

Correlation of Cat-Hair (Fel d1) Prick Skin Test to Airway Response Using a Live-Cat-Room Challenge Model

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ABSTRACT

The purpose of this study was to document the relationship between prick skin test, airway, and common allergy symptom responses to natural cat exposure. Twenty-nine volunteers with a history of cat-hair allergy and asthma were recruited. Subjects had spirometry and prick skin test with Fel d1 on Visit 1. On Visit 2, subjects had a live-cat-room challenge with airway responses and allergy symptoms monitored. All 29 subjects had a positive skin test (wheal ≥ 4 mm), but only 12 (41%) had a positive airway response (fall in FEV₁ $\geq 15\%$). There was no significant correlation between the fall in FEV₁ and wheal size. All symptom scores increased significantly from baseline, but the change was not significantly related to wheal size. In summary, prick skin test response is not a good predictor of airway response or changes in allergy symptoms using the live-cat-room challenge model. (Allergy and Asthma Proc 20:371–376, 1999)

Bronchial inhalation challenge with aerosolized allergen is sometimes performed in the routine clinical investigation of the allergic asthmatic, but more commonly it is performed in research. These allergen challenges pose a risk of significant immediate and/or late responses, which can be prolonged. Thus, the clinician or investigator should begin with an allergen concentration not likely to elicit severe or life-threatening responses. To accomplish the task of deter-

mining the starting allergen concentration, it has been recommended that immediately before the aerosolized allergen inhalation challenge, a skin (prick) test titration be performed with the specific allergen. For safety, it is recommended that the starting concentration for the inhalation challenge is that which causes a 2- to 3-millimeter (mm) wheal.^{1–3} This recommendation assumes a reasonable correlation between cutaneous and airway responses to the aerosolized allergen. However, this correlation has been described as fair to poor.^{4,5}

The live-cat-room challenge model has increasingly been used as a method for assessing the therapeutic effects of drugs in individuals with respiratory and systemic allergies.^{6–9} This model uses a small room to house one or more cats for extended periods, creating high levels of cat hair and dander allergen. Subjects are then placed in the room for various amounts of time. The purpose of this study was to document the relationship between prick skin test, airway, and common allergy symptom responses to natural cat exposure.

METHODS

Inclusion Criteria for Subjects

1. Male or female individuals >18 years of age with a history of airway symptoms after exposure to cats.
2. A baseline forced expiratory volume in one second (FEV₁) >65% of predicted.
3. Positive prick skin test (wheal ≥ 4 mm) to Fel d1 allergen (10,000 BAU/mL).
4. Not receiving antihistamines, corticosteroids, anti-inflammatory drugs or any immuno-modulator within 30 days of starting the study.

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Study Design

Retrospective review of data obtained from subjects being screened for a larger prospective clinical trial. There were two visits involved in the screening process.

Visit 1:

1. Subjects gave their written, informed consent.
2. Subjects had a prick skin test with cat hair and dander extract.
3. Subjects had spirometry according to the recommendations of the American Thoracic Society.¹⁰

Visit 2 (7 days $\pm$ 1 day after Visit 1):

1. Baseline spirometry, blood pressure, and symptom scores obtained.
2. Subjects entered the cat room for no longer than 60 minutes.
3. Spirometry, blood pressure, and symptoms were monitored at 10, 20, 30, 45, and 60 minutes after entering the cat room.
4. Subjects exited the cat room for spirometry.
5. If the FEV₁ fell by $\geq 20\%$, the cat-room exposure was ended.

Skin (Prick) Test

1. Fel d1 allergen (ALK Laboratories, Inc., Milford, CT) 10,000 BAU/ml, or 10 Fel d1 units/mL was used.
2. Diluent and histamine controls were used.
3. A blood lancet was used to prick the skin of the forearm underneath a single drop of allergen, diluent, and histamine.
4. Extent of the reaction was assessed 15 to 20 minutes after the skin prick.
5. Reactions were drawn-off using skin marking pen and trans-pore tape.
6. Reactions were measured by drawing a straight line on the tape through the longest diameter of the reaction (wheal).

Cat Room

The cat room is a modular 600 ft³ chamber. Two adult declawed male cats live in the room at all times and are free to move about except during challenges, at which time they are placed in a wire cage in the room. The cat room contained a bed with sheets, a stuffed-fabric chair, litter box, wire cage, area rug covering approximately 80% of the floor, and two metal folding chairs. The cats lived in the room for at least 3 months before starting the study.

Measurement of Cat Room Fel d1 Levels

Air samples were taken weekly using a small portable pump (Gilian Model HFS 513A Hi-flow sampler, Gilian Instrument Corp., Wayne, NJ). A flow rate of 4 L/min for 60 minutes was used during the sampling. The

pump was calibrated with a Buck calibrator (Model M-30, A.P. Buck, Inc., Orlando, FL). Samples were collected using a round 37-mm glass-fiber filter on a support pad. Sampling was performed when there was no activity in the cat room with the air conditioner turned off. Fel d1 was measured using a monoclonal based enzyme immunoassay.

Symptom Scores

Baseline symptom scores for five symptoms were taken using a standardized form before the subject entered the cat room. Scores were taken at 10, 20, 30, 45, and 60 minutes after entering the cat room. The symptoms monitored were:

1. Itchy and/or watery eyes
2. Rhinorrhea
3. Sneezing
4. Cough
5. Nasal congestion

The severity scores were as follows:

- 0 = No symptoms
- 1 = Barely noticeable
- 2 = Definitely present
- 3 = Annoying
- 4 = Very bothersome
- 5 = Very severe, incapacitating

Statistical Analysis

Results are presented as means $\pm$ one standard deviation. The statistical significance of the correlation was determined using the Spearman Correlation Coefficient. The statistical significance of differences was determined using the Wilcoxon ranked sign test.

RESULTS

The demographic characteristics of the 29 subjects who participated are shown in Table I. Of the 29 subjects, 27 claimed to have asthma (average $\pm$ SD number of years = 19.9 $\pm$ 14.7). Fourteen of the 29 subjects reported that they used a bronchodilator on an as-needed basis. All 29 subjects claimed to have airway symptoms when exposed to cats, and some subjects claimed multiple allergies. The average ($\pm$ SD) number of years the subjects claimed to have these allergies was 18.2 ($\pm$ 13.1) years. All 29 subjects were nonsmokers.

TABLE I

Demographic Characteristics of Subjects		
	Males	Females
Number of subjects	7	22
Age, years (Sd)	38.3 (8.3)	34.9 (8.2)
FEV ₁ , % predicted (Sd)	82.1 (12.7)	90.5 (14.5)

All 29 subjects had a positive prick skin test to Fel d1, defined as a wheal of at least 4 mm. The prick skin test response ranged from 4 mm to 20 mm with a mean ($\pm$ SD) for all subjects of 9.52 ($\pm$ 3.4) mm. Twelve of the 29 (41%) subjects had a positive airway response (defined as a fall in FEV₁ of at least 15%). The mean change in FEV₁ ($\pm$ SD) from baseline was -13.2 ($\pm$ 11.4)%, and the range was +6.6% to -31.2%. Table II and Fig. 1 show the percent change in FEV₁ and the relationship to the prick skin test wheal size. There was no significant correlation between wheal size and percent change in FEV₁ ($r = -0.19$; $p = 0.329$).

Scores for all five symptoms increased significantly (i.e., worsened) from baseline (Table III). There was no relationship between the wheal size and change in symptom scores (Table IV).

The Fel d1 allergen levels in the cat room varied and increased during the course of the study (Table V). During the first half of the study, the weekly levels ranged from 170–690 ng/m³ (mean $\pm$ SD = 357 $\pm$ 156 ng/m³). During the second half, the weekly levels ranged from 170–1260 ng/m³ (mean $\pm$ SD = 597 $\pm$ 376 ng/m³). There was no relationship between positive airway responses (i.e., fall in FEV₁ $\geq$ 15%) and allergen levels. The increase in allergen levels over the course of the study had little effect, as there were five positive airway responses (14 subjects assessed) in the first half of the study (a 9-week period), and seven positive airway responses (15 subjects assessed) in the second half of the study (a 10-week period).

DISCUSSION

The results of this retrospective review show no correlation between the wheal size of the cat allergen prick skin test and fall in FEV₁ when using a live-cat-room model. Moreover, there was no correlation between the

% Change in FEV₁ versus Wheal Size

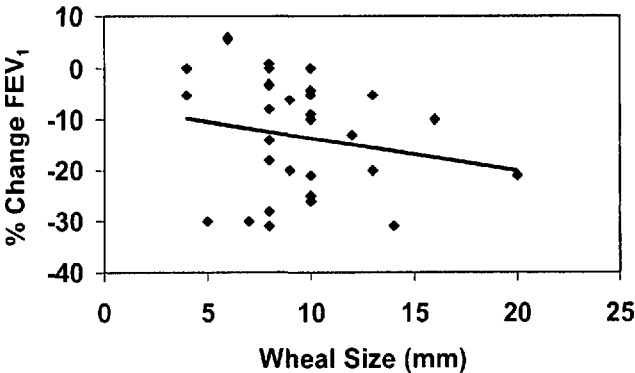


Figure 1. Relationship between maximum percent change in FEV₁ from baseline during cat room challenge and wheal size from prick skin test ($r = -0.19$, $p = 0.329$).

wheal size of the prick skin test and changes in allergy symptoms.

The correlation between prick skin test and airway responsiveness to aerosolized allergen has been assumed to be good.^{2,3} There is some support in the literature for this assumption. Bryant et al.¹¹ and Cockcroft et al.¹² reported a highly significant correlation between the degree of bronchial and cutaneous allergic reactivity. In contrast, others have reported poor or no correlation between airway and cutaneous responses.^{4,5,13–15} These studies compared the relationship of the response to inhaled aerosolized extracts to the responses of skin tests. Our findings indicate that the live-cat exposure model appears also to have a poor correlation.

The correlation between specific IgE antibodies in serum (RAST) and airway response has also been reported to be controversial. Bryant et al.¹¹ and Bruce et al.¹⁶ reported good correlation between allergen specific IgE levels and aerosolized allergen challenge. Pelikan and Pelikan-Filipak¹⁷ and Sicherer et al.¹⁸ reported poor correlation between RAST and airway response. We did not perform the RAST test in our study.

All five symptoms monitored had significant increases in severity after the cat room exposure. Surprisingly, we did not find a correlation between prick skin test response as determined by wheal size and changes in allergy symptoms. The intensity rating scale we used for each symptom was 0 to 5, with 5 being the worst. This scheme has been used previously.⁸ We did not compute a summary score of the five symptoms as was done by Norman et al.⁸ and speculate that a summary score might have provided a more sensitive symptom assessment.

We observed a relatively poor sensitivity (12 of 29 subjects, or 41%) of the prick skin test in predicting positive airway response after a live cat-room challenge in a population claiming to have asthma or airway symptoms after

TABLE II

Percent Change in FEV₁ and Fel d1 Prick Skin Test Wheal Size

Percent Fall in FEV₁ and Fel d1 Wheal Size

Number of Subjects	% Fall in FEV ₁	Mean (Sd) Wheal Size (mm)	Challenge Date* Period	
			First	Second
11	≥ 20	10.5 (4.3)	5	6
1	$\geq 15 < 20$	8.5 (0.7)	0	1
3	$\geq 10 < 15$	10.0 (2.0)	1	2
14	< 10	8.9 (3.2)	8	6

* Challenge date period grouped into first and second halves of the study with the number of subjects participating in each half.

TABLE III

Symptom Scores

Symptom	Baseline Mean Score (SD)	Final Mean Score (SD)	Mean Change	P value*
Itchy/watery eyes	0.14 (0.44)	1.66 (1.20)	1.52	<0.001
Rhinorrhea	0.48 (0.74)	2.59 (1.29)	2.11	<0.001
Sneezing	0.21 (0.77)	0.97 (1.09)	0.76	0.003
Cough	0.14 (0.35)	1.90 (1.45)	1.76	<0.001
Nasal congestion	0.72 (1.16)	2.51 (1.43)	1.79	<0.001

* Wilcoxon ranked sign test for change from baseline

TABLE IV

Allergy Symptom Score Change and Wheal Size Correlation

Symptom Score Change and Wheal Size Correlation			
Variable	N	SCC*	P value
Change in itchy/watery eyes	29	0.05	0.784
Change in rhinorrhea	29	-0.02	0.917
Change in sneezing	29	-0.13	0.514
Change in cough	29	-0.14	0.464
Change in nasal congestion	29	0.17	0.389

* SCC = Spearman Correlation Coefficients

exposure to cats. Sicherer et al.¹⁸ reported that 7 of 13 subjects (54%) with positive prick skin tests to cat allergen and a history of airway symptoms after exposure to cats had a positive airway response using a cat-exposure room. Wood et al.¹⁹ reported a positive challenge (fall in FEV₁ ≥ 15%) in 32 of 41 subjects (78%) with a positive skin test. Our data support these reports in that acute asthma is only found in a subgroup of individuals allergic to cats after a live-cat-room challenge.

There are several explanations for the poor relationship between the prick skin test response and airway response as measured by FEV₁ in our study using the live-cat-room model including false negative skin tests, nonasthmatic subjects, low cat allergen levels, and the particle size of airborne Fel d1 allergen.

The prick skin test is dependent on the technique and device used to introduce the allergen into the skin.²⁰ Additionally, inter-technician variability in pricking the skin is also a potential factor. In our study, a blood lancet was used that was not evaluated by Nelson et al.²⁰ However, the blood lancet is somewhat similar to the smallpox needle that produced among the smallest mean histamine wheal sizes in Nelson's study. Thus, it seems unlikely that the cutaneous responses were false positives. Only one technician performed all skin tests in our study.

TABLE V

Weekly Fel d1 Levels, Number of Subjects Assessed and Having a Positive Airway Response

Fel d1 Levels			
Week of Study	Number of Subjects Assessed	Fel d1 Level (ng/m ³)	Number of Subjects with + Airway Response*
1	1	336	1
2	0	170	0
3	1	364	0
4	1	420	0
5	4	690	2
6	2	336	1
7	4	224	1
8	0	ND	0
9	1	318	0
10	2	560	2
11	3	170	0
12	0	244	0
13	2	658	1
14	1	386	0
15	2	1187	1
16	1	529	1
17	2	261	0
18	1	714	1
19	1	1260	1

* Fall in FEV₁ ≥ 15%

ND = not done

Our protocol used a single-concentration of allergen (10,000 BAU) for the prick skin test. The use of multiple concentrations and possibly the intradermal skin test technique might have provided a better assessment of actual Fel d1 allergy, but this is controversial. Wood et al.¹⁹ reported that prick skin test and RAST values showed excellent efficiency in the diagnosis of cat allergy, and that intradermal skin test values added little to the diagnostic evaluation.

The inclusion criteria for the study required only a history of any airway symptoms after exposure to cats. A detailed questionnaire was used to screen subjects asking specific questions about their symptoms when exposed to cats. This was a self-reported history and unconfirmed by medical record, physician's examination, or previous challenge. Thus, it is possible that our subjects with negative airway responses did not have reactive airway disease. However, we speculate that this factor alone was not responsible for the lack of positive airway responses.

The measured cat allergen levels in our study were variable (170 to 1260 ng/m³). This variability is similar to that reported in other studies.^{7,8,21} Measurements of airborne Fel d1 levels were made weekly and increased from the first 9 weeks (357 ng/m³) to the last 10 weeks (597 ng/m³) of the study. However, there were about the same number of positive airway responses during the last half of the study (7) as during the first half (5).

The cat room allergen levels need to be high enough to elicit a response. The minimum airborne Fel d1 levels that can cause respiratory and nasal changes varies with the individual. Wood et al.⁹ reported that levels in the 1 to 3 ng/m³ range caused respiratory and nasal symptoms in a group of 35 cat-allergic subjects. Van Metre et al.²² reported airborne levels of cat allergen of -1.86 to -3.04 log FDA units caused respiratory and nasal symptom changes in 10 patients with cat asthma. Our cat allergen levels were clearly higher than those reported in these reports.

The airborne Fel d1 levels were measured weekly as opposed to being measured each time a subject was assessed. Thus, there is no assurance that the subjects were exposed to the quantities of Fel d1 measured. However, we have found in conducting these challenges for several years that the measurement of weekly levels of airborne Fel d1 allergen is adequate in estimating the usual allergy level in the chamber. This is true as long as the air exchange rate, traffic into and out of the chamber, and disruptive techniques (e.g., sheet-shaking) are kept constant. We followed a rigid protocol with regard to keeping these variables constant.

A small percentage (<14%) of cat allergen is carried on particles ≤ 2.5 μ m in diameter. Approximately 17 to 60% are carried on particles > 6 μ m in diameter.^{21,23} Larger airborne particles (i.e., particles > 5 μ m) are likely to be deposited in the nose and oropharynx. Thus, it is conceivable that a large portion of the airborne cat allergen did not reach the lungs resulting in a reduced airway response.

The fall in FEV₁ used to define a positive airway response may vary. Typically a 15% to 20% fall is used. We used a 15% fall. This more liberal criterion would favor more positive airway responses.

In conclusion, we found a poor correlation exists between the size of the wheal from a prick skin test and airway responses (i.e., fall in FEV₁), and that a positive prick skin

test may not be a good predictor of airway response using the live-cat-room model. Also, there was no significant correlation between the size of the wheal from the prick skin test and changes in symptom scores.

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