logarithm; PC₂₀ values were transformed to the base-2 logarithm, since this reflects doubling concentrations. Values are presented as mean $\pm$ 1 SE, unless stated otherwise.

Individual data plots of our patients showed that the change in PC₂₀ with time could appropriately be expressed by a linear function. Therefore, the rate of decline of PC₂₀ was assessed by calculating individual regression coefficients from linear regression of PC₂₀ on time for each subject, and expressed as PC₂₀ histamine slope. Patients were excluded from the analysis if less than three PC₂₀ measurements were available. The influence of treatment, initial level of lung function, age, smoking, serum IgE level and blood eosinophils on the PC₂₀ histamine slope was examined for each factor individually. Treatment effect on PC₂₀ histamine slope was analysed using ANOVA. For all other factors, patients were assigned to one of two strata: one containing values smaller than the (geometric) mean value and the other containing values equal to or greater than the (geometric) mean value of the factor involved. With regard to smoking, patients were classified as smokers or ex-smokers. Differences in PC₂₀ histamine slope between strata were analysed using unpaired *t*-tests.

As follow-up varied because of withdrawal before the end of the study, the estimates of the individual slopes have different variances. Therefore we performed additional analysis of PC₂₀ using the unbalanced repeated measures model from the BMDP (module 5 V) statistical package (random effects) [23]. This technique corrects for the fact that intra- as well as inter-individual comparisons are made and can handle time-varying covariates and missing data. In this way, all the available data are used. In the model, PC₂₀ was the dependent variable. Age, smoking (as a dichotomous variable: current or ex-smoker), serum IgE, and peripheral blood eosinophils, all as measured at the start of the study, pre-challenge FEV₁ (as percentage of predicted) at each time point, treatment, time since the start of the study, and interaction terms were entered as covariables to assess their independent influence on level and longitudinal change of PC₂₀. All covariables used in the model were entered at once. Again, patients were excluded from the analysis if less than three PC₂₀ measurements were available.

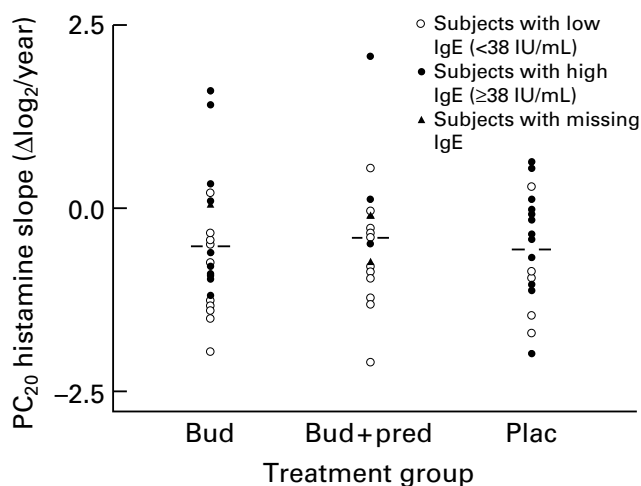


Fig. 1. Individual PC₂₀ histamine slopes per treatment group. The individual PC₂₀ histamine slopes (expressed as $\Delta\log_2$ PC₂₀ histamine/year) were calculated from linear regression of PC₂₀ histamine on time for each subject. Horizontal bars indicate the mean value in each treatment group.

Results

A group of 58 non-allergic patients with COPD was included in this study. Baseline characteristics were not significantly different in the three treatment groups (Table 1). Corticosteroid responsiveness, as assessed from the effect of a short course of oral prednisolone, was low in each treatment group: mean FEV₁ decreased on prednisolone. When response was expressed as an increase in FEV₁ of more than 20% from baseline, there were only three responders (Table 1). Sputum production was low (median production ≤ 5 mL/24 h) in all three groups. There was no significant difference in bronchodilator maintenance treatment among the three treatment groups (see Table 1). When patients were grouped according to actual smoking habit, no significant differences between smokers and ex-smokers were found with regard to age, pack years, lung function, reversibility of airway obstruction, baseline PC₂₀ histamine, serum IgE level and blood eosinophil number. Smoking habits remained remarkably constant during the study. The effects of long-term treatment with corticosteroids according to the protocol of this study on decline of FEV₁, symptoms and exacerbations have been published elsewhere [24].

Compliance

Weighing of the canisters and counting of the tablets showed that patient compliance was high. Mean use of tablets was not significantly different in the three treatment groups (100 ± 16 , 98 ± 17 and $102 \pm 21\%$ of the prescribed intake in the budesonide (bud), budesonide plus

prednisolone (bud + pred), and placebo (plac) group, respectively), nor was mean number of inhaled puffs (101 ± 23 , 99 ± 21 and $106 \pm 31\%$ of the prescribed intake in the bud, bud + pred, and plac group, respectively). Compliance was not significantly different between patients who completed the whole study and withdrawals (mean use of $100 \pm 17\%$ and $100 \pm 28\%$ in completers and withdrawals, respectively; mean number of inhaled puffs $101 \pm 23\%$ and $109 \pm 41\%$ in completers and withdrawals, respectively).

Withdrawals

Eleven patients dropped out of the study, two from the bud group (after 2 and 10 months of treatment, respectively), four from the bud + pred group (after 2, 4, 12 and 14 months, respectively), and five from the plac group (after 4, 12, 16, 20 and 22 months, respectively). Withdrawals were divided into two categories: patients who dropped out because of pulmonary problems (seven patients) and those who dropped out irrespective of pulmonary condition (four patients). Three patients of the latter category dropped out because they were unable to combine the intensive, 2-year study protocol with their usual daily activities; one patient withdrew because he turned out to be unwilling to take any medication.

Airways hyperresponsiveness

For the whole group ($n = 58$), the number of PC₂₀ histamine measurements obtained per patient during follow-up was distributed as follows: 34 patients had seven measurements, the maximum obtainable number, 11 had six, one had five, three had four, four had three, two had two, and three patients had one measurement. Individual values of PC₂₀ histamine slope (expressed as the annual change in $\log_2$ PC₂₀ histamine) per treatment group are shown in the figure. Mean (SE) values of the PC₂₀ histamine slope according to treatment and other subgroups are shown in Table 2. In the group as a whole and in every subgroup, the degree of hyperresponsiveness increased during the study. Mean PC₂₀ histamine slope was not significantly different in the three treatment groups. No significant differences in mean PC₂₀ histamine slope were found when patients were stratified for FEV₁, age, actual smoking habit or blood eosinophil number, all measured at baseline. In patients with a serum IgE level < 38 IU/mL, mean annual decline of PC₂₀ histamine was significantly larger than in patients with a serum IgE level ≥ 38 IU/mL (-0.85 ± 0.14 vs -0.18 ± 0.19 $\Delta\log_2$ PC₂₀ histamine/year).

Additional analysis of PC₂₀ histamine was performed using a random effects model (see Methods). Regression coefficients of the independent variables are shown in

Table 1. Patient characteristics

	Budesonide	Budesonide + prednisolone	Placebo
Number of patients	21	19	18
Smokers (<i>n</i>)	9	9	8
Age (years)	56 ± 8	58 ± 8	54 ± 10
Pack years	25 ± 21	30 ± 17	29 ± 20
FEV ₁ (L)	2.16 ± 0.58	1.86 ± 0.56	1.90 ± 0.66
FEV ₁ % pred (%)	67 ± 15	61 ± 15	60 ± 18
FEV ₁ % VC (%)	48 ± 11	44 ± 10	44 ± 10
RV % pred (%)	151 ± 35	158 ± 15	165 ± 39
TLC % pred (%)	111 ± 17	113 ± 15	113 ± 17
PC ₂₀ histamine (mg/mL)	5.94	4.66	4.90
ΔFEV ₁ [terb] % pred (%)	7 ± 7	6 ± 6	6 ± 5
ΔFEV ₁ [predn.] % pred (%)	-2 ± 11	-2 ± 13	-1 ± 8
Predn. responders (<i>n</i>)	1	2	0
Eosinophils (10 ³ /mL)	125	84	122
Total serum IgE (IU/mL)	39	22	59
Bronchodilator users (<i>n</i>)			
Anticholinergics	17	18	18
β-agonists	8	4	5
Theophylline	6	4	8

Values are expressed as mean ± SD, except PC₂₀ histamine, peripheral blood eosinophils, and total serum IgE which are presented as geometric mean. Pack years were calculated as the estimated average number of packs of 25 cigarettes smoked per day × number of years of smoking. FEV₁, forced expiratory volume in one second; FEV₁ % pred, forced expiratory volume in one second, expressed as a percentage of the predicted value; FEV₁ % VC, FEV₁ expressed as a percentage of slow inspiratory vital capacity, RV % pred, residual volume expressed as a percentage of the predicted value; TLC % pred, total lung capacity expressed as a percentage of the predicted value; PC₂₀ histamine, provocative concentration of histamine causing a 20% fall of FEV₁ from baseline after inhalation during 30 s; ΔFEV₁[terb] % pred, change in FEV₁ after inhalation of 2 × 250 μg terbutaline per mdi, expressed as a percentage of predicted FEV₁; ΔFEV₁[predn] % pred, change in FEV₁ after a short course of oral prednisolone (40 mg/day, during 8 days), expressed as a percentage of predicted FEV₁; predn responders, patients having an increase in FEV₁ greater than 20% from baseline on an 8-day prednisolone course.

Table 3. Pre-challenge level of lung function was weakly but highly significantly correlated with PC₂₀ histamine. No significant interaction effect of treatment and time on PC₂₀ histamine was found. In other words, there was no significant effect of treatment on change in the degree of hyper-responsiveness over time. Age was not significantly associated with level or decline of PC₂₀ histamine. Smoking had a negative effect on both level and decline of PC₂₀ histamine, but these effects did not reach statistical significance. Serum IgE level was significantly associated with the degree of airway responsiveness: a higher serum IgE level was correlated with a lower PC₂₀ histamine. Moreover, serum IgE level was a significant predictor of the change of PC₂₀ histamine over time: a higher serum IgE level was

associated with a smaller annual decline of PC₂₀ histamine. No significant interaction effects of IgE and age, smoking, FEV₁% prednisolone, or treatment group on level or decline of PC₂₀ histamine were found. When the number of peripheral blood eosinophils was entered in the model instead of serum IgE level, no significant effects of eosinophil number on level or decline of PC₂₀ histamine were found.

Although our study group was small, we performed a subgroup analysis with the same model in actively and placebo-treated patients separately. Analysis of the group of actively treated patients (*n* = 36) yielded the same results as the analysis of the whole group. Total serum IgE level showed a significant negative correlation with level of PC₂₀ histamine and a significant positive correlation with change

Table 2. Mean (SE) PC₂₀ histamine slope (expressed as $\Delta\log_2$ PC₂₀ histamine/year) per subgroup

Subgroups	Number of patients	PC ₂₀ histamine slope	P for differences between subgroups
<i>Treatment</i>			
Budesonide	20	−0.52 (0.21)	0.925
Budesonide + prednisolone	16	−0.45 (0.23)	
Placebo	17	−0.57 (0.19)	
<i>Baseline FEV₁</i>			
< 63% pred	27	−0.51 (0.18)	0.946
≥ 63%	26	−0.52 (0.16)	
<i>Age</i>			
< 56 years	27	−0.63 (0.16)	0.320
≥ 56 years	26	−0.39 (0.18)	
<i>Smoking</i>			
Current smokers	22	−0.64 (0.18)	0.390
Ex-smokers	31	−0.43 (0.16)	
<i>Serum IgE</i>			
< 38 IU/mL	26	−0.85 (0.14)	0.007
≥ 38 IU/mL	24	−0.18 (0.19)	
<i>Blood eosinophils</i>			
< 110 × 10 ³ /mL	22	−0.64 (0.18)	0.393
≥ 110 × 10 ³ /mL	28	−0.43 (0.17)	

For abbreviations and units of measurement, see Table 1.

of PC₂₀ histamine over time. In the group of placebo-treated patients ($n = 17$) the trends for the relation between serum IgE level and PC₂₀ histamine were the same, but the associations did not reach statistical significance. In both subgroups, as in the whole group, pre-challenge FEV₁ was weakly but highly significantly associated with level of PC₂₀ histamine.

Discussion

Our study shows that airways hyperresponsiveness increases over time in non-allergic patients with COPD. Long-term treatment with an inhaled corticosteroid, alone or in combination with oral prednisolone, does not change this increase. Like many other investigators, we found a significant correlation between pre-challenge level of lung function and histamine responsiveness. An important observation is that in this group of non-allergic COPD patients a higher total serum IgE level was significantly associated with a lower PC₂₀ histamine and a smaller decline of PC₂₀ histamine over time, independent of pre-challenge FEV₁ and other modulating factors.

Our knowledge about factors modulating the expression of airways responsiveness is mainly derived from cross-sectional

population studies. Factors detected thus far are the presence of allergy and the level of exposure to allergens, pre-existing airway narrowing, age, and smoking or other environmental irritants [9]. Longitudinal studies on this subject are very scarce. Lim *et al.* showed an accelerated decline of FEV₁ and an increase in histamine responsiveness in smokers over a 4-year period, whereas in ex-smokers both FEV₁ (as percentage prednisolone) and PC₂₀ histamine remained unchanged [25]. In a recently published study, Sparrow *et al.* showed a slight decrease of methacholine responsiveness after a 3-year period in a population sample of middle-aged and elderly men [26]. These studies, however, assessed airways responsiveness only twice: at the beginning and at the end of follow-up. We measured airways responsiveness every 4 months during a 2-year period. Our results show that in non-allergic patients with COPD, who are treated with bronchodilators with or without corticosteroids, the degree of airways hyperresponsiveness increases with time. Because of withdrawal the number of PC₂₀ measurements obtained per patient varied. Since the statistical model of BMDP can handle missing data and because PC₂₀ in itself was no reason for dropout, we think withdrawal has had little if any influence on our results.

Age did not relate significantly to level or decline of

Table 3. Regression coefficients $\pm$ SE in random effects model analysis of PC₂₀ histamine

Parameter	Regression coefficient	SE	P-value
Constant	1.86	1.23	0.13
Time	-0.30	0.20	0.15
Budesonide	0.14	0.40	0.71
Budesonide $\times$ time	-0.02	0.21	0.92
Budesonide + prednisolone	-0.72	0.44	0.10
(Budesonide + prednisolone) $\times$ time	0.39	0.24	0.11
Pre-challenge FEV ₁ % prednisolone	0.03	0.01	0.00
Age	0.01	0.02	0.84
Age $\times$ time	-0.01	0.01	0.58
Smoking	-0.15	0.33	0.64
Smoking $\times$ time	-0.31	0.18	0.09
Log ₁₀ IgE	-0.70	0.27	0.01
Log ₁₀ IgE $\times$ time	0.47	0.14	0.00

Number of patients included in the analysis: 50. All covariables used in the model were entered at once. Smoking and treatment (budesonide, budesonide + prednisolone) are entered as dichotomous variables. Time is expressed in years. For abbreviations and units of measurement, see Table 1.

PC₂₀ histamine in our patient group. A number of population studies have suggested an age-related increase in hyperresponsiveness, at least in individuals over 40 years of age [9]. The difference between these findings and ours may be due to the fact that we investigated a small number of patients who showed lower levels and a smaller range of PC₂₀ histamine than generally observed in population samples, which may have obscured a possible association.

Uncertainty exists whether smoking causes increased airways responsiveness or not. Our results show that actual smoking habits are negatively related with both level and annual change of PC₂₀ histamine. Both correlations, however, did not reach statistical significance. This may at least partially be explained by the fact that we compared current smokers with ex-smokers, since our study group contained no never-smokers. Although the period after smoking cessation varied, a number of patients had continued smoking until about 1 year before entering the study and one ex-smoker had stopped only 4 months before entry. Although the number of pack years was larger in smokers than in ex-smokers, smoking history was considerable and not significantly different between the two groups. This may also explain why total serum IgE level and blood eosinophil number were not different in our smokers and ex-smokers, in contrast with findings in other studies [27,28].

As observed in many other studies, pre-challenge FEV₁ (as percentage predicted) was significantly correlated with PC₂₀ histamine. The observed decrease of PC₂₀ histamine will therefore be partly explained by a concomitant decline in FEV₁ [24]. Interestingly, however, our results show that factors other than pre-challenge level of lung function alone may determine the level and decline of airways responsiveness in patients with COPD. Total serum IgE level was significantly and inversely associated with PC₂₀ histamine. In other words, patients with a higher total serum IgE are more hyperresponsive than patients with a lower serum IgE. This is a remarkable finding since we included only non-allergic patients without signs or symptoms of asthma and with a serum IgE level within the normal range. Since we corrected for treatment group, pre-challenge FEV₁, age, and smoking habits, the observed correlation exists independently from these factors. We also did not find a significant interacting effect of IgE and the above-mentioned factors on level of hyperresponsiveness.

The explanation for this finding is not clear. In the absence of clinical evidence of allergy, the level of total serum IgE may reflect non-specific immunological inflammation, which may for example explain the increased total serum IgE levels in non-allergic smokers [9,29]. It is also possible that the observed relation between IgE and PC₂₀ histamine reflects an individual susceptibility for the degree of hyperresponsiveness a person may develop, even in the absence of overt asthma or atopy. The finding of an identical relationship between IgE and airways hyperresponsiveness in two other studies supports this hypothesis. O'Connor *et al.* demonstrated a weak but significant correlation between total serum IgE and methacholine responsiveness in a population sample, even after adjustment for skin-test reactivity and exclusion of asthmatic subjects [11]. As in our patient group, the same association could not be demonstrated between blood eosinophil number and methacholine responsiveness. In a cross-sectional study of a birth cohort of Australian children, Sears *et al.* demonstrated a highly significant correlation between serum IgE level and methacholine responsiveness, even after exclusion of all asthmatic or allergic children [30]. A recently published study in siblings of asthmatic probands suggests that both an elevated level of total serum IgE and AHR may be determined genetically [8].

An important finding in our study is the significant positive effect of serum IgE level on change of PC₂₀ histamine over time. A higher serum IgE level was associated with a smaller annual decrease of PC₂₀ histamine. This association was found to be independent of treatment and confounding factors. Moreover, no significant interaction effect of IgE and treatment on decline of PC₂₀ was found. Our patients were selected on the basis of strict criteria for COPD. These criteria included careful history

and extensive lung function testing and also the exclusion of allergy on the basis of negative skin tests, eosinophilia $< 250 \times 10^3/\text{mL}$ and a serum IgE $< 200 \text{ IU/mL}$. Our findings suggest that even when serum IgE is below 200 IU/mL , a higher IgE level is associated with less decline of PC_{20} than a lower level. This could be related to a low but nevertheless relevant level of allergic inflammation resembling inflammation in asthma. If so, these data would be compatible with those of Burrows *et al.* who found that patients with chronic airflow obstruction and additionally asthmatic features had a more favourable course of disease [31]. We are aware of two other studies that examined the relationship between initial IgE level and change of airways hyperresponsiveness over time. In the Normative Aging Study, Sparrow *et al.* found no significant relationship between baseline IgE and longitudinal change in methacholine responsiveness in a population of middle-aged and older men [26]. This may be due to the fact that the change in airways responsiveness during follow-up was very small in this group. Kerstjens *et al.* investigating a group of patients with asthma and COPD, demonstrated that a higher initial IgE predicts a more favourable course of AHR in patients who are treated with an inhaled corticosteroid, in contrast with a more unfavourable course in patients who are not [32]. These relationships, however, were not present in the COPD group when analysed separately. When one regards a higher IgE level as a marker of some kind of immunological inflammation, it may be surprising that we did not find an interaction effect of IgE and treatment on decline of PC_{20} . It may be that an interaction effect was really absent, for instance because the type of inflammation in these patients is less or not sensitive to the anti-inflammatory action of corticosteroids. On the other hand, it is possible that our group was too small or follow-up too short to detect such an interaction.

Corticosteroids are first-line drugs in the treatment of asthma because of their well-documented capacity to improve symptoms, lung function and degree of AHR in these patients [13]. In contrast, their effectiveness in COPD remains controversial. If an effect on FEV_1 is found, it is usually smaller than in asthma. Studies investigating the effect on airways hyperresponsiveness in COPD are scarce. Short-term studies generally show no effect of oral or inhaled corticosteroids on level of airways hyperresponsiveness [14]. We are aware of only two long-term studies. Dompeling *et al.* showed no effect of a 12-month treatment with inhaled beclomethasone on PC_{20} histamine [16]. Kerstjens *et al.* observed an improvement of PC_{20} histamine in patients with COPD during long-term (≥ 21 months) treatment with inhaled beclomethasone, although the improvement was smaller than in patients with asthma [15]. Inclusion of allergic subjects in their COPD group may have contributed to the observed beneficial effect. Our results indicate that treatment with corticosteroids does not

improve the level of airways hyperresponsiveness in non-allergic patients with COPD. The lack of treatment effect cannot be explained from a lack of patient compliance, since drug intake was very high and not significantly different in the three treatment groups. It is possible that the dose of corticosteroids we gave was not high enough, but the fact that the combination of oral prednisolone and an inhaled corticosteroid was not more effective than an inhaled corticosteroid alone suggests that this was not the case.

Taken together, our findings contribute to the knowledge of AHR in COPD. AHR may progress unremittingly in COPD, even with bronchodilator and anti-inflammatory treatment. The increase in AHR over time is smaller in patients with higher serum IgE levels. The results underline the need for further studies into the role of IgE and other modulating factors in the development and progression of AHR in patients with COPD.

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References

- 1 Tashkin PT, Altose MD, Bleecker ER *et al.* The Lung Health Study Research Group. The Lung Health Study: Airway Responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. *Am Rev Respir Dis* 1992; 145:301–10.
- 2 Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. *Am Rev Respir Dis* 1992; 145:922–7.
- 3 Sluiter HJ, Koëter GH, de Monchy JGR *et al.* The Dutch Hypothesis (chronic non-specific lung disease) revisited. *Eur Respir J* 1991; 4:479–89.
- 4 Hopp RJ, Townley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. *Am Rev Respir Dis* 1990; 141:2–8.
- 5 Rijcken B, Schouten JP, Xu X, Rosner B, Weiss ST. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV_1 . *Am J Respir Crit Care Med* 1995; 151:1377–82.
- 6 Gerritsen J, Koëter GH, Postma DS, Schouten JP, Knol K. Prognosis of asthma from childhood to adulthood. *Am Rev Respir Dis* 1989; 140:1325–30.
- 7 Postma DS, de Vries K, Koëter GH, Sluiter HJ. Independent influence of reversibility of airflow obstruction and nonspecific hyperreactivity on the long-term course of lung function in chronic airflow obstruction. *Am Rev Respir Dis* 1986; 134:276–80.
- 8 Postma DS, Bleecker ER, Amelung PJ *et al.* Genetic susceptibility to asthma — bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995; 333:894–900.

- 9 O'Connor GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 140:225–52.
- 10 Dirksen A, Madsen F, Engel T et al. Airway calibre as a confounder in interpreting bronchial responsiveness in asthma. *Thorax* 1992; 47:702–6.
- 11 O'Connor GT, Sparrow D, Segal MR, Weiss ST. Smoking, atopy, and methacholine airway responsiveness among middle-aged and elderly men. *Am Rev Respir Dis* 1989; 140:1520–6.
- 12 Annema JT, Sparrow D, O'Connor GT et al. Chronic respiratory symptoms and airway responsiveness to methacholine are associated with eosinophilia in older man: The Normative Aging Study. *Eur Respir J* 1995; 8:62–9.
- 13 Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993; 148:S1–26.
- 14 Postma DS, Renkema TEJ. Corticosteroid treatment. In: Calverley P, Pride N, eds. *Chronic Obstructive Pulmonary Disease*. London: Chapman and Hall 1995: 447–59.
- 15 Kerstjens HAM, Brand PLP, Hughes MD et al. Study Group. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airway disease. *N Engl J Med* 1992; 337:1413–9.
- 16 Dompeling E, van Schayck CP, Molema J et al. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992; 5:945–52.
- 17 Cotes JE. *Lung function: assessment and application in medicine*. 4th Edn. Oxford: Blackwell Scientific Productions 1979; 114,118.
- 18 De Vries K, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyper-reactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20:93–101.
- 19 Ferron GA, Kerrebijn KF, Weber J. Properties of aerosols produced with nebulizers commonly used in medicine. *Am Rev Respir Dis* 1976; 114:899–908.
- 20 Cockcroft DW, Berscheid BA. Standardization of inhalation provocation tests. Dose vs. concentration histamine *Chest* 1982; 82:572–5.
- 21 Quanjer PH (ed.). *Standardized lung function testing*. *Bull Europ Physiopath Resp* 1983; 19 (Suppl. 5):1–95.
- 22 Norusis MJSPSS, /PC, + V. 3.0 Base manual. SPSS Inc, Chicago, IL, USA.
- 23 Schluchter MD. Unbalanced repeated measures models with structured covariance matrices. In: Dixon WJ, Brown MB, Engelman L, Hill MA, Jennrich RI, eds. *BMDP statistical software manual* (Vol. 2). Berkeley: University of California Press 1988: 1084–114.
- 24 Renkema TEJ, Schouten JP, Koëter GH, Postma DS. Effects of long-term treatment with corticosteroids in chronic obstructive pulmonary disease. *Chest* 1996; 109:1156–62.
- 25 Lim TK, Taylor RG, Watson A, Joyce H, Pride NB. Changes in bronchial responsiveness to inhaled histamine over four years in middle aged male smokers and ex-smokers. *Thorax* 1988; 43:599–604.
- 26 Sparrow D, O'Connor GT, Rosner B, Weiss ST. (with the technical assistance of Demolles D). Predictors of longitudinal change in methacholine airway responsiveness among middle-aged and older man. *The Normative Aging Study Am J Respir Crit Care Med* 1994; 149:376–81.
- 27 Gerrard JW, Heiner DC, Ko CG et al. Immunoglobulin levels in smokers and non-smokers. *Ann Allergy* 1980; 44:261–2.
- 28 Halonen M, Barbee RA, Lebowitz MD, Burrows B. An epidemiologic study of the interrelationships of total serum immunoglobulin E, allergy skin-test reactivity, and eosinophilia. *J Allergy Clin Immunol* 1982; 69:221–8.
- 29 Villar T, Holgate ST. IgE, smoking, and lung function. *Clin Exp Allergy* 1994; 24:508–10.
- 30 Sears MR, Burrows B, Flannery EM et al. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991; 325:1067–71.
- 31 Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med* 1987; 317:1309–14.
- 32 Kerstjens HAM, Schouten JP, Brand PLP et al. Study Group. Importance of total serum IgE for improvement in airways hyperresponsiveness with inhaled corticosteroids in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 151:360–8.