

Changes in bronchial responsiveness following nasal provocation with allergen

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The relationship between upper airway inflammation and asthma is controversial. In the current study, we sought to investigate the relationship between allergic rhinitis and lower airway dysfunction by performing double-blind, randomized nasal challenges with allergen or placebo. Subjects were selected for a prior history of asthma exacerbations after the onset of seasonal allergic rhinitis symptoms. After the induction of a marked nasal-allergic reaction (with a technique of nasal provocation that limited allergen delivery to the nose), there were no changes in FEV₁, specific conductance, or lung volumes either 30 minutes or 4½ hours after nasal allergen challenge, nor any changes in peak flow rates followed hourly until the next day. However, nasal provocation with allergen resulted in a relative increase in bronchial responsiveness to methacholine compared with that to placebo ($p = 0.011$ at 30 minutes and $p = 0.0009$ at 4½ hours after challenge). Our study suggests that, although a nasal-allergic response does not induce airflow limitation of the lower airways, it can alter bronchial responsiveness. (J ALLERGY CLIN IMMUNOL 1992;89:611-8.)

Key words: Asthma, rhinitis, airway hyperresponsiveness, antigen challenge, diurnal variations

It has been noted since the time of Galen that an association existed between nasal symptoms and chest disease.¹ More recently, epidemiologic studies have indicated that symptoms of AR coexist with, and may precede, the development of asthma.²⁻⁴ Furthermore, many investigators have noted that treatment of upper airway disease often resulted in an improvement of asthma symptoms.⁵⁻⁷ Although there appears to be an important association between upper airway disease and asthma, it remains controversial as to whether there is a direct cause-and-effect relationship.⁸

Studies with human subjects and animals support as association between upper airway processes and lower airway dysfunction. Kaufman and Wright⁹ instilled silica particles onto the human nasal mucosa and were able to demonstrate significant increases in

Abbreviations used

AR:	Allergic rhinitis
TLC:	Total lung capacity
NBI:	Nasal blockage index
PC ₂₀ :	Provocative dose of methacholine (milligrams per milliliter) causing a fall in FEV ₁ of 20%
BR:	Bronchial responsiveness
SG _{aw} :	Specific pulmonary conductance
V _{tg} :	Thoracic gas volume
PEFR:	Peak expiratory flow rate
AU:	Allergy unit

lower airway resistance. These same investigators later demonstrated that a prior resection of the trigeminal nerve could prevent this bronchoconstriction, suggesting the existence of a nasal-bronchial neural reflex.¹⁰ Many other substances, including petrolatum packing,¹¹ atomized histamine,¹² and cold air¹³ have also been demonstrated to cause immediate changes in lower airway function. However, several studies have been unable to detect lower airway obstruction immediately after nasal challenge with allergen.¹⁴⁻¹⁷ A recent study by Schumacher et al.¹⁶ using sensitive measures of pulmonary function, demonstrated no changes in lower airway function despite causing several-fold increases in nasal resistance induced by nasal

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challenge with grass pollen. These studies suggest that induction of an allergic nasal response does not elicit immediate bronchospasm.

There are several potential explanations for the failure of these previous studies with allergen to demonstrate a nasal-bronchial relationship. First, patient selection may be important. Previous studies randomly selected patients with AR and asthma without selection for clinical histories of worsening asthma after the onset of nasal symptoms. Second, these studies searched only for immediate changes in lower airway function. Finally, prior investigations measured only changes in indices of lower airway caliber (e.g., FEV₁). Although airway caliber may not change after a nasal-allergic reaction, bronchial responsiveness could, in fact, be altered.

Therefore, it was the purpose of the present study to investigate the relationship between AR and lower airway dysfunction by (1) selecting patients with histories of allergic nasal symptoms preceding or coinciding with exacerbations of asthma, (2) measuring pulmonary function at both early and late time points, and (3) assessing the response of the lower airways with both measures of pulmonary function as well as BR.

METHODS

Subjects

Eleven subjects (eight female and two male subjects) between 15 and 39 years of age (mean age, 31.4 years) were chosen for study. All patients gave histories (during the past 2 or more years) of rhinitis and asthma symptoms during May and June, with or without mild nasal and/or chest symptoms outside the pollen season. Additionally, all patients reported that seasonal exacerbations of rhinitis resulted in worsening of their asthma symptoms. All subjects had a positive skin prick test (≥ 3 mm wheal diameter¹⁸ to full-strength timothy grass-pollen extract (100,000 allergy units per milliliter, ALK America, Milford, Conn.). All subjects had airway hyperresponsiveness to inhaled PC₂₀ < 8 mg/ml.¹⁹ At the time of the study, all patients were free of both nasal and chest symptoms, had an FEV₁ of 90% of predicted or greater, and required either no medication or only occasional use of β -adrenergic agonist agents for symptom control. None of the subjects had experienced an upper respiratory illness in the 6 weeks before the study, had received allergy immunotherapy during the previous 3 years, or had any previous history of smoking. To reduce the likelihood of either nasal or bronchial priming by allergen, patients were studied out of the Colorado pollen seasons between November 1989 and February 1990. None of the patients were exposed to pets on a regular basis, nor was it likely that these subjects were exposed to house dust mites or other significant indoor allergen because of the altitude and dryness of the climate in Denver.²⁰ All subjects provided statements of informed consent, and the study protocol was

approved by the Institutional Review Board of the National Jewish Center for Immunology and Respiratory Medicine.

Allergen delivery

To establish that changes in pulmonary function were the result of a nasal allergic response, we sought to use a technique of nasal challenge that would not deliver allergen into the lower airways. We used a commercially available, hand-held atomizer used for topical nasal therapy (Nostrilla nasal spray; Boehringer-Ingelheim, Ridgefield, Conn.), which delivers 0.07 ml per activation. Analysis of the aerosol generated by this atomizer was performed with a particle analyzer (laser particle analyzer, model CSASP-100-HV, Particle Measuring Systems, Inc., Boulder, Colo.) and demonstrated that the mass-median particle diameter was approximately 30 μ m, a size not likely to penetrate the lower airways.²¹ Since deposition of inhaled aerosol into the lower airways requires airflow toward the lungs, the allergen was delivered at TLC during breath holding. Thus, by the use of a larger, less respirable particle size and breath holding, we hoped to avoid delivery of allergen to the lower airways.

To confirm that our technique of nasal challenge did not allow penetration of allergen into the lower airways, we performed the following preliminary study: Five volunteer, normal subjects were instructed to inspire to TLC. Two sprays (0.14 ml) of a radiolabeled solution were administered by the same atomizer to each nostril at end inspiration followed by 10 seconds of breath holding. The solution contained ^{99m}technetium-labeled diethylenetriaminepentaacetic acid (Syncor Corp., Denver, Colo.), delivering 0.5 mCi of radioactivity to each nostril. Scans of the head and chest with a gamma camera (Starcam 2000, IGE Medical Systems, Ltd., St. Albans, England) were performed at 140 keV with 20% windows for 90 seconds. There was no detectable deposition of ^{99m}technetium-labeled diethylenetriaminepentaacetic acid into the trachea or lungs in any of the five subjects at either 1 or 6 hours after administration of the solution.

Nasal provocation

Nasal challenges were performed in a double-blinded fashion with diluent (NaCl, 0.9%, and albumin, 0.03%) or timothy-grass extract (four tenfold dilutions ranging in concentration from 10 AU/ml to 10,000 AU/ml). Conventional short-acting antihistamines were withheld for 72 hours before nasal-challenge testing.²² Delivery of the allergen was accomplished in the same manner as described above. The challenge solution was administered every 10 minutes until the NBI doubled or the fourth dose of solution was administered.

Nasal patency was assessed with a mini-Wright peak expiratory flow meter (Clement Clarke International, Ltd., London, England) with an attached face mask. After nasal and oral PEFRs were determined in triplicate, the best values were used to calculate the NBI as follows²³:

$$\text{NBI} = \frac{\text{Oral peak flow rate} - \text{nasal peak flow rate}}{\text{Oral peak flow rate}}$$

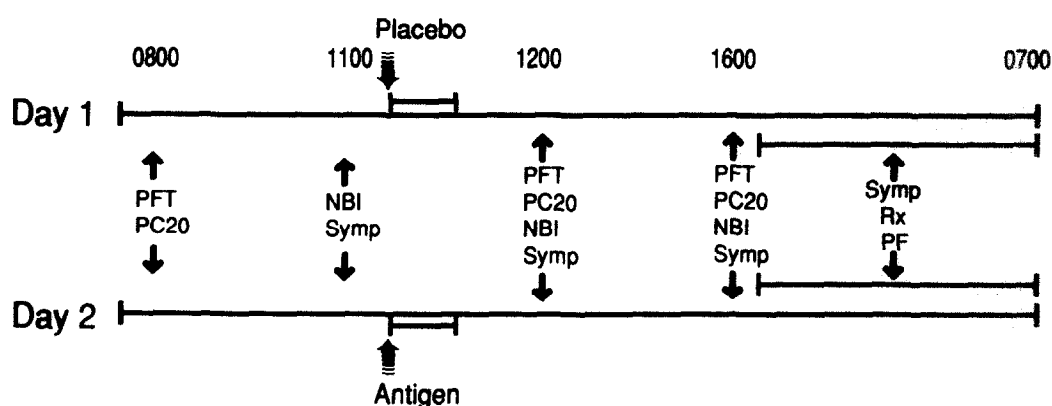


Fig. 1. Study protocol. *PFT*, complete pulmonary functions; *PC₂₀*, methacholine challenge; *NBI*, nasal blockage index; *Symp*, nasal and/or chest symptoms; *NC*, nasal challenge; *Rx*, medication use; *PF*, peak flow rate. Symptoms, medication use, and peak flow readings were recorded hourly after final methacholine challenge until 7 AM the following day.

This index has been demonstrated to be ≤ 0.4 in normal individuals.²⁴

Nasal symptoms were evaluated as follows: sneezing: 0, 0 points; 1 to 3, 1; >3 , 2; rhinorrhea: none, 0; mild, 1; abundant, 2; congestion: none, 0; mild, 1; complete (bilateral), 2; pruritus: none, 0; mild (eyes or throat), 1; severe (eyes and throat), 2. Scores were determined before beginning the nasal challenge, 10 minutes after each dose, and at 12 PM (1200) and 4 PM (1600). A total score of 4 points or more was defined as positive, since scores of this magnitude have been demonstrated to correlate with the activation of mast cells after nasal-allergen challenge.²⁵

Pulmonary-function and methacholine-challenge testing

All tests were performed by technicians who were unaware of whether subjects had received allergen or diluent nasal challenge. Flow was measured with a heated Fleisch-type pneumotachograph (size 3-0, Gould, Inc., Cleveland, Ohio) and differential pressure transducer (Validyne Corp., Northridge, Calif.). Volume was determined by either digital integration of the flow signal (for FEV_1 and FVC) or as the displacement of a Krogh-type spirometer of a volume-displacement plethysmograph (for TLC). V_{10} and lower airway resistance were measured with standard techniques.^{26,27} SG_{aw} was calculated by dividing the inverse of airway resistance by V_{10} . FEV_1 and FVC were derived from maximal expired flow-volume loops. PEFs were performed with a mini-Wright peak flow meter, as described above.

BR was assessed by methacholine-challenge testing, performed according to the guidelines of Chai et al.²⁸ Briefly, after establishing reproducible baseline FEV_1 (two efforts within 5% of each other), subjects inhaled nebulized solutions of either normal saline or increasing concentrations of methacholine generated from a DeVilbiss (DeVilbiss Co., Somerset, Pa.) 646 nebulizer. A Rosenthal-French (Laboratory for Applied Immunology, Baltimore, Md.) dosimeter, triggered by a solenoid valve set to remain open for 0.6 seconds and with pressurized air at 20 psi, was used to deliver

the aerosol. Each subject inhaled five inspiratory capacity breaths of normal saline followed by doubling concentrations of methacholine from 0.075 to 25 mg/ml at 5-minute intervals. Measurements of FEV_1 and FVC began 1 minute after each dose, and forced expiratory maneuvers were performed twice. Dose-response curves were constructed by plotting percent change in FEV_1 versus doses of methacholine. The PC_{20} was determined by linear interpolation from the dose-response curve.

Study design

We used a randomized, crossover design with two treatments and two periods (Fig. 1). Although we attempted to perform the study in a double-blind manner, this proved difficult, since a positive clinical response to nasal provocation was obvious to both the technician performing the nasal challenge and the study subjects. However, technicians performing pulmonary function were unaware of which treatment had been received. All patients were studied on 2 days, each separated by 2 weeks. Medications were withheld according to guidelines of the American Thoracic Society for at least 24 hours before each study visit in all subjects.²⁹ Thirty minutes after arriving at the Clinical Research Center, baseline pulmonary function testing and a bronchial methacholine-challenge test were performed at 8 AM (0800). At 11 AM (1100), after the FEV_1 had spontaneously returned to baseline, nasal-symptom scores and NBI were assessed. Patients were then randomized to undergo nasal-challenge testing with either placebo or allergen. Nasal-symptom scores, NBI, pulmonary function, and BR to methacholine were again assessed at both 12 PM (1200) and 4 PM (1600). No bronchodilator medications were administered after methacholine challenges throughout the study day, and patients were not allowed to leave the research area. After the final methacholine challenge, subjects returned home and were instructed to maintain an hourly record (while they were awake) of nasal and chest symptoms, medication use, and oral peak flow rates until the following day at 7 AM.

TABLE I. Characteristics of study patients

Patient	Age (yr)	Sex	Medication	FEV ₁ (L)	% Predicted FEV ₁	PC ₂₀
1	36	F	N	2.91	103	2.60
2	30	F	A	2.63	94	0.74
3	37	F	N	3.02	101	1.05
4	24	F	N	3.51	102	5.02
5	39	F	N	3.32	110	0.81
6	24	F	A	3.12	100	0.45
7	30	F	A	3.12	96	0.50
8	15	M	A	3.22	90	0.50
9	38	F	N	3.60	110	1.20
10	41	M	A	3.66	99	1.25
Mean	31.4			3.21	100.5	1.41
(\pm SD)	(8.4)			(0.32)	(6.4)	(1.41)

A, Albuterol; N, no medication.

Statistics

All variables were analyzed as change from baseline. Values of PC₂₀ were logarithmically transformed as log-base 2, since methacholine was administered in increasing two-fold concentrations. Changes in pulmonary-function parameters (baseline FEV₁, baseline SG_{aw}, FVC, V_{tg}, TLC, residual volume, and PEFR) and BR (PC₂₀) were assessed by an analysis of variance model specific for crossover data.³⁰ This model analyzes treatment (placebo or allergen challenge), period, and carryover effects. In the event of a carryover effect, the two treatments were compared with a two-sample Student's *t* test on the data collected during the first period of the study. Additionally, FEV₁, SG_{aw}, and PC₂₀, measured at 8 AM, were compared between the 2 study days with the Student's paired *t* test. Pearson's correlations were performed between change in PC₂₀ versus changes in both NBI and nasal-symptom scores. All tests of hypotheses were two-tailed and were performed at the 0.05 significance level.

RESULTS

Of 11 subjects who entered the study protocol, one subject withdrew for unspecified reasons. All 10 remaining subjects who completed the study (Table I) tolerated nasal provocation with allergen up to a dose of 10,000 AU/ml. The group of 10 patients demonstrated a significant increase from baseline (11 AM) in NBI 30 minutes after nasal challenge compared with increases with placebo (placebo [mean \pm SEM], -0.012 ± 0.22 ; allergen, 0.378 ± 0.058 ; $p = 0.0004$; Fig. 2). The difference was not statistically significant 4½ hours after challenge (placebo, -0.048 ± 0.033 ; allergen, 0.087 ± 0.061). Nasal-symptoms scores also increased significantly 30 minutes after nasal allergen challenge compared with increases after placebo (placebo, 0.2 ± 0.39 ; allergen, 6.4 ± 0.45 ; $p = 0.0001$; Fig. 3) and remained significantly elevated 4½ hours later (placebo,

-0.2 ± 0.36 ; allergen, 2.1 ± 0.55 ; $p < 0.01$). None of the subjects exhibited a positive response (symptom score, ≥ 4 or doubling of NBI) after placebo administration.

Baseline pulmonary function at 8 AM was comparable on the 2 study days (Figs. 4 and 5). There were no significant changes in FEV₁ (Fig. 4) or SG_{aw} (Fig. 5) either 30 minutes or 4½ hours after nasal allergen challenge. Other pulmonary-function measurements, including FVC, V_{tg}, TLC, and residual volume, were not significantly altered after nasal challenge (data not presented). PEFR measurements recorded hourly after the patients returned home and the following morning demonstrated no significant differences between allergen-challenge and placebo-challenge days (data not presented). Similarly, chest symptom and medication diaries demonstrated no significant difference between allergen-challenge and placebo-challenge days for any time point (data not presented).

The results of the bronchial methacholine challenges before and after nasal provocation with placebo and allergen are illustrated in Fig. 6. Lower airway responsiveness to methacholine was comparable at 8 AM on the 2 study days. Airway responsiveness appears to decrease throughout the placebo-challenge day, consistent with prior studies demonstrating diurnal variation in airway reactivity.³¹⁻³⁴ However, after nasal allergen challenge, there was an elimination of this diurnal decrease in responsiveness. These differences between placebo and allergen challenge were highly significant at both 30 minutes (change from baseline log₂ PC₂₀ for placebo, 0.701 ± 0.280 ; allergen, -0.228 ± 0.234 ; $p = 0.011$) and 4½ hours (placebo, 0.927 ± 0.317 ; allergen, 0.093 ± 0.221 ; $p = 0.0009$) after nasal provocation. Individual

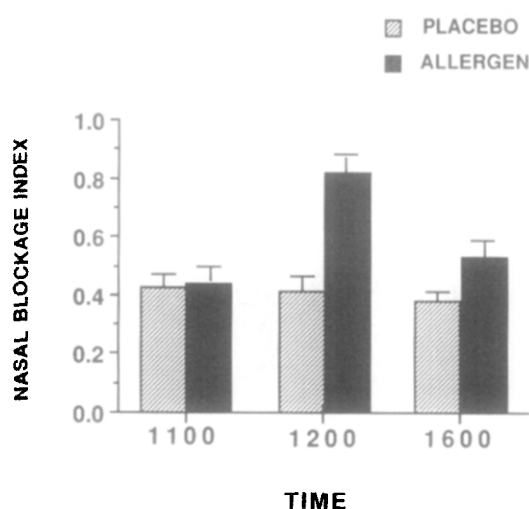


Fig. 2. Effect of nasal challenge with placebo or allergen on NBI. Data points are expressed as mean \pm SEM; $p = 0.0004$ at 1200 (12 PM), comparing change from baseline at 1100 (11 AM) for placebo versus allergen. No statistically significant change at 1600 (4 PM). $N = 10$ for both treatments.

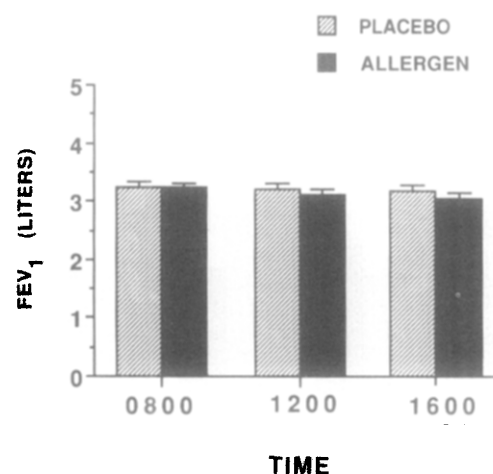


Fig. 4. Effect of nasal challenge with placebo or allergen on FEV₁. No significant changes for either treatment. $N = 10$ for both treatments.

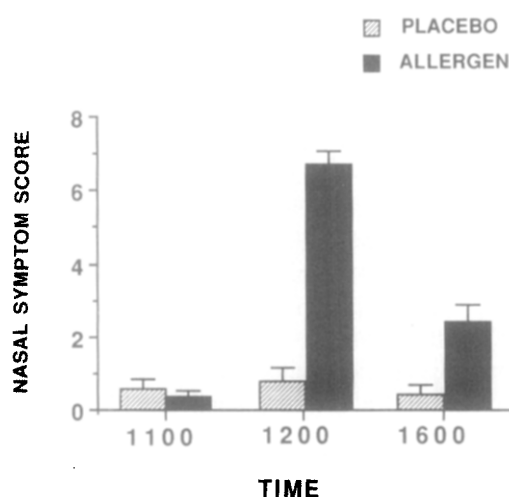


Fig. 3. Effect of nasal challenge with placebo or allergen on nasal-symptom scores; $p = 0.0001$ at 1200 (12 PM) and $p < 0.01$ at 1600 (4 PM), comparing change from baseline at 1100 (11 AM) for placebo versus allergen. $N = 10$ for both treatments.

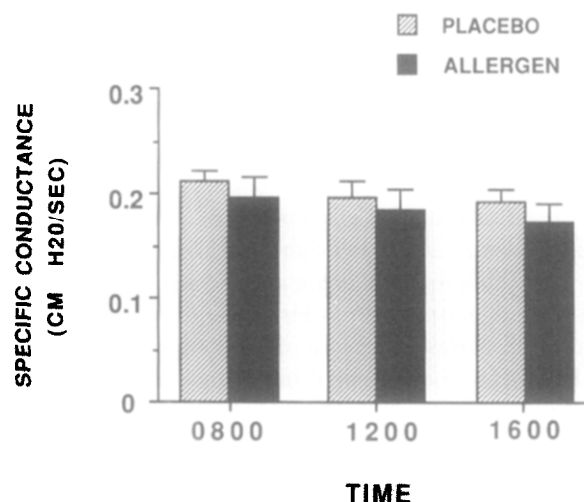


Fig. 5. Effect of nasal challenge with placebo or allergen on SG_{aw}. No significant changes for either treatment. $N = 10$ for both treatments.

changes in airway responsiveness after nasal challenge are presented in Fig. 7. For every individual at both times measured, BR was greater after nasal challenge with allergen than after placebo challenge, with some individuals demonstrating marked differences (approximately three doubling dilutions of methacholine) between placebo and allergen. Correlations between changes in FEV₁ and changes in PC₂₀ were not significant for placebo or allergen at either 30 minutes or 4½ hours.

Pearson's correlations of PC₂₀ versus NBI and nasal-symptom score demonstrated no significant correlations at either 30 minutes or 4½ hours after nasal challenge.

DISCUSSION

Our study was initiated to investigate the relationship between upper airway disease and asthma, since a relationship may be important to strategies of treatment. Previous studies have used several provocative substances and challenge techniques with varying effects on pulmonary function.⁹⁻¹⁷ Furthermore, these

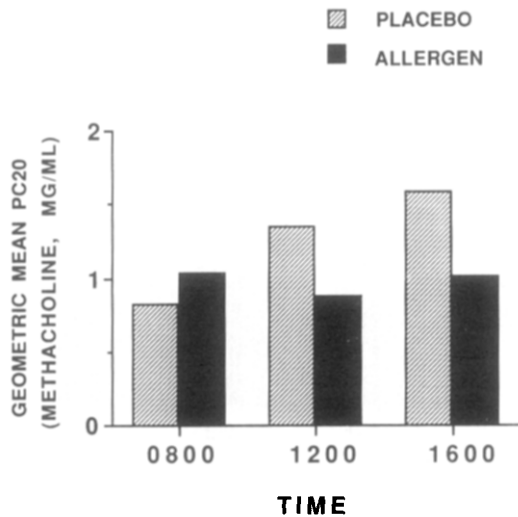


Fig. 6. Effect of nasal challenge on BR, expressed as the geometric means of PC₂₀ to inhaled methacholine; $p = 0.011$ at 1200 (12 PM) and $p < 0.0009$ at 1600 (4 PM), comparing change from baseline 0800 (8 AM) for placebo versus allergen. $N = 10$ for both treatments.

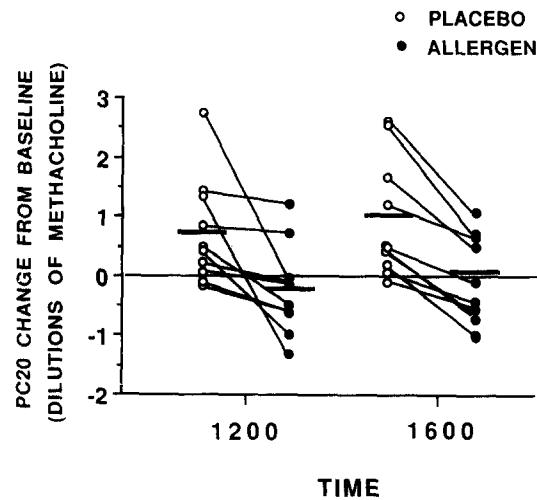


Fig. 7. Changes in PC₂₀ from baseline 0800 (8 AM) at 1200 (12 PM) and 1600 (4 PM) in individual subjects after nasal challenge. Data are expressed in doubling dilutions of methacholine, and means are indicated with horizontal bars. $N = 10$ for both treatments.

trials have studied patients both with and without perennial rhinitis, and none attempted to study patients who specifically implicated nasal symptoms as a trigger of their asthma. Finally, none of these studies investigated late changes in lower airway function, nor did any studies examine changes in airway responsiveness associated with nasal allergen challenge.

We chose to use allergen as the challenge material. Unlike agonists, such as histamine or methacholine, allergen causes the release of a spectrum of mediators that might be of potential importance in altering airway caliber or responsiveness.³⁵ We also chose to deliver allergen to both nostrils with an atomizer that distributed allergen to a larger surface area of nasal tissue as might be expected with natural pollen exposure. Since we demonstrated that this technique did not allow allergen to reach the lower airways, we can conclude that the changes in responsiveness observed originated from a process confined to the nose. Patients were selected for study only if they related worsening of their asthma to symptoms of AR to increase the likelihood of observing an effect, since this phenomenon may not occur in all subjects with asthma. The patients were studied out of their season of allergic symptoms to avoid day-to-day variability in pulmonary function and bronchial reactivity,³⁶ as well as any nasal priming effects.³⁷

Our results are in agreement with several prior studies that performed nasal challenges on patients out of pollen season and found no alteration of pulmonary function.¹⁴⁻¹⁷ In our study, despite the induction of

severe rhinitis, we were unable to detect any significant immediate (30 minutes) nor late (4½ hours) changes in pulmonary function after nasal allergen challenge. Since we initially hypothesized that a nasal late-phase response might be of importance in the nasal-bronchial relationship, patients were also instructed to record a diary of peak flows and chest symptoms until the following day. There were no changes in these parameters that might suggest a delayed reaction. Some investigators have suggested that preexisting chronic rhinitis is necessary to elicit bronchoconstriction after nasal challenge.¹² In a recent study, however, Small and Biskin¹⁷ were unable to document changes in pulmonary function after inducing a significant nasal-allergic response in subjects with perennial AR. Therefore, several studies, including our own, indicate that nasal provocation with allergen causes no change in baseline pulmonary function either in patients with or without perennial nasal symptoms. Our results do not disprove that naso-bronchial reflexes may result in bronchospasm^{9,10}; rather, these results suggest that the nasopharyngeal irritant receptors that may evoke this response are largely unaffected by mediators released and other processes that occur during the allergic nasal response.

The diurnal decreases in reactivity that followed the placebo nasal challenge are consistent with data from other studies that have demonstrated that BR is greatest at 4 AM and gradually decreases throughout the day to its lowest value at 4 PM.³¹⁻³⁴ de Vries et al.³¹ initially demonstrated that BR decreased significantly

between 8 AM and 12 PM in 11 patients with mild asthma. More recently, Bonnet et al.³² demonstrated similar findings, noting marked changes in airway reactivity between 6 and 10 AM and between 10 AM and 2 PM. Our study demonstrated that nasal allergen challenge eliminated the normal diurnal reduction in airway responsiveness. This alteration in BR after nasal allergen challenge corresponds with other preliminary studies.^{38, 39} In our study, the differences between placebo and allergen challenge were highly statistically significant for the entire group at both 30 minutes and 4½ hours. Although these differences were small in absolute terms (approximately one doubling dilution of methacholine at both 30 minutes and 4½ hours), some individuals demonstrated much larger differences (Fig. 7). Additionally, it must be kept in mind that these challenges were performed in minimally symptomatic patients without recent exposure to any type of inhaled allergen. Therefore, it appears probable that daily natural exposure to grass allergen throughout the course of an entire pollen season would produce significantly larger effects on BR than were observed after this single laboratory challenge.

We attempted to determine which aspect of the nasal response might be most closely linked to the increase in BR. We addressed this question by correlating the changes in responsiveness with the intensity of the nasal response (as measured by NBI and total nasal-symptom scores). Measures of the nasal response did not correlate with the changes in bronchial reactivity. Furthermore, for the group as a whole, NBI had decreased to normal levels by 4 PM, even though BR continued to be significantly increased as compared with placebo at that time. This finding would indicate that the degree of nasal blockage is probably not the eliciting factor in determining the change in lower airway responsiveness. Furthermore, although these data do not suggest which aspect of the nasal response could link a nasal-allergic reaction to the lower airways, these data do suggest that it is not related to the absolute magnitude of the nasal response.

A variety of mechanisms have been proposed to explain the link between upper and lower airway disease. These include (1) elicitation of a nasal-bronchial reflex, (2) absorption of mediators or chemotactic factors, (3) postnasal drainage of inflammatory material into the lower airways, (4) increased oral inhalation of cold, dry air or airborne allergen caused by nasal blockage, and (5) diminished β -adrenergic responsiveness.⁴⁰ The initial alteration in airway responsiveness observed in our study (occurring 30 minutes after nasal challenge) is most consistent with the effects of either a neural reflex or an inflammatory mediator released into the systemic circulation during the

nasal-allergic reaction. However, it is doubtful that changes in responsiveness persisting 4½ hours after nasal challenge could be due to neural effects. Rather, these persistent changes in bronchial reactivity more likely reflect the action of inflammatory products that have reached the lower airways either through postnasal drainage or via the systemic circulation. An animal model⁴¹ suggests that postnasal drainage of inflammatory material is the most likely explanation of persistent, late changes in BR associated with nasal inflammation. After inducing a granulocytic nasal/sinus infiltrate in rabbits, bronchial provocation with histamine demonstrated marked hyperresponsiveness of the lower airways with no change in baseline lower airway caliber 16 hours after initiation of the rhinitis. This increase in BR could be prevented by blocking drainage of nasal secretions into the lower airways. Although it is still controversial whether nasal secretions can be aspirated into the lower airways of humans,^{42, 43} postnasal drainage may prove to be an important mechanism contributing to airway hyperresponsiveness in patients with both rhinitis and asthma.

The association between inflammation of the upper and lower airways may have important therapeutic implications. Welsh et al.⁵ examined the efficacy of topical rhinitis treatment in a large group of patients having both seasonal AR and asthma. In addition to the marked improvement in nasal disease, nasal corticosteroid treatment also resulted in a significant reduction in asthma symptoms. Future studies will be needed to clarify the pathogenetic mechanisms linking upper airway disease and BR, as well as to define further the role of nasal treatment in the therapeutic approach to asthma.

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