

Bronchial and skin reactivity in asthmatic patients with and without atopic dermatitis

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ABSTRACT: It is unclear whether the presence and severity of atopic dermatitis (AD) is predictive for the occurrence and severity of early and late asthmatic responses to inhaled allergens. The aim of this study was to compare the bronchial effects of allergen inhalation challenge in allergic asthma (AA) and atopic dermatitis.

We therefore studied these responses in: nine patients with mild-to-moderate AA without AD; eight patients with mild-to-moderate AA and mild AD; eight patients with severe AD and mild AA; and eight patients with severe AD without AA. Allergen challenge was performed by inhaling doubling doses until the dose provoking a 20% fall in forced expiratory volume in one second (PC₂₀) was reached. The late asthmatic reaction (LAR) was defined as a fall of >20% in peak expiratory flow (PEF) between 3 and 8 h after the challenge.

All but four of the patients with severe AD without AA developed an early asthmatic response (EAR). A LAR was seen in all patients with severe AD and mild AA, in four patients with mild AD and mild-to-moderate AA, and in three patients with mild-to-moderate AA without AD. The LAR was most pronounced in patients with a combination of mild AA and severe AD. This could be explained, in part, by a decreased skin sensitivity in these patients, which made the Cockcroft formula for prediction of PC₂₀ allergen less accurate in such patients.

We conclude that patients with severe atopic dermatitis and mild asthma are at risk for developing pronounced late asthmatic responses after allergen exposure. This suggests that eosinophils activated in atopic dermatitis also predispose to airway inflammation.

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The term "atopy" was introduced in 1923 by COCA and COOKE [1] and refers to a hereditary predisposition to development of immunoglobulin E (IgE) antibodies to common environmental allergens, as expressed in atopic dermatitis (AD), allergic asthma (AA) and rhinitis. AD is a chronic inflammatory skin disease characterized by skin hyperreactivity, which is frequently (29–35%) associated with AA [2, 3]. An important pathophysiological aspect of asthma is bronchial hyperresponsiveness (BHR) [4, 5]. However, skin reactivity to cholinergic agonists has also been found in asthmatics [6], and BHR has been shown in AD patients without AA [4, 5, 7–9]. These studies strongly suggest a similarity between the pathophysiology of AD and AA.

Inhalation of allergens plays an important role in the pathogenesis of AA [10, 11]. The activity of AD can also be influenced by allergens. Exposure to environmental allergens may aggravate the eczema by inhalation [12–14] or skin contact [15], and an improvement of the skin lesions can be seen after allergen avoidance [16–18]. Immunological evidence supporting the significance of allergen exposure comes from the presence of elevated serum IgE levels to aeroallergens, the binding

of IgE to antigen presenting cells in the skin [19], and the presence of allergen specific T-cells in lesional AD skin [20, 21].

In contrast to allergen challenges in asthmatics, only a few allergen inhalation studies have been carried out in patients with AD. In previous reports, RAJKA [12] and BUTLER *et al.* [13] primarily investigated cutaneous effects of allergen inhalation challenge. RAJKA [12] reported that inhalation of mould extracts could induce eczematous skin reactions in 2 out of 5 patients with "pure" AD. BUTLER *et al.* [13] found that in Ascaris-sensitized asthmatic dogs a pruritic dermatitis developed after Ascaris antigen inhalation provocation which showed similarities with AD.

Bronchial effects of inhalation of allergens were investigated in studies by MORSBACH [22] and DOHI *et al.* [7]. MORSBACH [22] provoked bronchoconstriction in 12 out of 16 "pure" AD patients after experimental inhalation of different allergens. DOHI *et al.* [7] carried out allergen inhalation challenges in eight AA patients and eight AD patients with no history of asthma, to compare bronchial responsiveness to house dust mite allergen in these patients. They observed an early asthmatic response

(EAR) in all 16 patients. A late asthmatic response (LAR) was found in six asthmatic patients, whereas it was not observed in any AD patient [7]. These studies only describe bronchial effects of allergen inhalation challenge in patients with "pure" AD.

In a recent study by TUPKER *et al.* [14], respiratory and cutaneous symptoms were studied after double-blind, placebo-controlled bronchial provocation with house dust mite in 15 AD patients with and five AD patients without a history of asthma. Allergen inhalation induced-dermatitis was seen in nine AD patients with a history of asthma. An EAR was seen in eight of these patients and a LAR in three. One of the AD patients without a history of asthma showed an EAR after provocation, and none of them developed skin symptoms after challenge [14].

Because of the suggested existence of a similarity between the pathophysiological aspects of AD and AA, the effects of allergen inhalation challenge were studied in AD patients with or without clinical respiratory symptoms in comparison with AA patients with or without dermatitis. The aim of the present study was to evaluate whether the presence and severity of AD in asthma patients is relevant for the degree of bronchial hyper-responsiveness and the occurrence and severity of EARs and LARs. We therefore compared the degree of BHR to methacholine or histamine and EARs and LARs after allergen inhalation challenge in patients with either AD or AA, and in patients with both AA and AD.

Materials and methods

Patients

Four different patient groups were studied.

Patients with mild-to-moderate AA without AD. The diagnosis of mild-to-moderate AA was made according to the definition of the American Thoracic Society (ATS) [23]. These patients were free of eczematous skin lesions. Before entering the study, the patients were receiving daily therapy with inhaled β_2 -agonists. Six of them were also receiving daily therapy with inhaled corticosteroids (table 1).

Patients with mild-to-moderate AA and mild AD. AD was diagnosed according to the criteria of HANIFIN and RAJKA [25], and was considered to be mild according to the quick scoring system of COSTA *et al.* [26] (Costa score <15, see "severity score for atopic dermatitis" below). None of these patients were treated with topical corticosteroids. All patients were regularly using inhaled β_2 -agonists, and four of them were also receiving daily therapy with inhaled corticosteroids (table 1).

Patients with severe AD and mild AA. These patients were regularly using topical tar ointment (pix liquida) and oral antihistamines (hydroxyzine) as treatment for AD. AD was considered to be severe according to COSTA *et al.* [26] (Costa score >40). Seven patients were receiving inhaled β_2 -agonists *p.r.n.* (table 1).

Patients with severe AD without AA. All patients showed a Costa score >40 before entering the study, and used the same treatment for AD as the group with severe AD and mild AA. The patients in this group had no complaints or history of asthma (which was assessed by a standardized questionnaire), showed no diurnal variation in peak flow, and demonstrated a less than 10% reversibility in forced expiratory volume in one second (FEV₁) 15 min after inhalation of 100 μ g salbutamol.

The first group included nine patients and the other three groups included eight patients. Table 1 presents the patient characteristics and the values of total serum IgE. All patients had raised levels of specific IgE antibodies either to house dust mite, birch pollen, cat, dog or rabbit allergen (tables 2 and 3). They also showed positive immediate type skin-prick test reactions to these allergens, and hence were considered atopics. Eight patients with severe AD with or without mild AA had diagnosed IgE-mediated sensitization to food allergens. Clinically relevant food allergens were excluded from the diet of these patients. At the time of the study, all patients were in a stable state of their AA or AD. The FEV₁ was >60% of the predicted values without bronchodilator therapy [24]. During the study, all asthmatic patients used inhaled bronchodilators when needed. The asthmatic patients who were treated with inhaled corticosteroids had to stop this medication 6 weeks prior to

Table 1. – Characterization of study groups

Group	Pts n	Age [#] yrs	Sex F/M	IgE [‡] kU·L ⁻¹	FEV ₁ [#] % pred	Medication ⁺
Mild-to-moderate asthma	9	27 (22–38)	3/6	194 (69–800)	76 (62–92)	C: 6 S: 9
Mild-to-moderate asthma and mild atopic dermatitis	8	25 (19–32)	2/6	337 (53–1746)	75 (55–99)	C: 4 S: 8
Severe atopic dermatitis	8	26 (22–30)	5/3	4517** (1232–17198)	93** (80–107)	
Severe atopic dermatitis and mild asthma	8	26 (17–49)	4/4	14808** (2070–29578)	90** (65–116)	S: 7

[#]: values are presented as mean and range in parenthesis; [‡]: values are presented as median and range in parenthesis; ⁺: medication used in the year before entering the study and number of patients taking the medication. Pts: patients; F: female; M: male; IgE: immunoglobulin E; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted values, according to QUANJER *et al.* [24]. C: inhaled corticosteroids; S: inhaled salbutamol. **: significant difference between patients with severe atopic dermatitis (AD) regardless of the presence of mild atopic asthma (AA) and the patients with mild-to-moderate AA regardless of the presence of mild AD (p<0.01).

Table 2. – PC₂₀ and the effects of allergen inhalation challenge on lung function in mild-to-moderate asthma

Pts No.	PC ₂₀ histamine mg·mL ⁻¹	Allergen	Specific IgE kU·L ⁻¹	PC ₂₀ allergen BU·mL ⁻¹	% fall in PEF from baseline		
					% fall in FEV ₁ from baseline <20 min	<20 min	3–8 h
Mild-to-moderate asthma							
1	0.16	Dog	18	21	25	24	2
2	0.16	Cat	59	9	27	18	13
3	0.92	<i>Der p</i>	45	127	25	34	32
4	0.21	<i>Der p</i>	57	94	29	28	30
5	1.99	Dog	11	41	23	30	25
6	0.87	Cat	41	1470	23	19	7
7	0.19	<i>Der p</i>	17	7	32	28	14
8	0.17	<i>Der p</i>	16	17	27	22	9
9	0.41	<i>Der p</i>	25	39	22	25	19
Mean	-	-	-	-	25.9	26.4	16.8
SEM	-	-	-	-	1.1	2.2	3.5
Median	0.21	-	-	39	-	-	-
Mild-to-moderate asthma and mild atopic dermatitis							
10	1.55	<i>Der p</i>	93	394	36	26	30
11	0.21	<i>Der p</i>	75	21	21	33	8
12	0.20	<i>Der p</i>	77	42	23	30	10
13	0.31	<i>Der p</i>	26	152	21	8	22
14	2.06	Rabbit	3	1050	37	26	7
15	0.21	<i>Der p</i>	54	43	26	23	2
16	0.18	<i>Der p</i>	73	16	34	20	22
17	0.61	<i>Der p</i>	25	330	23	26	22
Mean	-	-	-	-	27.6	24.0	15.4
SEM	-	-	-	-	2.4	2.7	3.5
Median	0.26	-	-	98	-	-	-

Allergen inhalation challenge was performed with house dust mite (*Dermatophagoides pteronyssinus*), rabbit, dog or cat allergen. After PC₂₀ allergen challenge, percentage fall in FEV₁ from baseline within 20 min and percentage fall in PEF from baseline within 20 min and between 3 and 8 h were measured. PC₂₀: provocative concentration producing a 20% fall in FEV₁; BU: biological units; PEF: peak expiratory flow; *Der p*: house dust mite allergen. For further definitions see legend to table 1.

allergen inhalation challenge. The study was approved by the Hospital Ethics Committee and all patients gave their written informed consent.

Study design

Each subject was studied on four separate days. At enrolment, the Costa score (see "severity score for atopic dermatitis" below) was measured and a spirometric test was performed after inhalation of salbutamol. Two weeks later, an inhalation challenge was performed. To minimize the effect of the daily oral antihistamine therapy (given to the severe AD patients) on the bronchial challenge tests, the therapy was stopped 48 h before the inhalation test and the challenge was performed with methacholine and not with histamine, as is the routine procedure in our laboratory [27]. Comparisons in the clinic have shown that histamine and methacholine are equipotent in asthmatic subjects and in a population sample of adults [27–29]. Because the two agents are equipotent, it is possible to use either with equal effectiveness to determine bronchial hyperreactivity [28]. Two days after challenge with histamine or methacholine, an allergen inhalation challenge was performed. The allergen inhalation challenge started between 10.00 and 11.00 h. Inhalations were continued until the FEV₁ measured 10 min after each inhalation had fallen by more than 20%. The FEV₁ and

peak expiratory flow (PEF) were then monitored at 10 min intervals for 1 h, followed by hourly measurements of the FEV₁ and PEF. The EAR was defined as the maximal fall (>20%) in FEV₁ from the postcontrol value, occurring in the first hour after allergen inhalation [30]. The LAR was defined as a fall in PEF of ≥20% from baseline, occurring 3–8 h after allergen challenge. All patients were seen 24 h later to collect the daily record card with hourly PEF measurements after allergen inhalation challenge and to report the occurrence of pulmonary symptoms.

Allergens

Commercial preparations of SQ 503 house dust mite (*Dermatophagoides pteronyssinus*), SQ 197 tree pollen (a mixture of *Alnus glutinosa*, *Betula verrucosa*, *Corylus avellana*), SQ 553 cat (*Felis catus*), SQ 553 dog (*Canis familiaris*) and 15.07 rabbit (*Oryctolagus cuniculus*) for inhalation challenge and skin-prick tests were obtained from Allergologisk Laboratorium, Copenhagen, Denmark.

Severity score for atopic dermatitis

To evaluate the severity of AD, the simple scoring system described by COSTA *et al.* [26] was used. This method

Table 3. – PC₂₀ and the effects of allergen inhalation challenge on lung function in severe atopic dermatitis

Pts No.	PC ₂₀ Methacholine mg·mL ⁻¹	Allergen	Specific IgE kU·L ⁻¹	PC ₂₀ allergen BU·mL ⁻¹	% fall in FEV ₁ from baseline	% fall in PEF from baseline	
					<20 min	<20 min	3–8 h
Severe atopic dermatitis and mild asthma							
18	0.76	<i>Der p</i>	>100	206	32	17	42
19	0.38	<i>Der p</i>	>100	11 [§]	44	44	26
20	0.67	<i>Der p</i>	>100	56	41	45	22
21	0.43	<i>Der p</i>	>100	90	22	27	21
22	1.30	Tree pollen	>100	21 [§]	45	35	24
23	0.55	<i>Der p</i>	>100	12 [§]	33	27	29
24	0.55	<i>Der p</i>	>100	137	32	14	24
25	0.45	<i>Der p</i>	>100	250	43	30	30
Mean	-	-	-	-	37**	30***	27.3**
SEM	-	-	-	-	2.8	4.0	2.4
Median	0.55	-	-	73	-	-	-
Severe atopic dermatitis							
26	2.88	<i>Der p</i>	>100	938	30	5	+5
27	2.40	<i>Der p</i>	>100	1463	21	11	3
28	>76.80	Cat	50	>1500	7	2	0
29	4.90	<i>Der p</i>	>100	1153	29	21	4
30	3.15	Tree pollen	24	>1500	7	16	6
31	>76.80	<i>Der p</i>	>100	>1500	9	9	16
32	6.50	<i>Der p</i>	>100	1343	22	13	8
33	13.80	<i>Der p</i>	4	>1500	3	3	2
Mean	-	-	-	-	16*	10*	4.3*
SEM	-	-	-	-	3.8	2.3	2.2
Median	5.7*	-	-	1482*‡	-	-	-

‡: PC₂₀ allergen >1,500 BU·mL⁻¹ is calculated as 1,500 BU·mL⁻¹; §: the starting concentration for allergen inhalation was one doubling dilution above the measured PC₂₀ allergen in patients Nos. 19 and 22, and two doubling dilutions in patient No. 23. Allergen inhalation challenge was performed with house dust mite (*Dermatophagoides pteronyssinus*), tree pollen or cat allergen. After PC₂₀ allergen challenge, percentage fall in FEV₁ from baseline within 20 min, and percentage fall in PEF from baseline within 20 min and between 3 and 8 h were measured. *: significant difference between patients with severe AD without AA and all other groups (p<0.01); **: significant difference between patients with severe AD and mild AA and all other groups (p<0.01); ***: significant difference between patients with severe AD and mild AA and patients with severe AD without AA (p<0.01). For definitions see legends to tables 1 and 2.

consists of scoring 10 "severity" criteria (erythema, oedema, vesicles, crusts, excoriations, scales, lichenifications, pigmentation/depigmentation, pruritus, loss of sleep), and 10 topographic sites. To evaluate each "severity" criterion, the most severely affected areas were chosen and each was scored from 0 (no lesion) to 7 (extremely severe). The following topographic sites were scored from 0 to 3, according to the extent of the involvement: five symmetrical areas (feet, knees, legs, hands, arms; one value for each pair); and five nonsymmetrical areas: (face, scalp, buttock, anterior and posterior aspects of the trunk).

Lung function measurements

Salbutamol inhalation was stopped at least 8 h before all lung function tests. Lung function was measured with a water-sealed spirometer. Bronchodilatation was measured as the increase in FEV₁ 10 min after inhalation of 400 µg salbutamol from a pressurized metered-dose inhaler through a spacer device (Volumatic®; Allen and Hanbury's Ltd, Greenford, UK). Morning and evening PEF measurements were recorded with a mini-Wright peak flow meter. The best of three attempts was registered on a diary card. Bronchial responsiveness to methacholine in both patient groups with severe AD, and to

histamine in the other patient groups, was determined using a standard bronchoprovocation technique, as described by COCKCROFT and co-workers [31]. Briefly, an aerosol of saline followed by doubling concentrations of histamine (0.125–4.0 mg·mL⁻¹) or methacholine (0.3–76.8 mg·mL⁻¹) were inhaled for 2 min during tidal breathing. The aerosol was inhaled through a mouthpiece and the nose was clipped. The result was expressed as the provocative concentration causing a 20% fall in FEV₁ (PC₂₀) from postsaline value [32].

Airway response to allergen was determined by 2 min inhalations (tidal breathing) at 10 min intervals, as described previously [32]. The allergen challenge was preceded by 2 min inhalation of an initial aerosol of buffer (0.03% human serum albumin and 0.5% phenol in phosphate-buffered saline) to which none of the patients reacted with a fall in FEV₁ of more than 10% from initial value. Increasing concentrations of antigen aerosol were delivered with a nebulizer (Model 646; DeVilbiss Inc., Somerset, PA, USA). This nebulizer was connected to the central chamber of an inspiratory and expiratory three-way valve box, with an expiratory aerosol filter (Sterivent Filter; DAR Mirandola, Italy). The patients inhaled the aerosol through a mouthpiece while the nose was clipped. Antigen was diluted from stock solutions (10,000 biological units (BU)·mL⁻¹). The diluent

was the same buffer as used for the negative control. The predicted PC₂₀ allergen was calculated from the skin sensitivity, determined in the skin-prick test, and the preantigen PC₂₀ for histamine or methacholine, according to COCKCROFT and co-workers [33]. Allergen inhalation tests were routinely started two doubling dilutions below this prediction. The strongest allergen solution used in the challenge was 1,500 BU·mL⁻¹. Skin-prick tests were performed 2 h before allergen challenge. Inhalations were performed by stepwise doubling of the dose of antigen until the FEV₁ fell at least 20% following allergen exposure. PC₂₀ allergen was defined as the concentration of allergen which caused 20% fall in FEV₁ from postcontrol value.

Skin-prick test

This test was performed according to the technique described in the European Academy of Allergology and Clinical Immunology (EAACI) position paper [34]. A drop of test solution of the allergen used in the allergen inhalation challenge was applied to the skin of the volar side of the forearm, using a lancet with a 1 mm tip (ALK, Copenhagen, Denmark). The test was performed with allergen at five different concentrations (6, 24, 94, 375 and 1,500 BU·mL⁻¹). After 20 min, the reactions were evaluated. Skin sensitivity to allergen was defined as the smallest allergen concentration that gave a wheal of at least 2 mm in diameter [33].

Measurement of total and allergen specific serum IgE

Total IgE concentrations were measured using the paper radioimmunosorbent test (PRIST; Pharmacia, Uppsala, Sweden) [35], according to manufacturer's instructions. The results are expressed in kU·L⁻¹. Specific IgE antibodies to house dust mite, cat, dog, rabbit and birch pollen allergen were measured with the CAP method (Pharmacia, Uppsala, Sweden) [35], according to the manufacturer's instructions. The results are expressed in kU·L⁻¹.

Statistical analysis

The baseline lung function data are expressed as mean ± standard error of the mean (SEM). The data for total IgE, skin sensitivity, PC₂₀ histamine, PC₂₀ methacholine and PC₂₀ allergen are expressed as median values. When data were normally distributed, one-way analysis of variance (ANOVA) was used followed by least significant difference (LSD) test. When data were not normally distributed, a Kruskal-Wallis test was used. A p-value less than 0.05 was considered significant.

Results

Lung function measurements and bronchial provocation with histamine or methacholine

The mean value of the baseline FEV₁ was significantly lower in the patients with mild-to-moderate AA

with or without mild AD compared with the patients with severe AD regardless of the presence of AA (table 1). There was no significant difference in mean early morning PEF values between the four groups (not shown). Increased BHR to histamine or methacholine (PC₂₀ histamine or methacholine (Mch) ≤8 mg·mL⁻¹) (tables 2 and 3) was found in all patients, with the exception of three patients with severe AD without AA. Two of the latter patients did not respond to the highest concentration of methacholine used (PC₂₀ Mch >76.8 mg·mL⁻¹). The median value of the PC₂₀ Mch in the patients with severe AD without AA was significantly higher compared to the PC₂₀ Mch or PC₂₀ histamine in all other groups. On at least one occasion, a more than 20% increase in FEV₁ following 400 µg salbutamol was shown in all patients with mild-to-moderate AA with or without mild AD. On at least one occasion, all patients with severe AD and mild AA showed a >10% increase in FEV₁ following bronchodilator (not shown).

Allergen inhalation challenge

The allergen used in the challenge is presented in tables 2 and 3. All but four patients with severe AD without AA developed an EAR (table 3). The mean value of the maximal fall in FEV₁ within 1 h after challenge was significantly different between the groups (p=0.0001). The provocative allergen concentration causing an EAR (PC₂₀ allergen) is presented in tables 2 and 3. The median value of the PC₂₀ allergen was significantly higher in the patients with severe AD without AA compared to the other groups (p=0.0007).

After recovery from the EAR, all patients with severe AD and mild AA, four patients with mild-to-moderate AA and mild AD and three without mild AD showed a second decrease in PEF of ≥20% 3–8 h after allergen challenge (tables 2 and 3), indicating the occurrence of a LAR. None of the patients with severe AD without AA developed a LAR. LSD analysis of the mean percentage fall in PEF from baseline 3–8 h after challenge showed a significant difference between the groups (p=0.0001). The mean value of the maximal fall in PEF 3–8 h after challenge of the patients with severe AD without AA was significantly lower compared to the other groups, whereas the mean value of patients with severe AD with AA was significantly higher compared to the other groups.

Pulmonary symptoms after allergen inhalation challenge

In one patient with severe AD and mild AA, a prolonged LAR with a severe episode of asthma refractory to bronchodilators was observed. Therefore, an intramuscular injection with corticosteroids was given 24 h after onset of the EAR, which resulted in a fast relief of asthma symptoms. Three other patients in this group had an exacerbation of asthma symptoms (shortness of breath, wheezing, difficulty with expectoration) within 2 weeks after allergen inhalation challenge. In this period, a fall in FEV₁ of more than 20% from baseline values was measured. Two of these patients were, therefore, treated with inhaled corticosteroids and bronchodilators.

Table 4. – Skin sensitivity to the allergen used in the allergen inhalation challenge measured in all patient groups.

Patient groups	Pts n	Allergen concentration BU·mL ⁻¹				
		6	24	94	375	1500
Mild-to-moderate asthma	9	5	3	1	0	0
Mild-to-moderate asthma and mild atopic dermatitis	8	5	2	1	0	0
Severe atopic dermatitis and mild asthma	8	1	2	5	0	0
Severe atopic dermatitis	8	0	2	2	1	3

Skin sensitivity was defined as the smallest allergen concentration that gave a wheal of at least 2 mm in diameter. BU: biological units; Pts: patients.

The other patient showed signs of pneumonia on chest radiographic image and was treated with oral corticosteroids and antibiotics in combination with bronchodilators. Within 4 weeks of treatment, all patients showed significant improvement, with return to normal lung function. A tendency to a LAR (a fall in PEF within 3–8 h after allergen challenge of 16%) and complaints of shortness of breath were found in one patient with severe AD without AA. On this occasion, salbutamol was given for symptomatic relief. Surprisingly, this patient showed no EAR and did not respond to the highest concentration of methacholine. A prolonged LAR or exacerbation of asthma symptoms was not observed in the groups with mild-to-moderate AA with or without mild AD.

Skin-prick test

The skin sensitivity to the allergen used in the allergen inhalation challenge in all patient groups is presented in table 4. The median values of the skin sensitivity were significantly higher in the patients with severe AD with or without mild AA than in the patients with mild-to-moderate AA with or without mild AD ($p=0.0002$).

Discussion

In this study, early and late asthmatic responses after allergen inhalation challenge were compared in four different patient groups: 1) patients with mild-to-moderate AA without AD; 2) patients with mild-to-moderate AA with mild AD; 3) patients with severe AD with mild AA; and 4) patients with severe AD without AA. All patients with severe AD with mild AA, four patients with mild-to-moderate AA with and four without mild AD developed a LAR. The fact that none of the "pure" AD patients showed a LAR confirms other studies, and indicates that the LAR is a characteristic feature of AA [7, 14]. The mean value of the maximal fall in PEF 3–8 h after allergen inhalation challenge was significantly higher in the patients with severe AD with mild AA compared to all other groups. Furthermore, four patients in this group had an exacerbation of their asthma after allergen inhalation challenge, which had to be treated with corticosteroids. These results have clinical relevance, as they indicate that pronounced late responses

can be induced in severe AD patients with mild AA. Interestingly, the mean value of the maximal fall in PEF 3–8 h after challenge in this group was significantly higher compared to the mean values in the patient groups with mild-to-moderate AA with or without mild AD, despite the fact that patients in this group had less complaints of asthma (which was assessed by a standardized questionnaire). They showed better lung function and used less asthma medication, in diversity as well as in frequency (table 1). Furthermore, these patients are at risk for developing prolonged asthma after allergen inhalation challenge. There are several possible explanations for the finding that the mean value of the maximal fall in PEF from baseline 3–8 h after allergen challenge was significantly higher in this group compared to the other patient groups.

Firstly, the patients with severe AD with mild asthma showed significantly higher levels of total serum IgE and allergen specific serum IgE. In previous reports, the EAR and LAR have been shown to be dependent on the level of allergen specific serum IgE [30, 36]. Nevertheless, statistical analysis showed no significant correlation between allergen specific serum IgE (or total serum IgE) levels and the presence of asthmatic episodes, including development both of early and late asthmatic responses upon challenge.

Secondly, the patients with severe AD with mild AA showed significantly lower skin sensitivity to the allergen used in the allergen inhalation challenge compared to the other groups of patients with mild-to-moderate AA, although they had higher levels of specific serum IgE. This finding can probably be explained by a decreased skin sensitivity to histamine, which was described by DE MAAT-BLEEKER [37]. This latter study described a decreased skin sensitivity to histamine in patients with severe AD. As mentioned previously, the most diluted allergen solution used for the first inhalation was calculated from the skin-prick test and the preantigen PC₂₀ for histamine or methacholine [33]. In contrast to skin sensitivity, no difference was found in nonspecific and specific bronchial responsiveness. As a result of the decreased skin sensitivity, we found that the calculated starting concentration for allergen inhalation was one or two doubling dilutions above the measured PC₂₀ allergen for three patients with severe AD with mild AA (table 3). In relation to their calculated PC₂₀ allergen these three patients inhaled more allergen than the AA patients in the other groups. The absolute concentrations of the inhaled allergen in these three patients, however, were not higher compared to patients in other groups (tables 2 and 3).

Another possible explanation for the finding is the hypothesis that the courses of AA and AD may alternate [38]. At the time of allergen challenge, the skin lesions of all severe AD patients were in remission. Therefore, these patients could probably easily develop severe asthma symptoms after allergen inhalation challenge. To test this hypothesis, we should also challenge these patients when their skin lesions are in exacerbation, which was not possible for ethical reasons.

Finally, differences in lung function could possibly also explain the severity of the LAR in the patients with severe AD with AA. The FEV₁ in the patients with severe AD with AA was significantly higher compared to the

FEV₁ in the other asthmatics, which indicates that these patients showed less airways obstruction. Possibly, as a consequence of better penetration of higher amounts of allergens into the lung tissue, a more severe LAR can be induced in the patients with severe AD with AA.

Nonspecific BHR was found in four patients with severe AD without AA. The present data support the findings of several investigators, who found increased BHR in patients with AD without AA [4, 5, 7–9]. This finding suggests a latent predisposition to bronchial asthma in AD patients. Pathophysiologically, this predisposition might be explained by the strong activation of eosinophils in AD. Indeed, marked dermal deposition of eosinophil-granule major basic protein and occasional eosinophils were found in chronic lesions of AD patients [39], suggesting degranulation of eosinophils, which is consistent with a high degree of activation of eosinophils [40]. It is tempting to speculate that the BHR in AD is caused by extravasation of these highly activated eosinophils into lung tissue. The relationship between the appearance of extravasated eosinophils in the lung and increased bronchial responsiveness has been demonstrated previously by WEGNER *et al.* [41]. Affirmative data still remain to be established.

In all patients with asthma, regardless of the presence of AD, an EAR was observed. Only four patients with severe AD without asthma developed an EAR. All these patients showed increased bronchial hyperresponsiveness. This finding is in agreement with previous reports, in which early bronchoconstriction was provoked by allergen inhalation challenge. MORSBACH [22] reported that 12 out of 16 "pure" AD patients developed early bronchoconstriction after experimental inhalation of different allergens. DOHI *et al.* [7] observed early asthmatic responses after bronchial inhalation challenge with house dust mite in eight patients with AD without a history of asthma [7]. The PC₂₀ allergens in these patients without a history of asthma were significantly higher compared to patients with asthma, which is in agreement with the present findings [7]. These results suggest that the EAR is an IgE-dependent bronchospastic reaction which can be induced in any atopic patient, provided that they show increased bronchial responsiveness and adequate sensitivity to the allergen used in the allergen challenge.

In conclusion, we found that the mean value of the maximal fall in peak expiratory flow from baseline 3–8 h after allergen inhalation challenge was significantly higher in the patients with severe atopic dermatitis with very mild allergic asthma compared to all other groups. The presence of severe atopic dermatitis in asthma patients is probably relevant for the severity of the late asthmatic response. The present data suggests that the occurrence of a late response in patients with severe atopic dermatitis and mild allergic asthma is a result of fundamental differences from the other groups, such as significantly higher levels of total serum immunoglobulin E, allergen specific serum immunoglobulin E, and significantly lower skin sensitivity to the allergen used in the allergen inhalation challenge, and not because of higher exposure to inhaled allergen (tables 2 and 3). The finding that patients with severe atopic dermatitis and mild allergic asthma show decreased skin sensitivity compared to other asthmatic patients implies that the Cockcroft

formula used for prediction of allergen PC₂₀ is not accurate in these patients. The selection of a starting concentration for allergen inhalation should be made very carefully in this situation. The increased bronchial responsiveness and early asthmatic response in some patients with "pure" atopic dermatitis in the present study suggests a latent predisposition to bronchial asthma, and a careful follow-up should be considered in these patients.

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