

Allergen-induced changes in airway responsiveness are related to baseline airway responsiveness

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In the literature, bronchial allergen challenge is usually reported to result in an increase in histamine-induced airway responsiveness (AR). The present study investigated the relation between baseline AR and allergen-induced changes in AR. The effect of allergen challenge on AR was investigated in 21 atopic asthmatic patients. Allergen challenge resulted in a significant decrease in PC₂₀ histamine after 24 h. When the group was divided into three subgroups according to baseline PC₂₀ histamine, a significant decrease in PC₂₀ histamine was found only in patients with relatively high baseline PC₂₀ histamine (groups 1 and 2). A significant inverse correlation was found between baseline PC₂₀ and allergen-induced PC₂₀ histamine. The effect of repeated allergen challenge on AR was studied in eight patients. The first allergen challenge resulted in a significant decrease in PC₂₀ histamine; no further decrease in mean PC₂₀ histamine was seen after the second allergen challenge. These results suggest that allergen-induced changes in AR occur mainly in patients with relatively high baseline PC₂₀ values. Once an increase in AR is induced, further allergen challenge does not always result in further increase in AR.

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The bronchial response to inhaled allergen and the degree of histamine-induced airway responsiveness (AR) are considered to be interrelated. An increase in AR is found after natural exposure to allergen (1) and at various intervals after experimental allergen challenge (2–4). Cartier et al. (4) found a significant correlation between the allergen-induced increase in AR and the severity of the late asthmatic reaction (LAR), suggesting the same underlying mechanisms. These mechanisms may include inflammatory changes in the airways, as described by several authors during late responses and allergen-induced increases in AR (5–8). More recent studies show that the increase in AR precedes the development of the LAR (9, 10).

In an earlier study on the effect of cetirizine on early and late asthmatic reactions, we did not find a significant increase in AR after allergen challenge, despite the fact that all patients had late-phase responses (11). It was suggested that this could be related to the design of the study. Since in this study many included patients had a relatively low baseline PC₂₀ histamine, we also considered the

possibility that this patient characteristic might have influenced the results.

The aim of the present study was to investigate whether allergen-induced changes in AR are related to the pre-existing level of AR.

Material and methods

Patients

Twenty-one atopic, nonsmoking patients with mild to moderate asthma (15 women and six men, aged 17–44 years) participated in the study. The clinical data are presented in Table 1. Nineteen patients had positive skin tests and/or elevated specific IgE (Pharmacia Cap >0.7 PRU/ml) to house-dust mite (HDM), and two to grass pollen (GP). The pollen-allergic patients were tested at the end of the pollen season. All patients had asthma, well controlled by inhaled anti-inflammatory therapy, and FEV₁ values ≥70% of the predicted value. None of the patients gave a history of respiratory tract infections in the 6 weeks before the study or had received oral corticosteroids. All patients gave informed consent.

Table 1. Clinical data of patients

Patient	Age	Sex	FEV ₁	FEV ₁ % pred.	PC ₂₀ histamine mg/ml	Allergy	Regulatory steroids	Smokers
Group 1								
1*	44	F	2.80	89	8.00	GP	+	—
2*	20	F	2.92	103	7.74	HDM	+	—
3	21	M	4.40	109	12.08	HDM	+	—
4*	34	F	3.04	90	32.00	HDM	+	—
5	21	F	2.57	82	7.59	HDM		—
6	23	M	3.95	99	14.36	HDM		—
7*	26	F	3.20	96	5.50	HDM	+	—
Mean	27		3.27	95	12.47			
SD	9		0.66	9	9.13			
Group 2								
8*	27	F	2.80	88	1.45	GP	+	—
9*	24	F	3.72	99	3.00	HDM	+	—
10*	23	M	4.80	96	3.25	HDM	+	—
11	23	M	4.00	89	3.76	HDM	+	—
12	19	M	4.30	76	2.42	HDM	+	—
13	33	F	2.68	79	1.74	HDM	+	—
14	39	F	2.36	81	3.99	HDM		—
15	21	F	4.68	119	3.12	HDM	+	—
Mean	26		3.67	91	2.84			
SD	7		0.95	14	0.91			
Group 3								
16	19	F	3.27	81	0.83	HDM		—
17	22	F	3.09	99	0.93	HDM	+	—
18	32	F	3.36	92	0.77	HDM	+	—
19	17	F	3.56	86	0.63	HDM	+	—
20*	20	M	3.56	84	0.82	HDM	+	—
21	29	F	3.23	98	0.47	HDM	+	—
Mean	23		3.35	90	0.74			
SD	6		0.19	8	0.17			

* Patients who were rechallenged with allergen after 48 h.

The study was approved by the medical ethics committee of Asthmacentre Heideheuvel, The Netherlands.

Histamine challenge

Histamine phosphate solutions (doubling concentrations from 0.25 to 32 mg/ml) were administered through a De Vilbiss 646 nebulizer with a gauged output of 0.13 mg/ml. The nebulizer was mounted on a valve box with aerosol filter. The nebulization time was 30 s, during which the patient was instructed to breathe quietly. The test was started with inhalation of a phosphate-buffer aerosol. Before inhalation, three measurements of vital capacity (VC) and FEV₁ were taken with the portable electronic Printer Spirometer II (Micro Medical Ltd, Rochester, UK). Calibration of the spirometer was performed every 2 weeks. No adjustments were necessary. After each concentration, the FEV₁ value was measured. The PC₂₀ histamine was derived by linear interpolation.

Bronchial allergen challenge

Allergen solutions were prepared from stock solutions of *Dermatophagoides pteronyssinus* and mixed grass pollens, diluted in PBS with 0.03% human serum albumin and containing 0.5% phenol (SQ 503 and SQ 293, respectively, ALK Benelux), to produce a range of fivefold increasing concentrations from 80 to 10 000 BU/ml. The allergen solutions were administered through a De Vilbiss nebulizer mounted on a valve box with aerosol filter (output 0.13 mg/ml; see histamine challenge above). The patients were instructed to breathe quietly for 1 min for each dose. Increasing doses were given at 15-min intervals. The challenge procedure was terminated when the FEV₁ value fell $\geq 15\%$ below baseline value. After the last inhalation, FEV₁ was recorded at 10-min intervals for the first hour and every hour thereafter until 10 h after the last inhalation. FEV₁ values were corrected for diurnal variation; a fall in FEV₁ value $\geq 15\%$ from baseline value 3–10 h after challenge was considered a late phase reaction.

The early asthmatic reaction (EAR) and the

LAR were expressed by the mean fall in FEV₁ value during the early response (1–60 min after challenge) and during the late response (3–12 h after challenge).

Study design

The group of 21 patients was divided into three subgroups depending on the initial PC₂₀ histamine: group 1 with PC₂₀ histamine >4 mg/ml (*n*=7); group 2 with PC₂₀ histamine >1 mg/ml and ≤4 mg/ml (*n*=8); and group 3 with PC₂₀ histamine ≤1 mg/ml (*n*=6) (Table 1).

All patients underwent a bronchial challenge with allergen. Subjects were admitted to the hospital for 3 successive days. Histamine challenge was performed 72 h before admission to determine the PC₂₀ histamine before allergen challenge. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate were stopped 1 week before the study; theophyllines, oral β₂-adrenergic drugs, and antihistamines were stopped 48 h before the study; and inhaled β₂-adrenergic drugs were stopped 12 h before the tests. On admission day 1, the control solution was inhaled four times at 15-min intervals. FEV₁ was measured immediately and 15 min after each inhalation. After the fourth inhalation, FEV₁ was recorded at 10-min intervals for the first hour and then every hour until 11 h after the last inhalation. On day 2, subjects underwent the first allergen challenge with HDM or GP. Spirometry was performed as on day 1. On day 3, patients underwent a second histamine challenge to determine the PC₂₀ histamine after allergen challenge.

For study of the dynamics of allergen-induced changes in AR, a subgroup of eight patients (Table 2) was rechallenged with allergen 48 h after the first allergen challenge with the same dose of allergen. A third histamine challenge was performed 24 h after the second allergen challenge to determine the PC₂₀ histamine after the second allergen challenge. This group of patients stayed in the hospital for 5 successive days.

Table 2. PC₂₀ histamine (mg/ml) before and after repeated allergen challenge

Patient	PC ₂₀ 1	PC ₂₀ 2	PC ₂₀ 3
1	8.00	2.05	0.99
2	7.74	3.32	3.64
4	32.00	10.68	2.79
7	5.50	3.73	1.34
8	1.45	0.84	0.91
9	3.00	0.74	2.62
10	3.25	2.80	2.19
20	0.82	1.03	1.40
Mean	7.72	3.15	1.99
SD	10.17	3.25	0.98

We chose an interval of 48 h between the allergen challenges in order to secure baseline FEV₁ values comparable to those obtained before the first challenge, with inflammatory changes probably still present (12, 13).

Data analysis

Comparisons were made with the Wilcoxon signed rank test (WSR). Spearman's rank correlation test was used for correlation studies. *P* values less than 0.05 were considered significant.

Results

Allergen challenge resulted in EAR in all 21 patients (mean fall in FEV₁ 23.9±7.4%) and LAR in 19 patients (mean fall in FEV₁ 15.8±8.8%). Before allergen challenge, the PC₂₀ histamine of the patients varied from 0.47 to 32 mg/ml; the mean value was 5.45±7.20 mg/ml. Allergen challenge resulted in a significant decrease in PC₂₀ histamine, measured after 24 h (WSR log-transformed data, *P*=0.006).

The effect of allergen challenge on PC₂₀ histamine in the three subgroups is shown in Fig. 1. In groups 1 and 2, allergen challenge resulted in a significant decrease in PC₂₀ histamine (WSR log-transformed data, *P*=0.03; *P*=0.01, respectively). However, in group 3, no significant change in PC₂₀ histamine was found after allergen challenge.

When the entire group was evaluated, no significant correlation was found between the allergen-induced change in PC₂₀ histamine and the mean fall in FEV₁ (EAR) (Spearman, *r*=0.214; *P*=0.34; Fig. 2A). When the change in PC₂₀ histamine was compared with the mean fall in FEV₁ (LAR), a significant correlation was found (Spearman, *r*=0.474; *P*=0.03; Fig. 2B). The baseline PC₂₀ histamine (before allergen challenge) showed a significant *inverse* correlation with the allergen-induced change in PC₂₀ histamine (Spearman, *r*=−0.552; *P*=0.01; Fig. 2C).

In a subgroup of eight patients, repeated allergen challenge was performed with an interval of 48 h with the same dose of allergen. The first allergen challenge in this subgroup of patients resulted in EAR in all patients (mean fall FEV₁ 20.4±4.9%). This was followed by a definite late response in six patients. The mean fall in FEV₁ of all eight patients during the late-phase period was 9.9±8.0%. The second allergen challenge resulted in EAR in all patients (mean fall FEV₁ 22.3±8.0%) and LAR in seven patients. The mean fall in FEV₁ of all eight patients was 12.8±8.6%. Repeated allergen challenge did not result in significant changes in the severity of EAR and LAR, calculated as mean fall

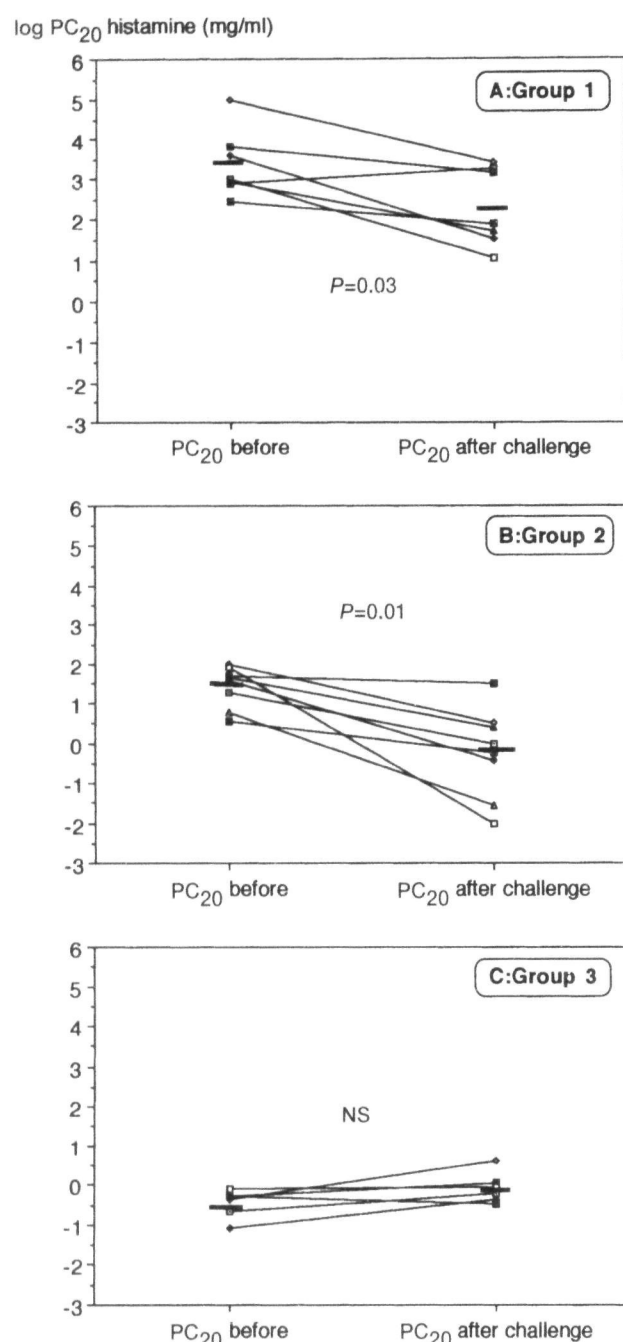


Fig. 1. PC₂₀ histamine before and after allergen challenge (log-transformed data): A) group 1; B) group 2; C) group 3.

in FEV₁ value during the early and late responses (WSR, $P=0.33$ and 0.33 , respectively).

PC₂₀ histamine before the first allergen challenge varied from 0.82 to 32 mg/ml; the mean value was 7.72 ± 10.17 mg/ml. The first allergen challenge resulted in a significant decrease in PC₂₀ histamine (WSR log-transformed data, $P=0.03$). The second allergen challenge did not result in a significant change in PC₂₀ histamine (WSR log-transformed data, $P=0.58$; Fig. 3).

Discussion

The present study was performed in order to investigate whether allergen-induced changes in AR are dependent on baseline AR. In an earlier study (11), we did not find a significant increase in AR after allergen challenge in a group of atopic asthmatic patients, and we speculated that this could be related to the rather low baseline PC₂₀ histamine (mean

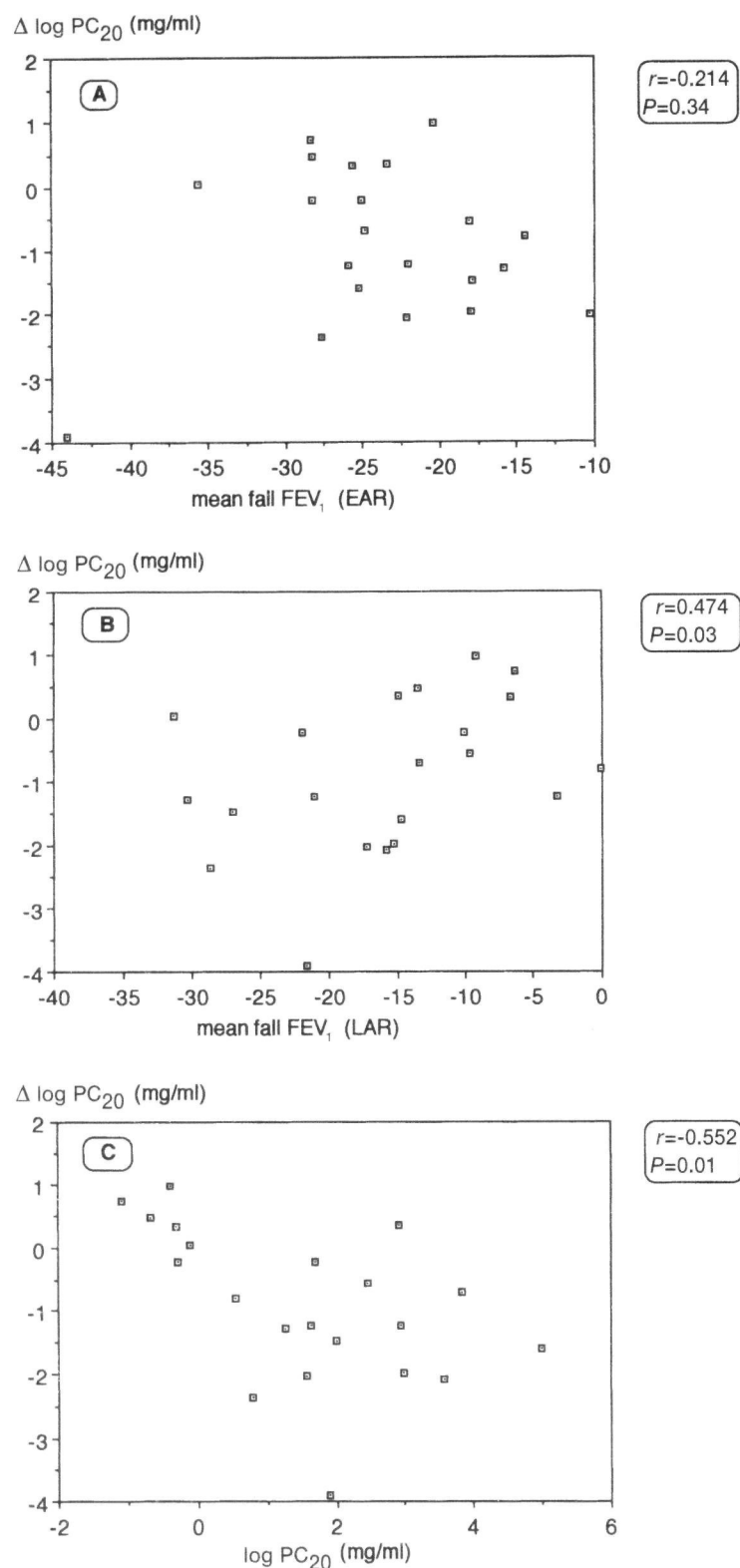


Fig. 2. Correlation between allergen-induced change in PC₂₀ histamine (Δ PC₂₀) and mean fall in FEV₁ (EAR) (A), mean fall in FEV₁ (LAR) (B), and baseline PC₂₀ histamine (log-transformed data) (C).

value 2.85 ± 4.43 mg/ml) of the patients in this group. In the present study, 21 atopic asthmatic patients with a higher baseline PC₂₀ histamine (mean value 5.45 ± 7.20 mg/ml) than in the former study were included, with the same study design, including 3 days of hospitalization. In contrast to the former study, allergen challenge in these 21 patients resulted in a significant decrease in PC₂₀ histamine 24 h after allergen challenge. The change in PC₂₀ histamine after allergen challenge showed a significant inverse correlation with baseline PC₂₀ histamine, suggesting a more pronounced increase

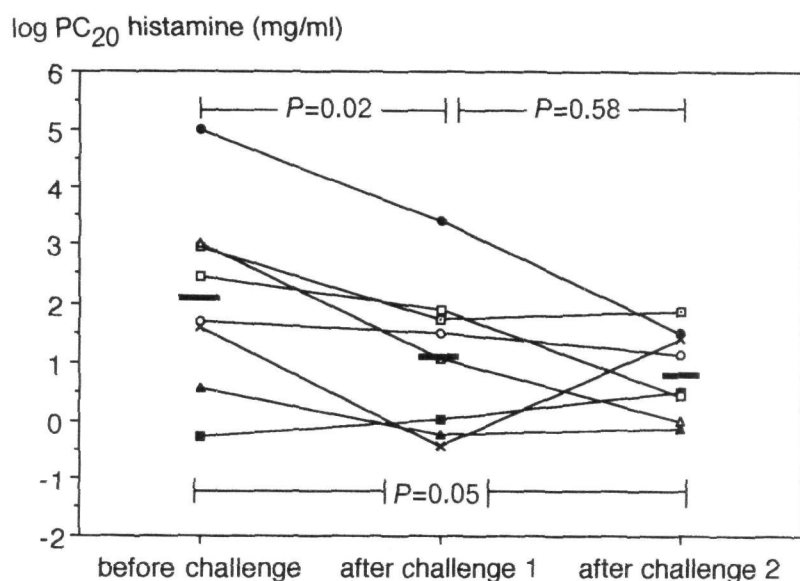


Fig. 3. PC₂₀ histamine before and after allergen challenges 1 and 2 (log-transformed data).

in allergen-induced AR in patients with an initially relatively high PC₂₀ histamine.

To explore further the relationship between baseline PC₂₀ histamine and allergen-induced changes in AR, we divided the group of 21 patients into three subgroups, depending on initial PC₂₀ histamine. In groups 1 and 2 (PC₂₀ histamine > 1 mg/ml), allergen challenge resulted in a significant decrease in PC₂₀ histamine, although the differences in group 1 (PC₂₀ histamine > 4 mg/ml) were rather small. The patients with the lowest baseline PC₂₀ histamine (group 3, PC₂₀ histamine ≤ 1 mg/ml) did not show a significant change after allergen challenge. This could not be attributed to a limited measuring range of the group with the lowest baseline PC₂₀ histamine. As shown in Table 1, in all patients PC₂₀ values were above the lowest histamine phosphate concentration (0.25 mg/ml) that was used. Also, differences in the allergen dose administered in the three groups could not explain the lack of significant change in PC₂₀ histamine after allergen challenge in group 1. Although there was a small difference between the mean allergen dose administered in the three groups, the patients with the lowest baseline PC₂₀ histamine did not receive the lowest dose of allergen. The mean dose of allergen in groups 1, 2, and 3 were 5.1, 4.3, and 5.0 BU/ml, respectively (log-transformed data). In order to study a possible relation between the dose of anti-inflammatory treatment before the tests and the allergen-induced change in PC₂₀ histamine, we calculated the correlation between the dose of inhaled steroids before the tests and the allergen-induced change in PC₂₀ histamine. We could not find a significant correlation ($r=0.27$). The mean dose of inhaled steroids in groups 1, 2, and 3 were 514, 487, and 800 µg, respectively; however, there were large differences within the groups.

In the past, many studies have been performed

on the effect of allergen challenge on the induction of AR. A significant decrease in PC₂₀ histamine 24 h after allergen challenge, as we found in our group of 21 patients, has been reported by several other authors (2–4, 9, 10). A significant correlation between the allergen-induced increase in AR and the severity of the LAR has earlier been reported (4, 10). No data have been reported on the relation between baseline AR and allergen-induced changes in AR.

In the second part of the present study, the relation between baseline AR and allergen-induced change in AR was studied in a longitudinal design. A subgroup of eight patients, who were willing and able to stay in hospital for 5 successive days, underwent two allergen challenges with an interval of 48 h and the same dose of allergen. The first allergen challenge resulted in a significant decrease in PC₂₀ histamine. This significantly lower PC₂₀ histamine after the first allergen challenge served as baseline value for the second allergen challenge. No significant further decrease in mean PC₂₀ histamine was found after the second allergen challenge, despite the fact that the intensity of the allergic reaction, expressed as mean fall in FEV₁ during EAR and LAR, did not differ significantly from the first. As shown in Table 2, in all patients, PC₂₀ values after the first challenge were above the lowest histamine phosphate concentration (0.25 mg/ml) that was used. Thus, the lack of a further decrease in PC₂₀ values after the second allergen challenge could not be attributed to a limited measuring range. This finding also suggests that in patients with relatively low baseline PC₂₀ histamine, no further fall in PC₂₀ value may occur.

The effect of repeated allergen challenge on AR in allergic patients was also studied by Ihre & Zetterström (14), who found a significant increase in AR after repeated inhalation of low doses of allergen. AR was not measured during the course of these repeated inhalations; therefore, it is possible that the increase in AR was already maximal after the first allergen challenge, as in our study.

Another finding in the second part of our study was that repeated allergen challenge did not lead to significant changes in the intensity of early and late asthmatic responses. Our findings on the EAR are in accordance with the findings of Rosenthal et al. (15), who performed repeated allergen challenges for 4 consecutive days in 13 ragweed-allergic patients outside the season and who also could not find significant changes in the intensity of the EAR. The effect of repeated allergen challenge on EAR and LAR was studied by Rasmussen (16), who used an interval of 14 days between the challenges. No significant changes in EAR were found, but a significant increase in the intensity of the LAR was

found, which was thought to be related to an enhanced specific reactivity. These findings are in contrast to a study performed by Bel et al. (17), who found reproducible EAR and LAR after allergen challenge with an interval of 2 weeks in 10 atopic asthmatic patients (18).

Our finding that allergen-induced change in AR shows an inverse correlation with baseline AR also has practical implications. For instance, when selecting patients for controlled medication studies on the effect on allergen-induced changes in AR, baseline AR should be comparable in each group.

In the second part of the study, we found that repeated allergen challenge did not induce further significant increase in AR, despite the fact that the LAR after both challenges was not statistically different. It seems that some patients have reached their individual maximal level of AR due to the first allergen challenge. In the literature, the occurrence of LAR is often associated with a subsequent increase in AR, which in turn could lead to a more severe LAR. The fact that in our study an increase in AR did not lead to an increase of the subsequent LAR suggests that not all patients deteriorate after repeated allergen exposure. Further studies in which AR is measured after several successive allergen challenges are needed to elucidate this problem.

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