

Nasal response to natural cat allergen exposure is significantly greater in patients with rhinitis and asthma than in patients with rhinitis alone

To the Editor:

Approximately 25% to 35% of patients with allergic rhinitis have clinical and physiologic evidence of asthma, and, conversely, upwards of 90% to 95% of patients with allergic asthma have symptoms of upper airway dysfunction.¹ Very importantly, a growing number of longitudinal population-based studies have shown that rhinitis precedes asthma in the majority of cases and that allergic rhinitis is a significant risk factor for developing asthma.¹ Taken collectively, these findings have led some investigators to postulate that respiratory allergy is a syndrome that begins in the nose in most patients and progresses over time to involve the lower airways.² As such, it has also been suggested that, as the syndrome evolves into bronchial asthma, the upper airway symptoms also gradually worsen. One small laboratory study demonstrated that nasal provocation using cold air evoked a greater clinical and physiologic response in the upper airways in patients with allergic rhinitis and concomitant asthma than in patients with allergic rhinitis alone.³ Employing a database of cat room challenges, we sought to confirm and extend these findings by comparing the nasal response to natural cat allergen exposure in patients with isolated cat-induced rhinitis (CIR) versus those with cat-induced allergic rhinitis and asthma (CIRA).

Our data base included cat room challenges performed between 1998 and 2002 on individuals with histories of cat-induced upper or lower respiratory symptoms and a positive prick skin test to standardized cat allergen. Subjects were defined as having CIR alone if they had histories (before challenge) of nasal symptoms without any chest symptoms immediately after exposure to cats, whereas subjects were classified as CIRA if they had histories of wheezing (with or without nasal symptoms) after cat exposure. Both groups were required to have cat allergy for at least 1 year before the challenge. At the time of challenge, all subjects were asymptomatic, and their composite nasal symptom scores were <1. The cat room challenge consisted of a 40-minute exposure to cats in a natural setting (10' × 10' room; cats kept in open-air cages set 3 feet from subject), during which time sneezes were counted and nasal symptoms (nasal congestion, sneezing, and rhinorrhea) were scored by the patient on a 0 to 3 scale before challenge and after 5, 10, 20, and 40 minutes of cat exposure. Fel D 1 levels were measured throughout the duration of the challenge. Mean values and SEs were calculated for the sneeze counts and composite nasal scores (sum of congestion, sneezing, and rhinorrhea). Repeated-measures ANOVA was used to compare means, and a *P* value of <.05 was considered significant.

Challenge data from 42 subjects with CIR and 39 with CIRA were available for analysis. Skin test reactivity and age were equivalent in the 2 groups, whereas sex and duration of rhinitis differed significantly (Table I).

TABLE I. Subject characteristics and cat challenge results (means ± SEMs)

Parameter	CIR (n = 42)	CIRA (n = 39)
Sex, % female	33	62*
Age, y	27.5 (1.40)	30.2 (1.44)
Skin test wheal diameter, mm	9.56 (0.81)	10.36 (0.66)
Duration of rhinitis, y	13.69 (1.69)	19.76 (1.58)*
Sneeze counts†	0.34 (0.10)	1.11 (0.31)*
Composite symptom score†	1.02 (0.27)	3.35 (0.67)*

**P* < .05.

†Measured at 40-minute time point.

Overall, nasal symptoms induced by cat room challenge began after 5 minutes of exposure and continued to increase through the end of the challenge period. At 40 minutes, subjects with CIRA had significantly higher mean sneeze counts and composite nasal symptom scores (Table I). Although the sneeze counts are low, only 51% of the subjects (CIRA, 59%; CIR, 43%) demonstrated at least 1 sneeze during the 40-minute challenge period. Fel D 1 levels were measured during 35 of the 42 cat challenges in subjects with CIR and 17 of 39 challenges in subjects with CIRA. Subjects in the CIR group had significantly higher median levels of Fel D 1 than the CIRA group (572 vs 401 ng/m³; *P* < .01). However, in the subset of subjects who had Fel D 1 measurements made during their challenges, the differences in composite scores were the same as those observed in the entire study cohort (composite nasal symptom scores, CIRA, 5.24; CIR, 3.34; *P* < .01).

Our analysis demonstrates that patients with CIRA experience more severe upper airway symptoms after a single, acute allergen exposure than patients with CIR alone. Although the basis for this observation is unknown, one possible explanation relates to the ability of allergic reactions in the upper and lower airways to modulate and potentially augment responses occurring in other regions of the respiratory tract. It has been shown that localized allergen instillation into the lower airways caused an increase in both blood and nasal mucosal eosinophilia as well as reductions in pulmonary peak expiratory flow.⁴ These laboratory observations indicate that the nose and lungs make significant contributions to inflammation and dysfunction in other portions of the airways in patients with allergic rhinitis and concomitant asthma.

Another interesting and unexpected finding in our analysis was the significantly longer duration of rhinitis in patients with CIRA than in those with CIR alone. Although these data support the notion that allergic airway disease represents a continuum that begins in the upper airway and progresses to the lungs, this finding will need to be reproduced in a larger series of patients.

Jonathan Corren, MD

Holly Fish

Jeanette Gumarange, RNP

Allergy Research Foundation

University of California, Los Angeles

Department of Medicine

11620 Wilshire Blvd, #200

Los Angeles, CA 90025

REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-334.
2. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;111:1171-83.
3. Stephens L, Proud D, Togias A. Nasal cold, dry air (CDA) challenge results in stronger nasal and pulmonary responses in asthmatics compared to patients with rhinitis. *J Allergy Clin Immunol* 1996;97:A315.
4. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161:2051-7.

Available online November 12, 2004.
doi:10.1016/j.jaci.2004.09.035

Dipyridamole (Persantin)-induced asthma during thallium stress testing

To the Editor:

Coronary artery disease and bronchial asthma commonly coexist in adults. The status of coronary myocardial perfusion is commonly evaluated with the thallium stress test (TST). A TST is performed during exercise or after injection of a coronary vasodilator when patients are unable to perform exercise. The need for a nonexercise or resting TST may be particularly common in patients with asthma whose exercise capacity is limited; however, it may present additional hazards to patients with asthma. The resting TST commonly includes a preceding intravenous infusion of dipyridamole (Persantin, Sicor Pharmaceuticals, Irvine, Calif), a purine nucleoside that blocks the reuptake of extracellular adenosine. The resultant transient increase of serum levels of adenosine causes coronary vasodilation, increasing the sensitivity of the TST. Adenosine can cause significant bronchoconstriction in patients with bronchial hyperresponsiveness. We report a case of a stable patient with asthma who developed sudden bronchospasm immediately after receiving intravenous dipyridamole during an elective TST. Our objective is to alert physicians to the possible risks involved when their patients with asthma undergo a resting dipyridamole TST.

S.K. is a 69-year-old nonsmoking woman with a 30-year history of cat allergy and mild persistent asthma. Her asthma has been well controlled with medications and cat avoidance. Because of atypical chest discomfort, she was referred to a cardiologist, who scheduled her for a TST. Three hours before the TST, she took her only medications: inhaled salmeterol and 88 μ g fluticasone. Within minutes of the intravenous dipyridamole injection, the patient had coughing, audible wheezing, and dyspnea typical of previous asthma. Oxygen saturation on room air was 89%. The cardiologist immediately infused 150 mg aminophylline intravenously. The pulmonary symptoms and hypoxemia resolved within 5 minutes before albuterol nebulization was needed. The stress test was completed and was normal.

The bronchospasm seen in patients undergoing the TST, although not commonly known, has been described in occasional reports. Ranhoskey and Rawson¹ reported 6 (0.15%) cases of acute asthma after intravenous dipyridamole in a retrospective multicenter review of 3911

unselected adults undergoing TST. Four of the 6 reactors were known to be patients with asthma. All 6 bronchospastic reactions were reversed with intravenous aminophylline. In addition, 19% of the patients in the same study population complained of dyspnea. It is unclear how many of them were actually experiencing bronchospasm. Shaffer et al² reported an acute increase in observed wheezing in 39% of 72 adults with asthma and/or COPD after intravenous dipyridamole despite pretreatment with albuterol. Thurnheer et al³ documented reductions in FEV₁ greater than 15% with spirometry in 9 of 20 patients with advanced COPD after a dipyridamole TST. We are not aware of pulmonary function studies to investigate whether there is reduction in expiratory airflow after intravenous dipyridamole infusion in patients with asthma.

Because dipyridamole injection results in increased extracellular levels of endogenous adenosine,⁴ we postulate that the bronchospasm in our patient after intravenous dipyridamole injection was induced by increased *in vivo* levels of extracellular adenosine. Most studies of adenosine effects in asthma use an inhalational model. Adenosine appears to induce bronchoconstriction in patients with asthma indirectly by the synthesis and release of autacoids from airway mast cells.^{5,6} Pretreatment with 10 mg montelukast for 2 days or 1000 μ g fluticasone propionate inhaled 2 hours before adenosine inhalational challenge provided significant protection against adenosine-induced bronchoconstriction.^{6,7}

The role of an increased concentration of serum adenosine as an *in vivo* cause of clinical bronchospasm is not well defined. The rapid intravenous infusion of adenosine to convert supraventricular tachyarrhythmias has been reported to cause bronchospasm when administered to patients with asthma. The package insert for a commercial adenosine product warns against using intravenous adenosine in patients with asthma.⁸ Intravenous adenosine infusion has been substituted for the intravenous dipyridamole injection on occasion in resting TST procedures. Mild airway obstruction, documented by pulmonary function tests, was reported in a selected group of 94 patients with COPD receiving a drip of intravenous adenosine before the TST.⁹ The airway obstruction occurred in these patients despite pretreatment with inhaled albuterol and persisted at least 15 minutes after adenosine was stopped. The bronchospasm occurring after intravenous dipyridamole can be reversed rapidly by treatment with intravenous aminophylline. Because methylxanthines competitively antagonize the physiological effects of extracellular adenosine through their interaction with specific cell surface purinoreceptors,⁴ this beneficial effect of aminophylline provides indirect evidence that dipyridamole-induced bronchospasm is adenosine-mediated.

Intravenous dipyridamole injection in the TST is considered relatively safe in the evaluation of coronary artery disease.¹ Awareness of the risk of bronchospasm in those with obstructive airways disease has resulted in most cardiologists having parenteral aminophylline available when performing a TST. Clinicians who do not perform TSTs may not be as knowledgeable about the risk of broncho-