

Bronchial responsiveness to inhaled histamine in both adults with intrinsic and extrinsic asthma: The importance of prechallenge forced expiratory volume in 1 second

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Background: Recent evidence suggests that both nonspecific bronchial hyperresponsiveness and degree of airflow obstruction may be involved in the deterioration of lung function observed in patients with bronchial asthma. To investigate to which degree the level of bronchial hyperresponsiveness reflects the size of the airways at the time of testing, we examined the relationship of nonspecific bronchial responsiveness to prechallenge pulmonary function in adult asthmatic patients.

Methods: Bronchial responsiveness to inhaled histamine was measured in 100 patients (age range, 28 to 79 years), of whom 62 had intrinsic and 38 had extrinsic asthma. Histamine responsiveness was analyzed by means of the dose-response slope (DRS).

Results: No significant difference in prechallenge forced expiratory volume expressed as a percentage of predicted value ($FEV_1\%$ pred), duration of asthma, smoking habits (pack years), or bronchial responsiveness (DRS) was found between the patients with intrinsic and those with extrinsic asthma. The patients had, in general, reduced pulmonary function, because 80% had a prechallenge FEV_1 less than 80%pred. The DRS displayed a significant inverse relationship to the prechallenge level of $FEV_1\%$ pred in both patients with intrinsic asthma and those with extrinsic asthma ($p < 0.000001$); the initial $FEV_1\%$ pred accounted for approximately 35% of the variance in measurements of histamine responsiveness. Excluding patients with abnormal prechallenge FEV_1 ($<70\%$ pred), or current and exsmokers (never smoked: $n = 67$) from the analysis did not change these findings.

Conclusion: Nonspecific bronchial responsiveness is to some extent determined by the prechallenge level of pulmonary function in both adults with intrinsic and extrinsic asthma. (J ALLERGY CLIN IMMUNOL 1993;91:120-6.)

Key words: Asthma, bronchial responsiveness, adults, histamine, prechallenge pulmonary function, intrinsic asthma, extrinsic asthma

Generalized hyperresponsiveness of the airways is one of the cardinal features of bronchial asthma.^{1, 2} Bronchial hyperresponsiveness (BHR) can, however, also be demonstrated in many patients with chronic obstructive pulmonary disease (COPD),^{3, 4} although this may reflect quite different underlying mechanisms.⁵ In patients with COPD, the degree of BHR

Abbreviations used

DRS:	Dose-response slope
$FEV_1\%$ pred:	FEV_1 expressed as a percentage of predicted value
BHR:	Bronchial hyperresponsiveness
COPD:	Chronic obstructive pulmonary disease
$PD_{20} FEV_1$:	The dose of agonist causing a 20% decline of FEV_1
$PC_{20} FEV_1$:	The concentration of agonist causing a 20% decline of FEV_1
HRB:	Histamine release from basophil leucocytes
CI:	Confidence interval
PEF:	Peak expiratory flow
VC:	Vital capacity

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is largely determined by the initial degree of airway obstruction; that is, the lower the initial forced expiratory volume in 1 second (FEV_1), the higher the degree of BHR.³ In patients with asthma, the relationship of prechallenge level of pulmonary function to nonspecific bronchial responsiveness is less clear.⁶ In a study by Yan et al.⁴ no significant correlation was found between prechallenge level of pulmonary function and $PD_{20} FEV_1$ in 17 asthmatic patients with abnormal prechallenge lung function. In contrast, Cockcroft et al.¹ observed a significant direct correlation between prechallenge FEV_1 and $PC_{20} FEV_1$ among 156 "well-controlled" asthmatic patients. Because it has been suggested that both BHR and degree of airflow obstruction may be involved in the deterioration of lung function of some patients with asthma,⁷ it is important to further investigate to which degree the level of BHR reflects the size of the airways at the time of testing.

Bronchial responsiveness is, like all measurable aspects of asthma, not a stable phenomenon.⁸ Furthermore, patients with extrinsic asthma may seem to have greater variability in pulmonary function than subjects with intrinsic asthma who might have permanent airway obstruction possibly caused by both inflammation and bronchoconstriction.⁹ These findings might suggest differences in the relationship of prechallenge FEV_1 to nonspecific BHR in patients with intrinsic asthma and patients with extrinsic asthma; however, this is at present unknown.

The purpose of this study was to examine the relationship between FEV_1 and bronchial responsiveness to inhaled histamine in adults with intrinsic asthma and those with extrinsic asthma.

MATERIAL AND METHODS

Subjects

In the years 1976 to 1979, 180 patients with bronchial asthma were referred to the Allergy Clinic and tested in the Laboratory of Respiratory Physiology at the University Hospital in Copenhagen (Rigshospitalet). The diagnosis of bronchial asthma was made on the basis of a combination of case history (symptoms of intermittent wheeze and/or breathlessness, subjective effect of β_2 -agonists) and laboratory tests (including significant reversibility in FEV_1 with salbutamol).^{10, 11}

Patients were divided into two groups: those with intrinsic asthma and those with extrinsic asthma. Patients with intrinsic asthma fulfilled the following criteria: (a) normal levels of serum IgE (<260 kU/l) (12) and (b) no evidence of extrinsic asthma from history, results of skin tests,¹² radioallergosorbent tests (AI-RAST),^{12, 13} histamine release from basophil leukocytes (HRB),¹⁴ and—when results of these were doubtful—specific bronchial provocations.¹² The remaining patients were defined as having extrinsic asthma.

In 1988 the 180 patients were invited to participate in the present study, of whom 143 (79%) were examined. Some of the subjects ($n = 43$) had such severe airways obstruction (baseline FEV_1 below 1.0 L) that it was not possible to do a bronchial challenge test with histamine,¹⁵ and they were therefore excluded from this analysis. Informed consent was obtained from all participating subjects, and the study was approved by the ethics committee of Copenhagen and Frederiksberg counties.

Exclusion criteria. All subjects were asked not to smoke for at least 2 hours before the examination. They were asked not to take theophylline or antihistamine for at least 24 hours, astemizole for 6 weeks, oral B_2 -agonist for 18 hours, and not to use inhaled bronchodilators for 6 hours before testing. Inhaled or oral steroids were continued, if used. In case of recent respiratory infection, the examination was postponed for at least 6 weeks.

Methods

History. The patients were interviewed by one person (C.S.U.) about respiratory symptoms (episodes of dyspnea and wheezing, cough, phlegm production, and frequency of symptoms), number of emergency room visits and hospital admissions caused by asthma within the last 5 years, duration of asthma, and use of antiasthma medication (medicaments and daily doses). Furthermore, all subjects reported whether they were current smokers, exsmokers, or had never smoked, and for the first two categories they reported the duration of smoking. Current and exsmokers reported their daily tobacco consumption, and an estimate of their lifetime tobacco exposure was calculated as pack years (current tobacco consumption [gm/day] $\times$ duration of smoking (year/20)).

Skin prick tests. Skin prick tests were performed with standard dilutions of allergens in 50% glycerol.¹² The standard allergens used were: birch, timothy grass, mugwort, animal hair and dander (cat, horse, and dog), house dust allergen, house dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*), and mold (*Alternaria iridis*, *Cladosporium herbarum*, and *Mucor racemosus*). Histamine hydrochloride, 1 mg/ml in 50% glycerol, was used as a positive reference for recording the skin prick test results; a negative reference was also included. The wheal was read after 15 to 20 minutes. The area of the wheal produced by each antigen was compared with the area of the histamine wheal and regarded as positive if it was at least the same size as the histamine wheal.

Total IgE. Total serum IgE levels were determined by paper radioimmunosorbent test (PRIST, Pharmacia, Uppsala, Sweden). Values below 260 kU/l (equal to 260 kIU/l) were regarded as normal.¹²

Radioallergosorbent test. Tests for allergen-specific IgE (AI-RAST) were performed with the aluminium radioallergosorbent test kit according to the method of Weeke.¹³ The patients were screened by a modification of this in which a mixture of four or five allergen extracts (a "pool") was used instead of one allergen only. The following

TABLE I. Characteristics of patients ($n = 100$) with bronchial asthma

	Intrinsic asthma	Extrinsic asthma	p values
No.	62	38	
Age (yr)	49.8 (11.9)	41.3 (10.9)	$p < 0.001$
Male/female	20/42	18/20	
Smoking status			
Current	12	8	
Former	10	3	
Never	40	27	
Pack years	3.8 (7.9)	5.3 (9.3)	$p = 0.41$
Duration of asthma (yr)	21.5 (12.3)	20.9 (9.5)	$p = 0.81$
FEV ₁ (L)*	1.88 (0.56)	2.22 (0.77)	$p < 0.05$
FEV ₁ (%pred.)*	63.5 (18.0)	64.5 (20.2)	$p = 0.80$
FEV ₁ /VC (%)*	54.0 (12.3)	59.9 (13.9)	$p < 0.05$
FEV ₁ reversibility (%)	17.3 (17.3)	30.4 (38.1)	$p < 0.05$

*Prechallenge values; mean values and (SD).

pools were used: pollen (birch, timothy grass, *Artemisia vulgaris* [mugwort], and *Leucanthemum vulgare* [oxeye daisy]); molds (*Alternaria iridis*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Mucor racemosus*); animals (horse, dog, cat, cow, and guinea pig); and "other" (house dust, *D. farinae*, *D. pteronyssinus*, and duck feathers). When the reaction to a pool was 10 sorbent units or above, each separate allergen within the pool was used for further RASTs; a reaction to one allergen of 20 sorbent units or more was regarded as a positive response.¹²

Histamine release from basophil leukocytes. The percentage of histamine released (out of the total histamine that could be released from the cells) was recorded according to the method described by Skov et al.¹⁴ The allergens used were the following: birch, timothy grass, mugwort, oxeye daisy, *Alternaria iridis*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Mucor racemosus*, horse, dog, cat, cow, guinea pig, house dust, *D. farinae*, *D. pteronyssinus*, and duck feathers.¹² A characteristic curve was obtained by expressing the released histamine as a percentage of the total histamine (ordinate) with four dilutions— 10^{-9} , 10^{-7} , 10^{-5} , and 10^{-3} —of the allergen extract (abscissa). A positive result was defined as release of 30% or more of the total cell content.¹⁴

Lung function test. All patients had their FEV₁, peak expiratory flow rate (PEF), and vital capacity (VC) measured. The highest of three technically acceptable FEV₁, PEF, and VC readings within 5% of one another was recorded.

When the FEV₁, after the bronchial challenge test with histamine, had returned to at least 95% of the baseline value (at least 45 minutes),¹⁶ the patients were tested for reversibility. The FEV₁, PEF, and VC were measured 15 minutes

TABLE II. Asthmatic patients ($n = 100$), 62 with intrinsic asthma and 38 with extrinsic asthma, divided according to their medication requirements

	Intrinsic asthma	Extrinsic asthma
Bronchodilators (inhaled and/or oral)	17 (72.6 ± 16.4)	16 (63.2 ± 22.2)
+ Inhaled steroids	24 (64.3 ± 20.0)	17 (65.1 ± 19.5)
+ Oral steroids	21 (55.2 ± 13.2)	5 (67.1 ± 19.0)

Number in parentheses are mean prechallenge FEV₁%pred. ± SD.

after inhalation of 1 ml (5 mg/ml) salbutamol. Reversibility in FEV₁ was calculated as (FEV₁ after − FEV₁ before)/FEV₁ before.¹⁰

Bronchial challenge test. The test was carried out by the method described by Cockcroft et al.¹ Aerosols of the test solution were generated by a Wright nebulizer (Aerosol Products Ltd., London, England) operated to give an output of 0.14 ml/min. Each aerosol was inhaled through the mouth by tidal breathing for 2 minutes. The first aerosol was saline (0.9%), and it was followed at 4-minute intervals by twofold increasing concentrations of histamine (0.075 to 8.0 mg/ml). The response was measured by the FEV₁ 1 minute after each inhalation. Determination of nebulizer output by weight indicated that the histamine inhalation schedule corresponded to the following doses of histamine in micromoles: 0, 0.11, 0.228, 0.456, 0.978, 1.825, 3.65, 7.302, and 12.169. The test was terminated when a 20% or more decline in FEV₁ from the postsaline value occurred or at the end of the dose schedule if such a decline did not occur.

For all subjects having at least 20% decline in FEV₁, the concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) was read from the individual log-dose response curve. Histamine responsiveness was also analyzed with use of an estimate of the overall slope of the dose-response relationship as described by O'Connor.¹⁷ The dose-response slope (DRS) was calculated as the decline in FEV₁ from the post-saline value (expressed as a percentage of the postsaline value) after the final dose divided by the dose of histamine administered.¹⁷

Statistical methods. Data were analyzed with use of the statistical package program Minitab (Minitab Inc., Birmingham, Great Britain). Predicted values for FEV₁, PEF, and VC were calculated with the regressions of Quanjer.¹⁸ Because of the skewed distribution, DRS values were logarithmically transformed (log₁₀) for all analyses and geometric mean values, and 95% confidence intervals (CI) are reported.¹⁹ The data were analyzed by means of two-sample t test, chi-square, and Pearson's correlation analysis. Factors of possible importance for the bronchial responsiveness

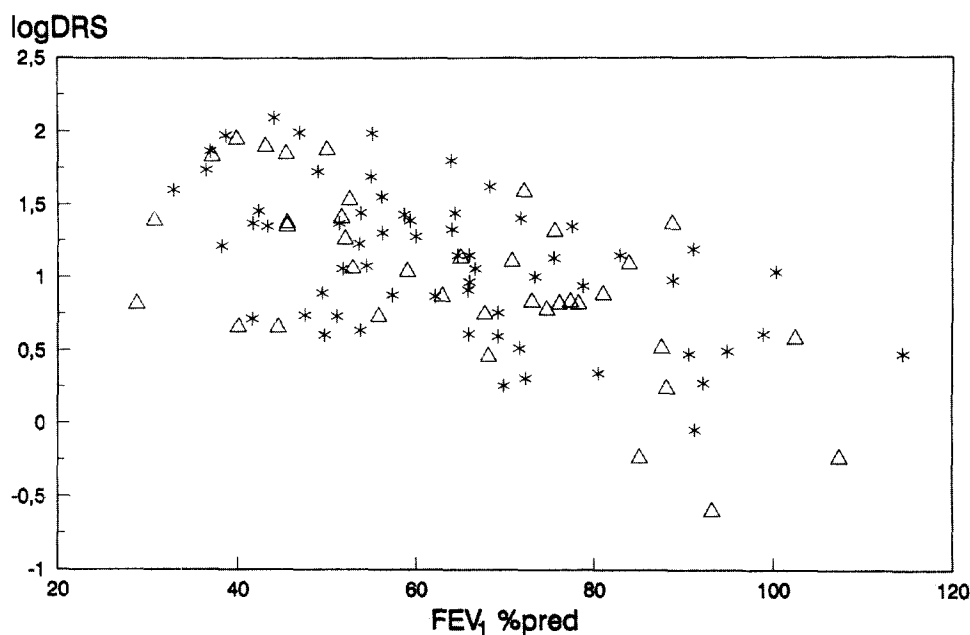


FIG. 1. Distribution of DRSs to inhaled histamine in patients ($n = 100$) with bronchial asthma.

(DRS) were entered into a multiple linear regression model, and nonsignificant variables were deleted by backward elimination to determine those associated with DRS. The data were further analyzed with type of asthma as an independent variable in the regression model and with interaction terms between type of asthma and other independent variables to test for differences in the influence of independent variables on patients with intrinsic asthma and those with extrinsic asthma.

RESULTS

Of the 100 patients studied, 62 had intrinsic asthma and 38 had extrinsic asthma; the characteristics of the patients are outlined in Table I. Five patients, three with intrinsic asthma, had unchanged FEV_1 after inhalation of bronchodilator; all of these patients had a prechallenge FEV_1 within the normal range (88% to 115% pred). As shown in Table I, the prechallenge level of $FEV_1\%$ pred was similar in the patients with intrinsic and extrinsic asthma ($p = 0.80$). The patients in this study had, in general, reduced level of pulmonary function, because 80% of the subjects had an initial (prechallenge) FEV_1 below 80% pred. Six patients, two with intrinsic asthma, had less than 20% reduction in FEV_1 from baseline (postsaline value) after inhalation of the highest concentration of histamine (8 mg/ml), the mean fall in FEV_1 being 9%, two of these patients had a 15% or more increase in FEV_1 after inhalation of salbutamol; all six patients were treated with inhaled corticosteroids (mean daily dose 0.8 mg), and four of the patients were on oral

corticosteroids (mean daily dose 7.5 mg prednisolone). In Table II, the patients are divided according to their medication requirements; two thirds of the patients were treated with inhaled or oral or both corticosteroids. Although there was a tendency toward an increased number of patients with intrinsic asthma receiving corticosteroids compared with the patients with extrinsic asthma, this difference did not reach statistical significance. Excluding the six patients for whom a PC_{20} value could not be determined, the DRS was nearly perfectly correlated with the dose causing a 20% decline in FEV_1 (PC_{20}) ($r > 0.99$, $p < 0.001$).

The distribution of DRS values is given in Fig. 1. No significant differences in DRS was found between the patients with intrinsic (mean 12.8, CI 9.6 to 17.1) and extrinsic (mean 9.8, CI 6.2 to 15.3) asthma ($p = 0.31$). The DRS displayed a significant inverse relationship to the prechallenge level of $FEV_1\%$ pred ($p < 0.00001$); the initial $FEV_1\%$ pred accounted for approximately 35% of the variance in measurements of histamine responsiveness. The relationship between DRS values and the prechallenge level of pulmonary function, expressed as $FEV_1\%$ pred, in patients with intrinsic and extrinsic asthma is shown in Fig. 2. Reanalyzing the data excluding current and exsmokers showed that the baseline $FEV_1\%$ pred accounted for 45% of the variance in measurements of histamine responsiveness among those who were lifelong non-smokers ($n = 67$). To explore if the relationship be-

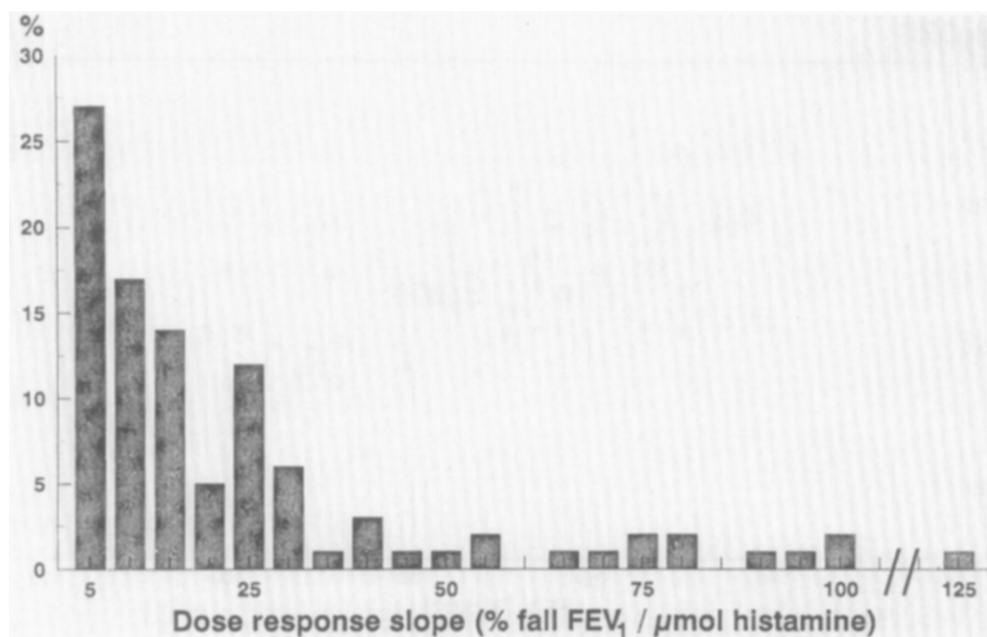


FIG. 2. The relationship between DRS and prechallenge level of pulmonary function, expressed as FEV₁% pred, in patients with intrinsic asthma ($n = 62$) and those with extrinsic asthma ($n = 38$).

tween bronchial responsiveness and prechallenge FEV₁ was caused by the high number of patients with reduced pulmonary function the data were reanalyzed excluding all patients with a prechallenge FEV₁ 70% pred or less. However, this did not abolish the significant relationship between prechallenge level of FEV₁ and degree of bronchial responsiveness (DRS) ($p = 0.007$).

Multiple regression analysis revealed that female gender ($p < 0.0001$) and more frequent symptoms of asthma ($p < 0.002$) were associated with a steeper DRS. Together with prechallenge FEV₁%pred, these variables accounted for 52% of the variance in measurements of bronchial responsiveness. No significant relationship could be demonstrated between smoking habits (pack years, daily tobacco consumption) and histamine responsiveness.

Decreasing prechallenge FEV₁%pred ($p < 0.0001$) and more frequent symptoms of asthma ($p < 0.05$) were associated with a steeper DRS in patients with both intrinsic and extrinsic asthma. Female gender was associated with a steeper DRS in patients with intrinsic asthma ($p < 0.003$), whereas no such relation was found for the patients with extrinsic asthma.

DISCUSSION

This study demonstrated that the prechallenge level of FEV₁ is an important determinant for the degree of

bronchial responsiveness to inhaled histamine in adults with bronchial asthma, even in patients with a prechallenge FEV₁ within the normal range. This is in keeping with findings by Cockcroft et al.,¹ as they observed a significant direct correlation between prechallenge FEV₁ and PC₂₀FEV₁ ($r = 0.49$) among 156 asthmatic patients. However, the group of patients studied by Cockcroft et al. differ in several ways from the patients in the present study. First, their patients were recruited from among both hospital volunteers and patients and, as assessed by their prechallenge level of pulmonary function, they most likely had less severe asthma than the patients in the present study. Second, their patients had a mean age of 35 years, and most were atopic, they were therefore both younger and more likely to have extrinsic asthma than the patients in the present study. Despite these differences between the patients in the two studies, the findings concerning the association between prechallenge FEV₁ and degree of bronchial responsiveness was similar. These findings, therefore, may suggest that the degree of bronchial responsiveness to inhaled histamine in asthmatic patients in general, to some extent reflects the size of the airways at the time of testing.

Prospective longitudinal data on nonspecific bronchial responsiveness and pulmonary function in population samples suggest that increased bronchial responsiveness is associated with accelerated longitudinal decline of pulmonary function²⁰; this relationship

has also been observed in subjects with bronchial asthma.⁷ However, in most studies concerning decline of lung function in adults with asthma, the degree of BHR has been measured at some point during the study and not at the start.²⁰ As the present study showed that the degree of nonspecific BHR in asthmatic patients is to some extent determined by the prechallenge airway caliber, these findings might not provide insight into the question of whether nonspecific BHR intrinsically is associated with accelerated decline in lung function. The high degree of nonspecific BHR observed in the patients who have had the steepest rates of decline in lung function might be a result of deterioration in the already established clinical disease instead of a true risk factor. However, when measurements of bronchial responsiveness are carried out in a standardized way, the results seem to reflect the severity of the disease.¹ High degree of nonspecific BHR, therefore, may be a marker of an abnormality in the airways, which might be associated with an accelerated decline in pulmonary function. It appears that interpretation of this "chicken-and-egg" relationship requires further studies of nonspecific BHR and decline of pulmonary function in subjects with bronchial asthma.

This study was performed in a selected population of clinic patients who may have had more severe asthma or may have been more difficult to treat than patients with asthma in the general population. This is supported by the relatively high proportion of patients with intrinsic asthma and the finding that 80% of the patients had reduced baseline (prechallenge) level of pulmonary function. However, although this population may not be representative of the asthmatic population at large, it offered an opportunity to study bronchial responsiveness in patients with a wide range of prechallenge levels of pulmonary function.

Nonspecific bronchial responsiveness to pharmacologic, bronchoconstricting agents has been described by use of various methods of summarizing dose-response data. Most commonly, the dose-response relationship is described as the concentration or dose of bronchoconstricting agent that causes a specific decline in lung function, for example, $PC_{20}FEV_1$. Because most nonasthmatic subjects have a normal degree of bronchial responsiveness, it has recently been suggested that the DRS should be used as a quantitative measure of bronchial responsiveness in epidemiologic studies.¹⁷ However, as it was also found in the present study, some subjects with current asthma have a $PC_{20}FEV_1$ histamine above 8 mg/ml²¹; and therefore, to avoid censoring of data, the DRS was used instead of PC_{20} to describe each subject's responsiveness.

There is no generally accepted definition of bronchial asthma²²; probably partly because in some cases it is difficult to separate bronchial asthma, especially intrinsic asthma, from COPD (also referred to as non-asthmatic COPD). The role of smoking, especially cigarette smoking, in the etiology of COPD has been well established for many years.²³ In the present study the estimated cumulative tobacco exposure was relatively low in both patients with both intrinsic and extrinsic asthma. Furthermore, no differences in the number of current and former smokers were found between the two groups of asthmatic patients. It therefore seems unlikely that the findings in this study are due to admixture of patients with COPD. However, as pointed out by the American Thoracic Society²⁴: "Patients with COPD may have significant reversibility after treatment, and patients with asthma may develop airflow obstruction with little to no reversibility. The separation of these overlap patients is often arbitrary and difficult." Some of these overlap patients might be among the asthmatic patients in this study, but they may as well be among the patients with extrinsic asthma as among the patients with intrinsic asthma. This is supported by the finding that bronchial responsiveness was similar in patients with intrinsic asthma and those with extrinsic asthma, as it has earlier been shown that the degree of bronchial responsiveness is less pronounced in patients with COPD than in asthmatic patients.⁴

In conclusion, the degree of nonspecific bronchial responsiveness is to some extent determined by the prechallenge level of pulmonary function in adults with bronchial asthma, even in patients with a prechallenge FEV_1 within the normal range.

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