

THE JOURNAL OF Allergy AND Clinical Immunology

January 1997 • Volume 99 • Number 1

Treatment with hot, humid air reduces the nasal response to allergen challenge

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Ten subjects with asymptomatic seasonal allergy, outside of their allergy season, underwent allergen provocation following 1 hour of exposure to air at either 20° C and 30% relative humidity (RH) or air at 37° C and 90% RH. The ipsilateral changes following antigen challenge were compared under the two conditions. Conditioning of the nose to 37° C, 90% RH reduced total histamine release (7.9 ± 1.8 ng vs 4.2 ± 1.3 ng; $p \leq 0.05$), sneezes (6 ± 2 vs 3 ± 1 ; $p \leq 0.05$), pruritus (score of 17.4 ± 6.0 vs score of 2.0 ± 1.8 out of a total score of 100, $p \leq 0.01$), nasal airway resistance (1.4 ± 0.8 kPa/L/sec vs 0.2 ± 0.1 kPa/L/sec; $p \leq 0.05$), human serum albumin levels (389.6 ± 53.4 µg vs 242.2 ± 37.9 µg; $p \leq 0.05$), and congestion (score of 23.8 ± 4.8 vs score of 10.6 ± 5.4 out of a total score of 100, $p \leq 0.01$). It had no effect on the volume of secretions ($p = 0.8$), lactoferrin levels ($p = 0.3$), or rhinorrhea ($p = 1.0$). Thus air at 37° C and 90% RH partially reduces the early response to antigen. Its effects are greatest on histamine release, the vascular response, and neural responses, with no effect on the glandular response. The mechanisms underlying these effects are unknown. (J Allergy Clin Immunol 1997;99:77-86.)

HHA	Hot, humid air
HSA	Human serum albumin
LTC₄	Leukotriene C ₄
NAR	Nasal airway resistance
PGD₂	Prostaglandin D ₂
RA	Room air
RH	Relative humidity

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Key Words: [Humidity](#), [heat](#), [nasal provocation](#), [nasal airway resistance](#), [allergic rhinitis](#)

Our interests in the potential effects of environment on the allergic reaction were triggered from our review of the literature. In 1980 Yerushalmi and Lwoff¹ reported that treatment of the nasal mucosa with supersaturated air at 44° C leads to a beneficial effect on the nasal symptoms of subjects with allergic and perennial rhinitis. Additional studies duplicated these findings and showed improved nasal patency and decreases in the levels of total protein and albumin in nasal secretions following antigen challenge.²⁻⁶ There is also evidence that treatment with supersaturated, heated, air can reduce the symptoms of experimental and naturally occurring colds caused by rhinovirus^{1,7,8} and seems to have a protective effect on lower airway reactivity.⁹ In contrast to these reports, Oppenheimer et al.¹⁰ found that treatment with supersaturated, hot air had no effect on symptomatology or nasal patency in a population of patients with perennial rhinitis nor did it have a protective effect on nasal challenge with antigen.

Early studies evaluated symptoms and nasal blockage but did not attempt to measure secretions,

histamine levels, or markers of vascular permeability or glandular activity in nasal secretions. Later studies that did address these questions used nasal lavage techniques for sample collection, allowing measurement of mediators and markers of glandular activity and vascular permeability but not simultaneous measurement of physiologic parameters such as nasal airway resistance (NAR) and rhinorrhea. These studies also evaluated superphysiologic environments. We preferred to evaluate conditions that exist within nature and within the body. Previous work in our laboratory suggested that 1 hour of whole body exposure to air at 37° C and 90% relative humidity (RH) partially reduced the biochemical response to nasal allergen provocation.¹¹ In this report we extend our findings by studying the effect of environmental alterations on both physiologic responses and biochemical markers produced after allergen provocation.

Methods

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Subjects

Twelve volunteers with seasonal allergy were recruited (9 men and 3 women; ages 23 to 41 years; mean age, 30.9 years). Allergic status was confirmed by history and positive skin puncture test results (wheal diameter of 3 mm or greater). Subjects with allergies to *Dermatophagoides farinae* and *D. pteronyssinus* were excluded, as were those with nasal symptoms outside of their pollen season. All subjects had previously reacted to nasal allergen challenge with sneezing and increased nasal secretions but had no reaction to a sham challenge with the diluent for the allergen extract (phenol buffered solution, 0.5%; Greer Laboratories, Lenoir, N.C.). All subjects were free of symptoms at the time of study and had had no upper respiratory tract infections within the preceeding 2 weeks. Subjects had not taken antihistamines within the past week, astemizole within the past 3 months, or intranasal steroids, cromolyn, or systemic corticosteroids within the past month. No significant septal deviation or other mechanical obstruction was present. Written informed consent was obtained from each subject prior to study entry, and the protocol was approved by the Institutional Review Board for Human Subjects Research of the Johns Hopkins Bayview Medical Center.

Experimental protocol

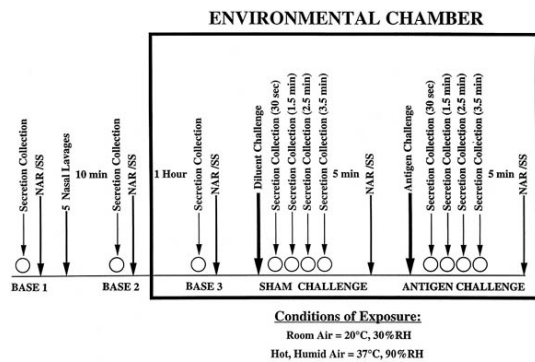
We performed a two-way, crossover study comparing the effects of exposure to air at 37° C and 90% RH (hot, humid air [HHA]) to that of air at 20° C and 30% RH (room air [RA]) on nasal antigen provocation. An environmental chamber (Environmental Sciences, Raleigh, N.C.) capable of regulating temperature and humidity conditions precisely was used.

At least 2 weeks separated the challenges to avoid an effect of one challenge on another, and the order of the challenges was randomized. Mediator measurements were performed in a blinded fashion. One subject was eliminated because review of his allergic history showed a previous strong reactivity to skin prick tests with *D. farinae* and *D. pteronyssinus*, and repeat testing confirmed this reactivity. Another was dropped from the study because of repeated failure to return for the second visit. Thus, 10 subjects completed all areas of the study, and results are reported only for them.

Allergen challenge

Localized allergen challenges were performed using 8 mm diameter filter paper disks (Shandon Inc., Pittsburgh, Pa.) as previously described.¹² The protocol was begun with a first series of baseline measurements (Base 1) (Fig. 1).

Fig. 1. Protocol. The different challenges, collection time points, and times of assessment of nasal airway resistance and symptoms are depicted by *arrows*. The time intervals between different sets of arrows are indicated in the space between them. The *solid box* represents challenges performed and time spent within the environmental chamber. *BASE*, Baseline measurements; *NAR*, nasal airway resistance; *SS*, symptom scores.



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Filter paper disks were used to collect secretions and were placed on the anterior portion of the nasal septum just posterior to the mucocutaneous junction for 30 seconds. NAR was then measured, and symptom scores were recorded by the subjects. Five nasal lavages with 10 ml of 0.9% saline (McGaw Inc., Irvine, Calif.) (5 ml in each nostril) were then performed to bring mediator levels to a stable baseline. After a 5-minute waiting period, a second series of baseline measurements were taken (Base 2). Subjects were then seated in an environmental chamber set to either 37° C and 90% RH or to 20° C and 30% RH for a 1-hour conditioning period. At the end of the conditioning phase, the subjects remained in the chamber and the baseline measurements were repeated (Base 3). Nasal challenge with diluent was then performed to control for nonspecific reactivity of the nasal mucosa. Fifty microliters of 0.5% phenol-buffered saline were placed on a filter paper disk and applied to the anterior nasal septum for 60 seconds under direct visualization by using a headlight, nasal speculum, and duckbill forceps. After a 30-second wait, dry disks were applied to the anterior nasal septum at the site of challenge and kept in place to collect nasal secretions for a 30-second period (time point, 0.5 minute). By this method, secretions were also collected at 1.5, 2.5, and 3.5 minutes. After a 5-minute waiting period, NAR was measured and symptom scores recorded. An allergen challenge employing disks containing 50 µl of either ragweed or mixed grass (Timothy, June, Meadow Fescue, and Orchard) extract at a concentration of 6667 PNU/ml (Greer Laboratories) was then performed. The quantity of antigen in 50 µl was 333 PNU, or approximately 1.2 µg of Amb a 1, for ragweed extracts. Secretions were then collected at the same time points as for diluent challenge.

Histamine was measured in the eluate from the time of measurement of baseline points and from the 0.5- and 1.5-minute time points after both diluent and allergen challenge. Lactoferrin and human serum albumin (HSA) were assayed on disks from baseline points and at the later time points (2.5 and 3.5 minutes) after both the diluent and allergen challenge. The choice of time points for measurement were based on previous data (unpublished) that showed that the peak level of histamine preceded the peak level of HSA. The limited volume of secretions obtained precludes the ability to measure multiple biochemical markers simultaneously.

Collection of nasal secretions

The collection disks were kept in 1.5 ml microtubes (Sarstedt, Newton, N.C.) and the disk-tube combinations were weighed before collection of secretions with a Mettler AE 240 Analytical Balance (Mettler Instruments, Highstown, N.J.). The disks were then placed on the nasal septum for a period of 30 seconds to collect secretions. After this, they were immediately replaced in the original microtubes. The disk-tube combination was weighted again, and the precollection weight was subtracted from the postcollection weight to determine the weight of secretions collected in 30 seconds. Exposure of disks to the ambient conditions used in this experiment for similar periods as in the actual experiments did not cause increases in disk weights.

Symptom scores, sneezes, and NAR

Symptoms were recorded by the subjects on a visual analog scale. Rhinorrhea and congestion were evaluated separately for each nostril, and pruritus was evaluated in a combined fashion for the nose and throat. Subjects indicated the severity of their symptoms by making a vertical mark through a 100 mm line that represented the range of symptoms from no sensation to the worst possible sensation. Scores were obtained by measuring the distance along the scale in millimeters. Sneezes were counted by the investigator. Anterior rhinomanometry with a digital rhinomanometer (Allergopharma, Ganza KG, Germany) was used to measure NAR at rest over a 10-second period of nasal breathing with the mouth closed. Results are reported in kilopascals per liter per second.

Mediator assays

Levels of histamine, HSA, and lactoferrin were assayed in recovered secretions to allow evaluation of mast cell degranulation, plasma leakage, and glandular secretion, respectively. After collection of nasal secretions, all disks were eluted in 300 μ l of phosphate-buffered 0.9% saline. Disks for histamine were eluted for 24 hours at 4° C, and those for lactoferrin and HSA were eluted at room temperature for 30 minutes. After elution, disks were removed, and the eluate was frozen and stored at -20° C until assayed. Samples obtained from the same subject during exposure to the different environmental conditions were always measured in the same assay to eliminate interassay variability. Histamine was measured by using a radioenzymatic assay with a sensitivity of 250 pg/ml.¹³ Lactoferrin and HSA were measured with noncompetitive ELISAs that used a modification of a previously published method.¹⁴ The usable range of the assay is 1 to 200 ng/ml for lactoferrin and 1 to 800 ng/ml for HSA. All markers are reported as the total amount in the eluate. This value was obtained by multiplying the concentration obtained from the assay by the volume of secretions plus the volume of eluate used. One milligram of secretions was assumed to be equivalent to 1 μ l of fluid for this calculation.

Statistical analysis

The change in parameters after exposure to the environmental conditions was obtained by subtracting the baseline measurements after the nasal washes from the measurement after exposure to HHA or RA prior to diluent challenge. For both diluent and allergen challenges, secretion weights and histamine, lactoferrin, and albumin levels were expressed as the sum of the values for each of the time points. Nonspecific responses to sham challenge were obtained by subtracting the immediately preceding baseline values from those obtained after challenge with the diluent solution. Changes in parameters after allergen challenges under the different conditions were obtained by subtracting values obtained after diluent challenge from those after allergen challenge. Comparisons between the antigen-induced changes after exposure to either environmental condition were performed by comparing changes from diluent for all the parameters between the two conditions. Statistical analysis used nonparametric methods. For descriptive purposes, data are reported as mean $\pm$ standard error of the mean (SEM). Differences between the changes from diluent were also compared for HHA and RA conditions with the Wilcoxon Signed Rank test. A *p* value (two-tailed) of 0.05 or less was considered significant. All statistical analyses were performed using the Statview II data analysis program (Abacus Concepts Inc., Berkeley, Calif.) on a Macintosh microcomputer (Apple Computer, Cupertino, Calif.).

Results

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The results are grouped into secretory, neural, and vascular responses (Figs. 2 to 4).

Fig. 2. Ipsilateral secretory responses after allergen challenge. **Left,** Responses at each of the individual time points after exposure to either room air (*closed circles*) or hot humid air (*open circles*). The protocol of the challenge is shown on the abscissa. Depending on the parameter monitored, the measurements are made at four time points after allergen challenge, two time points after challenge, or one time point after challenge as detailed in the text and in Fig 1 ■. Data are mean $\pm$ SEM values of 10 subjects. *B*, baseline measurement; *Dil*, diluent for the allergen extract; *Ag*, allergen challenge. **Right,** Individual data for the net change from diluent challenge for each parameter after exposure to each of the environmental conditions specified on the abscissa. The *solid bars* represent median values. *RA*, Room air; *HHA*, hot humid air; *NS*, not significant.

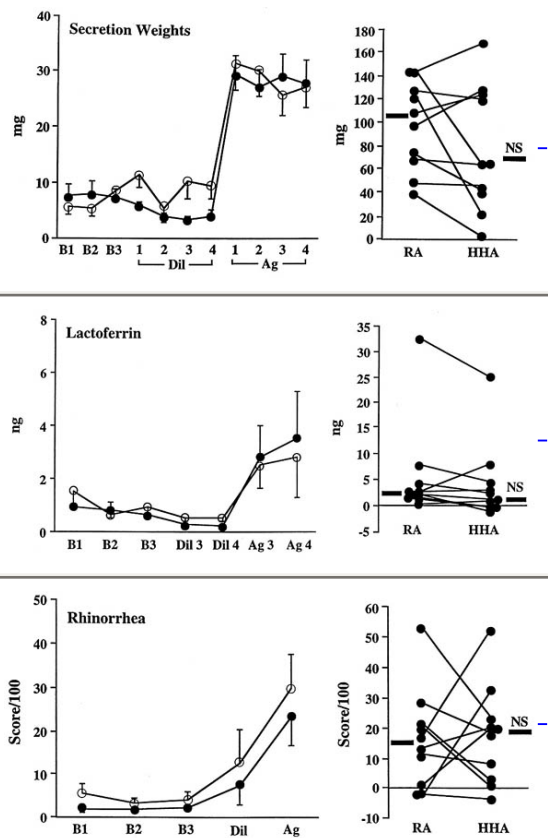
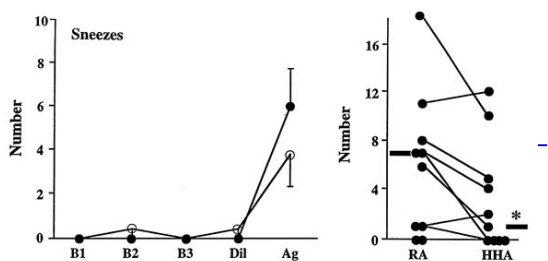
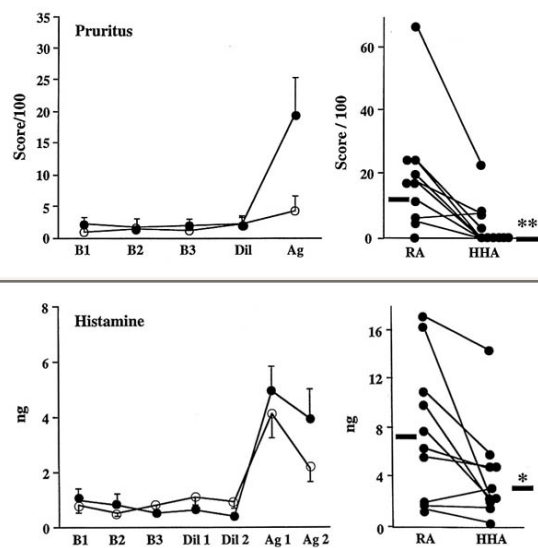


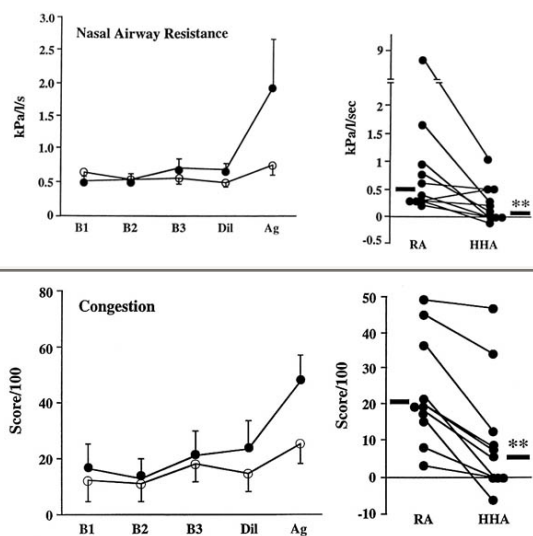
Fig. 3. Neural responses and ipsilateral histamine levels after allergen challenge. **Left,** Responses at each of the individual time points after exposure to either room air (*closed circles*) or hot humid air (*open circles*). The protocol of the challenge is similar to that in Fig. 2 ■. Depending on the parameter monitored, measurements are made at one or two time points after allergen challenge. Data are mean $\pm$ SEM values of 10 subjects. **Right,** Individual data for the net change from diluent challenge for each parameter after exposure to each of the environmental conditions specified on the abscissa as in Fig. 2 ■. * $p < 0.05$ and ** $p < 0.01$ compared with RA.

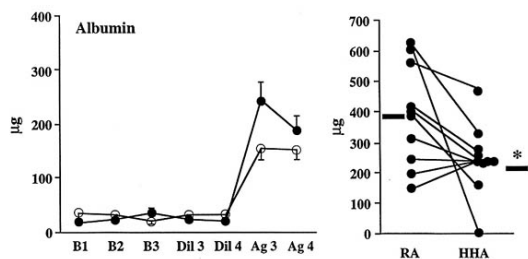




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Fig. 4. Vascular responses. Vascular responses after allergen challenge. **Left** Responses at each of the individual time points after exposure to either room air (*closed circles*) or hot humid air (*open circles*). The protocol of the challenge is similar to that in Fig. 2 ■. Depending on the parameter monitored, measurements are made at one or two time points after allergen challenge. Data are mean $\pm$ SEM values of 10 subjects. **Right** Individual data for the net change from diluent challenge for each parameter after exposure to each of the environmental conditions specified on the abscissa as in Fig. 2 ■. * $p < 0.05$ and ** $p < 0.01$ compared with RA.





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Baseline values for all parameters measured were comparable on both days and remained unaffected by nasal lavage. Exposure to RA was associated with a slight, but significant, increase in ipsilateral NAR (from 0.55 ± 0.08 kPa/L/sec to 0.75 ± 0.14 kPa/L/sec; $p = 0.03$). This increase was not accompanied by a contralateral increase in NAR and did not occur after exposure to HHA. All other parameters remained unaffected by the preconditioning period. No significant changes from baseline were recorded after diluent challenge.

As expected, challenge with allergen in RA provoked a marked increase, compared with challenge with diluent, for all parameters ipsilaterally. The sum of the values for each time point after either diluent or allergen challenge are reported here. Data obtained for each of the collection time points are shown in Fig. 2 ■ to Fig. 4 ■. The values for the various parameters after diluent and allergen challenge, respectively are as follows: secretion weights (16.4 ± 1.7 mg and 113.1 ± 12.9 mg; $p \leq 0.01$), lactoferrin levels (0.5 ± 0.1 ng and 6.3 ± 3.1 ng; $p \leq 0.01$), rhinorrhea (7.3 ± 4.7 and 23.2 ± 7.0 ; $p \leq 0.01$), sneezing (0 ± 0 and 6 ± 2 ; $p \leq 0.01$), histamine levels (0.9 ± 0.3 ng and 8.9 ± 2.0 ng; $p \leq 0.01$), pruritus (2.3 ± 0.9 and 19.7 ± 6.0 ; $p \leq 0.01$), NAR (0.7 ± 0.1 kPa/L/sec and 2.1 ± 0.8 kPa/L/sec; $p \leq 0.01$), HSA levels (41.2 ± 15.6 µg and 430.8 ± 63.0 µg; $p \leq 0.01$), and congestion (23.6 ± 10.1 and 47.4 ± 10.1 ; $p \leq 0.01$).

The response to allergen challenge was altered during exposure to HHA. Allergen challenge did not produce significant increases in NAR or in the sensation of pruritus compared with diluent, and the increases in some responses were less than those obtained after RA exposure. Comparisons of the responses obtained after preconditioning with RA and HHA were made by comparing the net change from the diluent challenge for all parameters during the two conditions. HHA exposure had no effect on allergen-induced secretion weights (HHA: 77.9 ± 17.1 mg; RA: 96.7 ± 12.1 mg; $p = 0.37$), lactoferrin levels (HHA: 4.4 ± 2.5 ng; RA: 5.8 ± 3.1 ng; $p = 0.32$) or rhinorrhea (HHA: 17.3 ± 5.4 ; RA: 15.9 ± 5.3 ; $p = 0.96$). However, HHA led to significant reductions in allergen-induced sneezing (HHA: 3 ± 1 ; RA: 6 ± 2 ; $p \leq 0.05$), histamine levels (HHA: 4.2 ± 1.3 ng; RA: 7.9 ± 1.8 ng; $p \leq 0.05$), pruritus (HHA: 2.0 ± 1.8 ; RA: 17.4 ± 6.0 ; $p \leq 0.01$), NAR (HHA: 0.2 ± 0.1 kPa/L/sec; RA: 1.4 ± 0.8 kPa/L/sec; $p \leq 0.01$), congestion (HHA: 10.6 ± 5.4 ; RA: 23.8 ± 4.8 ; $p \leq 0.01$) and HSA levels (HHA: 242.2 ± 37.9 µg; RA: 389.6 ± 53.4 µg; $p \leq 0.05$).

Discussion

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In a previous study, in which nasal lavage was used to monitor the response to antigen, we found a significant decrease in antigen-induced levels of N- α -tosyl-L-arginine methyl ester–esterase activity and HSA after treatment with air at 37° C and 90% RH when compared to treatment with air at 22° C and 50% RH and air at 4° C and 30% RH.¹¹ The current study extends those observations and

shows that preconditioning the nasal mucosa with HHA inhibits certain components of the nasal response to antigen challenge as compared with preconditioning at room temperature. Nasal antigen challenge after preconditioning with air at 20° C and 30% RH allowed increases in secretion weights, histamine levels, HSA levels, lactoferrin levels, NAR, and the subjective sensations of congestion, rhinorrhea, pruritus, and sneezing. Pretreatment with air at 37° C and 90% RH reduced the increases in sneezes, pruritus, histamine levels, NAR, HSA levels, and congestion. Secretory responses and lactoferrin levels, which reflect glandular activity, remained unaffected.

Our previous work with hot, humid air showed a tendency toward decreased production of histamine and sneezing after allergen challenge, but these differences did not attain statistical significance. In that study allergen challenge was performed with progressively increasing doses of either ragweed or grass extracts (10, 100, and 1000 PNU). While there seemed to be a reduction in sneezes and histamine levels after the lower antigen doses in HHA, these parameters were not decreased after the highest dose, suggesting a possible dose-response effect. In the present study a decrease in allergen-induced histamine production was shown after HHA exposure, and this was accompanied by decreases in sneezing and nasal pruritus. Since sneezing and pruritus occur through a reflex mechanism initiated by stimulation of H₁ receptors on sensory nerves of the nasal mucosa, the decreased sneezing observed in HHA probably reflects decreased histamine release. Increased HSA in nasal secretions reflects increased vascular permeability. Because blood vessels possess H₁ receptors, whose occupancy increases permeability, the decreased HSA after HHA may be attributed to decreased stimulation of H₁ receptors; however, numerous other mediators can cause increased vascular permeability. HHA essentially abolished the antigen-associated increase in NAR. Histamine is not considered the main mediator responsible for increased nasal congestion after allergen exposure because systemically administered antihistamines have no protective effect on this parameter after allergen challenge.¹⁵ Other mediators, such as PGD₂, LTC₄, and bradykinin, have been shown to provoke nasal congestion when applied to the nasal mucosa. Decreased vascular responses in HHA may be due to decreased production of these mediators, increased metabolism, decreased end organ response, or generation of a mediator that opposes the effects of vasopermeability and vasodilation.

Our data showing that HHA decreases physiologic and biochemical responses to allergen provocation agree with the observations of others who have studied the effect of higher temperatures and humidity. Ophir et al.^{3 4} have found an immediate decrease in symptoms and improvement of nasal patency in a group of symptomatic subjects with perennial and seasonal allergy who wore an apparatus delivering super-saturated air at 44° C to the nasal mucosa.^{3 4} In a blinded study comparing the effects of this same apparatus and a placebo device emitting room air at 21° C on symptomatic patients with perennial allergic rhinitis, Yerushalmi et al.² demonstrated an absence of symptoms in 75% and 68% of actively treated subjects at 1 week and 1 month after treatment, respectively, versus an absence of symptoms in 28% and 17% of the placebo-treated subjects. Johnston et al.⁵ compared the effects of pretreatment with air at either 44° C and 100% RH or air at 31° C and 100% RH, delivered by face mask, on antigen challenge in a population of subjects with out-of-season allergy. Using a lavage technique for sample collection and posterior rhinomanometry for evaluation of nasal blockage, they reported an attenuation of the response-to-antigen challenge after exposure to the conditioning with air at 44° C. Significantly fewer antigen-associated increases in NAR, total protein, and albumin in nasal lavages were noted, but no decrease in the number of sneezes, secretion production, or tryptase levels in nasal lavages

occurred. This study reinforces our conclusions as to the inhibitory effect of HHA exposure on nasal vascular responses. The lack of inhibition of the secretory response also agrees with our observations. However, their study differs from ours in that there was no inhibition of mast cell degranulation (reflected by tryptase levels in nasal lavages) or sneezing after exposure to HHA. These differences might be due to the design of the two studies. Johnston et al. exposed the subjects to the differing conditions for 30 minutes via a face mask and performed the allergen challenges 30 minutes after the end of exposure. In our study the subjects underwent whole body exposure to the different conditions and were challenged while still undergoing exposure. Therefore it is possible that any inhibitory effect of HHA on mast cell degranulation might be short lived and would have disappeared 30 minutes after termination of exposure as seen in Johnston's study, whereas the continuation of exposure to HHA led to the detection of inhibition of the nasal mast cells in our experiments. It is also worth noting that mediators in nasal lavages and the physiologic changes after allergen challenge were measured on two different days in Johnston's study. The use of the localized nasal challenge technique with filter paper disks allowed us to bypass the use of lavage for mediator measurements, and therefore we were able to perform all measurements simultaneously during one visit after allergen provocation.

Georgitis⁶ compared the effects of treatment with large-particle molecular water vapor at 44° C, molecular water vapor at 43° C, and nasal irrigation with 400 ml of 0.9% saline solution delivered by a Water-Pik device in a population of patients with perennial rhinitis. He showed decreased symptoms and a slight improvement in nasal patency during the 6-hour observation period after treatment with both molecular water vapor and large-particle water vapor. Nasal irrigation produced an initial increase in symptoms and had no effect on nasal patency. However, initial baseline symptoms were higher in both the molecular water vapor and the large-particle water vapor groups. Thus our study is the only one that tested subjects continually in the same environment.

Some investigators have questioned the benefits of HHA. A recent study in which a prototype version of the Rhinotherm apparatus was used conflicts with descriptions of the beneficial effects of this type of device in perennial rhinitis.¹⁰ In individuals with symptomatic dust allergy, Oppenheimer et al.¹⁰ were unable to demonstrate any difference in immediate or long-term symptom scores or nasal blockage indices after treatment with the active or placebo devices. In a second experiment they were unable to show any beneficial effects of the device on pollen antigen challenge performed immediately after treatment with the device, as measured by symptom scores and nasal expiratory indices. However, the placebo device in this case emitted room-temperature air that remained supersaturated with water droplets 4 to 8 µl in size. Any differences arising from the water content of the inspired air would thus be obviated. Interestingly, Konno et al.¹⁶ have reported that exposure to cold decreases the response to antigen challenge. They demonstrated a decrease in the quantity of ipsilateral nasal secretions produced following antigen challenge after preexposure to air at 1° C and 81% RH as compared to air at 22° C and 83% RH. There was no modification in sneezes. No challenge after conditioning under hot and humid conditions was performed for comparison, and mediators and symptoms were not recorded. We attribute the discrepancies in the various results to differences in experimental design—they used an antigen challenge immediately preceding the RA conditions as the control for the subsequent challenge performed in cold, dry air conditions, rather than comparing results from 2 days separated by a rest period in order to avoid the influence of one challenge on another.

Mechanisms underlying the beneficial effects of hot, humid conditions on the nasal mucosa have

been suggested, but none has gained universal acceptance. In this study the lower histamine levels measured after allergen challenge performed in HHA suggest that mast cell degranulation decreased. Decreases in histamine and other mediators or decreased end organ sensitivity to these mediators may be responsible for the decrease in responses. How the decrease in mast cell degranulation occurred is not addressed by our experiments, but several hypotheses exist. Conditioning of RA by the nose requires both heating and humidification of inspired air. Humidifying air requires the addition of water through a process of evaporation from the nasal mucosa.

Evaporation increases the osmolality of nasal secretions.¹⁷ Hot, humid air resembles air found at the alveolar level and does not need conditioning by the nasal mucosa. In the 37° C, 90% RH environment, the osmolality of secretions may have been reduced, allowing the nasal mucosa to attain temperatures higher than normal. There is evidence that changes in both osmolality and temperature can reduce mast cell degranulation. Nasal provocation with hyperosmolar stimuli provokes mast cell degranulation and mediator release with accompanying symptomatology in susceptible persons.¹⁷ Mann et al.¹⁸ showed that inspiration of hot, fully saturated air decreased the osmolality of tracheal secretions in dogs to an isoosmolar level. It is conceivable that, in HHA, osmolality decreased sufficiently to alter a potential synergistic effect of osmolality and antigen on the mast cell. Alternatively, osmolality changes might have affected nerves and other nasal end organs directly, making them less responsive to antigen provocation.

Increased temperature can also decrease histamine release from mast cells. Studies of histamine release from guinea pig lung and small-bowel tissue in vitro both showed decreases at temperatures above 40° C.¹⁹ All of these tissues differ from nasal tissue in that they are normally subject to an ambient temperature of 37° C. Since the temperature of the nasal mucosa under normal ambient conditions is between 30.4° C at inspiration and 32.0° C at expiration,²⁰ we propose that the optimal functioning temperature of mast cells of the nasal mucosa is probably in this range and that increasing nasal mucosal temperature above 32° C may have inhibited histamine release. How increased temperature decreases mast cell degranulation is unknown. Modification of a temperature-dependent enzymatic reaction is a possibility. Production of heat shock proteins can also have a protective effect, but their production has only been described at temperatures higher than the ones used in our experiment.²¹ In human macrophages, production of cytokines has been shown to be suppressed by exposure to a temperature of 39° C.²² It is possible that both modifications of temperature and osmolality act synergistically in decreasing mast cell mediator release. HHA may also directly affect the nerves, blood vessels, and glands within the nose. With regard to decreased nasal congestion in response to allergen challenge under HHA conditions, it may depend on phenomena other than decreases in mast cell release of histamine alone. Inhibition of other mediators such as prostaglandins, leukotrienes, and kinins, not measured in this study, may have contributed to the observed inhibitory effect of HHA on increases in nasal congestion after allergen challenge. We can not exclude the possibility that the whole-body exposure to higher temperature and not the local effects of inspired air were responsible for our observation. Additional experiments are needed to study this effect.

Mast cells have been shown to produce a variety of cytokines with actions on recruitment, adhesion, and eosinophil migration. If HHA has the same effect on induction of cytokine production as it does on histamine release, there may be a potential role for HHA in decreasing late-phase reactions and in relieving the symptoms of perennial rhinitis. Since allergic rhinitis involves more than mast cell degranulation and the early response to nasal challenge, the effect of HHA should be studied on these late events. The duration of the beneficial effects of exposure to hot, humid air

after exiting the chamber were not studied. In a subsequent study there was no effect on antigen challenge of prior conditioning in subjects tested 22 hours after exiting the chamber.²³

Because our experimental conditions differ from those obtained with supersaturated moist air, the results of this study should not be used to ascertain any clinical benefit.

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Publishing and Reprint Information

TOP

- *From ^athe Department of Medicine, the Johns Hopkins University School of Medicine; and ^bthe Section of Otolaryngology–Head and Neck Surgery, the University of Chicago.*
- *Supported in part by National Institutes of Health grants RO1 DC02714-01 and AI 08270. Dr. Baroody is the recipient of the 1993 combined American Academy of Otolaryngic Allergy/ American Academy of Otolaryngology–Head and Neck Surgery Research Award.*
- *Received for publication July 10, 1995.*
- *Accepted for publication June 11, 1996.*
- *Reprint requests: Robert Naclerio, MD, The University of Chicago, 5841 S. Maryland Avenue/ MC1035, Chicago, IL 60637.*
- **1/1/76108**
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Warming of feet elevates nasal mucosal surface temperature and reduces the early response to nasal challenge with allergen

Journal of Allergy and Clinical Immunology, The August 1999, part 1 • Volume 104 • Number 2

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