

Natural and induced allergic responses increase the ability of the nose to warm and humidify air

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Background: We have previously shown that subjects with seasonal allergic rhinitis out of season had a reduced ability to warm and humidify air compared with normal subjects.

Objective: We sought to investigate whether allergic reactions induced by either seasonal exposure or nasal challenge with antigen would decrease the capacity of the nose to condition cold, dry air.

Methods: We performed two prospective studies comparing the effects of allergic inflammation, induced by either seasonal exposure or nasal challenge with antigen, on nasal conditioning capacity (NCC). The total water gradient (WG) across the nose was used to represent the NCC. In the first study, the NCC was measured and compared before and during the allergy season in 10 subjects with seasonal allergic rhinitis. In the second study, 20 subjects with seasonal allergic rhinitis were recruited outside of the allergy season. NCC was measured and compared before and 24 hours after challenge with antigen.

Results: In the first study, seasonal allergic subjects in season showed a significant increase in NCC when compared with their preseason baseline (total WG in season: 2050 ± 138 mg vs total WG preseason: 1524 ± 100 mg; $P < .01$). In the second study, antigen challenge led to early-phase and late-phase responses. There was a statistically significant increase in NCC 24 hours after antigen challenge compared with that before antigen challenge (total WG after antigen challenge: 1938 ± 101 mg vs total WG before antigen challenge: 1648 ± 84 mg; $P = .01$).

Conclusion: Allergic reactions induced by either seasonal exposure or antigen challenge increase the ability of the nose to condition inspired air. We speculate that allergic inflammation increases this ability by changing the perimeter of the nasal cavity. (*J Allergy Clin Immunol* 2000;106:1045-52.)

Key words: Allergic inflammation, nasal conditioning, water gradient, humidification, allergy

Abbreviations used

CDA: Cold, dry air
ECP: Eosinophil cationic protein
NCC: Nasal conditioning capacity
WC: Water content
WG: Water gradient

Allergic rhinitis is a chronic disease that has a prevalence of between 15% and 20% and affects nearly 40 million people in the United States. It is the sixth most prevalent chronic health condition experienced by the American population, outranking heart disease.¹ Additionally, it has been shown that its prevalence is increasing.²

A major function of the nose is to warm and humidify air.³ The influence of allergic reactions on the air-conditioning capacity of the nose is unexplored. We previously showed that subjects with seasonal allergic rhinitis out of season had a reduced ability to warm and humidify air compared with normal subjects.⁴ In this article, we report the results of two studies of the effect of allergic responses induced by either seasonal exposure or nasal challenge with antigen on nasal conditioning of cold, dry air (CDA). We hypothesized that allergic inflammation caused by ragweed exposure during the season in the first study and antigen challenge in the second study would decrease the ability of the nose to warm and humidify inspired air.

METHODS

Subjects

In the first study, 10 subjects with seasonal allergic rhinitis who had positive skin test responses to ragweed were studied (8 men and 2 women; age range, 20-38 years; mean age, 29 years; 7 white and 3 African American subjects) during and outside their allergy season. The inclusion criteria were positive symptoms during the ragweed season, no perennial symptoms, and a positive skin puncture test response to ragweed. In the second study, 20 volunteers with a history of seasonal allergic rhinitis were recruited (16 men and 4 women; age range, 18-41 years; mean age, 25 years; 14 white, 2 African American, 2 Asian, and 2 Hispanic subjects). Their allergic status was confirmed by history, a positive skin puncture test response to either ragweed or timothy grass, and a positive nasal challenge with antigen, defined by sneezing two or more times and by a 2-fold or greater increase in the weight of generated nasal secretions and albumin levels compared with the diluent challenge

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(0.4% phenol-buffered saline solution). In addition, subjects had to have an increase in the number of eosinophils in nasal secretions 24 hours after antigen challenge. No subjects had asthma or were taking medications within 2 weeks of the evaluation. All subjects in the second study were studied out of season. Both studies were approved by the Institutional Review Board of the University of Chicago, and written informed consent was obtained from each subject before study entry.

Experimental protocol

In the first study, we compared the ability of the nose to condition air before and during the allergy season to determine whether allergic inflammation affected that ability. Subjects were brought to the laboratory on two separate occasions. During the first visit, 1 to 4 weeks before the beginning of the ragweed season, the ability of the nose to condition CDA (see below) was examined. After that, the subjects received diary symptom score sheets to keep track of their symptoms during the season. They returned during the ragweed season when they were symptomatic, and the measurement of nasal conditioning was repeated. The measurement of nasal conditioning during the allergy season was performed 19 to 48 days after the start of the season, as evidenced by increased ragweed counts.

In the second study, subjects were brought to the laboratory on 3 separate occasions (Fig 1). On the first and third visits, nasal conditioning was measured, and during the second visit, an antigen challenge was performed. The time interval between the first and second visits varied between 1 and 7 days, and the interval between the second and third visits was approximately 24 hours. On all visits, the subjects came to the laboratory and were allowed to rest for 15 minutes so that equilibration of the nasal mucosa with the environmental conditions of the laboratory was achieved (25°C and 30% relative humidity). During the first visit, symptoms of nasal congestion, itching, and rhinorrhea were recorded by the subjects. The number of sneezes was counted and recorded by the investigators. Nasal secretions were collected and weighed. After that, baseline nasal lavage was performed, and the measurement of nasal conditioning was begun. After the end of exposure, symptom score evaluation, secretion weight collection, and nasal lavage were repeated. During the second visit, a diluent challenge was performed followed by challenge with two increasing doses of antigen. Twenty-four hours later, during the third visit, subjects were brought back for measurement of nasal conditioning, which was performed in a manner identical to that of the first visit.

Nasal conditioning

Evaluation of the ability of the nose to condition CDA has been described in detail previously.⁴ In brief, the more patent nostril (probe side) was sprayed with 3 puffs (0.3 mL) of 0.05% oxymetazoline hydrochloride (Nostrilla; Ciba Self-Medication, Inc, Woodbridge, NJ), followed by 3 puffs (0.3 mL) of 4% lidocaine (Roxane Laboratories, Columbus, Ohio). Five minutes later, a probe containing temperature and humidity sensors was inserted through the nose along the floor of the nasal cavity, so that the tip touched the posterior nasopharyngeal wall, and the sensors were suspended in the air stream facing the opposite nostril. Flexible nasopharyngoscopy (Flex View Nasopharyngoscope; Smith and Nephew ENT, Bartlett, Tenn) was then performed for verification of the proper position of the probe in the nasopharynx. The nostril containing the probe was occluded anteriorly with a wax plug (Mack's Earplug; McKeon products Inc, Pleasant Ridge, Mich). A nasal CPAP mask (Respironics Inc, Murrysville, Pa) was then applied to the face over the probe with head straps. A second probe containing both temperature and humidity sensors was inserted into the mask through a hole made at the bottom of the mask and positioned just outside the nasal cavity. Silicone wax was used to provide an airtight seal around the probes where they entered the mask.

Air from compressed air tanks (Gas Tech, Inc, Hillside, Ill) was passed through a flowmeter into a cold air machine (FTS Systems, Stone Bridge, NY). Cold air at 0% relative humidity was then delivered to the patient's nose through the mask at increasing flow rates of 5, 10, and 20 L/min. Its temperature was approximately 19°C, 10.5°C, and 0.8°C at 5, 10, and 20 L/min, respectively. The subjects were instructed to breathe in and out through the mouth, while air was blown through the nose at the 3 different flow rates. Exposure to each flow rate lasted 22 minutes. Temperature and relative humidity were measured simultaneously by the sensors located in the mask and in the nasopharynx. The first 7 minutes at each flow rate allowed the temperature in the nasopharynx to reach a steady state, and we used the last 15 minutes at each flow rate to calculate the water content (WC) of the air. Water vapor content of air is a function of its temperature and relative humidity, and was calculated with the following formula: $WC = [2.32 + (0.59 \times T) - (0.011 \times T^2) + (0.00063 \times T^3)] \times RH / (100 \times D)$, where WC is the water content of air in milligrams per kilogram; T and RH are the temperature (in degrees Celsius) and relative humidity (%) values of air at 760 mm Hg, respectively; and D is the density of air (1.2 g/L at 20°C).⁴ The difference between the WC of air before entry into the nose and that in the nasopharynx is the water gradient (WG) across the nose; it represents the amount of water evaporated by the nose to condition air, which is a measure of nasal conditioning capacity (NCC).

Antigen challenge

We began the antigen challenge in the second study by obtaining a symptom score evaluation and a baseline nasal lavage sample. After subjects blew their noses to clear any accumulated secretions, two puffs of 0.05% oxymetazoline were sprayed into each nostril. After a 5-minute waiting period, 2 puffs of diluent for the allergen extracts (0.4% phenol-buffered saline solution; Bayer Corporation, Spokane, Wash) were sprayed into each nostril to control for non-specific reactivity of the nasal mucosa. Symptom score evaluation and nasal lavage were performed 10 minutes later. Next, two consecutive allergen challenges were performed, 10 minutes apart, by spraying two puffs of either ragweed or timothy grass extracts (Bayer Corporation, Elkhart, Ind) at two concentrations (1:2000 and 1:200 wt/vol) into each nostril. Symptom score evaluation and nasal lavage were performed 10 minutes after each challenge.

Collection of nasal secretions

Secretions were collected in the second study from the anterior nasal septum beyond the mucocutaneous junction by using filter paper disks (Shandon Inc, Pittsburgh, Pa), as previously described.⁵ Disks used for secretion collection were kept in Eppendorf tubes (Fisher Scientific, Pittsburgh, Pa), and the disk-tube combinations were weighed before collection of secretions. After the collection, the disks were replaced in the Eppendorf tubes and weighed on a Mettler AE 240 analytical balance (Mettler Instruments, Highstown, NJ). We subtracted the pre-collection weight from the post-collection weight to determine the weight of secretions collected in 30 seconds.

Sneezes and symptom scores

In the first study the subjects received a symptom diary to record their symptoms every day after the first visit. The number of sneezes, rhinorrhea score, congestion score, and pruritic score were recorded by the subjects. The symptom score was also recorded on the day the subjects came to the laboratory before the measurement of nasal conditioning was begun. The symptom scores were graded on the following scale: 0, none; 1, mild; 2, moderate; and 3, severe.

In the second study the number of sneezes before and after nasal conditioning of CDA and after antigen challenge was counted and recorded by the investigator performing the challenges. After the

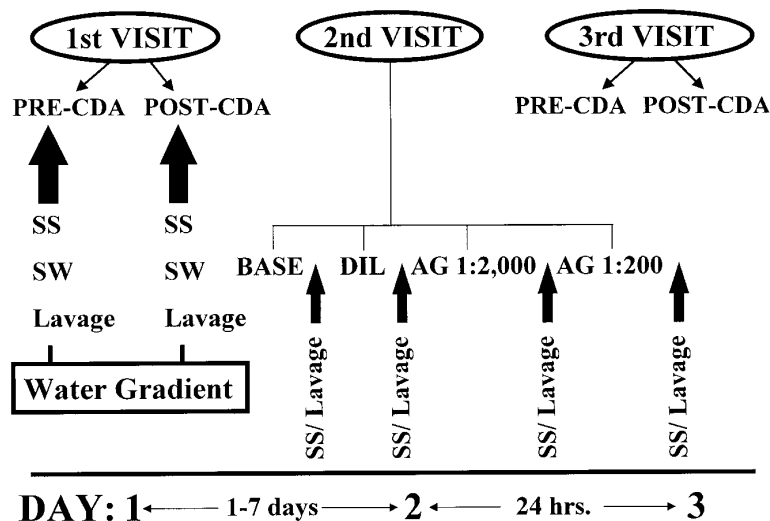


FIG 1. Protocol of the second study. The different interventions (symptom scoring, nasal secretion collection, and nasal lavage) in each visit are depicted by arrows. Antigen challenge was performed on the second visit. The third visit was identical to the first visit. The WG values were obtained from the first and third visits. The time intervals between visits are indicated below. SS, Symptom score; SW, secretion weight; BASE, baseline measurement; DIL, diluent challenge; AG, antigen challenge (1:2000 wt/vol and 1:200 wt/vol).

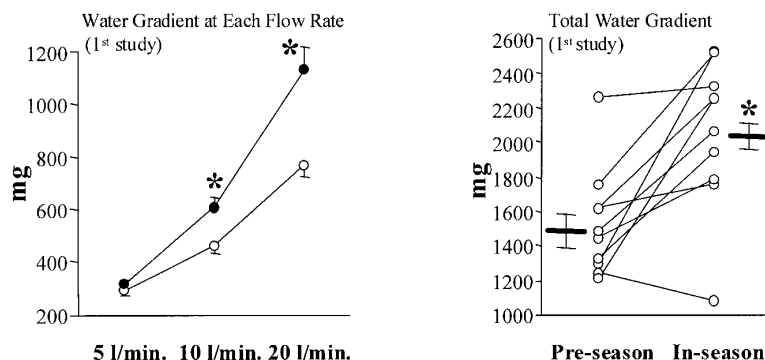


FIG 2. WG in the first study. **Left,** WG values across the nose before (open circles) and during (filled circles) allergy season at 3 flow rates (5, 10, and 20 L/min). Data are means $\pm$ SEM for 10 subjects (* P < 0.01 vs pre-season). **Right,** Individual data of total WG across the nose before and during allergy season. The time points are shown on the abscissa. Solid bars represent means $\pm$ SEM of the individual data points. Pre-season, Before allergy season; In-season, during allergy season. * P < .01 compared with pre-season.

measurement of nasal conditioning of CDA, only the nonprobe nostril (the less-patent one) was evaluated by the subjects. The rhinorrhea score and congestion score for each nostril and a combined sensation of pruritus for both nostrils were graded by the subjects on the same scale as in the first study.

Nasal lavage and cell collection

Lavages were performed in the second study by introduction of 2.5 mL of 37°C lactated Ringer's solution (Baxter Healthcare Corporation, Deerfield, Ill) into each nostril, as previously described.⁶ Subjects kept the solution in the nose for about 10 seconds and then expelled the lavage solution into a plastic receptacle. The volume of the lavage fluid was recorded, and then the sample was vigorously

shaken and stored in plastic tubes. The total number of cells was counted with a hemocytometer. The lavage solution was then placed on ice until centrifugation at 5000 rpm for 15 minutes at 4°C. The cell pellet was resuspended in an adequate volume of buffer and cytospun onto one or more slides. The cells were then dried, fixed, and stained with a Diff-Quick Stain Set (Dade Behring Inc, Newark, Del) to allow enumeration of different types of cells. The percentage of eosinophils was counted by using a Zeiss microscope (Carl Zeiss Inc, Thornwood, NY), and the total number of eosinophils was calculated by multiplication of that percentage by the total cell count. Two hundred cells were counted. If the total number of countable cells was more than 50 but there were no eosinophils present, the number of eosinophils was arbitrarily assigned to be 500.

TABLE I. Indices of early-phase responses after antigen challenge in the second study (n = 20)

Parameters	Early allergic response		Diluent vs antigen challenge
	Diluent challenge	Antigen challenge (1:200 wt/vol)	
Rhinorrhea score	0.5 (0-1)	2 (1.5-3)	<i>P</i> = .0001
Congestion score	0 (0-0.5)	2 (1-2)	<i>P</i> = .00009
No. of sneezes	0 (0-0)	7.5 (3.5-10.5)	<i>P</i> = .0001
Pruritic score	0 (0-0)	1.5 (0.5-2)	<i>P</i> = .0007

Data are presented as median with 25th-75th percentiles in parentheses.

TABLE II. Indices of late-phase responses after antigen challenge in the second study (n = 20)

Parameters	Late allergic response		Before vs after challenge
	Before antigen challenge	24 h after antigen challenge	
Congestion score	0 (0-1)	1 (0-1)	<i>P</i> = .03
Albumin levels (μg/mL)	16.7 (8-42)	28.5 (19.7-72)	<i>P</i> = .0001
ECP levels (μg/mL)	2.4 (1-3.9)	7.4 (3.6-25)	<i>P</i> = .002
No. of eosinophils	500 (500-767)	6074 (1142-20,792)	<i>P</i> = .0001

Data are presented as medians with 25th-75th percentiles in parentheses.

The supernatant was stored at -20°C until assayed for albumin and eosinophil cationic protein (ECP).

Nasal secretion osmolality measurement

Osmolality values were measured in the returned lavage fluids with a Vapro vapor pressure osmometer (Wescor, Inc, Logan, Utah) in the second study. This instrument provides an accuracy of ± 3 mOsm/kg H_2O . The returned nasal lavage fluid was well homogenized by vigorous shaking. Ten microliters was then transferred to a filter paper disk. All measurements were performed in triplicate. The average values are reported.

Albumin assay

In the second study, levels of human serum albumin were assayed in nasal lavage fluid for evaluation of plasma leakage. Samples obtained from the same subject on each visit were always measured in the same assay, so that interassay variability was eliminated. Human serum albumin was measured by using an ELISA sensitive to 1 ng/mL of albumin.⁷

ECP assay

In the second study, ECP was assayed in nasal lavage fluid for evaluation of eosinophil activation. Samples obtained from the same subject on each visit were always measured in the same assay, so that interassay variability was eliminated. ECP was assayed by means of an RIA technique (Pharmacia ECP RIA; Pharmacia & Upjohn Diagnostics, Kalamazoo, Mich). A standard curve was constructed for each assay by using known concentrations of ECP, and the ECP value of the samples was obtained by extrapolating from the standard curve. The sensitivity of the assay was 2 μg/L.

Statistical analysis

For the WG, statistical analysis was performed with parametric statistics on the basis of the results of prior studies.⁴ Total WG was calculated as the sum of nasal WG values during each of 3 flow rates tested (5, 10, and 20 L/min). Multiple repeated measurements were compared by using ANOVA, and post hoc analysis was performed with the Fisher test of least significant difference. Comparison of results within the same group of subjects was done by paired *t* test. To study the effect of allergic inflammation on the conditioning capacity of the nose, we compared the total WG values obtained before and during the allergy season in the first study and before

and 24 hours after antigen challenge in the second study by using a paired *t* test.

For other parameters, nonparametric statistics were used for analysis. If the selected values of parameters were more than two, those values were first analyzed by using Friedman ANOVA. If a significant difference was found, post hoc analysis between two selected values was performed with the Wilcoxon signed-rank test. The total symptom scores on the day the subjects came to the laboratory before and during the allergy season in the first study were compared by using the Wilcoxon signed-rank test. In the second study, evidence of an early allergic reaction was analyzed by comparison of the number of sneezes and of symptom scores after the highest dose of antigen to those after diluent challenge. Evidence of a late allergic reaction was analyzed by comparison of albumin levels and total eosinophils in pre-CDA lavage samples before antigen challenge with those 24 hours after antigen challenge and ECP levels in baseline sample before antigen challenge (second visit) with those in pre-CDA samples 24 hours after antigen challenge (third visit). These indices of allergic inflammation were analyzed by use of the Wilcoxon signed-rank test. The rhinorrhea score, congestion score, secretion weight, and nasal secretion osmolality obtained from the first and third visits were also compared before and after CDA exposure by use of the Wilcoxon signed-rank test.

Correlations were performed by using the Spearman rank method. A *P* value (two-tailed) of less than .05 was considered significant. The data of WG values to which parametric statistics were applied are presented as means $\pm$ SEM. The data of other parameters to which nonparametric statistics were applied are presented as medians, with 25th-75th percentiles in parentheses.

RESULTS

In the first study, there were significantly higher total symptom scores on the day that subjects came to the laboratory during the ragweed season compared with the preseason baseline (preseason: 0.5 [25th-75th percentile, 0-2] vs in season: 5 [25th-75th percentile, 3-8]; *P* < .01). The WG across the nose during exposure to CDA was calculated for all 3 flow rates before and during the ragweed season. Before the ragweed season, the WGs at 5, 10, and 20 L/min were 295 ± 25 mg, 462 ± 30 mg, and

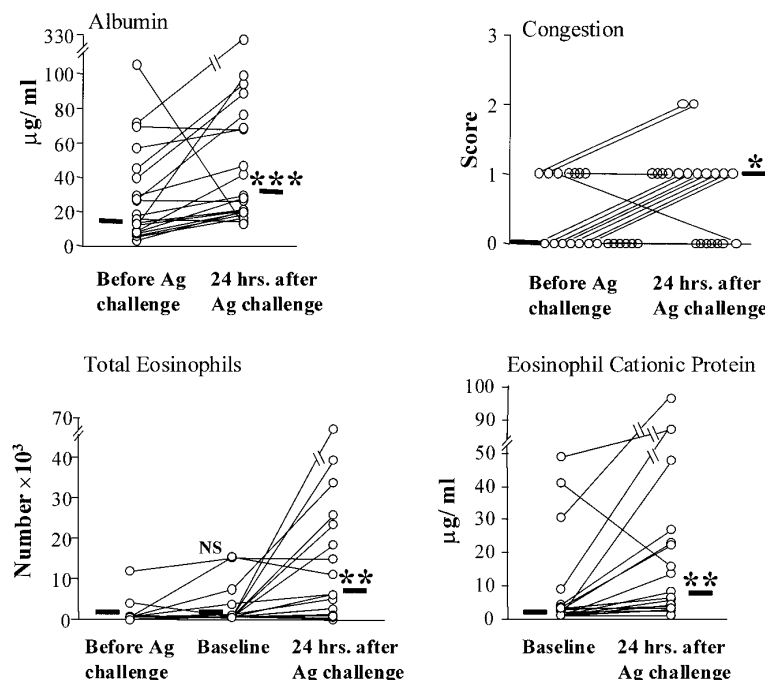


FIG 3. Albumin, congestion score, total eosinophils, and ECP in the second study. **Above left,** Individual data of albumin levels before nasal conditioning of CDA (pre-CDA time point) before and 24 hours after antigen challenge. The time points are shown on the abscissa. **Above right,** Individual data of congestion score at pre-CDA time point before and 24 hours after antigen challenge. **Below left,** Individual data of total eosinophils at pre-CDA time point before antigen challenge (first visit), baseline time point before antigen challenge (second visit), and pre-CDA time point 24 hours after antigen challenge (third visit). **Below right,** Individual data of ECP levels at baseline time point before antigen challenge (second visit) and pre-CDA time point 24 hours after antigen challenge (third visit). Solid horizontal bars represent median values. Ag, Antigen. * $P < .05$; *** $P < .01$; NS, not significant compared with before antigen challenge; ** $P < .01$ compared with baseline.

767 ± 46 mg, respectively, and the total WG was 1524 ± 100 mg. ANOVA and post hoc analysis showed significant differences between the WGs at 5 and 10 L/min ($P < .01$), between the WGs at 5 and 20 L/min ($P < .0001$), and between the WGs at 10 and 20 L/min ($P < .0001$) flow rates. During the ragweed season, the WGs at 5, 10, and 20 L/min and the total WG were 320 ± 15 mg, 605 ± 37 mg, 1125 ± 90 mg, and 2050 ± 138 mg, respectively. Again, ANOVA and post hoc analysis showed significant differences between the WGs at 5 and 10 L/min ($P < .01$), between the WGs at 5 and 20 L/min ($P < .0001$), and between the WGs at 10 and 20 L/min ($P < .0001$) flow rates. Allergic inflammation caused by natural seasonal exposure resulted in a statistically significant increase in WG values obtained at 10 and 20 L/min, as well as in the total WG ($P < .01$) compared with the pre-season baseline values (Fig 2).

In the second study allergen challenge was associated with early and late allergic responses. The early allergic response was indicated by significant increases in the rhinorrhea score, congestion score, number of sneezes, and pruritic score after the highest dose of allergen (1:200 wt/vol) compared with diluent challenge (Table I). The late allergic response, occurring 24 hours later, was doc-

umented by significant increases in congestion score, albumin levels, ECP levels, and total eosinophils compared with baseline levels (Table II and Fig 3).

The WGs across the nose after conditioning of CDA in the second study were also calculated for all 3 flow rates before and after antigen challenge. Before antigen challenge, the WGs at 5, 10, and 20 L/min and the total WG were 293 ± 13 mg, 495 ± 25 mg, 860 ± 55 mg, and 1648 ± 84 mg, respectively. ANOVA and post hoc analysis showed significant differences between the WGs at 5 and 10 L/min ($P < .001$), between the WGs at 5 and 20 L/min ($P < .0001$), and between the WGs at 10 and 20 L/min ($P < .0001$) flow rates. Twenty-four hours after antigen challenge, the WGs at 5, 10, and 20 L/min and the total WG were 321 ± 7 mg, 561 ± 18 mg, 1055 ± 94 mg, and 1938 ± 101 mg, respectively. Again, ANOVA and post hoc analysis showed significant differences between the WGs at 5 and 10 L/min ($P < .0001$), between the WGs at 5 and 20 L/min ($P < .0001$), and between the WGs at 10 and 20 L/min ($P < .05$) flow rates. Antigen challenge resulted in a statistically significant increase in WG values obtained at 5 ($P < .05$) and 10 L/min ($P < .01$), as well as the total WG ($P < .05$), compared with those before antigen challenge (Fig 4).

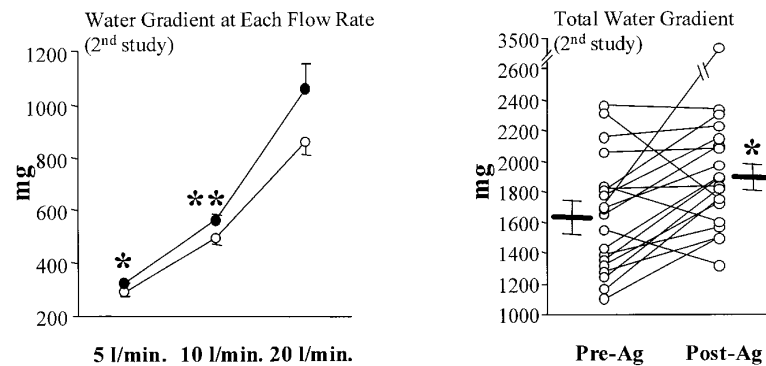


FIG 4. WG in the second study. **Left**, WG values across the nose before (open circles) and 24 hours after (filled circles) antigen challenge at 3 flow rates (5, 10, and 20 L/min). Data are means $\pm$ SEM for 20 subjects. * $P < .05$ vs before antigen challenge (Ag); ** $P < .01$ vs before antigen challenge. **Right**, Individual data of total WG across the nose before and 24 hours after antigen challenge. The time points are shown on the abscissa. Solid bars represent means $\pm$ SEM of the individual data points. Pre-Ag, Before antigen challenge; Post-Ag, 24 hours after antigen challenge. * $P < .05$ vs before antigen challenge.

TABLE III. Comparison of each parameter before and after exposure with CDA at the first and third visits of the second study (n = 20)

Parameters	Before antigen challenge (first visit)			24 h after antigen challenge (third visit)		
	Pre-CDA	Post-CDA	Pre-CDA vs post-CDA	Pre-CDA	Post-CDA	Pre-CDA vs post-CDA
Rhinorrhea score	0 (0-0)	1.5 (1-2.5)	$P = .0003$	0 (0-1)	1 (1-2)	$P = .002$
Congestion score	0 (0-1)	1 (1-2)	$P = .005$	1 (0-1)	1.5 (1-2.5)	$P = .001$
Secretion weight (mg)	7.3 (4.6-9.4)	28.5 (17.3-40.6)	$P = .00009$	6.9 (3.6-9.9)	28.8 (17.5-39.7)	$P = .00009$
Nasal secretion osmolality (mOsm/kg H ₂ O)	284 (281-286)	288 (283-293)	$P = .04$	284 (281-288)	286 (281-296)	$P = .048$

Data are presented as medians with 25th-75th percentiles in parentheses.

There was no significant correlation between total WG and measures of albumin, total eosinophils, or congestion score obtained 24 hours after antigen challenge in the second study ($P > .05$ for all).

After nasal exposure to CDA in the second study, there were significant increases in subjective symptoms, as shown by the rhinorrhea score and congestion score, and the objective parameter, as shown by the nasal secretion weight compared with those before CDA exposure at both the first and third visits (Table III). There was also a significant increase in nasal secretion osmolality after CDA exposure at both the first and third visits (Table III). There were no significant differences in rhinorrhea score, pruritic score, and number of sneezes before and 24 hours after antigen challenge ($P > .05$ for all). Furthermore, there were no significant differences in net change of secretion weights after CDA exposure before and 24 hours after antigen challenge (before antigen challenge: 20.4 mg [25th-75th percentile, 12.8-34.1 mg] vs after antigen challenge: 23.2 mg [25th-75th percentile, 10.9-32.6 mg]; $P = .5$).

DISCUSSION

In both studies, we used the inhalation of CDA at different temperatures and flow rates to assess the NCC,

and we investigated how naturally occurring or induced allergic inflammation affected the ability of the nose to warm and humidify air. We have previously shown that our nasal conditioning measurement model is reproducible in the same individuals whether they are allergic or nonallergic on different days.⁴ Thus, this model can be used for assessment of allergen-induced changes. In the first study, our results demonstrated that allergic inflammation induced by seasonal exposure increased the ability of the nose to condition CDA in contrast to our hypothesis. The increased conditioning capacity of the nose during the allergic response was surprising. Because we had previously shown the reproducibility of the response in nonallergic individuals, we did not follow a parallel group of nonallergic subjects in and out of season. Instead, we chose to reproduce our observation by using nasal provocation.

In the second study, we used nasal challenge with antigen to induce allergic inflammation and studied its effect on the ability of the nose to condition air. In this study, there was a significant response to antigen challenge, as evidenced by increases in the rhinorrhea score, congestion score, number of sneezes, and pruritic score after the highest dose of antigen compared with the diluent challenge. There were also significant increases in congestion score, albumin levels, the number of total

eosinophils, and ECP levels in nasal lavage fluid 24 hours after antigen challenge compared with those before antigen challenge, suggesting the presence of a late inflammatory response. Both the early and the late allergic responses are consistent with previous reports.^{6,8-14}

Our data demonstrated that there was a significant increase in the total WG 24 hours after antigen challenge compared with that before antigen challenge. This finding complemented our result in the first study and enhanced its validity. We can conclude from both studies that the allergic response caused by either natural seasonal exposure or nasal challenge with antigen improves the ability of the nose to condition inhaled air. Whereas the groups showed a significant increase, only one individual in the first study and 5 in the second study had the opposite response. These findings probably represent variability in studying human subjects but could represent a subgroup with a different response. Our data do not distinguish these possibilities.

The mechanisms by which allergic inflammation improves the NCC remain unclear. Our favorite hypothesis is that allergic inflammation leads to an increase in blood flow, which increases the amounts of heat and water for conditioning inspired air. This is supported by the structural components of the nasal lining tissue, which is the dense subepithelial capillary network with fenestration polarized toward the luminal surface.¹⁵ In one study, the moisture that contributed to the humidification process of inspired air was found to be provided by this vascular network, and the water continuously diffused through the epithelium.¹⁶

A second hypothesis is that allergic inflammation can cause engorgement of the nasal mucosa and may increase the nasal surface area for contact with the air stream, resulting in an increased conditioning capacity of the nose. Alternatively, allergic inflammation may increase glandular secretions, leading to a greater fluid supply available for conditioning air.

In our study there was no correlation between the antigen-induced increase in vascular permeability, total eosinophils, or congestion score and total WG. The lack of such a correlation suggests that there might be other mechanisms responsible for this finding or that we failed to choose the relevant response parameter for correlation.

In the second study, our results also showed that there was a significant increase in the rhinorrhea score, congestion score, nasal secretion weight, and nasal secretion osmolality after CDA exposure at both the first and third visits. These results are in agreement with those of previous studies.¹⁷⁻²² During inspiration of CDA, the nasal mucosal surface is cooled, and water is evaporated to condition the air. The loss of water is presumed to cause transient increases in the osmolality of the nasal surface liquid, as we showed here.²³ Hyperosmolality of nasal secretions has been proposed to result in sensory nerve activation.²⁴

Our study failed to show an increase in response to CDA after antigen challenge. This contrasts with studies showing that allergic inflammation causes an increase in sensitivity or hyperresponsiveness to antigenic and

nonantigenic stimuli after allergen challenge.²⁵⁻²⁷ In one study, when 18 subjects with allergic rhinitis were exposed to CDA, an increase in N- α -tosyl-L-arginine methyl ester-esterase levels, a marker of vascular permeability, was observed compared with baseline values. Twenty-four hours after allergen challenge, the response to CDA was significantly enhanced ($P = .008$).²⁸ This indicates that allergic inflammation induces hyperresponsiveness to CDA, one of the nonantigenic stimuli. The difference between that study and ours probably relates to the differences in the technique of CDA challenge used in each study and the different endpoint evaluated (secretion versus vascular permeability).

We have shown that the allergic response caused by either seasonal exposure or allergen challenge, specifically the late-phase response, increases the ability of the nose to condition inspired air. The mechanism for the increase in conditioning and the potential benefit to the lower airway from the drying effect of unconditioned air need to be explored.

REFERENCES

1. Collins JG. Prevalence of selected chronic conditions, United States, 1983-85. Advance data from vital and health statistics. No. 155. Hyattsville (MD): Public Health Service; 1988. DHHS publication No. (PHS) 88-1250.
2. Smith JM. Epidemiology. In: Mygind N, Naclerio RM, eds. Allergic and non-allergic rhinitis: clinical aspects. Copenhagen: W.B. Saunders Company; 1993. p. 15-22.
3. Proctor D, Anderson IB, Lundqvist GR. Human nasal mucosa function at controlled temperatures. *Respir Physiol* 1977;30:109-24.
4. Rouadi P, Baroody FM, Abbott DJ, Naureckas E, Solway J, Naclerio RM. A technique to measure the ability of the human nose to warm and humidify air: allergic subjects out of season are less able to warm air than normals. *J Appl Physiol* 1999;87:400-6.
5. Baroody FM, Ford S, Proud D, Kagey-Sobotka A, Lichtenstein L, Naclerio RM. Relationship between histamine and physiological changes during the early response to nasal antigen provocation. *J Appl Physiol* 1999;86:659-68.
6. Naclerio RM, Meier HL, Kagey-Sobotka A, Adkinson NF Jr, Meyers DA, Norman PS, et al. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis* 1983;128:597-602.
7. Chung JH, Detenoe ML, Naclerio RM, Sorrentino JV, Winslow CM, Baroody FM. Low dose clemastine inhibits sneezing and rhinorrhea during the early nasal allergic reaction. *Ann Allergy Asthma Immunol* 1997;78:307-12.
8. Pelikan Z. Late and delayed responses of the nasal mucosa to allergen challenge. *Ann Allergy* 1978;41:37-46.
9. Dvoracek JE, Yunginger JW, Kern EB, Hyatt RE, Gleich GJ. Induction of nasal late-phase reactions by insufflation of ragweed-pollen extract. *J Allergy Clin Immunol* 1984;73:363-8.
10. Pipkorn U, Proud D, Lichtenstein LM, Schleimer RP, Peters SP, Adkinson NF Jr, et al. Effect of short-term systemic glucocorticoid treatment on human nasal mediator release after antigen challenge. *J Clin Invest* 1987;80:957-61.
11. Walden SM, Proud D, Bascom R, Lichtenstein LM, Kagey-Sobotka A, Adkinson NF Jr, et al. Experimentally induced nasal allergic responses. *J Allergy Clin Immunol* 1988;81:940-9.
12. Iliopoulos O, Proud D, Adkinson NF Jr, Norman PS, Kagey-Sobotka A, Lichtenstein LM, et al. Relationship between the early, late and rechallenge reaction to nasal challenge with antigen: observation on the role of inflammatory mediators and cells. *J Allergy Clin Immunol* 1990;86:851-61.
13. Bisgaard H, Gronberg H, Mygind N, Dahl R, Lindqvist N, Venge P. Allergen-induced increase of eosinophil cationic protein in nasal lavage fluid: effect of the glucocorticosteroid budesonide. *J Allergy Clin Immunol* 1990;85:891-5.

14. Davies RJ, Lozewicz S, Manolitsas N, Calderon M, Devalia JL. Inflammatory cell recruitment following allergen exposure. In: Godard PH, Bousquet J, Michel FB, eds. *Advances in allergology and clinical immunology*. Carnforth (Lancs), UK: The Parthenon Publishing Group, Casterton Hall; 1992. p. 233-43.
15. Cauna N. Fine structure of the arteriovenous anastomosis and its nerve supply in the human nasal respiratory mucosa. *Anat Rec* 1975;181:1-16.
16. Cauna N. Blood and nerve supply of the nasal lining. In: Proctor DF, Anderson IB, eds. *The nose*. Oxford: Elsevier Biomedical Press; 1982. p. 44-69.
17. Togias AG, Proud D, Kagey-Sobotka A, Norman PS, Lichtenstein LM, Naclerio RM. The effect of a topical tricyclic antihistamine on the response of the nasal mucosa to challenge with cold, dry air and histamine. *J Allergy Clin Immunol* 1987;79:599-604.
18. Cruz AA, Togias AG, Lichtenstein LM, Kagey-Sobotka A, Proud D, Naclerio RM. Steroid-induced reduction of histamine release does not alter the clinical nasal response to cold, dry air. *Am Rev Respir Dis* 1991;143:761-5.
19. Philip G, Jankowski R, Baroody FM, Naclerio RM, Togias AG. Reflex activation of nasal secretion by unilateral inhalation of cold, dry air. *Am Rev Respir Dis* 1993;148:1616-22.
20. Jankowski R, Philip G, Togias AG, Naclerio RM. Demonstration of bilateral cholinergic secretory response after unilateral nasal cold, dry air challenge. *Rhinology* 1993;31:97-100.
21. Togias AG, Proud D, Lichtenstein LM, Adams GK III, Norman PS, Kagey-Sobotka A, et al. The osmolality of nasal secretions increases when inflammatory mediators are released in response to inhalation of cold, dry air. *Am Rev Respir Dis* 1988;137:625-9.
22. Togias AG, Lykens K, Kagey-Sobotka A, Eggleston PA, Proud D, Lichtenstein LM, et al. Studies on the relationships between sensitivity to cold, dry air, hyperosmolar solutions and histamine in adult nose. *Am Rev Respir Dis* 1990;141:1428-33.
23. Cole P. Respiratory mucosal vascular responses, air conditioning and thermoregulation. *J Laryngol Otol* 1954;68:613-22.
24. Anderson SD, Togias AG. Dry air and hyperosmolar challenge in asthma and rhinitis. In: Busse WW, Holgate ST, eds. *Asthma and rhinitis*. Oxford: Blackwell; 1995. p. 1178-95.
25. Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. *J Allergy Clin Immunol* 1989;84:492-501.
26. Walden SM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Antigen-provoked increase in histamine reactivity: observations on mechanisms. *Am Rev Respir Dis* 1991;144:642-8.
27. Klementsson H, Andersson M, Baumgarten CR, Venge P, Pipkorn U. Changes in non-specific nasal reactivity and eosinophil influx and activation after allergen challenge. *Clin Exp Allergy* 1990;20:539-47.
28. Naclerio RM. Pathophysiology of perennial allergic rhinitis. *Allergy* 1997;52(Suppl 36):7-13.

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