

Determinants of airway responses to cat allergen: Comparison of environmental challenge to quantitative nasal and bronchial allergen challenge

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Background: Why allergic subjects may have asthma or rhinitis on allergen exposure remains unclear.

Objective: This study was carried out to compare airway responses during environmental allergen challenge (EAC) with quantitative allergen provocation challenges of the upper and lower airways.

Methods: Thirteen subjects with allergy to cats underwent EAC to cats. Lower airway responses during EAC were compared with bronchoprovocation with allergen. Nasal mucosal challenge with allergen-soaked disks were compared with EAC nasal responses. Nonspecific bronchial reactivity was assessed with methacholine; allergen sensitivity was assessed by skin prick tests, RAST, and end-point skin titration.

Results: During EAC, the maximal fall in FEV₁ ranged from 6% to 57% (median, 18%) and correlated closely with allergen bronchoprovocation PD₂₀ (Spearman's correlation coefficient [R_s] = -0.85, $p < 0.0002$). EAC asthmatic responses and allergen bronchoprovocation correlated with methacholine PD₂₀ (R_s = -0.85, $p = 0.0002$ and $R_s = 0.83$, $p = 0.0004$, respectively). Nasal provocation and EAC nasal responses correlated with each other but not with lower airway responses. On the basis of EAC and allergen bronchoprovocation responses, seven participants with asthma were identified. This group was significantly more sensitive to inhaled methacholine but was similar to the nonasthmatic group in IgE-mediated sensitivity and nasal responses.

Conclusions: The lower respiratory tract is less responsive to allergic and nonallergic stimuli in persons with allergic rhinitis. In persons with asthma during EAC, the response to nebulized cat allergen is also abnormal and correlates closely with their abnormal responsiveness to nonimmunologic stimuli. (J Allergy Clin Immunol 1997;99:798-805.)

Key words: Environmental allergen challenge, cat, asthma, rhinitis, bronchoprovocation, airway hyperreactivity

Among the several arguments supporting a relationship of asthma to IgE-mediated allergy¹ is the ability to induce acute asthma with inhaled allergen.²⁻⁵ These

Abbreviations used

BU:	Breath units
BAU:	Biologic allergen units
EAC:	Environmental allergen challenge
HSA:	Human serum albumin
PIPES:	Piperazine-N,N'-bis-[2-ethanesulfonic acid]
PRU:	Pharmacia RAST units
R_s :	Spearman's correlation coefficient

bronchoprovocation studies have, however, been confusing, because most investigators find that the acute responses to allergen exposure do not reflect the state of chronic respiratory disease.²⁻⁶ In these studies the acute asthmatic response can be induced by similar doses of allergen in sensitized individuals with a history of allergic rhinitis or with asthma, despite wide differences in clinical symptoms.¹⁻⁷

In environmental challenges with rat⁸ and cat⁹ allergens, we found that all individuals with positive skin prick test or RAST responses to these allergens had acute rhinitis, whereas only half of the individuals had acute asthma. Those persons with an asthmatic response almost always had an abnormal response to methacholine challenge, although their skin test and RAST responses to cat allergen were not significantly different from those of subjects with an isolated nasal response. Because animal allergens are carried on particles of diverse sizes¹⁰ and are likely to be widely distributed in the respiratory tract,¹¹ our results suggested that the airways in persons with allergic rhinitis or asthma respond differently. However, because our results disagreed with earlier reports that demonstrated that all sensitized persons experience acute asthma after specific allergen inhalation challenges, regardless of their history of chronic asthma,²⁻⁶ we believed that these distinctive responses should be examined more closely.

We hypothesized that the distinctive lower airway responses we observed after environmental challenge occurred either because the lower airways responded in a distinct manner in persons with an asthmatic response or because the nose may have filtered the allergen and reduced lower airway exposure. Therefore we compared airway responses of patients with allergy to cats during the environmental allergen challenge (EAC) with their

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responses during bronchial and nasal allergen challenge and during methacholine inhalation challenge.

METHODS

Subjects

Adult volunteers with allergy to cats who were in generally good health were recruited by advertisement, and a detailed history of allergy was obtained by questionnaire. The study was approved by the Joint Committee for Clinical Investigation of Johns Hopkins University, and all participants gave informed consent. The following tests were performed in all subjects: screening skin prick tests with 10 common allergens, RAST with cat allergen, intradermal end-point skin titration with cat allergen, exposure to cats in an environmental challenge, bronchial provocation inhalation challenges with both methacholine and cat allergen, and quantitative nasal challenges with cat allergen.

A positive history of rhinitis was defined by nasal pruritis, congestion, and rhinorrhea occurring seasonally or perennially or being precipitated after exposure to cats. A positive history of asthma was defined by the presence of two of three symptoms consisting of wheezing, chest tightness, or cough for at least 3 months per year and 1 to 3 days per month.

Blood tests

IgE levels to cat allergen were determined with the Phad-eym RAST system (Pharmacia, Uppsala, Sweden). Results are expressed as Pharmacia RAST units (PRU)/ml.

Skin testing

Skin prick tests (with a bifurcated needle) were performed with a battery of allergens including those from dust mites, molds (a mix of *Aspergillus*, *Penicillium*, *Mucor*, and *Fusarium*), orchard grass, maple, oak, ragweed, plantain, cockroach, and furred animals with glycerin:saline (50:50) and histamine (5 mg/ml) controls. A positive test result was defined as a wheal greater than one half of the diameter of the histamine control and at least 2 mm larger than the diameter of the glycerin:saline control. All subjects had at least a positive skin prick test response to cat extract. Intradermal skin titration with cat allergen was performed by using serial 10-fold and half-logarithmic dilutions of cat hair extract (5000 biologic allergen units [BAU]/ml, equivalent to 7.5 units Fel d 1/ml; ALK laboratories, Inc., Hørsholm, Denmark) prepared in sterile normal saline solution with 0.4% phenol and 0.03% human serum albumin (HSA) (Miles Laboratories, Spokane, Wash.) creating dilutions ranging from 5×10^{-7} BAU/ml to 50 BAU/ml. All diluted samples were stored at 4° C and were made fresh monthly from the same lot of allergen. Serial dilutions of cat allergen were injected intradermally, in duplicate, in a volume of 0.05 ml along with histamine controls (0.1 mg/ml) with a 27-gauge needle, and the results were read at 15 minutes. Wheal-and-flare circumferences were traced and transferred with tape to paper. The maximal diameter of the flare was averaged with its perpendicular diameter and plotted on semilogarithmic paper. The concentration of allergen causing a flare equal to the histamine flare was considered the end point of titration and was expressed in BAU/ml.¹² The weakest dilution causing a 1 cm wheal with a 2 to 3 cm flare was used as the starting dose for bronchial provocation testing.¹³

Environmental challenge procedure

A cat-exposure room with a total volume of 13.7 m³ and containing two female cats that roam freely has been exten-

sively characterized and studied.¹⁰ The room contained a bed with an encased mattress, an upholstered chair, and a small carpet. Before challenge, the cats were placed in a cage in the room, the chair was removed, bedding was shaken to disturb allergen, the litter boxes were removed, and ventilation was turned off. Spirometry was performed in an adjacent clean room by standard techniques with a Stead Wells spirometer (Warren Collins, Inc., Braintree, Mass.) and by using published norms to establish predicted spirometric values. Baseline spirometry was performed and repeated every 15 minutes during the 1-hour challenge. Challenges were terminated early if subjects became too uncomfortable or had a drop in FEV₁ of greater than 50%. Upper respiratory symptoms (congestion, rhinorrhea) and lower respiratory symptoms (tightness, wheezing) were scored on a scale of 0 to 3 at baseline and every 2 to 3 minutes during the challenge. These scores were averaged over the time of the challenge, and upper and lower airway scores were averaged separately to obtain a mean upper airway score and a mean chest symptom score, each with a maximum value of 3.

Air sampling was performed during the challenge procedure by using a small portable pump with a flow rate of 3.5 to 4.2 L/min (Gilian Instrument Corp., Wayne, N.J.) and 25 mm round glass-fiber filters on a support pad (Millipore Corp., Bedford, Mass.) attached to the subject's lapel as previously described.¹⁰ Pumps were calibrated before each use with a Buck calibrator (A.P. Buck, Orlando, Fla.). Filters were kept frozen at -10° C until overnight extraction at 4° C in 1.5 ml of piperazine-N,N'-bis-[2-ethanesulfonic acid] (PIPES) Tween as previously described.¹⁰ Fel d 1 levels were quantified with a two-site monoclonal antibody assay as previously described.¹⁴

Inhalation bronchial challenge with cat extract and methacholine

All EACs and provocation tests with allergen were performed at least 7 days apart. Inhaled β -agonists were avoided for 4 hours, theophylline was withheld for 24 hours, and the subject using terfenadine avoided it for 7 days before any testing. Challenges were performed in the winter months for patients who displayed sensitivity to seasonal allergens based on prick testing and at least 4 weeks after any upper respiratory infection. Subjects were not specifically instructed to avoid perennial allergens but were required to be free of symptoms at the time of each challenge as determined by FEV₁ values being within 20% of predicted values and mean symptom scores being less than 0.5. If environmental allergen exposure was performed more than 45 days after other bronchial challenges, a methacholine test was repeated, and the value had to fall within one dilution of that obtained from a previous methacholine test to qualify the patient for continuation in the experiment.

The identical cat allergen extract used for skin testing was diluted in HSA-saline and was administered in increasing concentrations by inhalation until a fall in FEV₁ of 20% or greater was observed.^{13, 15} Each concentration of aerosolized extract was inhaled five times, the dose being delivered through a DeVilbiss No. 646 nebulizer (DeVilbiss Co., Somerset, Pa.) attached to a dose-metering device with an air source at a pressure of 20 psi.¹³ For each subject, the initial concentration of cat extract used for bronchial provocation testing was at least 10-fold higher than the weakest dilution causing a 1 cm wheal after intradermal skin testing, as described above. Subsequent concentrations were administered in twofold increments up to a

TABLE I. Characteristics of the study population

Subject	Age (yr)	Sex	Cat ownership	FEV ₁ (% predicted)	Methacholine PD ₂₀ (BU)	RAST response with cat allergen (PRU/ml)	End-point skin titration with cat allergen (BAU)	Positive screening skin tests	Medications
1	22	M	No	79	1.5	2.2	10	4/10	Albuterol prn, theophylline 300 mg qd
2	31	F	No	94	2.8	10.6	0.37	4/10	Albuterol prn, theophylline 300 mg bid
3	36	F	Yes	90	1.5	54.4	0.03	7/10	Albuterol prn
4	34	F	Yes	88	5.8	7.1	0.05	5/10	Albuterol prn
5	23	F	No	83	37	0.1	50	8/10	None
6	32	F	Yes	80	8	1.0	0.16	3/10	Albuterol prn
7	26	F	No	111	4	5.8	1.2	6/10	Albuterol prn
8	20	F	No	84	100	0.5	5	4/10	Albuterol prn
9	49	F	Yes	96	12	4.0	0.08	7/10	None
10	27	M	No	87	26	18.2	0.23	6/10	Albuterol prn
11	34	F	No	99	100	0.8	1.25	7/10	None
12	27	M	No	96	100	0.3	0.03	9/10	Albuterol prn, terfenadine
13	34	F	Yes	104	100	0.1	50	3/10	Albuterol prn

bid, Two times a day; *prn*, as needed; *qd*, daily.

maximal concentration of 625 BAU/ml. After determination of a baseline FEV₁ value, which had to be at least 70% of the predicted value, a control aerosol of diluent (HSA-saline) was administered. The FEV₁ value obtained after diluent challenge had to fall within 10% of the baseline value and represented the baseline value for the determination of a 20% fall in FEV₁. Pulmonary function tests (forced vital capacity and FEV₁) were performed 10 minutes after each test solution. The cumulative dose of cat extract in BAU was plotted on semilogarithmic paper to determine the cumulative dose causing a 20% fall in FEV₁. Subjects without a 20% fall in FEV₁ after the highest dose were assigned a value of 120 BAU.

Methacholine was administered in a similar fashion¹⁵ by starting at 0.075 mg/ml and using doubling concentrations at 3-minute intervals until a fall in FEV₁ of 20% or greater was obtained. Aerosols were delivered by the methods described above for cat extract. Results are expressed as cumulative breath units (BU), where 1 BU is equivalent to one breath of a solution containing 1 mg of methacholine per milliliter. Subjects who did not achieve a 20% fall in FEV₁ at the highest concentration of methacholine (25 mg/ml) were assigned a value of 100 BU.

Nasal disk challenge with cat allergen

The method of allergen challenge of the nasal mucosa with paper disks was adapted from the methods of Baroody et al.^{16,17} Eight-millimeter diameter filter paper disks were punched from Shandon filter paper cards (Shandon Inc., Pittsburgh, Pa.). Disks used for collection were placed in 1.5 ml microtubes (Sarstedt, Inc., Newton, N.C.) and weighed with a Mettler AE 240 electronic balance (Mettler Instrument Corp., Hightstown, N.J.). The disks were able to retain 50 to 55 μ l of test solution or secretion. Test reagents were as described above, and dilutions of cat extract were prepared in HSA-saline. A dry disk was placed on the middle portion of the left anterior third of the nasal septum, just posterior to the mucocutaneous junction, by

using a surgical headlight, nasal speculum, and duckbill forceps. The first disk was kept in place for 30 seconds and was then sealed in a microtube. Nasal lavage was then performed five times with 5 ml of warm saline solution to reduce secretions to a stable baseline. After 5 minutes, another collection disk was placed for 30 seconds to confirm that secretions were reduced from baseline. The disks were placed 5 minutes later in the following sequence: (1) a disk soaked with 50 μ l of diluent was placed for 60 seconds and removed; (2) a dry collection disk was next placed 30 seconds after removal, left in place for 30 seconds, and then placed in its microtube and sealed; (3) after 90 seconds, a second collection disk was placed in the same location for 30 seconds and then removed. This series of events was repeated after an 8-minute rest period to test each dilution (50 BAU/ml, 500 BAU/ml, and 5000 BAU/ml) of cat allergen. The 8-minute waiting period was shown to allow the nasal secretion to return to baseline.^{16,17}

Immediately after the challenge, the capped tubes containing the disks were reweighed. The difference from the original weight represents the milligrams of secretion elicited. The mean secretion weight was calculated from the two disks obtained at each concentration of challenge solution corrected for secretion weight after diluent challenge. Symptom scores were also measured after each challenge (a rating from 0 to 3 of congestion, drainage, and pruritis) and recorded as a total symptom score for each challenge after correction for diluent challenge, with a maximum score of 9.

Statistics

Spearman correlation coefficients (R_s) and Kruskal-Wallis analysis of variance were used for statistical analysis by using GraphPad Instat Mac Software (GraphPad Software, San Diego, Calif.). Student's two-tailed *t* test or Fisher's exact test was used to compare group differences, and data that were not normally distributed were log-transformed before analysis. A *p* value less than 0.05 was considered significant.

TABLE II. Results of environmental challenge

Subject No.	Maximum % fall in FEV ₁ during EAC	Mean chest symptom score during EAC	Mean upper respiratory symptom score during EAC	Fel d 1 level in room during EAC (ng/m ³)
1	57	1.4	1.3	346
2	56	2.3	1.1	1461
3	48	1.6	2.1	9349
4	45	1.9	1.1	993
5	35	0.9	1.2	1209
6	34	1.4	1.9	3250
7	18	0.4	0.9	590
8	13	0	1.7	2967
9	10	1.6	1.7	928
10	10	0.8	1.4	378
11	7	0	1.1	302
12	6	0.1	1.6	442
13	6	0	0.6	289

RESULTS

Characteristics of subjects

The characteristics of the subjects (10 women and 3 men) are presented in Table I. The ages of the subjects ranged from 20 to 49 years (mean, 30 years). There were no smokers. Although inclusion in the study required only a positive skin prick test response to cat allergen and a history of any airway symptoms after exposure to cats, all of the subjects had asthma and rhinitis, and all listed exposure to cats as a precipitant. Five subjects had cats in the home. Baseline FEV₁ values ranged from 80% to 111% of predicted values (mean, 91%). Methacholine PD₂₀ values ranged from 1.5 BU to more than 100 BU (geometric mean, 14.6 BU), with four subjects not experiencing a 20% fall in FEV₁ at the highest concentration tested. RAST responses with cat allergen ranged from 0.1 to 54.4 PRU/ml (geometric mean, 1.9 PRU/ml), and cat end-point skin titration values ranged from 0.03 BAU to 50 BAU (geometric mean, 0.70 BAU). End-point skin tests correlated with cat allergen-specific RAST tests ($R_s = -0.55, p = 0.05$). On average, subjects had six positive skin test responses (range, 4 to 9 positive results), seven subjects had positive skin test responses to dust mites, three subjects had positive skin test responses to molds, and nine subjects had positive skin test responses to pollen. Three subjects did not use medications for asthma, whereas the remainder used albuterol as needed; two subjects used theophylline daily, and one subject used terfenadine.

Results of environmental allergen exposure

The results of the EAC to cats are shown in Table II. Eleven subjects completed the 1-hour challenge. Subjects 1 and 2 terminated their challenges at 24 and 15 minutes, respectively, because of a greater than 50% fall in FEV₁ and discomfort. All 13 of the volunteers experienced nasal symptoms during EAC. Average nasal symptom scores (for congestion and rhinorrhea) ranged from 0.6 to 2.1 (mean, 1.3). Table III summarizes

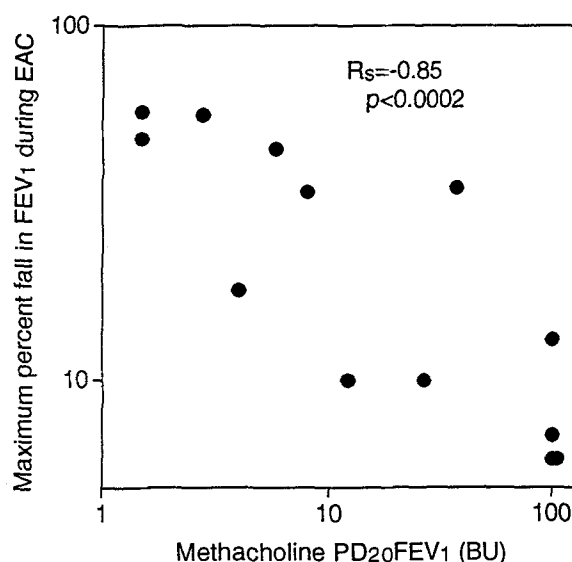


FIG. 1. The maximal percent fall in FEV₁ during EAC to cats was highly correlated inversely with the methacholine PD₂₀ value ($R_s = -0.85, p < 0.0002$) among the 13 subjects with cat allergy. The PD₂₀ values for four subjects with values greater than 100 BU were plotted as 100 BU.

correlations between the variables tested in the study. Nasal symptom scores in the EAC were not correlated with RAST responses to cat allergen ($R_s = 0.22, p = 0.48$), intradermal end-point titration to cat ($R_s = -0.53, p = 0.06$), or results of screening prick tests with allergen ($R_s = 0.19, p = 0.53$).

There was a wide range of lower airway responses during the EAC (Table II). The maximum fall in FEV₁ ranged from 6% to 57% (mean, 25%). Mean chest symptom scores during the challenge ranged from 0 in three subjects to 2.3 (mean, 0.9). The maximum fall in FEV₁ correlated with the mean chest symptoms ($R_s = 0.74, p = 0.004$); however, the fall in FEV₁ was not related to nasal symptoms during the EAC ($R_s = 0.12, p = 0.70$). Asthmatic responses after EAC were highly correlated with nonspecific bronchial reactivity ($R_s = -0.85, p < 0.0002$) (Fig. 1). Changes in FEV₁ after EAC were not significantly correlated with tests of IgE-mediated sensitivity as shown in Table III. Fel d 1 level in the room varied between the individual challenges from 289 to 9349 ng/m³ (geometric mean, 938 ng/m³) and correlated significantly only with nasal symptoms ($R_s = 0.60, p = 0.03$).

Bronchial inhalation challenges with cat extracts

To test the hypothesis that lower respiratory responses are quantitatively different among subjects with acute asthmatic responses after EAC, bronchial inhalation challenges were performed with cat allergen. In contrast to the EAC, this inhalation challenge bypasses the nose so that nasal filtration of allergen does not play a role in the ultimate deposition of allergen in the lower airway. The PD₂₀ for cat allergen ranged from 2.2 to 120 BAU (median, 25 BAU), with five subjects not experiencing a

TABLE III. Correlation of challenge results and patient characteristics

	Intradermal titration end point with cat allergen	RAST response with cat allergen	Methacholine PD ₂₀	Fall in FEV ₁ during EAC	Chest symptoms during EAC	Nasal symptoms during EAC	Cat allergen bronchoprovocation PD ₂₀
RAST response with cat allergen	-0.55*						
Methacholine PD ₂₀	0.27	-0.74†					
Fall in FEV ₁ during EAC	-0.01	0.51	-0.85‡		0.74†		
Chest symptoms during EAC	-0.46	0.66*	-0.78‡			0.23	
Nasal symptoms during EAC	-0.53	0.22	-0.14	0.12			
Allergen bronchoprovocation PD ₂₀	0.23	-0.53	0.83‡	-0.85‡	-0.69†	-0.25	
EAC airborne allergen concentration	-0.37	0.33	-0.37	0.52	0.51	0.60*	-0.54
Nasal challenge secretion weight at 5000 BAU	-0.68*	0.42	-0.27	0.06	-0.12	0.67*	-0.14

* $p < 0.05$.† $p < 0.01$.‡ $p < 0.001$.

20% fall in FEV₁ at the highest concentration tested. Like the EAC asthmatic responses, the cumulative dose of allergen causing a 20% fall in FEV₁ was highly correlated with methacholine challenges ($R_s = 0.83$, $p = 0.0004$) but was not correlated with RAST responses with cat allergen ($R_s = -0.53$, $p = 0.06$), intradermal end-point titration results with cat allergen ($R_s = 0.23$, $p = 0.45$), or the number of positive screening skin prick test results ($R_s = 0.23$, $p = 0.45$). As shown in Fig. 2, when the cat allergen PD₂₀ responses are compared with asthmatic responses during EAC (reflected by the maximum fall in FEV₁), subjects responded almost identically ($R_s = -0.85$, $p < 0.0002$). By inspection, it appears that the lower airway responses to both challenges can be categorized as asthmatic (>15% fall in FEV₁ during EAC and PD₂₀ < 60 BAU) or nonasthmatic.

Challenges of nasal mucosa with cat allergen

As a control for airway responses to allergen exposure, we performed quantitative nasal allergen provocation tests by using allergen-soaked disks. Nasal lavage reduced mean baseline secretion weight from 6.7 mg to 2.6 mg and symptom scores from 1 to 0.5. The postlavage values were subsequently subtracted from challenge values for each individual. The secretion weights (mean $\pm$ SEM) at 0 (diluent), 50, 500, and 5000 BAU/ml were: 3.2 ± 1.1 mg, 4.2 ± 1.7 mg, 7.4 ± 2.8 mg, and 16.7 ± 4.4 mg, respectively. Symptom scores at each dose were: 0.6 ± 0.2 , 0.7 ± 0.2 , 2.1 ± 0.5 , and 3.1 ± 0.7 , respectively. There was a significant dose-response relationship in nasal responses to allergen among the subjects as a group both in the amount of secretion elicited ($p < 0.05$) and in the extent of symptoms provoked ($p < 0.01$) during this challenge (Fig. 3). There were no significant correlations between the nasal provocation test responses and RAST results, but there was a significant correlation of intradermal skin titration with cat allergen and secretion weight at 500 BAU/ml ($R_s = -0.68$, $p = 0.02$) and at 5000 BAU/ml ($R_s = -0.68$, $p = 0.01$) and with symptom scores at these two doses ($R_s = -0.59$, $p = 0.04$ and $R_s = -0.56$, $p = 0.04$, respectively).

Nasal symptom scores during EAC correlated with the symptom scores elicited by each of the three incremental doses of allergen applied to the nasal mucosa ($R_s = 0.65$ to 0.78 , $p < 0.02$) and with the amount of secretion elicited at the highest concentration of allergen used for provocation, 5000 BAU/ml ($R_s = 0.67$, $p = 0.01$). In contrast to the correlations between this nasal mucosal challenge and nasal responses in the EAC, there were no correlations between the nasal challenge and the lower airway responses elicited during EAC or with bronchial provocation to allergen.

To further delineate the determinants of lower airway responses to allergen, the seven subjects who manifested an asthmatic phenotype (defined by EAC resulting in greater than 15% fall in FEV₁ and PD₂₀ less than 60 BAU) were compared with the remaining six subjects who experienced only nasal responses. As shown in Table IV, the groups manifested significant differences in fall in FEV₁ during EAC ($p = 0.0001$), EAC chest symptom scores ($p = 0.019$), bronchial allergen challenge PD₂₀ ($p = 0.0001$), and methacholine PD₂₀ ($p = 0.01$). However, they did not differ in cat allergen-specific RAST responses, intradermal skin titration with cat allergen, the number of positive screening prick test results, nasal responses to allergen challenge, allergen levels in the EAC, or demographic variables, including cat ownership.

DISCUSSION

The finding that acute asthma could be demonstrated only in a subgroup of individuals allergic to cats after environmental challenge was not surprising because it reproduced our earlier experience with challenges of unselected volunteers allergic to rats⁸ or cats.⁹ However, these results differ from those of other investigators who compared allergen and methacholine or histamine challenges in persons with a history of allergic rhinitis or asthma. Several studies compared patients with pollen allergy and rhinitis with and without a history of asthma in the pollen season and found that these groups had responses to inhalation challenge with pollen extract

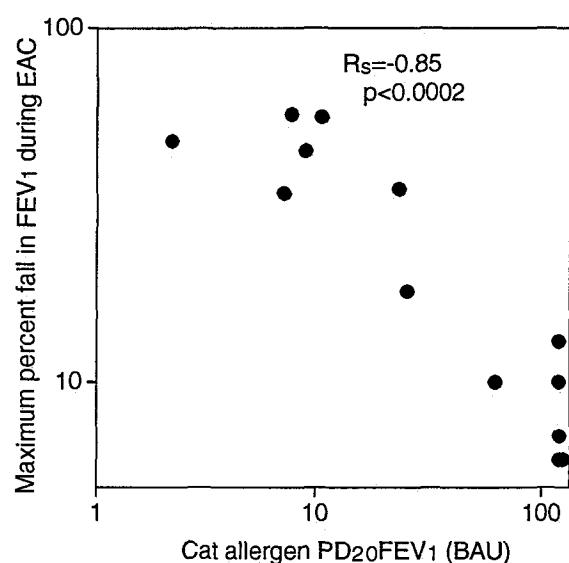


FIG. 2. The maximal percent fall in FEV₁ during EAC to cats was highly correlated inversely ($R_s = -0.85$, $p < 0.0002$) with the cat allergen bronchial inhalation challenge among the 13 subjects with cat allergy. The PD₂₀ values for five subjects with values greater than 120 BAU were plotted as 120 BAU.

that were identical or almost identical.²⁻⁶ In studying another group of allergic patients with asthma, Cockcroft et al.¹⁸ found that the response to allergen inhalation could be predicted by a combination of allergen sensitivity judged by skin test results and bronchial hyperresponsiveness. Muller et al.⁵ recently compared a group of allergic patients who were responsive to methacholine challenge but who reported no symptoms of asthma with a group of allergic patients with asthma and found that their response to allergen inhalation challenge was identical. We propose that the differences between all of these studies and our own relate to the fact that the environmental challenge allowed a more accurate definition of clinical asthma and rhinitis than did patient recall, even after a careful clinical history was obtained.

There were a number of methodologic differences between previous studies and our own, which may account for the discrepancies in the results. For example, the subjects studied by Stevens and Vermeire⁶ were evaluated with allergen bronchoprovocation only if the history of allergic asthma was unclear, thereby selecting for less allergic subjects among those tested; and comparisons by Muller et al.⁵ were made with subjects who were more similar in their methacholine sensitivity, among those with a history of asthma or rhinitis, than were those in our group. Another difference is the type of allergen studied, because these previous studies used grass pollen,⁶ dust mites,^{5,6} ragweed,^{2,5} and several other allergens,⁵ but not primarily cat allergen. Most importantly, however, many of these studies defined asthma by clinical history but did not attempt to follow up patients through the season of their natural exposure to the allergen in question.^{2-4,6} By EAC to cats, we were

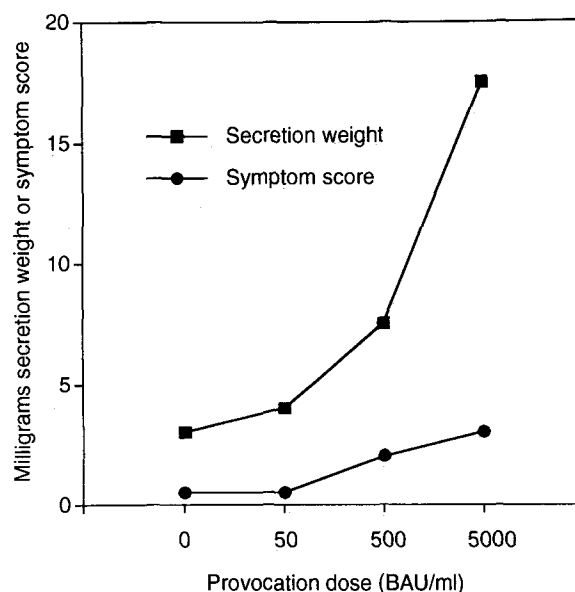


FIG. 3. Diluent and three concentrations of cat allergen were applied to the nasal mucosa of the 13 subjects. Mean secretion weight and symptom score increased in a dose-response relationship, with $p < 0.05$ and $p < 0.01$, respectively (Kruskal-Wallis analysis of variance).

able to emulate natural exposure to the allergen, which leads to a more precise definition of the clinical reactivity of our group of subjects. In fact, despite a history of asthma in all 13 subjects in our study, only seven demonstrated a lower airway response during the EAC.

We have chosen to study cat allergen in an environmental challenge because this is a clinically important, well-characterized airborne allergen, which has a particle size spectrum that ensures that the entire respiratory tract will be exposed to allergenic particles during the environmental challenge. In measurements in the cat challenge room, we have reported that from 15% to 20% of cat allergen is carried on particles that are less than 10 μm in diameter¹⁰; others have reported that as much as 50% of airborne cat allergen is associated with particles of this size.¹⁹ From 10% to 20% of particles of this size can be expected to pass through the nose and be deposited on the lower respiratory mucosa, whereas at least 50% should be deposited in the nose. Fifty to eighty-five percent of airborne cat allergen is carried on particles larger than 10 μm , almost all of which should be deposited in the nose.²⁰

Despite this potentially broad exposure of the respiratory tract to allergenic particles, our results show distinct individual responses to this exposure, with a well-defined subgroup of subjects manifesting a lower respiratory tract response. We have considered two explanations for this observation. First, because particles containing cat allergen must pass through the nose before being deposited in the lower respiratory tract, it is possible that allergen clearance in the nose (nasal scrubbing) is deficient in persons with an asthmatic response to the environmental challenge. Second, it is possible

TABLE IV. Comparison of groups responding with asthma or rhinitis alone

	Asthmatic subjects (n = 7)*	Nonasthmatic subjects (n = 6)	p Value
Bronchial responses			
EAC fall in FEV ₁ (%)†	39.4 (18-57)	8.3 (6-13)	0.0001
EAC chest symptom score	1.4 ± 0.2	0.4 ± 0.3	0.019
Methacholine PD ₂₀ (BU)†	4.6 (1.5-37)	56.1 (12->100)	0.001
Allergen PD ₂₀ (BAU)†	9.5 (2.2-25)	107.0 (62.2- >120)	0.0001
Allergen sensitivity			
RAST response with cat allergen (PRU)†	3.5 (0.1-54.4)	1.0 (0.1-18.2)	0.26
Intradermal titration with cat allergen (BAU/ml)†	0.6 (.03-50)	10.7 (.03-50)	0.94
Screening prick tests (no. positive)	5.3 ± 0.7	6.0 ± 0.9	0.54
Nasal responses			
EAC nasal symptoms	1.4 ± 0.2	1.3 ± 0.2	0.91
50 BAU/ml challenge			
Weight of secretions (mg)	0.7 ± 0.2	7.8 ± 2.9	0.06
Symptom score	0.5 ± 0.3	0.8 ± 0.3	0.48
500 BAU/ml challenge			
Weight of secretions (mg)	6.3 ± 2.9	8.8 ± 5.4	0.72
Symptom score	1.7 ± 0.6	2.5 ± 0.9	0.47
5000 BAU/ml			
Weight of secretions (mg)	14.9 ± 5.9	18.9 ± 7.2	0.67
Symptom score	2.7 ± 0.8	3.5 ± 1.1	0.58
Cat allergen (Fel d 1) level during EAC (ng/m ³)†	1406 (346-9349)	585 (289-2967)	0.15
Demographics			
Age (yr)	29 ± 2	31 ± 4	0.57
Baseline FEV ₁ (%)	89 ± 4	94 ± 3	0.33
Cat ownership	3	2	0.59

Except as indicated, results are expressed as arithmetic means ± SE.

*Subjects were considered asthmatic if the fall in FEV₁ during EAC was greater than 15% and if the allergen bronchoprovocation PD₂₀ value was less than 60 BAU.

†Results are expressed as geometric means (range).

that the upper and lower airway mucosal responsiveness differs among sensitized individuals.

Our earlier experiments showed that the asthmatic response is not exaggerated when the nose is occluded during the EAC²¹ and suggested that nasal scrubbing was not an essential determinant of lower airway responses. In this study, we again bypassed nasal scrubbing with an allergen inhalation challenge delivered through a mouthpiece and found that the relative sensitivity to cat allergen in this inhalation challenge was highly correlated with the occurrence of asthma during the environmental challenge. Thus the two experiments are consistent in their exclusion of nasal allergen particle scrubbing as an important determinant of the acute asthmatic response to naturally occurring allergenic particles.

These experiments support the idea that the lower respiratory tract response to allergen exposure is quantitatively different in persons who have acute asthma as compared with those who have rhinitis only. Our results would seem to confirm those of Cockcroft et al.¹⁸ who showed that nonspecific bronchial hyperresponsiveness was a principal determinant of acute asthma in allergen bronchoprovocation challenges. Our volunteers differed considerably in their nonspecific responsiveness to methacholine, and these differ-

ences correlated closely with their lower airway responses to both the environmental challenge and the allergen bronchoprovocation response. However, nonspecific bronchial hyperresponsiveness has been shown by others to be associated with more intense bronchial inflammation as judged by numbers of mast cells and eosinophils^{22, 23} and concentrations of histamine²⁴ and other mast cell products^{23, 25-27} in bronchoalveolar lavage fluid. In addition, the release of mast cell mediators^{26, 27} and eosinophil products²⁵ during the immediate inflammatory response to segmental allergen challenge has been shown to be significantly greater in allergic patients with a history of asthma and an abnormal response to methacholine or histamine inhalation challenge when compared with patients who have rhinitis only. Thus it would appear that increased nonspecific bronchial hyperresponsiveness is inextricably associated not only with increased numbers of mucosal inflammatory cells in allergic asthma but also with an exaggerated response by these cells to allergen exposure. The relative importance of increased mediator release and nonspecific bronchial hyperresponsiveness to acute asthma cannot be determined from the presently available data.

This study also compared nasal allergen challenges

with nasal responses during the environmental challenge and after bronchial allergen challenges. We included this comparison because it was possible that upper and lower respiratory tract responses were quantitatively different in persons with asthma, and we were aware of no data that compared upper and lower airway responses to allergen challenge. Even the recent demonstration by Svensson et al.²⁸ that tryptase, α_2 -macroglobulin, and albumin increase in airway lavage fluids after both upper and lower respiratory tract allergen challenges did not include a comparison of challenge results in the two sites. We found that nasal allergen challenge responses were highly correlated with nasal symptom scores during the environmental challenge but that there was no correlation with differences in lower respiratory tract responses in patients with asthma and nonasthmatic subjects. Thus the nasal allergen challenge results demonstrate that the increased allergen responsiveness after EAC and allergen bronchoprovocation challenge is limited to the lower airway.

We conclude from these studies that allergen responsiveness in the upper and lower respiratory tract differs in persons with allergic rhinitis and asthma. In persons with allergic rhinitis, the lower respiratory tract is relatively unresponsive to allergen exposure and to nonallergic stimuli. In persons who experience allergic asthma on exposure to natural environmental allergen particles, the response to nebulized allergen aerosols is accentuated and correlates closely with the abnormal responsiveness to nonimmunologic stimuli.

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