

The importance of maximal airway response to methacholine in the prediction of asthma development in patients with allergic rhinitis

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Summary

Background Allergic rhinitis is a known predictor and correlate of asthma incidence. However, it is not clear which patients with allergic rhinitis are at greater risk of the development of asthma.

Objective The aim of this study was to investigate whether airway hypersensitivity and/or increased maximal response on the dose–response curve to methacholine would predict the development of asthma in subjects with allergic rhinitis.

Methods One hundred and forty-one children with allergic rhinitis were prospectively studied for 7 years. At the initiation of the study, bronchial provocation test with methacholine using a stepwise increasing concentration technique was performed to measure PC₂₀ (provocative concentration causing a 20% fall in FEV₁) and maximal response. Each subject was evaluated at least every 6 months and details of asthmatic symptoms or signs experienced during the intervening period were taken.

Results Twenty of 122 subjects available for the follow-up developed asthma. Nine (19.6%) of 46 hypersensitive (PC₂₀ < 18 mg/mL) subjects developed asthma, compared with 11 (14.5%) of 76 normosensitive subjects ($P=0.462$). Eight (32%) of 25 subjects without maximal response plateau developed asthma, compared with 12 (12.4%) of 97 subjects with maximal response plateau ($P=0.018$). Score test for trend revealed a significant association between the level of maximal response ($P=0.007$), but not the degree of methacholine PC₂₀ ($P=0.123$), and the future development of asthma.

Conclusion An increased maximal airway response to methacholine is shown to be a better predictor for the future development of asthma in patients with allergic rhinitis, than airway hypersensitivity to methacholine.

Keywords allergic rhinitis, asthma, airway hyper-responsiveness, methacholine, maximal airway response, PC₂₀

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Introduction

Allergic rhinitis and asthma are closely related disorders that commonly occur together [1]. About two-thirds of patients with atopic asthma have concomitant allergic rhinitis symptoms, while asthma has been shown to afflict about one-third of patients with allergic rhinitis [2]. It has also been suggested that allergic rhinitis is a risk factor for the development of asthma [3]. In a long-term follow-up study, Settiple et al. found that three times as many individuals diagnosed with allergic rhinitis developed asthma than individuals without rhinitis [4]. However, it is not clear which patients with allergic rhinitis are at greater risk of developing asthma symptoms.

Airway hyper-responsiveness (AHR) to pharmacological agents, such as histamine or methacholine, is a characteristic feature of subjects with current asthma [5]. However, patients with allergic rhinitis and no clinical evidence of asthma frequently exhibit AHR [6–8]. This high incidence of AHR has caused some investigators to postulate that AHR may be a marker for the subsequent development of asthma in patients with allergic rhinitis. Several studies have been performed on this issue [6, 8–10] but the results are controversial.

AHR is usually defined as an increased sensitivity of the airways to inhaled histamine or methacholine [11]. However, there is accumulating evidence that AHR is a more complex functional abnormality that comprises more than just hyper-sensitivity [12]. When exposed to high concentrations of inhaled histamine or methacholine, asthmatic patients show an excessive airway narrowing, as reflected by an elevated or absent maximal response plateau. It can be argued that the latter is clinically a more relevant component of AHR than the former *per se* because it reflects the potential severity of airways obstruction in each individual [13]. An elevated or absent maximal

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response plateau has also been demonstrated in patients with allergic rhinitis [14] and its determination may add relevant information to airway hypersensitivity [15].

The aim of this study was to investigate whether airway hypersensitivity and/or increased maximal response to methacholine predicts the development of asthma in subjects with allergic rhinitis.

Subjects and methods

Subjects

Subjects were recruited consecutively from children with perennial allergic rhinitis, aged 10 to 16 years, at the allergy clinic of Seoul National University Children's Hospital. The diagnosis of allergic rhinitis was made on the basis of the patient's history, rhinological examination, and skin prick test [16]. Candidates showed symptoms of sneezing, nasal stuffiness, rhinorrhea and/or nasal itching throughout the year (lasting for at least 2 years). In all candidates the prick method showed at least one positive reaction to a panel of 12 common aeroallergens in the presence of positive and negative controls. Most subjects showed a positive reaction to house dust mites. The clinical records of candidates, who had responded at the initial visit negatively as to whether they had ever had asthma or whether they had ever been diagnosed as having asthma by a doctor, were reviewed. Candidates were considered as subjects for this study only when two doctors at our clinic agreed that the candidate had no history of symptoms suggestive of asthma.

Supplementary questions, which were modifications of those by Verdiani et al. [17], were asked concerning any current or past history of the following asthma-related symptoms: (i) attacks of chest tightness; (ii) difficulty breathing; (iii) occasional or a persistent wheeze; (iv) breathlessness or cough after exposure to cold air or exercise; (v) chest noises while breathing; (vi) chronic cough that persists for more than 3 weeks; and (vii) nocturnal symptoms that disturb sleep. Candidates were included in the study only when their parents responded negatively to all the questions. Candidates were excluded from the study if any of the questions were answered positively or their parents could not answer confidently. Physical examination, as well as spirometry, was normal at each time of the clinic visits.

Study design

A prospective study was carried out between December 1992 and February 2000. At the initiation of the study, spirometry and methacholine bronchoprovocation test were performed. Each subject was required to have an FEV₁ (the best of three consecutive measurements that agreed within 5%) of at least 80% of the predicted value [18]. Antihistamines and nasal topical medications (cromolyn sodium or corticosteroid) were withheld for at least 72 h and 2 weeks before the bronchoprovocation test, respectively. No other medication was taken. In view of the fact that most of the subjects were sensitized predominantly to house dust mites, it was decided to perform the bronchoprovocation test during the winter season (December to February), when the levels of house dust mites have been found to be the lowest and least changing in our country [19].

For the follow-up, subjects were treated as usual (antihistamines and/or nasal topical medications) and were asked to attend our clinic at least every 6 months. They had been given

peak flow meters and inhaled bronchodilator (salbutamol) and were asked to record symptoms of asthma (wheeze, shortness of breath, chest tightness, nocturnal cough, exertional wheeze, chest noises while breathing, or any other breathing problem) and to measure peak expiratory flow (PEF) rate before and after salbutamol (200 µg) inhalation when they occurred. At each attendance, subjects were evaluated by one of the authors (YYK), who did not have knowledge of the methacholine challenge test results, concerning their experiences in the interim and a physical examination was performed, if appropriate. A diagnosis of asthma was made according to a criterion modified from that of Prieto et al. [9], that is, if a subject had typical symptoms (episodic wheezing or dyspnoea) or successive 3-day nocturnal cough, and at least a 15% increase in PEF after inhaled salbutamol.

Those subjects who developed asthma were treated with an intermittent bronchodilator and some of them were additionally given inhaled cromolyn sodium or inhaled corticosteroid according to the National Institute of Health (NIH) guidelines [20]. These patients were withdrawn from further follow-up and repeated bronchial provocation test was performed at the end of year in which they developed asthma. From those who did not develop asthma, 15 with measurable PC₂₀ (provocative concentration causing a 20% fall in FEV₁) and maximal response plateau on the initial test were randomly selected and the test was repeated at the end of their follow-up period.

Parents gave written informed consent for their children to participate in the study. The study protocol was approved by the hospital ethics committee.

Methacholine inhalation test

High-dose methacholine inhalation tests were carried out using a modification of the method described by Chai et al. [21]. The methacholine (Sigma Diagnostics, St Louis, MO, USA) solutions were prepared at different concentrations (0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, 25, 50, 100, 150, 200 mg/mL) in buffered saline solution (pH 7.4). A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, MD, USA), triggered by a solenoid valve set to remain open for 0.6 s, was used to generate the aerosol from a DeVilbiss 646 nebulizer (DeVilbiss Health Care, Somerset, PA, USA), with pressurized air at 20 psi. Each subject inhaled five inspiratory capacity breaths of buffered saline solution and increasing concentrations of methacholine at 5-min intervals. This gave an output of 0.009 ± 0.0014 mL (mean $\pm$ SD) per inhalation. FEV₁ was measured 60 to 90 s after inhalation of each concentration level. The procedure was terminated when FEV₁ fell by more than 50% from baseline, or when a maximal response plateau had been established. This was considered to occur if three or more data points at the highest concentrations fell within a 5% response range [22]. An additional 5 or 10 inhalations of the 200 mg/mL solution were taken if the last three data points of less than a 50% FEV₁ fall did not satisfy the above criteria. For safety reasons, subjects were given the opportunity to stop the challenge test if they felt too much discomfort.

Response was expressed as the percentage fall in FEV₁ from the post-saline solution value and was plotted against the log of the concentrations of inhaled methacholine. The dose-response curves were characterized by their position and maximal response. Position was expressed as PC₂₀, which was calculated by log-linear interpolation between two adjacent data points,

and maximal response was defined as the level of maximal response plateau by averaging the consecutive points on the plateau, or as the last data point of the dose-response curve if a plateau could not be obtained.

Statistical analysis

Results are expressed as mean $\pm$ SD, unless otherwise stated. All PC₂₀ values were log-transformed before analysis and are expressed as geometric mean and range of 1 SD. Values or prevalences of two groups were compared with Student's *t*-test or the chi-square test. Score test for trend was used to evaluate potential relationships between the degree of PC₂₀ or the level of maximal response and the development of asthma. Changes in PC₂₀ or maximal response were analysed using either the paired *t*-test or the Wilcoxon signed rank test. All analyses were made using Stat View II (Abacus Concept Inc., Berkeley, CA, USA) on a Macintosh computer (Apple Computer Inc., Cupertino, CA, USA). A *P*-value of less than 0.05 was considered statistically significant.

Results

One hundred and forty-one subjects were enrolled in the study but 19 were lost to follow-up although every effort was made to continue the regular check-ups. The characteristics of the subjects who completed the study, and of the subjects who were lost, are summarized in Table 1. Those who developed asthma during the course of follow-up (*n* = 20) were designated as group 1, and those who did not (*n* = 102) were designated as group 2. Among the group 1 patients, three subjects developed asthma in the first year, four in the second year, three in the third year, four in the fourth year, two in the fifth year, three in the sixth year, and one in the seventh year. The two groups did not differ with respect to age, sex, duration of rhinitis symptoms, FEV₁ level or atopic status, as assessed by total serum IgE and the pattern of positive skin test responses. On the initial methacholine challenge test, 51 (36.2%) of our original 141 subjects showed airway hypersensitivity (PC₂₀ < 18 mg/mL) and 30 (21.3%) showed no evidence of a maximal response plateau. The difference between groups 1 and 2 was not significant in terms of the prevalence of airway hypersensitivity (45% vs. 36.3%, *P* = 0.462), but significant for

the prevalence of an absent maximal response plateau (40% vs. 16.7%, *P* = 0.018).

To further evaluate the association between airway sensitivity or maximal response and asthma development, subjects were classified according to the PC₂₀ level or maximal response and the risk for the development of asthma was assessed. In the analysis of groups with different levels of PC₂₀ (Fig. 1), nine (19.6%) of the 46 hypersensitive subjects developed asthma, compared with 11 (14.5%) of the 76 normosensitive subjects (*P* = 0.462). Score test for trend, with subdivision of the hypersensitive group into those with the asthmatic range PC₂₀ (< 8 mg/mL) and those with the non-asthmatic range (8 mg/mL (PC₂₀ P 18 mg/mL), and subdivision of the normosensitive group into those with a measurable range (18 to 200 mg/mL) and those with an immeasurable range (> 200 mg/mL) of PC₂₀, showed that asthma development was not predicted by the degree of PC₂₀ (*P* = 0.123).

In the analysis of groups with different levels of maximal response (Fig. 2), eight (32%) of the 25 subjects without maximal response plateau developed asthma vs. 12 (12.4%) of 97 subjects with maximal response plateau (*P* = 0.018). Score test for trend in the four groups with different maximal response levels showed a significant association between the level of maximal response and the development of asthma (*P* = 0.007).

Table 2 shows results of sensitivity, specificity and predictive values of different cut-off points of methacholine PC₂₀ or maximal response levels in predicting the development of asthma. Obviously, as the cut-off limit of methacholine PC₂₀ is lowered, specificity improves but sensitivity becomes low. In contrast, as the cut-off limit of maximal response levels is lowered, sensitivity improves but specificity becomes low. At all cut-off points of methacholine PC₂₀ or maximal response levels, however, positive predictive values remain very poor.

The changes in PC₂₀ or maximal response from the initiation to the end of the study in 20 subjects who developed asthma are shown in Fig. 3. Geometric mean (range of 1 SD) of PC₂₀ decreased from 16.22 (3.02 to 87.10) mg/mL at the initial evaluation to 4.27 (1.10 to 16.60) mg/mL after the development of asthma symptoms (*P* = 0.009), with a PC₂₀ value of 200 mg/mL assigned to the occasion of > 200 mg/mL. In terms of maximal response values, seven subjects had immeasurable (> 50%) values on both occasions, thus making estimate of change impossible. Excluding these seven subjects, maximal response

Table 1. Baseline characteristics of study groups at the initiation of study

	Group 1	Group 2	Dropped-out
<i>n</i>	20	102	19
Age (yr)	9.7 $\pm$ 1.4	10.1 $\pm$ 1.3	10.0 $\pm$ 1.2
Sex (M/F)	12/8	64/38	12/7
Duration of rhinitis symptoms (yr)	3.2 $\pm$ 0.7	3.3 $\pm$ 0.8	3.1 $\pm$ 0.7
Serum IgE (IU/mL)*	245.5 (74.1–812.8)	234.4 (79.4–691.8)	251.2 (100.0–631.0)
Pattern of positive skin test response†	19/8/4/3/7	96/35/19/18/34	16/7/5/2/8
Bronchial provocation test			
FEV ₁ (% predicted)	98.3 $\pm$ 3.2	96.5 $\pm$ 5.7	96.5 $\pm$ 7.8
Methacholine PC ₂₀ < 18 mg/mL (<i>n</i>)	9	37	5
Absence of maximal response plateau (<i>n</i>)	8	17	5

*Geometric mean (range of 1 SD). †Number of cases positive to house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), animal dander (cat and dog), mould (*Aspergillus* and *Alternaria* species), pollen (oak, alder, rye grass, and mugwort) or cockroach.

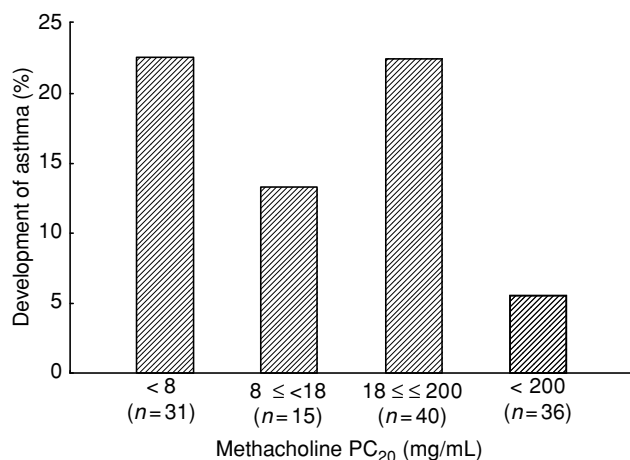


Fig. 1. The risk for development of asthma according to the degree of methacholine PC₂₀ at the initiation of study. No significant association between the degree of PC₂₀ and the development of asthma was found (score test for trend: $P = 0.123$).

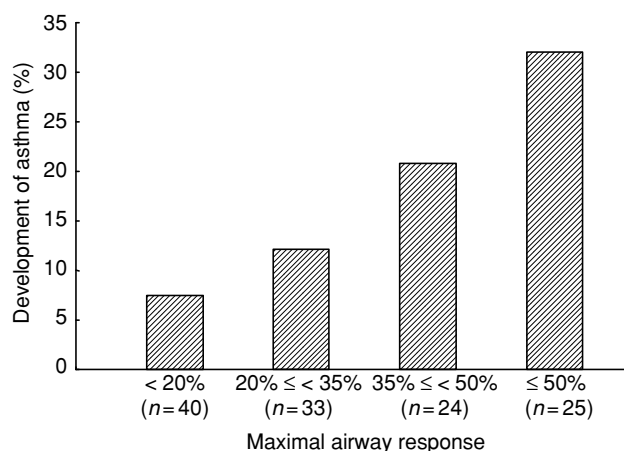


Fig. 2. The risk for development of asthma according to the level of maximal airway response to methacholine at the initiation of study. The level of maximal airway response and the development of asthma were significantly associated (score test for trend: $P = 0.007$).

Table 2. Different cut-off points of methacholine PC₂₀ or maximal response levels in relation to development of asthma

	Methacholine PC ₂₀			Maximal response level		
	< 200 mg/mL	< 18 mg/mL	< 8 mg/mL	≥ 50%	≥ 35%	≥ 20%
Sensitivity	90.0	45.0	35.0	40.0	65.0	85.0
Specificity	33.3	63.7	76.5	83.3	64.7	36.3
Positive predictive value	20.9	19.6	22.6	32.0	26.5	20.7
Negative predictive value	94.4	85.5	85.7	87.6	90.4	92.5

All values are percentages.

increased from $32.2 \pm 12.1\%$ to $40.8 \pm 10.9\%$ ($P = 0.014$), despite a possible underestimation of the change which resulted from assigning the censored value (50%) to the occasion of $> 50\%$. On the contrary, in the 15 subjects who did not develop asthma (Fig. 4), PC₂₀ at the end of the study, namely 19.50 (4.27 to 89.13) mg/mL, was not significantly different from the initial value of 19.05 (5.62 to 64.57) mg/mL (NS). Neither did the maximal response change significantly from the initiation ($32.8 \pm 6.8\%$) to the end of the study ($33.8 \pm 8.1\%$; not significant).

Discussion

Our results show that neither the presence nor the degree of airway hypersensitivity proved a reliable marker of subsequent asthma development in patients with allergic rhinitis. In contrast, subjects with an absent or elevated maximal response plateau were found to be at increased risk of the development of asthma. To our knowledge this is the first study that has addressed the importance of maximal airway response for predicting asthma development in patients with allergic rhinitis.

There have been several investigations of airway sensitivity to pharmacological stimuli, such as histamine or methacholine in patients with allergic rhinitis [6–8]. In the present study, the prevalence of airway hypersensitivity in our original 141

subjects was 36.2%, a figure that is similar to those reported by other studies, when differences in the challenge method [7] and the criteria for airway hypersensitivity [8] are taken into account. In fact, there is a continuous unimodal distribution of airway sensitivity in the general population [23] and a cut-off point of 18 mg/mL separating normal from increased airway sensitivity appears arbitrary. We have previously found that a PC₂₀ greater than 18 mg/mL virtually rules out the possibility of current symptomatic asthma [24], and for this reason this concentration was chosen as the criteria for airway hypersensitivity.

Previous investigators have suggested that patients with allergic rhinitis and AHR may be in a latent phase of asthma that may become clinically active over the course of time [6, 8]. Townley et al. [6] were the first to appreciate subsequent development of asthma in two subjects with allergic rhinitis and marked airway hypersensitivity. In a follow-up study of 40 patients with ragweed-sensitive allergic rhinitis, Brame et al. [8] showed that three of the 14 subjects with methacholine hypersensitivity developed asthma, whereas no patient developed asthma in the normosensitive group. On the contrary, other studies have shown that methacholine hypersensitivity is not a reliable marker of the subsequent development of asthma in patients with allergic rhinitis [9, 10]. In our study, 9 (19.6%) of 46 hypersensitive subjects developed asthma, compared with 11 (14.5%) of 76 normosensitive subjects. Further subdivision of hypersensitive and normosensitive groups into the respective

Fig. 3. Individual values for PC₂₀ (left panel) and maximal airway response (right panel) at the initiation and end of the study in 20 subjects who developed asthma. Mean and 1 SD are shown by horizontal bars. Censored values (PC₂₀: 200 mg/mL; maximal airway response: 50%) were assigned to the immeasurable ones. Seven subjects with immeasurable maximal airway response on both occasions were excluded from the analysis.

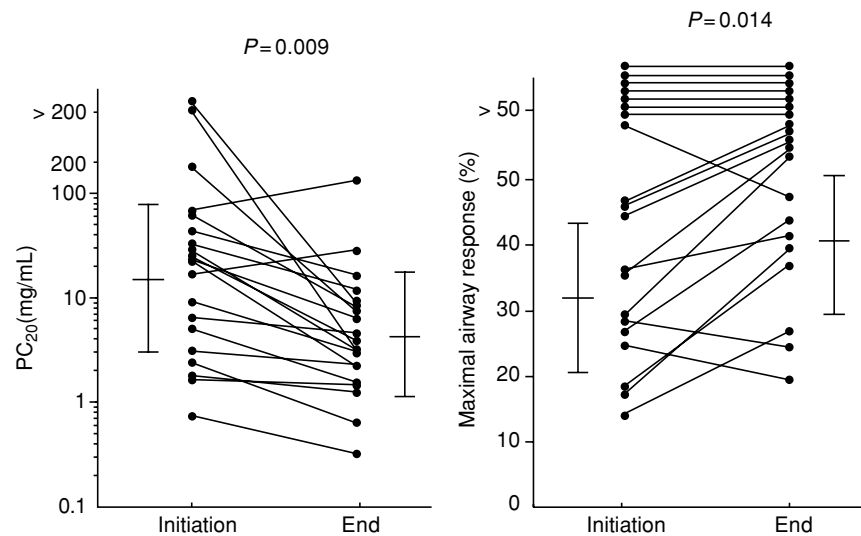
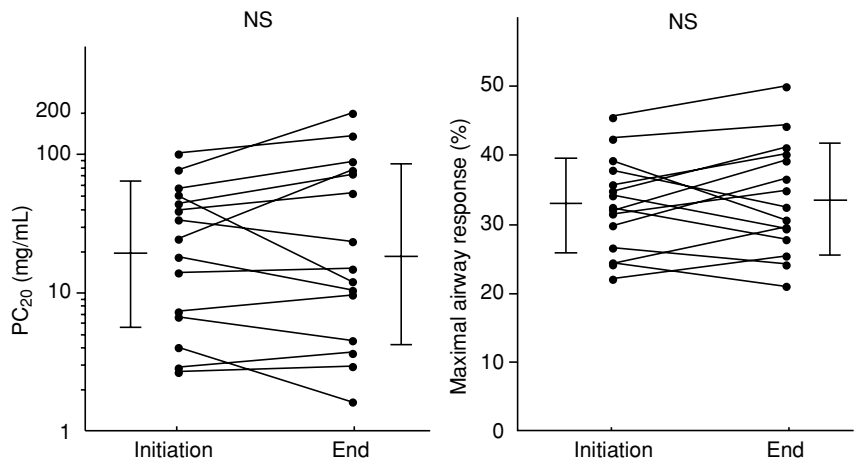


Fig. 4. Individual values for PC₂₀ (left panel) and maximal airway response (right panel) at the initiation and end of the study in 15 subjects who did not develop asthma. Mean and 1 SD are shown by horizontal bars. Censored values (PC₂₀: 200 mg/mL; maximal airway response: 50%) were assigned to the immeasurable ones.



two subgroups did not change the statistical non-significance (score test for trend; $P = 0.123$). Our study therefore confirms that the degree of airway sensitivity is a poor predictor of asthma development in patients with allergic rhinitis.

Excessive airway narrowing without evidence of plateau on the dose-response curve of methacholine was observed in 21.3% of our subjects with allergic rhinitis and therefore our results confirm that the absence of a plateau is not an exclusive characteristic of asthmatic subjects [14, 15]. Previous reports have indicated that subjects with allergic rhinitis have a prevalence and level of the plateau intermediate between that of asthmatics and normals [15, 25]. It is not known whether the increased maximal airway response is associated with airway inflammation [26] or if it is linked to other mechanisms. The proportion of subjects without evidence of plateau in this study is lower than that reported previously [14, 15]. This may be due to the method of measurement adopted, in as much as we stopped the challenge procedure when the FEV₁ fell by > 50%, and due to the fact that it was measured in the winter season, when the levels of relevant allergens for the majority of subjects (house dust mites) have been found to be the lowest and the least changing in our country [19]. We observed unlimited airway narrowing in a

small number of subjects with normal airway sensitivity as reflected by PC₂₀, and vice versa, which supports the viewpoint that airway sensitivity is not an adequate measure of maximal airway response [12]. A significant association was found between the degree of maximal response and the development of asthma at follow-up, whether the response was evaluated as a dichotomous (presence/absence of maximal response plateau) or as a stratified (four groups of different maximal response levels) variable.

In order to study the development of asthma prospectively in patients with allergic rhinitis, we believed it extremely important to select only those subjects who are not considered to have asthma. Our patients were carefully screened at the onset of the study for any current or past history of asthmatic symptoms to eliminate hidden asthmatics from the study group. The questionnaire that we used had already been demonstrated in a previous study to be sensitive in this respect [27]. The development of asthma was accepted if the subject had typical symptoms (episodic wheezing or dyspnoea) or a successive 3-day nocturnal cough, and at least a 15% increase in PEF after inhaled salbutamol (200 µg). These strict criteria undoubtedly excluded some mild episodes of asthma, but greatly reduced the

chance of identifying non-specific respiratory symptom as asthma. A 7-year period was chosen for follow-up. It is possible that further follow-up may have revealed additional cases of asthma development and that other prognostic factors could have been identified. Despite this possible deficiency, we believe that our results provide valuable information on the prognostic factors for asthma development.

Our observations show that subjects with an elevated or an absent maximal response plateau are at increased risk of developing asthma. The maximal airway response on the dose-response curve to methacholine is assumed to reflect the potential degree of airways obstruction in individual patients irrespective of the level of sensitivity [13, 28]. Indeed, it has been demonstrated that the maximal degree of airway narrowing is associated with the severity of asthma symptoms [29]. In non-asthmatic subjects with allergic rhinitis, maximal airway response, but not airway sensitivity, was found to have a correlation with PEF variation [14], and natural allergenic exposure may cause an increase in maximal airway response in a significant number of patients with allergic rhinitis [30]. On the basis of our results, we speculate that subjects with allergic rhinitis and elevated maximal airway response are at increased risk of asthma development if they are exposed to a sufficiently strong allergenic stimulus.

In our patients who developed asthma, maximal airway responses as well as airway sensitivity increased after the first asthma symptoms, whereas neither of the two parameters changed significantly in 15 of our subjects who did not develop asthma. The estimation of changes in maximal airway response or airway sensitivity was complicated because some subjects had either parameter above the upper limit of measurement (maximal airway response > 50%, $PC_{20} > 200$ mg/mL), and thus subjects with immeasurable values on both occasions made an estimate of change impossible. However, the different pattern of changes in PC_{20} or maximal airway response in subjects who developed asthma and those who did not was evident, when subjects with immeasurable values on both occasions were excluded and subjects with an immeasurable value on one occasion were included by assigning censored values (maximal airway response: 50%; PC_{20} : 200 mg/mL). Our findings expand those of previous reports of an association between the development of asthma and an increase in airway sensitivity [8, 9, 31], by showing that maximal airway response also increases significantly as patients with allergic rhinitis develop asthmatic symptoms. We cannot exclude that these changes precede the development of asthma, as our patients were not re-challenged at regular intervals. The reasons why airway responsiveness increases remain obscure, but may include a genetically determined factor, an increased exposure to relevant allergens, and frequent episodes of respiratory viral infections [31].

In conclusion, an increased maximal airway response to methacholine is expected to be a better predictor for the future development of asthma in patients with allergic rhinitis, than airway hypersensitivity to methacholine.

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