Warming of feet elevates nasal mucosal surface temperature and reduces the early response to nasal challenge with allergen

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Background: We have previously shown that hot, humid air partially reduces the early allergic response. Mechanisms for this effect have been suggested, but none has gained universal acceptance. The most likely explanations are a modification of mucosal temperature or a reduction in nasal secretion osmolality.
Objective: We sought to investigate whether increasing the nasal mucosal surface temperature by immersing feet in warm water (WW) could decrease the immediate nasal response to challenge with allergen.
Methods: We performed a randomized, 2-way crossover study on 14 subjects with seasonal allergic rhinitis outside of their allergy season. They immersed their feet in either WW (42°C) or room-temperature water (RW; 30°C) for 5 minutes before and during nasal challenge with diluent for the allergen extract, followed by 2 increasing doses of allergen.
Results: There was a statistically significant increase in nasal mucosal temperature from baseline after warming of feet (WW, 1.9 ± 0.1°C, vs RW, 0.2 ± 0.1°C; *P* = .001), but there were no significant differences in body temperature (WW, 0.1 ± 0.1°C, vs RW, 0.4 ± 0.1°C; *P* = .1). Net changes from diluent challenge for all parameters were compared between immersion of feet in WW and RW. Immersion of feet in WW significantly inhibited allergen-induced sneezes (WW, 5.7 ± 1.1, vs RW, 11.6 ± 3.2; *P* < .01), human serum albumin levels (WW, 941.7 ± 172.2 μg/mL vs RW, 1524.8 ± 220.6 μg/mL; *P* < .01), and secretion weights (WW, 30.5 ± 7.2 mg, vs RW, 41.8 ± 6.8 mg; *P* < .01).
Conclusion: Our data show that warming of feet decreases the early response to nasal challenge with antigen. This inhibitory effect is probably related to the increase in the nasal mucosal temperature. (J Allergy Clin Immunol 1999;104:285-93.)

Key words: *Warming of feet, nasal mucosal surface temperature, nasal provocation, allergic rhinitis*

Abbreviations used
GRP: Glucose-regulated protein
HSA: Human serum albumin
HSP: Heat shock protein
RW: Room-temperature water
WW: Warm water

The response to nasal challenge with allergen is less severe in a chamber containing hot, humid air (temperature, 37°C; >90% relative humidity) compared with the response at room temperature.[1] The mechanism by which preconditioning of the nose with hot, humid air reduces the early allergic response is unknown. There are 2 possible mechanisms that might lead to a reduced response: (1) a change in the osmolality of nasal secretions or (2) a change in the temperature of the nasal mucosa. Fully saturated air at 37°C would be expected to increase the normal nasal mucosal temperature during inspiration.[2] Thus inhaling warm, moist air would raise the surface temperature, alter chemical reactions, and reduce the responsiveness to antigen. Inhaling fully saturated air at 37°C prevents evaporation of water from the mucosal surface and the increase in osmolality of nasal secretions that occurs during evaporation of partially saturated air. This effect on osmolality might reduce mast cell activation or other mechanisms involved in the early reaction. It is also possible that modifications of both temperature and osmolality act synergistically in decreasing the early allergic response.[1] To evaluate the effects of mucosal temperature elevation, we sought a mechanism to raise temperature without affecting osmolality.

Cole[2] demonstrated that body heating resulted in changes in the surface temperature of the nose. After a subject was wrapped in blankets and his legs were placed in water at 45°C for 20 minutes, body temperature rose only 0.5°C, whereas the nasal expiratory air temperature rose 2°C to 3°C. He also found that localized skin heating resulted in an increase in the temperature of exhaled air. When subjects had their dorsal thoracic skin exposed

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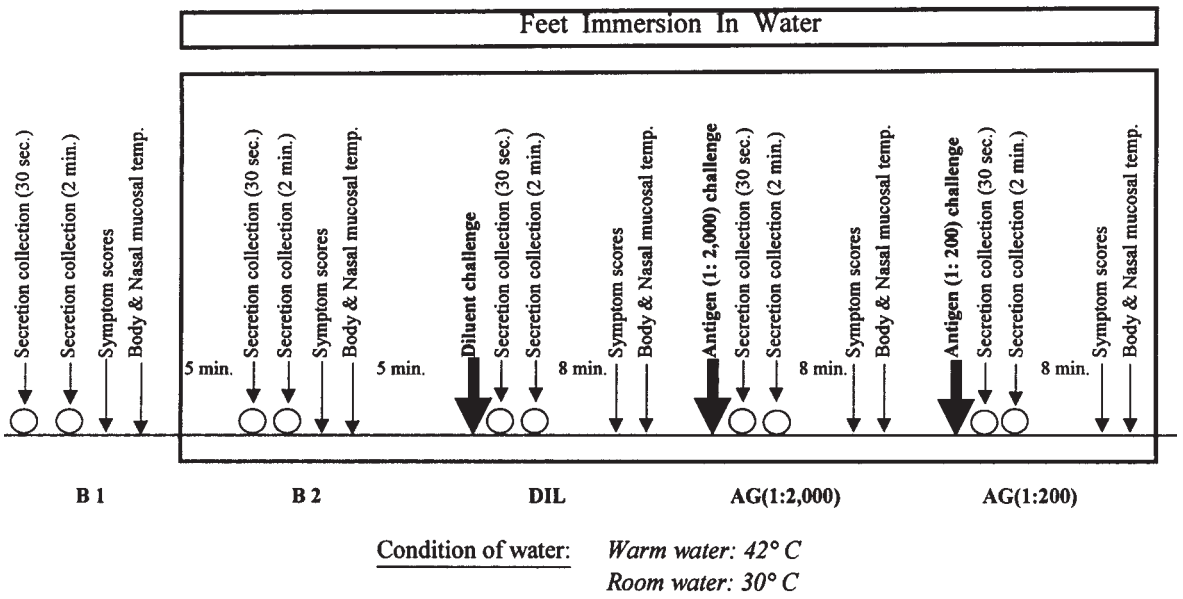

FIG 1. Protocol. The different interventions, including nasal secretion collection at both time points, symptom scoring, body and nasal mucosal temperature measurements, and diluent and antigen challenges, are depicted by *arrows*. The time intervals between different sets of arrows are indicated in the space between them. The *rectangle* at the top represents time spent during immersion of feet in either WW or RW. *B1* and *B2,* baseline measurements; *DIL,* diluent challenge; *AG,* antigen challenge. *Arrows* indicate events on time line.

alternately to an electric fire and a cooling fan, they showed an increase in nasal expiratory air temperature up to 2°C to 3°C during a 5-minute period in which the fire was turned on. The temperature returned to baseline within 5 minutes of the fire being turned off. These observations suggest that nasal expiratory air temperature changes in response to thermal stimulation of the skin. Cole also measured the nasal mucosal temperature by inserting the tip of a hypodermic needle into the turbinate submucosa. With a temperature-measuring circuit, submucosal turbinate temperature changes were recorded in response to thermal stimulation of the body. When the fan and fire sequence was used, changes similar to those found in expiratory air temperature occurred in the turbinates.

There is also experimental evidence in animals supporting these results. After a heat stimulus was applied to dogs for 15 minutes, the rectal temperature was found to vary no more than 0.2°C from the initial reading, but the nasal expiratory air temperature increased by about 3°C. After a cooling stimulus was applied, the nasal expiratory air temperature dropped about 5°C.[2]

We hypothesized that changing the skin temperature of allergic subjects by immersing their feet in warm water (WW) would increase the nasal mucosal temperature and lead to a decrease in the immediate response to allergen challenge.

METHODS

Subjects

Fourteen volunteers with a history of seasonal allergic rhinitis were recruited (7 men and 7 women; age, 18 to 39 years; mean age, 24 years). Their allergic status was confirmed by history, a positive skin puncture test reaction to either ragweed or timothy grass, and a positive nasal challenge with allergen defined by sneezing 2 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 (4% phenol-buffered saline). All subjects were studied out of season. The study was approved by the Institutional Review Board of the University of Chicago, and written informed consent was obtained from each subject before entry into the study.

Experimental protocol

We performed a randomized, 2-way, crossover study comparing the effects of mucosal temperature change on the acute response to allergen challenge by immersing feet in WW (42°C) or room-temperature water (RW; 30°C). On the day of challenge, 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 (temperature 25°C, 30% relative humidity). They immersed their bare feet in either WW or RW for 5 minutes before and during localized allergen challenge. The order of the conditions was assigned by a predetermined randomization code. At least 2 weeks separated the challenges to avoid any priming effect of one challenge on the other.

To evaluate the possibility that feet warming changed the osmolality of nasal secretions, we performed a second study in 14 asymptomatic allergic subjects outside of their allergy season. The technique for measuring osmolality involved performing nasal lavage. Because of the concern that lavage of the nose with warm (37°C) lactated Ringer's solution (Baxter Healthcare Corp, Deerfield, Ill) could affect the mucosal temperature, we did not incorporate these measurements in the first study. Lavages were performed with 5 mL of lactated Ringer's solution (2.5 mL in each nostril) before and 5 minutes after feet immersion in WW. The recovered lavage fluid was shaken vigorously and centrifuged. Ten-milliliter aliquots of the supernatant were placed in a Vapro vapor pressure osmometer

(Wescor, Inc, Logan, Utah). All measurements were done in triplicate. The sensitivity of the osmometer is ±3 mosm/kg H_2O.

Allergen challenge

Each challenge was begun with a series of baseline measurements (baseline 1; Fig 1). Preweighed filter paper discs (Shandon Inc, Pittsburgh, Pa) were placed on the anterior portion of the nasal septum just posterior to the mucocutaneous junction for 30 seconds for collection of nasal secretions (30-second time point). This was accomplished under direct visualization by use of a headlight, a nasal speculum, and a duckbill forceps. After a 1-minute wait, another disc was placed for collection of nasal secretions for 30 seconds (2-minute time point). Symptoms of nasal congestion, itching, and rhinorrhea were recorded by the subjects. Body and nasal mucosal surface temperatures were obtained with an oral thermometer and a nasal thermometer (see below), respectively. Subjects were then instructed to immerse their bare feet in one of the 2 conditioning water baths for 5 minutes. After that, a second series of baseline measurements was obtained (baseline 2). Five minutes after the second set of baseline measurements were obtained, a nasal challenge with diluent was performed to control for nonspecific reactivity of the nasal mucosa. Fifty microliters of the diluent for the allergen extracts (4% phenol-buffered saline; Bayer Corp, Spokane, Wash) were placed on a filter paper disc and applied to the anterior nasal septum for 60 seconds. Thirty seconds after removal of the challenge disc, a dry, preweighed disc was applied to the anterior nasal septum at the site of challenge and kept in place for collection of nasal secretions for 30 seconds (30-second time point). Similarly, secretions were collected at the 2-minute time point. After 8 minutes, symptoms were recorded by the subject, and the number of sneezes during the past 10 minutes was recorded by the investigator. Next, measurements of body temperature and nasal mucosal surface temperature were obtained. The subjects were then asked to blow their nose to clear any accumulated secretions before starting the next challenge, and then 2 consecutive allergen challenges were performed, 10 minutes apart, by application of 50 μL of either ragweed or timothy grass extracts (Bayer Corporation, Elkhart, Ind) at 2 concentrations (1:2000 and 1:200 wt/vol). Secretion weights, sneezes, symptoms, and body and nasal mucosal temperature were measured by the same technique as used after diluent challenge.

Collection of nasal secretions

Collection discs were kept in Eppendorf tubes (Fisher Scientific, Pittsburgh, Pa), and the disc/tube combinations were weighed before collection of secretions. After collection of secretions from the nose, the discs were replaced in the Eppendorf tubes and weighed with a Mettler AE 240 analytical balance (Mettler Instruments, Highstown, NJ). The precollection weight was subtracted from the postcollection weight for determining the weight of secretions collected in 30 seconds.

Sneezes and symptom scores

The number of sneezes after each challenge was counted and recorded by the investigator performing the challenges. Symptoms of runny and stuffy nose for each nostril and a combined sensation of itchy nose and throat were graded on a scale as follows: 0, no symptoms; 1, very mild symptoms; 2, mild symptoms; 3, moderate symptoms; 4, severe symptoms; and 5, very severe symptoms.

Albumin assay

After collection of nasal secretions, all discs were eluted in 300 μL of lactated Ringer's solution (Baxter Healthcare Corp). Discs for human serum albumin (HSA) were eluted at room temperature for 30 minutes. The discs were then squeezed to the bottom of the tubes, and the eluate was removed, frozen, and stored at –20°C until assayed. Levels of HSA were assayed in recovered secretions to allow evaluation of plasma leakage. HSA was assayed in the eluate from discs at the 2-minute time point. The choice of time point for albumin measurements was based on previous data, which showed that HSA levels peaked 2 minutes after removal of the allergen disc on the side of challenge.[3] Samples obtained from the same subject during immersion on the 2 days were always measured in the same assay, and therefore interassay variability was eliminated. HSA was measured by an ELISA sensitive to 1 ng/mL of albumin.[4]

Nasal mucosal temperature measurements

A nasal probe was developed for measurement of mucosal surface temperature. It consisted of a 14-Fr suction catheter (Kendall Healthcare Products Co, Mansfield, Mass) approximately 4 mm in diameter and 15 cm long. The distal part of the catheter was cut in half longitudinally for 1 cm. The temperature sensor, a 10-kω glass bead thermistor (Thermometrics, Edison, NJ), was attached to electrical wires and then inserted into the catheter through the proximal end. Silicone wax was used to stabilize the sensor in its position at the tip of the catheter and to anchor it to the remaining half of the catheter. The temperature sensor can measure temperatures from –20°C to 60°C with an accuracy of ±1°C. The output signals from the temperature sensor are amplified by an electronic module that develops signal levels compatible with typical computer data acquisition plug-in cards in an IBM-compatible computer. The Atlantis for Windows program (Lakeshore Technologies, Inc, Chicago, Ill) was used as the software for data acquisition.

The nasal probe was calibrated before each use. It was inserted into the anterior part of the nasal cavity by means of a nasal speculum and a headlight. The sensor at the end was placed in contact with the nasal mucosa of the anterior part of the nasal septum just posterior to the mucocutaneous junction, the location where collection and challenge discs were placed, and it sampled the mucosal temperature at a rate of 1 measurement per second for 30 seconds. We also measured the nasal mucosal temperature in the contralateral, nonchallenged nostril at the same time points in the equivalent site. The mean of the collected data during this period was analyzed with an Excel spreadsheet. The mean nasal mucosal temperature was determined.

Water conditioning

A water basin was put into an Isotemp waterbath (Fisher Scientific), which was set at 45°C for the WW and 33°C for the RW experiments. The resulting temperatures of the water in the basin were 42°C and 30°C, respectively. The top portion of the water basin and Isotemp waterbath was shielded by plastic wrap to prevent heat loss during the experiment.

Statistical analysis

For both diluent and allergen challenges, secretion weights were expressed as the average values of the 2 collection time points. Changes in nasal mucosal temperature were calculated by subtraction of values obtained after immersion of feet from those obtained before immersion. Net changes in other parameters after allergen challenge under the 2 different conditions were calculated by subtraction of values obtained after diluent challenge from those obtained after both allergen challenges (net change over diluent) and obtaining the sum of these values. Because the data were not distributed normally, nonparametric statistics was used. The values of each parameter at all time points after exposure to each of the conditions were analyzed by Friedman ANOVA. If a significant difference was found, post hoc analysis between diluent and the 2

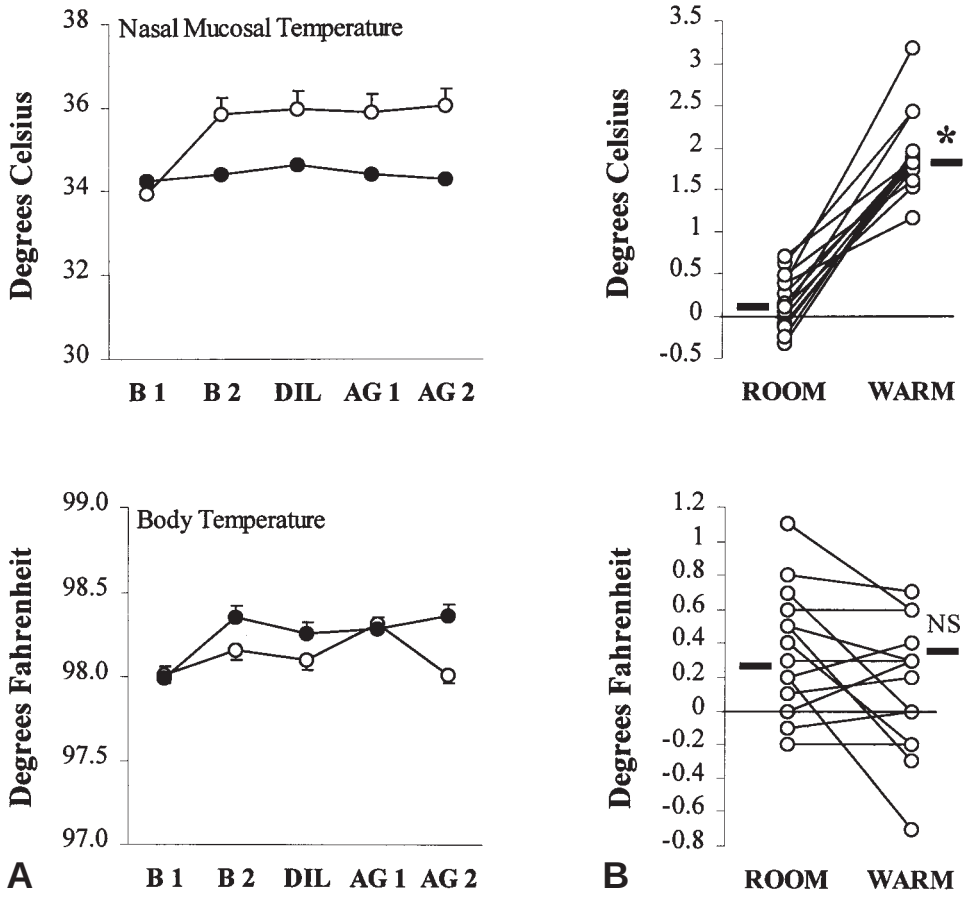

FIG 2. Nasal mucosal temperature *(top)* and body temperature *(bottom).* **A,** Temperature measured in the ipsilateral, challenged nostril or oral cavity at each of the individual time points after immersion of feet in either WW *(open circles)* or RW *(filled circles).* The challenge protocol is shown on the abscissa. Data are means ± SEM for 14 subjects. *B1* and *B2,* Baseline measurements; *DIL,* diluent for allergen extract; *AG1,* allergen challenge (1:2000 wt/vol); *AG2,* allergen challenge (1:200 wt/vol). **B,** Individual data for the net change from baseline after immersion of feet in 2 different water conditions specified on the abscissa. *Solid horizontal bars* represent median values. *ROOM,* RW; *WARM,* WW; *NS,* not significant. **P* = .001 compared with RW.

antigen challenges was performed by means of the Wilcoxon signed-rank test. To compare differences in the parameters between exposures, we compared net changes for each parameter after exposure to each of the 2 conditions by using the Wilcoxon signed-rank test. A *P* value (2-tailed) of less than .05 was considered significant.

RESULTS

Immersion of feet in WW was associated with a significant increase in nasal mucosal temperature over baseline, which began within 2 seconds of immersion and reached a plateau within 30 seconds (WW, 1.9°C ± 0.1°C, vs RW, 0.2°C ± 0.1°C; *P* = .001). There was no significant change in body temperature, as measured by oral thermometer (WW, 0.1°C ± 0.1°C, vs RW, 0.4°C ± 0.1°C; *P* = .10; Fig 2). We measured the nasal mucosal surface temperature at the anterior portion of the nasal septum on the side on which we performed nasal challenges; we also measured it in the contralateral nostril. There were no significant differences in nasal mucosal surface temperature between the sides (ipsilateral vs contralateral at all time points, *P* > .05). The osmolality of recovered nasal lavage fluid before and 5 minutes after immersion in WW was 286 ± 0.7 mosm/kg H_20 versus 286 ± 1.0 mosm/kg H_20 (n = 14, *P* = .22).

The results of the early nasal response after allergen provocation are grouped into secretory, neural, and vascular responses (Figs 3 to 5). All of these parameters were unaffected when the feet were immersed in the water bath. Likewise, there were no significant changes from baseline after diluent challenge.

Challenge with increasing doses of antigen caused significant increases in all parameters compared with diluent challenge during both exposures (Figs 3 to 5), except for body and mucosal temperature.

Warming of feet had no significant effects on allergen-induced rhinorrhea (WW, 6.1 ± 1.2, vs RW, 6.5 ± 1.3; *P* = .94), pruritus (WW, 1.5 ± 0.5, vs RW, 2.0 ± 0.6; *P* =

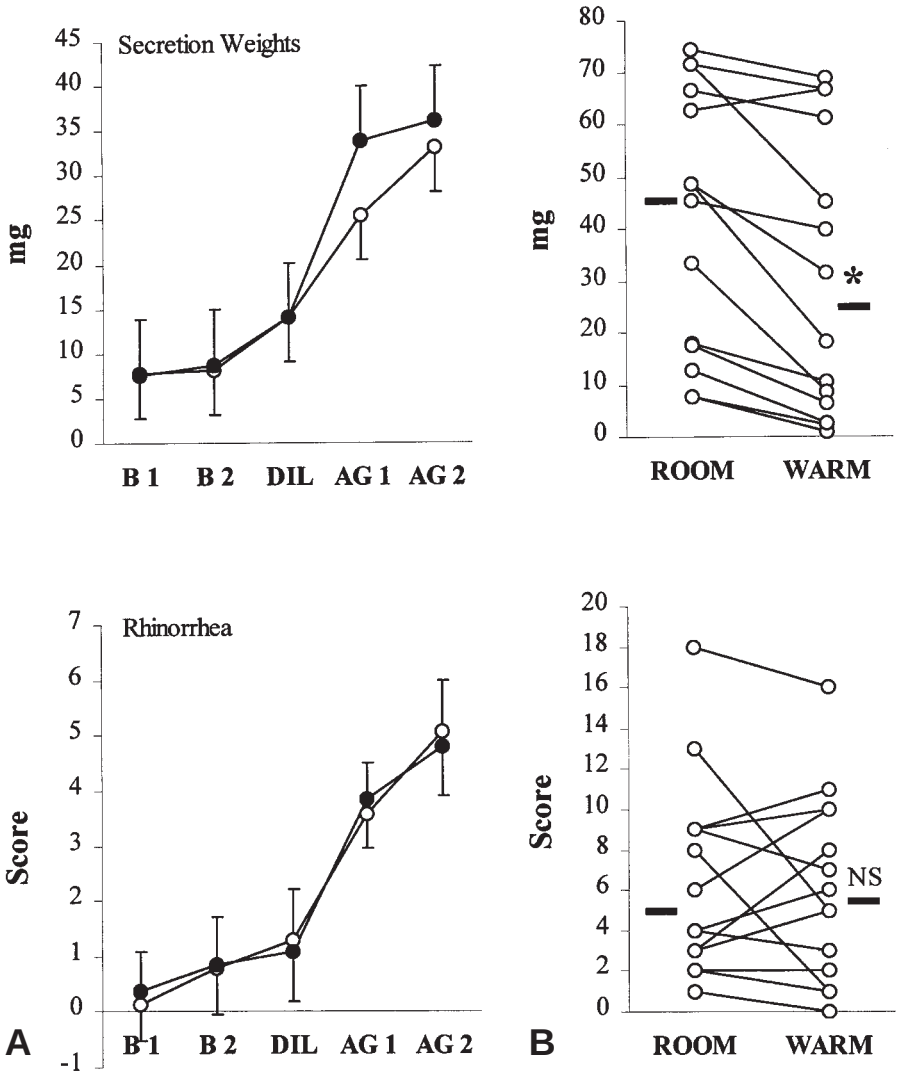

FIG 3. Secretory response. **A,** Responses at each of the individual time points after immersion of feet in WW *(open circles)* or RW *(filled circles)*. The challenge protocol is shown on the abscissa. Data are means ± SEM for 14 subjects. *B1* and *B2,* Baseline measurements; *DIL,* diluent for allergen extract; *AG1,* allergen challenge (1:2000 wt/vol); *AG2,* allergen challenge (1:200 wt/vol). **B,** Individual data for the net change from diluent challenge for each parameter after immersion of feet in 2 different conditions of water specified on the abscissa. *Solid horizontal bars* represent median values. *ROOM,* RW; *WARM,* WW; *NS,* not significant. **P* < .01 compared with RW.

.39), or nasal congestion (WW, 4.9 ± 0.9, vs RW, 6.1 ± 1.3; $P = .26$) but led to significant reductions in allergen-induced secretion weights (WW, 30.5 ± 7.2 mg, vs RW, 41.8 ± 6.8 mg; $P < .01$), sneezes (WW, 5.7 ± 1.1, vs RW, 11.6 ± 3.2; $P < .01$), and albumin levels (WW, 941.7 ± 172.2 μg/mL, vs RW, 1524.8 ± 220.6 μg/mL; $P < .01$).

DISCUSSION

Our results demonstrate that immersion of feet in WW causes a significant increase in nasal mucosal surface temperature without a significant change in body temperature or nasal secretion osmolality. These results are in agreement with Cole's study,[2] which showed that submucosal turbinate temperature rose approximately 2°C in response to a thermal stimulus to the body. The magnitude of the temperature rise in Cole's experiments is similar to our findings (1.9°C ± 0.1°C). The nasal mucosal temperature did not change in response to allergen challenge.

The nasal mucosa contains abundant vessels (eg, resistance vessels, capacitance vessels, exchange capillaries, and shunt vessels).[5] The arteriovenous anastomoses are considered to be specialized thermoregulatory organs both in the nose[6] and in the skin of the extremities.[7] The vessels in the nasal mucosa are innervated mainly by the sympathetic nervous system. The capacitance and resistance vessels possess α-receptors. Stimulation of these receptors leads to a decrease in blood flow by an increase

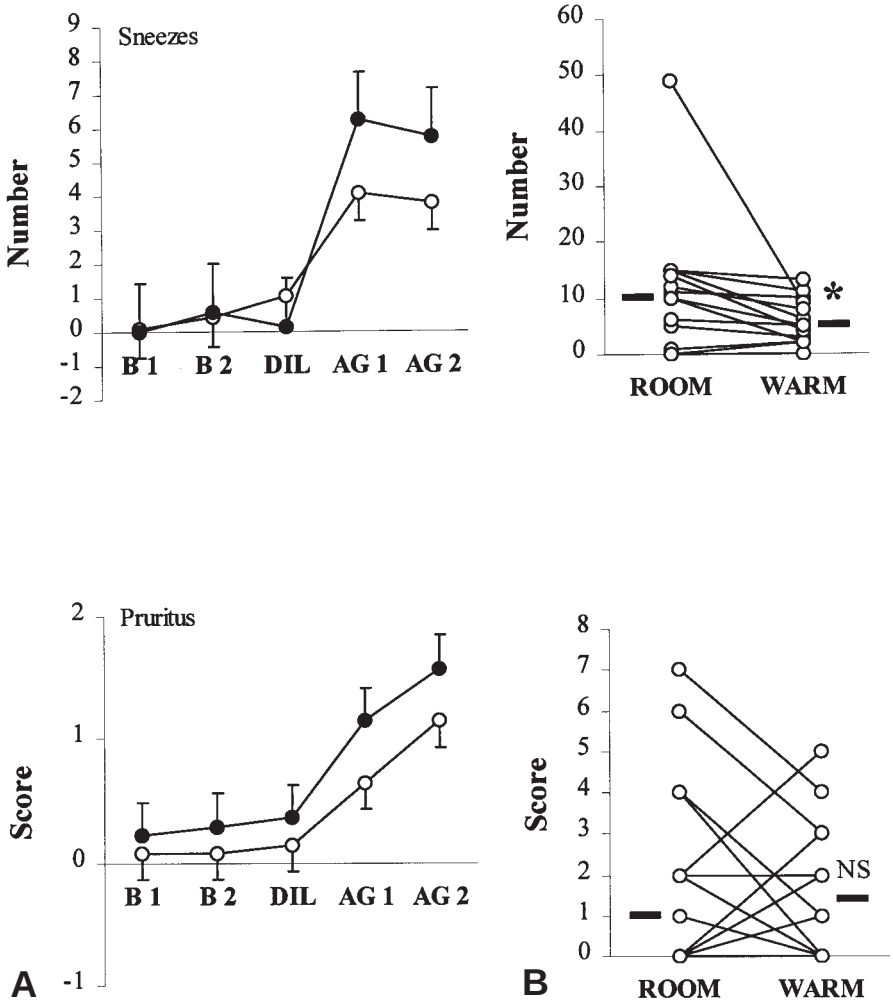

FIG 4. Neural response. **A,** Responses at each of the individual time points after immersion of feet in WW *(open circles)* or RW *(filled circles)*. Symbols and challenge protocol are identical to those in Fig 3. Data are means ± SEM for 14 subjects. **B,** Individual data for the net change from diluent challenge for each parameter after immersion of feet in 2 different conditions of water specified on the abscissa. *Solid horizontal bars* represent median values. *ROOM,* RW; *WARM,* WW; *NS,* not significant. **P* < .01 compared with RW.

in the precapillary resistance and a constriction of venules and capacitance vessels. Stimulation of the β_2-receptors leads to dilatation of the arterioles and the capacitance vessels.[8] The central vasomotor regulation is located in the hypothalamus,[9] which coordinates the responses to stimulation of peripheral and central thermoreception.

Vasomotor responses of the respiratory tract mucosa in response to thermal changes on the surface of the body were described long ago. The best known response is that of cooling the nape of the neck by wearing an ice pack and the resultant induction of a reflex vasoconstriction of blood vessels in the nasal mucosa. This maneuver has been used as an adjunctive treatment for epistaxis.

Human nasal mucosal blood volume has been shown to decrease with skin cooling[10] and to increase with skin warming.[11] These changes in volume were demonstrated by changes in nasal cavity volume, as assessed by acoustic rhinometry.[12,13]

Cole[14] demonstrated that when thermoelements were placed in the turbinate submucosa and on the skin of a finger, and adequate thermal stimuli were used, blood flow changes in the finger paralleled those in the turbinate mucosa, suggesting that turbinate vascular responses to remote thermal stimulation parallel those that occur in the extremities.

Drettner[15] found that the local temperature on the septal wall decreased rapidly during cooling of the feet with ice. The temperature of the nasal mucosa also decreased in response to cold stimulation on the skin of the back and feet[2,16,17] and increased in response to heat stimulation on various regions along the spine and body surface.[16] Simon[18] demonstrated that the nasal mucosal temperature and degree of swelling of the inferior nasal concha responded to caloric stimulation on the upper and lower extremities. These findings indicate a close reflex relationship between the nasal mucosa and the extremities.

Because of the rapidity of changes in both nasal

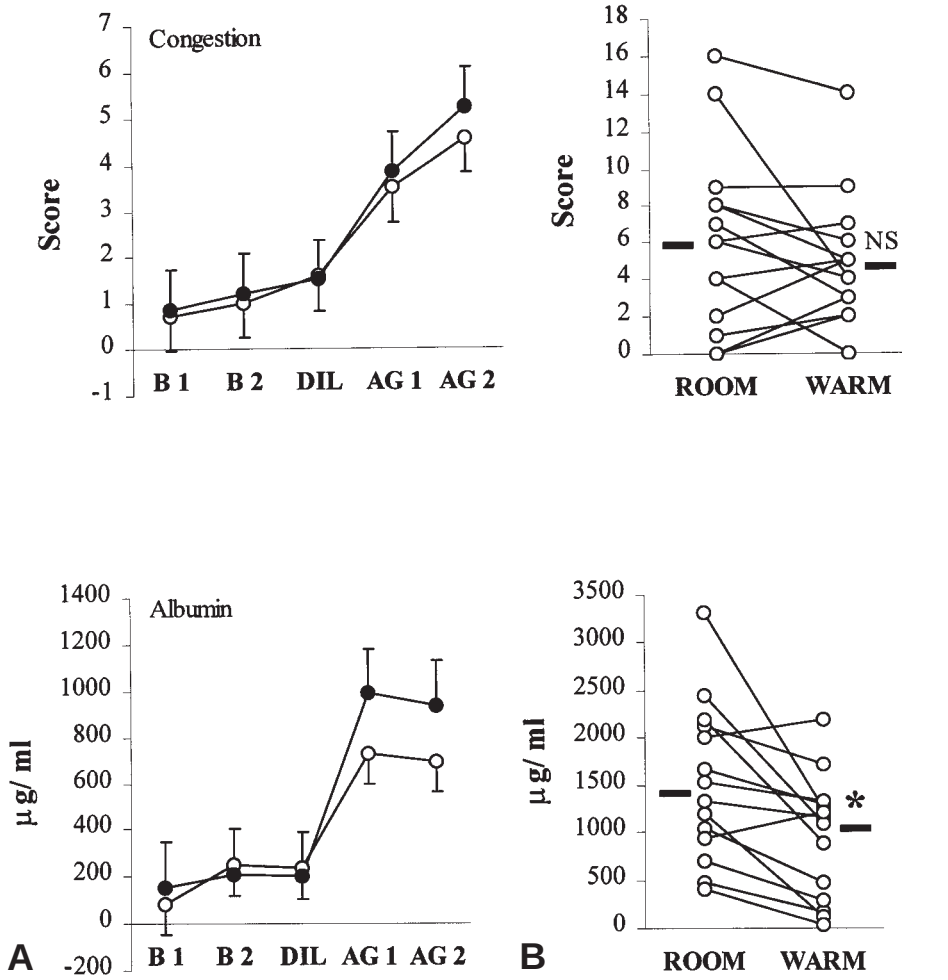

FIG 5. Vascular response. **A,** Responses at each of the individual time points after immersion of feet in WW *(open circles)* or RW *(filled circles)*. Symbols and challenge protocol are identical to those in Fig 3. Data are means ± SEM for 14 subjects. **B,** Individual data for the net change from diluent challenge for each parameter after immersion of feet in 2 different conditions of water specified on the abscissa. *Solid horizontal bars* represent median values. *ROOM,* RW; *WARM,* WW; *NS,* not significant. **P* < .01 compared with RW.

mucosal blood flow and nasal mucosal temperature in response to skin thermal change, the change in nasal mucosal temperature after skin thermal stimulation is probably mediated by neurovascular reflexes. Thermal stimulation of the skin of the feet produces a localized vasodilatation by loss of sympathetic neural activity of the vasoconstrictive α-adrenergic receptors of blood vessels. This change sends signals to the central vasomotor center in the hypothalamus and affects the regulation of vascular tone and blood flow to the nose. The resultant decrease in sympathetic neural activity causes passive vasodilatation of the nasal vascular bed and leads to an increase of nasal blood flow and temperature.[19] In our study we manipulated this system to study the effects on the early allergic reaction.

We compared the effect of immersion of feet in WW and RW on the early response to nasal challenge with allergen. Our results showed that immersion of feet in WW significantly inhibited allergen-induced sneezes, HSA levels, and secretion weights. The absence of an effect on symptoms possibly reflects the mild nature of the allergen challenge. Alternatively, the changes in the objective parameters were not of sufficient magnitude to impede the subjective measures of rhinorrhea, pruritus, and nasal congestion, or the subjects were insensitive in their perceptions.

Previous studies have demonstrated the beneficial effect of hot, humid air in patients with allergic rhinitis both during the season and after antigen provocation.[1,3,20-22] Inhaling hot, humid air through a face mask for 1 hour before and during an antigen challenge inhibited the secretory (secretion weights), neural (sneezes), and vascular (congestion score) responses after challenge.[23] We hypothesized that this inhibition could be the result of either an increase in nasal mucosal temperature or a reduction in the osmolality of the nasal secretion. Our data presented here suggest that raising the mucosal temperature can decrease the early allergic response.

Allergic reactions are triggered by the interaction between an allergen and a specific IgE bound to mast cells in the nasal mucosa. When stimulated, mast cells degranulate, with the subsequent release of histamine and other mediators. These mediators interact with neural elements, blood vessels, and mucosal glands to produce the physiologic responses associated with allergic rhinitis. Sneezing occurs through a reflex mechanism initiated by stimulation of H1 receptors on sensory nerves of the nasal mucosa, and the decrease in the number of sneezes after warming of feet may reflect a decrease in histamine release or a change in the sensitivity of nerves to released histamine. Albumin levels in nasal secretions, an indicator of increased vascular permeability, were reduced when feet were immersed in WW, reflecting either an indirect effect of reduced mast cell activation or a direct effect of increased mucosal temperature on the blood vessels. Other mediators that alter vascular permeability, such as prostaglandins, leukotrienes, and bradykinins, could have been affected. Furthermore, decreased glandular activation, as reflected by the reduced secretory response, may also be the result of reduced mast cell activation or decreased end organ response.

The mechanism by which increasing the nasal mucosal temperature reduces the early allergic response has not been defined. There are several possible explanations. One of these is that an increase in nasal mucosal temperature can decrease histamine release from mast cells. The nasal mucosal temperature under normal ambient conditions is between 30.4°C during inspiration and 32.0°C during expiration[24]; therefore the optimal temperature for nasal mucosal mast cells may be between 30°C and 32°C. An increase in nasal mucosal temperature above this optimum range may reduce histamine release. In support of this concept, there is in vitro evidence that temperatures of 40°C can reduce both mast cell[25] and basophil[26] histamine release. The mechanism by which increased temperature reduces mast cell degranulation is unknown. Histamine release from mast cells is a temperature-dependent enzymatic reaction; thus inactivation of enzymatic activity is a possibility.

Moreover, Dorrington and Bennich[27] found that the Fc portion of IgE is particularly temperature sensitive. The ability of IgE to bind to the membrane of basophils and mast cells is progressively lost with increasing temperature. Therefore increased temperature might affect IgE binding because of thermally induced structural changes, but so far this has been described only at 56°C, which is much higher than the increased nasal mucosal temperature observed in our experiment.

The production of cytokines from activated human mononuclear cells was found to be reduced at 39°C.[28] It is possible that increased temperature reduces cytokine production in the nose and subsequent intercellular communication. However, this would probably not affect the immediate response.

Increased temperature has also been shown to induce the formation of heat shock proteins (HSPs).[29] One of the current hypotheses for the pathogenesis of allergic rhinitis includes an increased expression of tachykinins either by their increased production or by reduced metabolism.[30] Substance P, one of the tachykinins, is a neuropeptide with proinflammatory effects that can increase vascular permeability, neutrophil adhesion and chemotaxis, mucus secretion, and smooth-muscle contraction. It exerts its effects by binding with substance P–receptor protein coupled to a glucose-regulated protein (GRP). GRP78, a member of the HSP70 family, was found to bind with low affinity to substance P receptor during purification.[31] Interaction between GRPs/HSPs and substance P may modify substance P activity and affect allergic inflammation. There also is evidence that HSP induces a gradual decrease in cellular responses to allergen[32] and can reduce allergic inflammation by modulation of steroid-receptor activity.[33]

Hastie et al[34] found that HSP27 was increased significantly in bronchial epithelium from subjects who had allergic rhinitis, with mild inflammatory responses after allergen challenge, and that there was little H_2SO_4–induced ciliary dysfunction at pH 5. This indicates that mild inflammation in response to allergen elevates HSP27 stress protein levels, thereby potentially protecting epithelial function from additional adverse conditions. HSP induced by increased nasal mucosal temperature may have a role in protecting the nasal epithelium from allergic inflammation. Further studies are needed for clarification of this mechanism and exclude the possibility that raising the temperature was unrelated to the mechanism for the reduction of the allergic response.

We have shown that increasing the nasal mucosal surface temperature by immersing feet in WW partially decreases the immediate nasal response to antigen challenge. This observation may better explain the effects of change in the external thermal environment on allergic inflammation.

REFERENCES

1. Jankowski R, Kagey-Sobotka A, Proud D, Lichtenstein LM, Baroody FM, Naclerio RM. Hot, humid air partially decreases the response to nasal challenge with antigen. Am J Rhinol 1995;9:241-5.
2. Cole P. Respiratory mucosal vascular responses, air conditioning and thermoregulation. J Laryngol 1954;68:613-22.
3. Desrosiers M, Baroody FM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Treatment with hot, humid air reduces nasal response to allergen challenge. J Allergy Clin Immunol 1997;99:77-86.
4. Chung JH, Detineo 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.
5. Malm L. Resistance and capacitance vessels in the nasal mucosa. Rhinology 1975;13:84-9.
6. Cauna N. The fine structure of the arteriovenous anastomosis and its nerve supply in the human nasal respiratory mucosa. Anat Rec 1970;168:9-22.
7. Folkow B, Neil E. Circulation. London: Oxford University Press; 1971. p. 448-65.
8. Anggard A, Lundberg JM, Lundblad L. Nasal anatomic innervation with special references to peptidergic nerves. Eur J Respir Dis 1981;64(Suppl 128):143-8.
9. Eccles R, Lee RL. The influence of the hypothalamus on the sympathetic innervation of the nasal vasculature of the cat. Acta Otolaryngol (Stockh) 1981;91:127-34.

10. Olsson P, Bende M. Influence of environmental temperature on human nasal mucosa. Ann Otol Rhinol Laryngol 1985;94:153-5.
11. White MD, Cabanac M. Nasal mucosal vasodilatation in response to passive hyperthermia in humans. Eur J Appl Physiol 1995;70:207-12.
12. Yamagiwa M, Hilberg O, Pedersen OF, Lundqvist GR. Evaluation of the effect of nasal cooling on nasal airway volume by acoustic rhinometry. Am Rev Respir Dis 1990;141:1050-4.
13. Lundqvist GR, Pedersen OF, Hilberg O, Nielsen B. Nasal reaction to changes in whole body temperature. Acta Otolaryngol (Stockh) 1993;113:783-8.
14. Cole P. Modification of inspired air. In: Proctor DF, Andersen IB, editors. The nose. Oxford: Elsevier Biomedical Press; 1982. p. 366.
15. Drettner B. Vascular reactions of the human nasal mucosa on exposure to cold. Acta Otolaryngol 1961;166:1-109.
16. Spiesman IG. Vasomotor reactions of the mucosa of the upper respiratory tract to thermal stimuli. Am J Physiol 1936;115:181-7.
17. Ralston HF, Kerr WMJ. Vascular responses of the nasal mucosa to thermal stimuli with some observations on skin temperature. Am J Physiol 1945;144:305-10.
18. Simon H. The nose as reacting organ to thermal skin irritations. Laryngol Rhinol Otol (Stuttg) 1980;59:808-19.
19. Grayson J. Responses of the microcirculation to hot and cold environments. In: Schonbaum E, Lomax P, editors. Thermoregulation: physiology and biochemistry. New York: Pergamon Press; 1990. p. 221-34.
20. Yerushalmi A, Karman S, Lwoff A. Treatment of perennial allergic rhinitis by local hyperthermia. Proc Natl Acad Sci U S A 1982;79:4766-9.
21. Ophir D, Elad Y, Fink A, Fischler E, Marshak G. Effects of elevated intranasal temperature on subjective and objective findings in perennial rhinitis. Ann Otol Rhinol Laryngol 1988;97:257-63.
22. Ophir D, Elad Y, Dolev Z, Geller-Bernstein C. Effects of inhaled humidified warm air on nasal patency and nasal symptoms in allergic rhinitis. Ann Allergy 1988;60:239-42.
23. Baroody FM, Assanasen P, Chung J, Naclerio RM. Hot, humid air partially inhibits the nasal response to allergen [abstract]. J Allergy Clin Immunol 1998;101:96.
24. Willatt DJ. Continuous infrared thermometry of the nasal mucosa. Rhinology 1993;31:63-7.
25. Mongar JL, Schild HO. Effect of temperature on the anaphylactic reaction. J Physiol (Lond) 1957;135:320-38.
26. Middleton E, Shermen WR, Fleming W, Van Arsdel PP. Some biochemical characteristics of allergic histamine release from leukocytes of ragweed-sensitive subjects. J Allergy 1960;31:448-54.
27. Dorrington KJ, Bennich H. Thermally induced structural changes in immunoglobulin E. J Biol Chem 1973;248:8378-84.
28. Dinarello CA, Dempsey RA, Allergratta M, et al. Inhibitory effects of elevated temperature on human cytokine production and natural killer activity. Cancer Res 1986;46:6236-41.
29. Kaufman SHE. Heat shock proteins and the immune response. Immunol Today 1990;11:129-36.
30. Dusser DJ, Djokic TD, Borson DB, Nadel JA. Cigarette smoke induces bronchoconstrictor hyperresponsiveness to substance P and inactivates airway neutral endopeptidase in the guinea pig. J Clin Invest 1989;84:900-6.
31. Oblas B, Boyd ND, Luber-Narod J, Reyes VE, Leeman SE. Isolation of the polypeptide in the HSP70 family that binds to substance P. Biochem Biophys Res Commun 1990;166:978-83.
32. Binaghi RA, Demeulemester C. Influence of the medium on the heat and acid denaturation of IgE. J Immunol Methods 1983;65:225-33.
33. Sanchez ER. HSP56: a novel heat shock protein associated with untransformed steroid receptor complexes. J Biol Chem 1990;265:22067-70.
34. Hastie AT, Everts KB, Zangrilli J, et al. HSP27 elevated in mild allergic inflammation protects airway epithelium from H2SO4 effects. Am J Physiol 1997;273:L401-9.