

The value of acoustic rhinometry in assessing nasal responses to cat exposure

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Background: Acoustic rhinometry (AR) uses sonar principles to map the anatomy of the nasal cavity and has been used in other studies to assess acute airway responses to allergen exposure.

Objective: The purpose of this study was to evaluate the utility of AR in assessing acute airway responses to cat allergen exposure by using a well-characterized cat exposure model.

Methods: Thirty subjects with a history of cat-induced rhinitis and a positive skin prick test response to cat allergen underwent an environmental cat challenge. Of these 30 subjects, 10 also had repeat challenges at lower levels of antigen to determine whether there was a dose response. Five subjects with negative skin test responses to cat were recruited as control subjects. During the 1-hour cat exposure, upper and lower respiratory symptoms were scored every 5 minutes, and spirometry and AR were obtained every 15 minutes.

Results: Although 29 of 30 subjects had changes in AR measurements, no correlations were detected between upper respiratory symptom scores and any of the changes observed in AR. In comparing the baseline challenges with lower antigen level challenges, upper respiratory symptom scores differed significantly ($P = .002$), whereas AR responses were nearly identical. Subjects without cat allergy did exhibit less response by AR ($P = .05$ to $.13$), but the greatest differences remained in the upper respiratory symptoms scores ($P < .0001$).

Conclusion: We conclude that although AR does provide an objective measure of nasal response to allergen exposure, it has significant limitations. These are evidenced by the lack of correlation with symptoms, the inability to measure a dose response, and the changes noted even among the control subjects. (*J Allergy Clin Immunol* 1998;102:896-901).

Key words: *Acoustic rhinometry, cat challenge, cat allergen*

Abbreviations used

AR:	Acoustic rhinometry
BU:	Breath units
LRSx:	Lower respiratory symptoms
MCA:	Minimum cross-sectional area
URSx:	Upper respiratory symptoms
V1:	Volume 1
V2:	Volume 2

A variety of measures have been developed to provide objective assessments of nasal response in allergic disease.¹ All have certain limitations. Acoustic rhinometry (AR) was first introduced in 1989 by Hilberg et al² and has been studied in a variety of settings over the last 10 years. This device uses sonar principles by means of reflection of sound waves transmitted into the anterior nares to map the anatomy of the nasal cavity, providing both minimal cross-sectional areas and nasal volumes. AR is noninvasive, rapid, easily reproducible,^{3,4} and in the past has been shown to correlate well with other measurements of nasal anatomy, such as computed tomography, rhinomanometry, and water displacement.⁴

Several studies in the past have used AR to assess changes in nasal airway geometry after nasal antigen challenge in sensitive subjects.⁵⁻⁸ These studies have yielded conflicting results, particularly regarding the relationship of AR to symptoms. In this study we applied AR to our well-characterized cat challenge model, which provides simultaneous exposure of both the upper and lower airways to naturally generated allergen particles. We believe that this model best represents natural allergen exposure and should therefore provide the most accurate test of the acoustic rhinometer to date.

METHODS

Thirty adult volunteers with a history of cat-induced rhinitis who were in generally good health were recruited by advertisement. Five additional subjects with cat allergy were recruited as control subjects. The study was approved by the Joint Committee for Clinical Investigation of Johns Hopkins University School of Medicine, and all participants gave informed consent.

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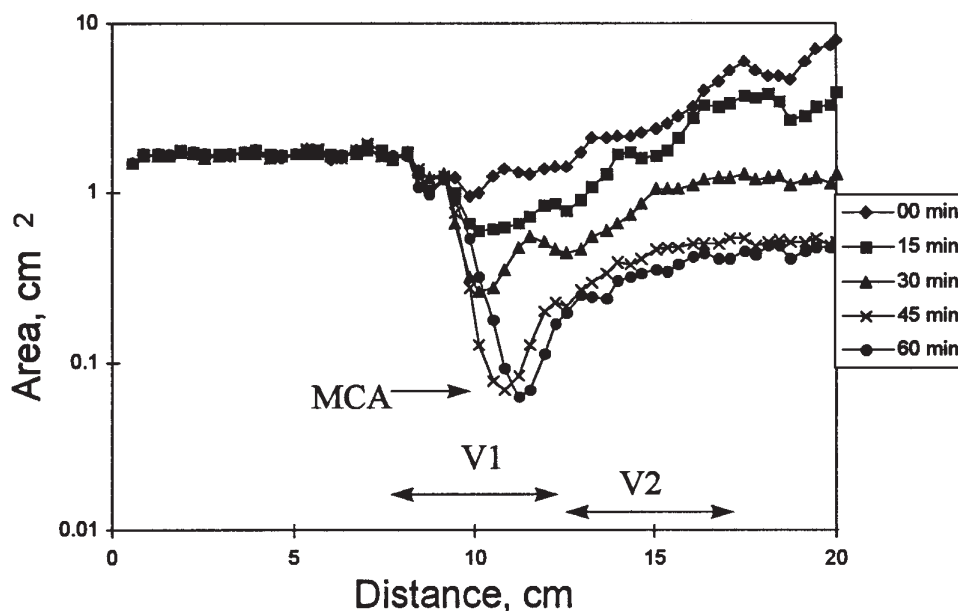


FIG 1. Rhinometry output for 1 subject's left nares over time at baseline, 15, 30, 45, and 60 minutes. The lowest point on each curve is MCA. V1 and V2 are determined as a product of area and distance. Percent change in MCA from baseline was 61.29%, 83.23%, 95.4%, and 96.77% at times 15, 30, 45, and 60 minutes, respectively. V1 had percent changes over time of 57.7%, 66.0%, 72.3%, and 73.5%, and V2 had percent changes of 81.4%, 91.9%, 96.2%, and 97.2%.

On recruitment, subjects were evaluated by a questionnaire regarding their medical history, their history of asthma or allergic rhinitis, and current medications. After a physical examination, subjects had prick-puncture skin tests for dust mite, cat, dog, cockroach, molds (2 mold mixes, including *Aspergillus*, *Penicillium*, *Mucor*, *Fusarium*, *Alternaria*, *Helminthosporium*, *Hormodendrum*, and *Botrytis* species), and grass (orchard), tree (oak and maple), and ragweed pollens. A positive test response 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 avoided short-acting antihistamines for 72 hours, long-acting antihistamines for 7 days, and tricyclic antidepressants for 6 weeks before skin testing.

Subjects then underwent spirometry (Model DECpc spirometer; Warren Collins Inc, Braintree, Mass) and a methacholine challenge test using previously described methods.⁹ The methacholine challenge was considered positive if the $PD_{20}FEV_1$ was less than 80 breath units (BU).

Cat exposure challenges were performed as previously described.¹⁰ In brief, challenges were performed in a 13.7-m³ room containing 2 cats, a bed, and a small carpet. Before the challenge, the cats were placed in a cage, and bedding was shaken to disturb allergen. In addition, baseline symptoms scores, spirometry, and acoustic rhinometry were performed. The subject then entered the cat room for a 1-hour exposure. During the challenge, upper respiratory symptoms (URSx) (congestion, rhinorrhea, and pruritis) and lower respiratory symptoms (LRSx) (tightness and wheezing) were scored by the subject on an arbitrary scale of 0 to 3 every 5 minutes, and coughs and sneezes were counted. Repeat AR and spirometry were obtained every 15 minutes. Challenges were terminated early if the subject became too uncomfortable or had a drop in FEV_1 of greater than 50%. Airborne Fel d 1 was collected during each chal-

lenge with a personal air sampler (Gilian Instrument Corporation, Wayne, NJ), and levels were quantified as previously described.^{10,11}

AR made use of a system similar to that described by Hilberg et al.² A spark generator produces a sound wave that is transmitted through a 7.5-cm long brass nose piece, which is briefly placed into the subject's nose. The subject is instructed not to breathe for a 2-second interval while the spark is generated. The nose piece is chosen with a cross-sectional area to provide an acoustic seal when placed 0.5 cm into the subject's nostril. The intensity of the impulse and reflected sound wave are measured by a microphone and amplifier, and a computer inversion program converts this reflected signal into an area-distance function. Fig 1 illustrates AR output, with each line representing different time points. These data are processed to determine the minimum cross-sectional area (MCA) and values for volumes of designated areas in the nose. MCA is represented by the lowest part of each curve. Volume 1 (V1) measures 7.5 to 12.5 cm behind the nasal entrance and represents the anterior portion of the nose. Volume 2 (V2) measures 12.5 to 17.5 cm behind the nasal entrance and represents the posterior portion of the nose.¹² Measurements were made in triplicate before and after challenge; however, because of time constraints, only single measurements were obtained during the challenge. Averages of the pretriplicate and posttriplicate measures were used for analysis. To determine reproducibility and ensure accuracy of the single measurements used during the challenge, coefficients of variation were determined among triplicate prechallenge measurements for all 30 subjects. These ranged from 1.5% to 15% (median, 7%).

The rhinometry data from the cat challenges were analyzed as follows. The MCA, V1, and V2 were determined every 15 minutes. The percent change from baseline was calculated at each data point, and the left and right sides were averaged. Then mean maximum changes for MCA, V1, and V2 were calculated for analysis. For

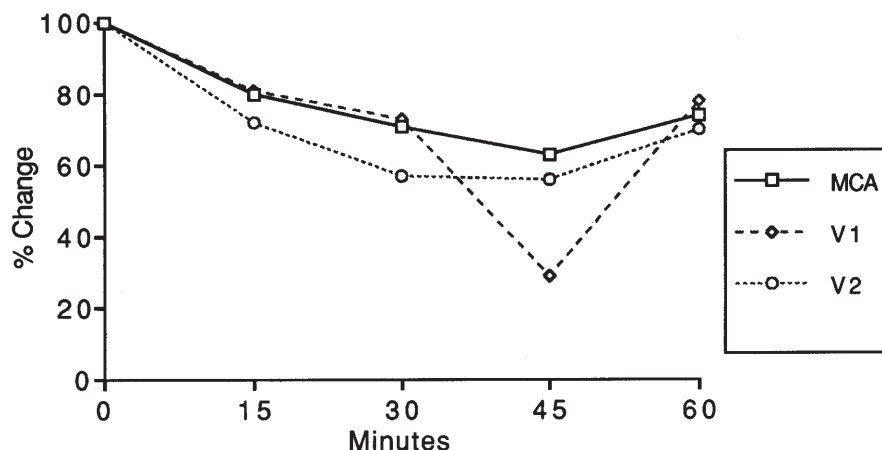


FIG 2. Median percent change from baseline for MCA, V1, and V2 over time. The N represented at each time point was 30, 25, 23, and 21 at times 15, 30, 45, and 60 minutes, respectively. The mean percent changes were as follows: MCA: 24.8%, 32.6%, 36.3%, and 29.9%; V1: 22.5%, 28.4%, 58.1%, and 24.3%; and V2: 31.6%, 42.1%, 44.1%, and 34.9% at times 15, 30, 45, and 60 minutes, respectively.

TABLE I. Correlation of rhinometry with clinical outcome

	Spearman's correlation coefficients		
	Mean maximum MCA	Mean maximum V1	Mean maximum V2
Mean URSx	0.14	0.18	0.16
Mean LRSx	-0.12	0.18	0.12
FEV ₁ (% change)	-0.22	0.012	-0.061

Data are correlation coefficients. The MCA, V1, V2, and FEV₁ values represent the maximum percent changes from baseline.

symptom scores, each symptom was rated on a scale of 0 to 3, and then these were averaged to provide URSx and LRSx scores at each time point. Those scores were then averaged to provide mean symptom scores for each 15-minute interval and for the entire challenge.

To determine whether a dose response could be determined, 10 of the individuals with cat allergy were rechallenged at a lower antigen level. This was accomplished by eliminating the shaking of the bedding. In addition, 5 control subjects without cat allergy were challenged and compared with the 30 subjects with cat allergy.

Statistical analysis

The relationships between AR and other challenge outcome measures were determined by calculating Spearman's correlation coefficients (R_s). The Wilcoxon signed-rank test was used to compare differences between baseline and low antigen challenges. The Mann-Whitney U test was used to compare differences between control subjects and subjects with cat allergy. The Kruskal-Wallis ANOVA was used to compare changes in AR over time. A P value less than .05 was considered significant.

RESULTS

Thirty subjects with a history of cat-induced rhinitis were enrolled in the study. The ages of the subjects ranged from 23 to 66 years (median, 33.5 years). Cat skin test wheal size ranged from 4 to 15.5 mm (median, 7

mm). Twelve of the 30 subjects had a history of asthma, and there were no smokers. Five of the 30 were cat owners. Baseline FEV₁ ranged from 70% to 105% of predicted value (mean, 87.5%). Thirteen of the 30 subjects had methacholine reactivity, with PD₂₀ values ranging from 1.9 to 70 BU (median, 18 BU). Five individuals were also enrolled as control subjects. All of these had negative prick and intradermal skin test responses to cat allergen and had a history of asthma. Three of the 5 had positive skin test responses to other inhalant allergens. One of the 5 was a cat owner. Two of the 5 had methacholine reactivity with PD₂₀ values of 5.1 and 27.

In the baseline challenges all 30 subjects had URSx. Mean URSx ranged from 0.19 to 2.56, with a median of 1.21. Twenty-two subjects had LRSx (range, 0.13 to 2.67; median, 1.1). Eighteen had a greater than 15% fall in FEV₁ (range, 17% to 72.5%). Nine subjects were unable to complete the 60-minute challenge because of a greater than 50% fall in FEV₁ or significant discomfort. Airborne Fel d 1 levels ranged from 1106 to 24,390 ng/m³ (median, 5196 ng/m³).

Fig 1 illustrates the progression of changes in AR in 1 subject during the challenge. At baseline, the MCA occurred in all subjects 2 to 3 cm behind the vestibule,

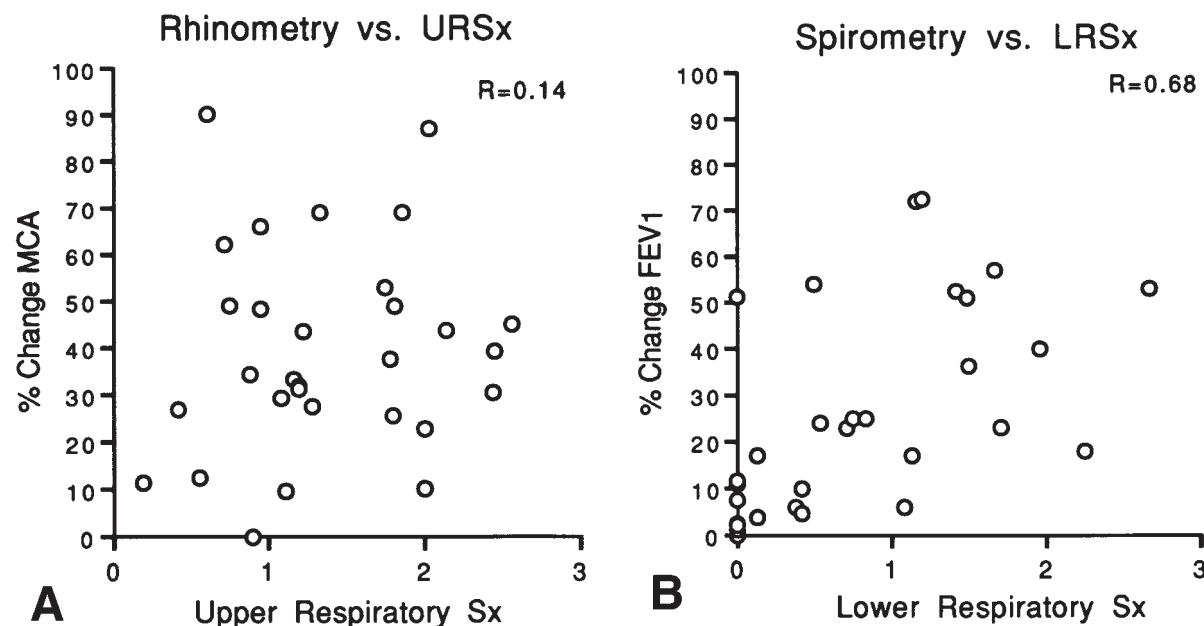


FIG 3. Comparison of rhinometry/URSx with spirometry/LRSx. **A**, Mean URSx versus maximum change in MCA ($r = 0.14$, $P = .23$). **B**, LRSx versus maximum percent change in FEV₁ ($r = 0.68$, $P = .0002$).

consistent with the nasal valve. The baseline MCA ranged in the left nostril from 0.27 to 2.52 cm² (median, 1.02 cm²) and in the right nostril from 0.40 to 1.37 cm² (median, 0.93 cm²). In the challenge 29 of 30 subjects had a fall in their MCA with a mean maximum percent change from baseline ranging from 9.6% to 90% (median, 36%). The change in MCA was significant compared with prechallenge values ($P < .0001$). As seen in Fig 2, changes in AR occurred within 15 minutes and generally progressed over the challenge (median percent change in MCA: 20.2%, 29.08%, 37.04%, and 26% at 15, 30, 45, and 60 minutes, respectively; $P < .0001$, Kruskal-Wallis ANOVA). V1 had median mean percent changes over time of 19.9%, 27.4%, 70.8%, and 21.5%, and V2 had median percent changes over time of 28%, 42.4%, 42.9%, and 30.9% ($P < .00001$). Each of the measurements therefore had their maximal change occurring at 45 minutes. The improvement at the 60-minute time point can be accounted for by the fact that 9 of 30 subjects were no longer in the challenge because of excessive reactivity. MCA, V1, and V2 all correlated with one another at each time point and in their mean maximum percent change from baseline, with correlation coefficients ranging from 0.81 to 0.92 (all P values $< .0001$).

When results from AR were compared with the other measures of challenge outcome, no significant correlations were detected (Table I). Correlation coefficients for mean URSx with MCA, V1, and V2 were 0.14, 0.18, and 0.16, respectively. Similarly, there was no correlation between AR and LRSx or maximum change in FEV₁. In addition, when the single component of congestion in the URSx was analyzed separately, there was still no corre-

TABLE II. Comparison of high-antigen versus low-antigen challenges

	High	Low	P value
Antigen level (ng/m ³)	4211	209	.002
Mean URSx	1.76	0.74	.002
Mean LRSx	0.81	0.33	.19
FEV ₁	18	9.1	.08
MCA	38.5	34.1	.44
V1	35.6	25	.19
V2	47.3	44.1	.15

Median values for high- and low-level challenges are displayed. The FEV₁, MCA, V1, and V2 values represent maximum percent changes from baseline.

lation (R_s MCA vs congestion = 0.21). We also compared URSx with the side that had the maximum change in AR, and there was again no correlation (mean URSx vs side of maximum change MCA $R_s = 0.14$, $P = .23$).

The relationship between MCA and URSx is also represented in Fig 3, which compares this measure of upper airway response to the relationship between LRSx and spirometry. Whereas there was no correlation between mean URSx and the mean maximum percent change in MCA ($R_s = 0.14$), there was a significant correlation between LRSx and the maximum FEV₁ change ($R_s = 0.68$, $P = .0002$).

To determine whether a dose response in AR could be detected, 10 individuals with cat allergy were rechallenged at lower allergen levels. Airborne Fel d 1 levels in these challenges ranged from 89 to 394 ng/m³ (median, 208 ng/m³). These levels differed significantly from the

baseline challenges ($P = .002$). Of these 10 repeat challenges, 9 subjects had URSx (mean URSx: range, 0.33 to 2.36; median, 0.74), 6 had LRSx (range, 0.13 to 2.41; median, 0.33), and 3 had a greater than 15% fall in FEV₁ (range, 15.8% to 37%; median, 18%). As shown in Table II, URSx differed significantly between the baseline and low level challenges ($P = .002$). LRSx and FEV₁ changes were also greater in the baseline cat challenges, although these differences were not statistically significant ($P = .19$ and $.08$ for LRSx and FEV₁, respectively). Changes in AR were not significantly different at any time point. For example, P values for the mean maximum changes in MCA, V1, and V2 were $.44$, $.19$, and $.15$, respectively. Furthermore, there were still no significant correlations between mean URSx and mean maximum changes in MCA, V1, and V2 in the low level challenges ($P = .098$, $.35$, and $.9$ for MCA, V1, and V2, respectively).

Five individuals without cat allergy were challenged as controls and compared with the subjects with cat allergy. Only 1 of the 5 reported any URSx, with a mean URSx of 0.14. This same individual had lower respiratory symptoms, with a mean of 0.21. Her maximum fall in FEV₁ was 26%. None of the other individuals had symptoms or FEV₁ changes during the challenge. Table III illustrates the comparison of the control subjects with the subjects with cat allergy. Antigen levels were similar for both groups, with median airborne Fel d 1 levels of 5782 and 5196 ($P = .5$). Small differences were noted in rhinometry, with P values of $.05$ for MCA, $.11$ for V1, and $.13$ for V2, but the greatest differences remained in the symptoms scores (URSx, $P < .00001$; LRSx, $P = .019$). Furthermore, it should be noted that the control subjects had modest changes in rhinometry with maximum percent changes of 27%, 11.5%, 37.2% for MCA, V1, and V2, respectively.

DISCUSSION

In this study we have shown that acoustic rhinometry provides an objective measure of nasal response to airborne cat allergen exposure. Changes in all 3 measurements occurred within 15 minutes in most subjects and progressed over the subsequent 30 to 45 minutes. Changes in many subjects were substantial, with a mean maximum percent change from baseline in MCA ranging from 9.6% to 90%. In addition, the tool provided rapid reproducible results and was easily incorporated into a busy challenge protocol.

However, it was disappointing that there were absolutely no correlations between the AR and other measures of clinical response. Even when we compared rhinometry with congestion alone, we still were unable to detect any significant correlation. We would therefore suggest that factors other than airway narrowing must play a more important role in symptom generation. These may include mucus production, pruritis, or other effects of nasal mediators that will require further investigation.

In the 10 repeat challenges performed at lower allergen levels, there was a significant difference in URSx scores. There were also trends toward differences in LRSx and FEV₁ changes. The lack of difference in lower

TABLE III. Comparison of nonallergic control subjects versus subjects allergic to cats

	Control	Allergic	P value
Antigen level (ng/m ³)	5782	5196	.50
Mean URSx	0	1.2	<.0001
Mean LRSx	0	0.6	.019
FEV ₁	4.4	24	.08
MCA	27	36	.05
V1	11.5	35.6	.11
V2	37.2	47.4	.13

Median values for the control and cat allergen challenges are displayed in this table. The FEV₁, MCA, V1, and V2 values represent maximum percent changes from baseline.

airway responses is most likely due to the fact that the subjects that were rechallenged were those who were able to complete the entire 1-hour baseline challenge because they did not have significant chest symptoms or asthma. With regard to rhinometry, however, there were no significant differences between the 2 challenges in any of the measurements. The AR was therefore less efficient in detecting a dose response than symptom scores. This suggests that AR may be too sensitive a tool to use clinically in that it appears to detect changes in nasal anatomy long before the subject experiences symptoms.

In the comparison of the control subjects with the subjects with cat allergy, there were significant differences in URSx and LRSx and spirometry. Rhinometry was able to detect statistically significant differences, but there were still substantial changes in rhinometry measurements among control subjects. Therefore although we are encouraged that there was at least a statistical difference between the control subjects and the subjects with cat allergy, we are again concerned about the utility of this tool if even the control subjects had changes in rhinometry without symptoms. The most likely explanation for this is that the cat room is a noxious environment, and a certain degree of congestion may occur just because of the strong odors and particulates in the room. In addition, the control subjects were recruited from an allergy clinic (a history of asthma), and they may therefore have been more prone to nonspecific respiratory responses.¹³

Other studies have evaluated AR by using a variety of challenge models, including tobacco smoke in smoke-sensitive subjects,¹² direct intranasal challenge with antigen in allergic subjects,^{5,7} and during a pollen season in allergic subjects.¹⁴ These studies have generated conflicting results regarding the relationship of symptom scores and AR. In their study of intranasal allergen challenges in 8 allergic subjects, Lane et al⁵ noted no correlation between nasal airway caliber and concomitant subjective congestion. Although those subjects that had the most nasal congestion also had the greatest change in rhinometry, these symptoms often preceded the greatest decrease in nasal volume and MCA by as long as 40 minutes. On the other hand, using a similar intranasal challenge model in 5 allergic subjects, Zweiman et al⁷ noted

a significant correlation between subjective congestion and MCA at 15 minutes ($P = .005$) and 6 hours after challenge ($P = .01$) but no correlation at 1 and 3 hours. Subjective rhinorrhea correlated with MCA at 15 minutes ($P = .02$) but not at other time points. Our study differs from these studies in that we have a much greater subject number, and in the fact that our model uses a natural allergen challenge that is more likely to yield clinically relevant results.

Other studies have also shown changes in AR in control challenges^{5,7} with buffered diluent with as much as 17% and 22% declines in volume and MCA, respectively.⁵ Although these control subjects are not necessarily analogous to our nonallergic control subjects, they again raise concern about the utility of this tool. Previous studies have suggested that normal nasal cycling and nonspecific effects of spraying or preservatives may play a role in this regard.^{5,13}

In a study of tobacco smoke exposure, Kesavanathan and Swift¹² did not find a correlation with bilateral measures but did find a correlation when unilateral AR changes and symptoms were analyzed. Similar results were obtained in the same patients by using posterior rhinomanometry. Roithman et al¹⁵ had similar results when comparing symptoms scores and AR before and after pharmacologic decongestion, showing correlation only among unilateral measures. Our study looked only at bilateral symptoms scores, and it is therefore possible that we would have detected a correlation if we had evaluated unilateral symptoms scores. We would argue, however, that the overall symptom score used in our study is far more clinically relevant.

It is also possible that our study was limited by the high antigen exposure in the cat room. Airborne Fel d 1 levels in the majority of homes with cats range from 10 to 200 ng/m³,¹⁶ whereas levels in our baseline challenges were much higher. Further studies looking at lower allergen exposure may be useful. One such study was done by Nielson et al¹⁴ who used AR in a trial comparing nasal steroids with placebo during a pollen season. Their results found significant differences in AR measures of volume between the placebo and nasal steroid groups but no significant differences in MCA. Symptom scores also improved among the nasal steroid groups, but correlations between symptoms and AR were not reported. With regard to our study, it should be noted that there were still no correlations between symptom scores and AR in our low level challenges, which had allergen levels more similar to those seen in homes.

We conclude that although AR does provide an objective measure of nasal response to allergen exposure, it has significant limitations. These are evidenced by the lack of correlation with symptoms, the inability to measure a dose response, and the changes noted even among the control subjects. Therefore we are still lacking a tool that objectively measures nasal response to allergen as effectively as spirometry measures lower airway responses.

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