

Observations on the ability of the nose to warm and humidify inspired air*

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SUMMARY

The major function of the nose is to warm and humidify air before it reaches to the lungs for gas exchange. Conditioning of inspired air is achieved through evaporation of water from the epithelial surface. The continuous need to condition air leads to a hyperosmolar environment on the surface of the epithelium. As ventilation increases, the hyperosmolar surface moves more distally, covering a larger surface area of the airway, and stimulates epithelial cells to release mediators that lead to inflammation. This inflammation is not identical to allergic inflammation, but causes both short-term and long-term changes in the epithelium. In the short term, it increases paracellular water transport in an attempt to enhance conditioning, and it stimulates sensory nerves to initiate neural reflexes. It also disrupts channels in the cellular membrane, which might permit greater penetration of foreign proteins, such as allergens, leading to further inflammatory cascades. The long-term inflammation induced over time by the hyperosmolar milieu could worsen the ability of the nose to condition air, requiring more of the conditioning to occur in the lower airway and leading to adverse consequences for the respiratory system.

Key words: humidity, nose, allergic rhinitis, temperature, water transport

Adults condition more than 14,000 liters of air per day; this requires more than 680 grams of water, approximately 1/5 of our adult daily water intake⁽¹⁾. The mechanisms, by which the nose conditions inspired air and how this ability is altered in patients with allergic rhinitis and asthma, are the subject of this review.

Water transport: a fundamental biological process

The regulation of the transport of water across biological membranes is fundamental to the maintenance of homeostasis between bodily fluid compartments, to the preservation of organisms under adverse conditions, and, indeed, to life itself⁽²⁾. Higher organisms could not exist without epithelial barriers that separate the internal and external milieus. To separate these compartments, cell membranes are composed of lipid bilayers that are relatively impermeable to ions. Therefore, to facilitate biological processes, ions must cross these membranes or pass between cells to exert their effects.

Membrane proteins known as ion channels, pumps, and transporters mediate water transport. Ion channels enable rapid passive movement of selected ions across cell membranes. More than 100 families of channel-forming proteins/peptides exist in prokaryotes and eukaryotes⁽³⁾. Transcellular transport through specific membrane pumps and channels actively generates

electro-osmotic gradients that are critical for a variety of cellular functions⁽⁴⁾. Tight junctions, located between cells, are the main routes for passive ion permeation. Inflammatory mediators, such as histamine, can alter tight junctions, allowing macromolecules to pass from the external to the internal environment^(5,6).

Aquaporins and channelopathies

Besides the classic Na⁺ and Cl⁻ ion transporters, other proteins can be involved in water transport, such as the glucose transporter, the c-AMP-activated cystic fibrosis transmembrane conductance regulator, the urea transporter UT3, and multiple Na⁺-solute cotransporters. Aquaporins (AQs), a family of small membrane-spanning proteins, are expressed in plasma membranes of many cell types involved in fluid transport⁽⁷⁾. The expression of many AQs is functionally significant for movement of water across cell membranes. Interestingly, they respond to osmotic gradients, and their activity is generally measured by an osmotic swelling assay⁽⁸⁾. Mutation in the AQP2 water channel causes the rare non-X-linked form of hereditary nephrogenic diabetes insipidus⁽⁹⁾ and shows the requirement of the human renal water channel aquaporin-2 for vasopressin-dependent concentration of urine⁽⁹⁾. Aquaporins have been implicated in respiratory disease. For example, AQP1, -4, and -5 are expressed in lung tissue. Transgenic aqua-

porin knockout mice with targeted gene disruption in AQP1 and AQP5 have very low lung water permeability⁽²⁾. Additionally, AQP-5-deficient mice have been shown to show bronchial hyperreactivity⁽¹⁰⁾. These data implicate water transport in related respiratory disease in the lower airway, which may also characterize the upper airway.

Channelopathies, diseases that result from defects in ion channel function, are being discovered with increasing frequency. Channelopathies arise through a number of mechanisms, such as mutations in the promoter and coding region of ion channel genes, defects in genes encoding molecules that regulate channel function, or the development of autoantibodies to channel proteins that inhibit their function. Additionally, many drugs and mediators such as phosphodiesterase inhibitors, nitric oxide, VIP, and leukotrienes have effects on ion channels, affording another mechanism by which they can develop acquired or secondary dysfunctions that can cause disease⁽¹¹⁾. Many diseases also have secondary effects on ion channel activity, for example, maturity-onset diabetes. Hence, the role of water transport proteins and ion channels is relevant to a number of diseases through a wide variety of mechanisms.

The epithelial barrier function and beyond

There is growing evidence that the respiratory epithelium has a number of functions in addition to its role as a barrier between the internal and external environments. It produces multiple cytokines that participate in airway inflammation, such as granulocyte macrophage colony-stimulating factor, for which the epithelium is the principal source⁽¹²⁾. The epithelium also makes metalloproteases that may be involved in airway remodeling⁽¹³⁾. Holgate hypothesized that a primary defect in the epithelium, which causes abnormal responses to various stimuli and cannot undergo the normal repair process, is responsible for asthma⁽¹⁴⁾. The epithelium is also now recognized as a critical component of the innate immune system.

Epithelial defects may be secondary to chronic inflammation. To illustrate this point, an analogy can be drawn to inflammatory bowel disease. In the gut of patients with this disorder, inflammation affects water transport and leads to diarrhea⁽¹⁵⁾. For years, the mechanism postulated to underlie the diarrhea was an inflammation-induced increase in secretions. We now know that the diarrhea is actually caused by increased production of interferon, which diminishes absorption of Na⁺. This is an example of the interaction between inflammation and epithelial water/ion transport that can cause disease.

Another component of epithelial function is nasal mucociliary transport, an important factor in heat and water exchange and protection of the mucosal interface. This process requires an aqueous periciliary fluid layer of a height that allows cilia to move the viscoelastic mucus on its surface. Too much or too little periciliary fluid leads to ineffective mucociliary transport,

which can lead to disease. For example, dryness leads to increased bacterial adherence and is believed to play a role in the development of sinusitis.

How might these processes be affected to cause disease in the upper and lower airway? A number of studies have suggested that decreased water transport in the upper airway causes conditioning to occur lower in the airway. McFadden and colleagues showed that air not fully conditioned by the nose will have to be conditioned further by the lower airway⁽¹⁶⁾. Annensi et al. showed that subjects reporting nasal sensitivity to cold dry air (CDA) had a more rapid decline in FEV₁ over five years compared to those without such sensitivity⁽¹⁷⁾. Inhalation of the same volume of dry air through the mouth, in contrast to the oronasal route, causes a greater reduction in FEV₁ in asthmatic subjects^(18,19). Moreover, prolonged repeated exposure of the airways to inadequately conditioned air can induce inflammation in the lower airways⁽²⁰⁾, the penultimate example being the changes that occur in the trachea after a total laryngectomy.

Dehydration injury of the epithelium includes epithelial desquamation, leukocyte infiltration, vascular leakage, and mast cell degranulation, all of which can worsen inflammation. Furthermore, a change of the epithelium from ciliated to squamous nonciliated leads to a further decrease in its ability to transport water. Hence, the study of nasal conditioning has both a fundamental basis in the critical function of water transport, an important relationship to inflammation, and direct clinical relevance to a variety of diseases, including those of the upper and lower airway.

Models of nasal conditioning

We have been interested in understanding nasal function in health and disease. Toward this goal, we have developed several *in vivo*, human models of nasal function. We have consistently used the relevant organ in the relevant species to address questions about the mechanisms that underlie nasal air conditioning.

Nasal provocation with cold, dry air

We were interested in studying the mechanism by which the inhalation of cold, dry air induces rhinorrhea. We reasoned that the inhalation of dry air caused drying of the nasal mucosa and creation of a hyperosmolar milieu, which can activate mast cells *in vitro*, leading to mediator release and subsequent symptoms⁽²¹⁾.

We thus allowed subjects to breathe CDA and monitored the subsequent response by scoring symptoms and measuring the levels of mediators in nasal lavage. CDA resulted in an increase in symptoms compared to baseline and in the release of inflammatory mediators. The pattern of these recovered mediators suggests that mast cells participate in this nasal reac-

tion. Because the early response to CDA produces the same pattern of mediator release, as does the early response to antigen, we asked whether a late-phase reaction follows the response to CDA. In fact, significantly more symptoms and higher histamine and TAME levels (a marker of vascular permeability) than in control exposures were recovered in the first ten hours after CDA, showing a late inflammatory response⁽²²⁾. Additionally, epithelial cells in the lavage fluid were found in increased numbers compared to those in appropriate controls, suggesting that tight junctions are disrupted⁽²³⁾.

We then undertook several studies to establish a mechanism for mast cell activation. To address the hypothesis that the hyperosmolar milieu generated by the drying of the nasal mucosa stimulated the release of mast cell mediator, we followed two directions: we evaluated the effect of nasal mucosal provocation with a hyperosmolar stimulus, and we attempted to determine changes in the osmolality of surface secretions after CDA challenge.

Healthy human volunteers underwent nasal challenge with isosmolar and hyperosmolar mannitol solutions. We found that hyperosmolar challenge caused histamine and leukotriene C4 release⁽²⁴⁾. Dose-response curves between increasing osmotic loads and histamine recovery in lavage fluids were obtained. We concluded that hyperosmolar stimuli cause histamine release *in vivo*, possibly from mast cells.

Although a spectrum of responsiveness to CDA probably exists in the general population, we were able to select both individuals who respond and those who do not respond to the CDA challenge, based on the presence or absence of a typical history of nasal symptoms upon exposure to a cold and windy environment. This criterion has a specificity of 94% in selecting a CDA responder. To assess whether the reactivity to hypertonic loads of the two extreme groups differs, we challenged 11 CDA responders and 19 non-responders with isosmolar and hyperosmolar mannitol solutions⁽²⁴⁾. The results indicated that CDA responders released more histamine in their nasal secretions after hyperosmolar provocation than did CDA non-responders, possibly because of impairment of water transportation across the mucosa.

The second approach to linking hyperosmolarity to the CDA-induced response involved measurement of the osmolality of nasal secretions after CDA challenges. We initially measured the osmolality of returned lavage fluids (25). In each of 9 CDA responders, this index was increased after CDA challenge, compared to baseline, from 288 ± 3 to 306 ± 5 mOsm/kg H₂O ($p < 0.01$). In contrast, the returned-fluid osmolality of six CDA non-responders did not differ from baseline. Significant correlations were found between mediator concentrations and the osmolality of recovered lavages ($r_s = 0.617$, $p < 0.02$; $r_s = 0.679$, $p < 0.01$ for histamine and TAME, respectively). As a

control, we measured the osmolality of nasal secretions obtained after allergen challenge of atopic individuals and found no significant changes. These studies provided the first evidence in human subjects that inhalation of CDA increased the osmolality of respiratory secretions. Although the changes were statistically significant and different from those in appropriate controls, the increments in osmolality were small, most likely secondary to the dilutional effect of the isosmolar saline lavage used for collecting secretions. We sought, therefore, to measure the osmolality of surface secretions directly.

We collected secretions directly from the mucosas of CDA-sensitive individuals with filter paper discs before and after challenge. The limitation of this method was that, except on rare occasions, we could not obtain a sufficient volume of nasal secretions at baseline to perform osmolality measurements. We therefore chose to compare the osmolality of CDA-induced secretions to that of methacholine- and histamine-induced secretions. Because CDA non-responders have little or no secretion on their mucosal surface after CDA challenge, only CDA responders were evaluated with these protocols⁽²⁵⁾. The osmolality of nasal secretions (mOsm/kg H₂O) (mean \pm SEM; $n = 8$) after provocation with CDA was 381 ± 5.6 ; with methacholine, 337 ± 3.5 ; and with histamine, 315 ± 3.1 . Histamine, which, in addition to glandular stimulation, induces vascular permeability, resulted in the lowest osmolality. In contrast, methacholine, a glandular secretagogue, produced slightly hyperosmolar secretions. Cold, dry air led to significantly higher osmolality compared to either methacholine or histamine ($p < 0.05$), confirming our hypothesis that the osmolality of nasal secretions is increased after inhalation of CDA. These data also suggest that nasal glandular secretions are hyperosmolar. This finding is in agreement with the data of Mann and colleagues in dogs⁽²⁶⁾. More importantly, these combined observations were consistent with our overall hypothesis that individuals vary in their ability to condition air, and those with the least ability to condition air develop hyperosmolar secretions and a clinical response to CDA inhalation.

The model used in the above experiments involves the inhalation of air through the nose and exhalation through the mouth. Strohl and colleagues showed that the inhalation of air through the nose and exhalation through the mouth induced an increase in nasal airway resistance, but when the same subjects inhaled and exhaled air through the nose, their airway resistance did not increase⁽²⁷⁾. They interpreted their experiment to imply that the pattern of breathing influences the response, and that the recovery of heat during expiration prevents the response. This work appeared to negate our studies.

To address this concern, we performed experiments in which we assessed the response of subjects to CDA when it was both inhaled and exhaled through the nasal cavity⁽²⁸⁾. In contrast to Strohl, we performed our experiments in 10 subjects who gave

a history of clinical sensitivity to cold, windy environments and who had previously responded to our standard CDA challenge. The subjects were randomized to breathe either CDA or warm moist air (WMA) in and out through the nose for 45 minutes during two separate visits. The total change in secretion weight from baseline after the CDA exposure was 30 ± 10 mg compared to 0 ± 1 mg for WMA, the difference being highly significant ($p < 0.009$). During the WMA challenge, the levels of histamine and TAME esterase did not change significantly from baseline. In contrast, after breathing of CDA, there was a significant increase ($p < 0.01$) from baseline in the levels of both histamine (3.9 ± 1.2 to 10.6 ± 2.7 ng/ml) and TAME (3.8 ± 1.4 to 4.6 ± 1.6 cpm). Although significantly increased, these levels did not change to the extent of those reported previously when the subjects inhaled the CDA through the nose and exhaled it through the mouth. This difference was anticipated based on the reduction of the stimulus, the amount of air to be conditioned. The fact that there was a significant change implies that the nasal mucosa does respond to conditioning CDA even though there is an estimated 30% recovery during exhalation. We believe that our protocol of breathing in through the nose and out through the mouth represents a means to augment the stimulus so that it is easier to study it. An analogy is that the inhalation of air with 5% CO₂ at 140 liters through the mouth while seated wearing nose clips serves as a model of exercise-induced asthma.

We then switched our focus from studying the mechanism of the CDA response to measuring the mechanics of the ability of the nose to condition air by using a nasal probe as our model.

Development of a nasal probe

The nose functions to warm and humidify air from ambient conditions that range from temperatures of -42 to 48°C and relative humidities from 0 to 100%⁽²⁹⁾. Nasal conditioning occurs from a resting ventilation of approximately 5 liters per minute (l/min) to sustained flow rates of 20 to 30 l/min before nasal breathing is supplemented with oral breathing. We reasoned that, if we could measure the temperature and relative humidity of inhaled air at the nasal inlet and then in the nasopharynx, we would be able to calculate the water content of the air at these two locations. The posterior (nasopharynx) measurements sample the airstream immediately after it exits the nose, thus providing information regarding the end results of nasal function. The difference between these contents (nasal inlet and nasopharynx) represents the amount of water invested by the nose into inhaled air, a good reflection of the conditioning capacity of the nose. Furthermore, because there is strong evidence that exhaled air is fully saturated, it would be necessary only to measure conditioning after inhalation⁽²⁹⁻³²⁾. We therefore developed a probe for measuring the temperature and humidity of inhaled air within the nasopharynx and a similar one for measuring the same parameters at the nasal inlet.

In a typical experiment, one of the patient's nostrils was decongested and anesthetized with oxymetazoline and lidocaine, and the probe was inserted through that nostril and positioned such that the tip of the probe bearing the temperature and humidity sensors was suspended in the nasopharynx, sampling air exiting the nasal cavities. This was confirmed by nasal endoscopy. That nostril was then occluded with a wax plug, and the other nasal cavity was exposed to air of different temperatures and humidities via a mask applied over the nose. The patients were instructed to breathe through their mouth while air was blown continuously and unidirectionally through the nose at flow rates of 5, 10, and 20 l/min. The temperature and humidity of the inhaled air were continuously sampled via a similar sensor placed in the mask at the inlet of the nasal cavity. This experimental design permitted the development of steady-state conditions that were easily measurable by the probe and circumvented the potential problems associated with exhalation.

The nostril used as a conduit for the probe was not studied, because pre-medication of that nostril (to facilitate insertion of the probe) as well as probe-induced distortions of airflow patterns within the nostril could interfere with the conditioning function of that nostril. Thus, sensors were placed at the nasal inlet and in the nasopharynx, and they sampled air entering and exiting the open, non-manipulated nostril, allowing us to evaluate the conditioning capacity of that nostril. The range of flow rates from 5 to 20 l/min spans flows at rest to values at which most individuals switch from nasal to oronasal breathing. It should also be noted that air blown unidirectionally prevents air exiting from the lung at 37°C and 100% RH from condensing on the probe and interfering with sampling in the nasopharynx. The duration of air sampling in the mask and nasopharynx was 22 min, with data collected only during the last 15 min of each challenge used for analysis. The initial 7-minute period of each challenge was disregarded because it reflects the time necessary for the temperature in the nasopharynx to reach a steady state.

To ensure that the probe sensors retained an adequate response time when positioned in the nasopharynx, the subjects forcefully inhaled room air through the nose with the mouth closed. This maneuver created an airflow transiently exceeding 100 l/min. A rapid change in both temperature and RH readings during the sniffs reflected adequate calibration and response times for the studies presented here. Subjects were asked to breathe room air and perform the "sniff" test periodically during the experiments to ensure proper functioning of the probe.

The nasopharyngeal temperatures at 5, 10, and 20 l/min for all subjects during exposure to CDA were $33.4 \pm 0.7^\circ\text{C}$, $30.5 \pm 1.1^\circ\text{C}$, and $25.9 \pm 1.4^\circ\text{C}$, respectively. The temperature fell sig-

nificantly with increasing flow rates ($p = 0.0001$). Post-hoc analysis of the nasopharyngeal temperatures obtained at different flow rates showed a statistically significant difference between the temperatures obtained at 5 l/min compared to those obtained at both 10 and 20 l/min ($p < 0.05$), as well as a significant difference between temperatures obtained at 10 l/min compared to 20 l/min ($p < 0.05$). Furthermore, nasopharyngeal temperatures during exposure to CDA were consistently lower than those during exposure to WMA at each flow rate ($p < 0.01$).

Individuals showed a wide variability in their ability to condition air, but the RH of air in the nasopharynx was consistently at 100%, irrespective of the temperature and RH of the inhaled air. There was no correlation among nasal airway resistance or nasal volume obtained prior to challenge, nasopharyngeal temperature, and the slight variability in body temperature. Proctor, in discussing the wide variability among individuals, speculated that prior viral infections may have altered the epithelium, thus producing the variability⁽²⁹⁾. As mentioned below, we think that heritability plays a role in this variability.

Because the temperature and RH of inhaled air as well as air exiting the nasal cavity into the nasopharynx were known, we were able to calculate their respective water contents and subsequently the water gradient (WG) between inhaled and conditioned air. The WG represents the amount of water invested by the nasal mucosa to condition inspired air. After exposure to CDA, the WG at 5, 10, and 20 l/min. was 297.6 ± 12.6 mg, 509.1 ± 32.0 mg, and 794.1 ± 62.1 mg, respectively, showing a statistically significant increase in the amount of water generated by the nose for conditioning inspired air with increasing air flow rates. The reproducibility of the nasal response to conditioning CDA was studied in 8 nonallergic subjects on 3 separate visits. During all three visits, there were flow-dependent significant increases in the water gradient across the nose. After exposure to CDA the difference in mean total water gradient (TWG) values for the three visits was not statistically significant ($p = 0.56$). The coefficient of variation in % (standard deviation/mean $\times 100\%$) of the TWG obtained during the three visits ranged between 5.1% and 33.8% and averaged 14.7%.

Once we were confident in our ability to measure the conditioning capacity of the nose in a reliable and reproducible fashion, we turned our attention to investigating factors that might influence this conditioning capacity by contributing to the amount of water delivered to inspired air. Among these, the geometry of the nasal cavity and the temperature of the nasal mucosa appear to be key⁽³³⁾. Therefore, we first studied the effects of raising the nasal mucosal surface temperature by immersion of the feet in warm water. This technique was based on observations in 1954 by Cole, who showed that the nasal mucosal temperature rose approximately 2°C when a fan

blew heat from an open flame onto the dorsal skin of subjects⁽³⁴⁾. This increase occurred without a concurrent increase in the body core temperature.

Studies of the microcirculation of skin and its contribution to heat exchange predict that the increase in nasal mucosal temperature after external thermal stimulation is secondary to a neural reflex⁽³⁵⁾. Our method of heating the feet by immersion in a warm water bath reproduced that of Cole. Six subjects were randomized to immersion of the feet in 30°C and then 40°C water, and their nasal mucosal temperature was measured by gentle application of the temperature sensor against the nasal mucosa (36). The nasal mucosal temperature increased significantly, to $32.2 \pm 1.3^\circ\text{C}$ after immersion of feet in 30°C water and to $33.1 \pm 1.2^\circ\text{C}$ after immersion of feet in 40°C water ($p < 0.05$). There was no concomitant change in nasal volume, as measured by acoustic rhinometry, between the two exposure groups (30°; 17.8 ± 4.5 cc; 40°; 17.7 ± 5.3 cc). There was a significant increase in the conditioning capacity of the nose in response to cold-air challenge during the 40°C immersion (1669 ± 312 mg water) when compared to the 30°C immersion (1324 ± 152 mg water) ($p < 0.05$). From these data, we deduced that warming the nasal mucosa improves the ability of the nose to condition inspired air without a concomitant change in the volume of the nasal cavity. These findings are consistent with the theoretical model of heat and water vapor transport across the nose developed by Hanna, and they support the accuracy of our setup for measuring nasal air conditioning⁽³⁷⁾.

Effect of allergic inflammation on the ability of the nose to condition inspired air

After establishing our ability to measure nasal conditioning, we studied the effect of allergic inflammation on that function. In prior studies, asymptomatic subjects with seasonal allergic rhinitis outside their season showed no alteration in their nasal functions and in their indices of inflammation when compared to normal subjects. Therefore, we first compared the nasal conditioning capacity of these 2 groups. The response to inhalation of CDA was compared between 11 nonallergic subjects and 22 allergic subjects out of season. Allergic subjects had significantly lower nasopharyngeal temperatures than did nonallergic subjects at 5 l/min ($31.7 \pm 0.5^\circ\text{C}$ vs $34.6 \pm 0.9^\circ\text{C}$, $p = 0.0004$) and 10 l/min ($28.2 \pm 0.5^\circ\text{C}$ vs $32.2 \pm 1.5^\circ\text{C}$, $p = 0.003$). Comparing allergic to nonallergic subjects, there was a significant difference in WG values obtained at 5 and 10 l/min as well as in the TWG (Figure 1). The reason for the difference was not apparent.

To examine the effect of allergic inflammation, we studied the ability of seasonal allergic subjects to condition air in and out of their allergy season. We selected 10 individuals with seasonal allergic rhinitis and measured their ability to warm and humidify air before the ragweed season and then slightly past

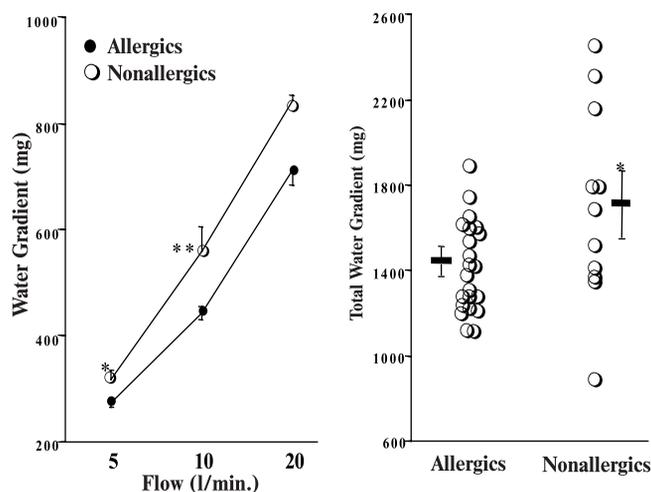


Figure 1. Comparison of the response to CDA exposure of allergic subjects out of season (n=22) and nonallergic (n=11) subjects. The left panel demonstrates the mean \pm SEM of the water gradient across the nose at each of the exposure flow rates used. Closed circles represent the response of the allergic subjects and open circles that of the nonallergic subjects. The right panel depicts the total water gradient across the nasal cavity for all three flow rates of CDA. Solid bars represent mean \pm SEM of the individual data points. *p < 0.05 and **p < 0.01 vs allergic subjects.

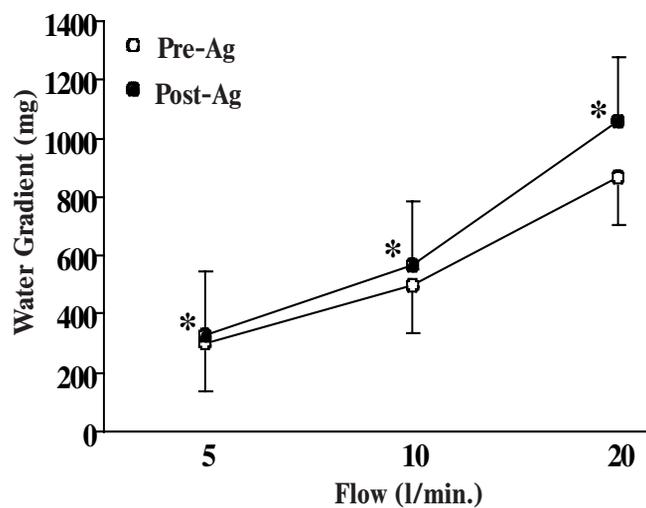


Figure 2. Comparison of the response to CDA exposure of allergic subjects out of season (n=20) before (open circles) and 24 hours after (closed circles) allergen challenge. The graph depicts mean \pm SEM of water gradient expressed in mg across the nose at each of the exposure flow rates used. *p < 0.05 vs pre-antigen.

the pollen peak. The TWGs before vs. during the season were 1523 ± 315 vs. 2050 ± 438 mg ($p < 0.01$)⁽³⁶⁾. Therefore, the presence of allergic inflammation improved the ability of the nose to condition air.

For better control of the factors that could be responsible for this change, we initiated a trial involving nasal challenge with antigen⁽³⁸⁾. Twenty subjects with seasonal allergic rhinitis were

investigated outside their season. We measured their ability to condition air before and 24 hours after challenge. We quantitated the degree of inflammation by counting eosinophils, measuring the level of albumin in nasal lavages, and recording symptoms. Twenty-four hours after allergen challenge, there was an increase in the number of eosinophils and in the level of albumin in recovered nasal lavages. As in the seasonal study, allergic inflammation increased the ability of the nose to condition inspired air (Figure 2). There was no significant relationship between the indices of allergic inflammation that we assessed and the change in conditioning capacity.

Changing nasal volume

Allergic rhinitis is consistently associated with nasal congestion, which results from pooling of blood in the cavernous sinusoids and a subsequent decrease in nasal volume. Therefore, an allergen-induced increase in nasal congestion seems like a logical explanation of the increase in the conditioning capacity of the nose observed in allergic inflammation.

We tested the hypothesis that increasing nasal congestion improves nasal air conditioning. We performed a randomized, 2-way crossover study on 6 healthy subjects to investigate the effect of decreased nasal volume, induced by placement of subjects in the supine position, on the conditioning capacity of the nose⁽³⁹⁾. Subjects underwent nasal conditioning measurement in both upright and supine positions at each visit. The order of which position was first and which was second was randomly assigned, and, on the second visit, the order was reversed. The same technique as detailed above was used for measurement of the conditioning capacity of the nose in response to a CDA stimulus, and acoustic rhinometry was used for assessment of nasal patency. The nasal volume decreased significantly from baseline without a change in the mucosal temperature when subjects were placed in the supine position ($p < 0.01$). The TWG in the supine position was significantly lower than that in the upright position ($p < 0.001$) (Figure 3). There were no significant differences in the percentages of CDA-induced decrease in the nasal volume between the two positions ($p = 0.5$). In the supine position, however, the nasal mucosal temperature after CDA exposure was significantly lower than that in the upright position ($p < 0.01$). Our data showed that placing a subject in the supine position decreased the ability of the nose to condition CDA compared to that in the upright position. We speculate that the decreased nasal conditioning capacity in the supine position is related to the decrease in nasal mucosal temperature induced by an increase in air pressure and speed.

According to a theoretical model of localized heat and water vapor transport in the nose, the two most important parameters predicting the air-conditioning process are the nasal mucosal temperature and the volume of the nasal cavity⁽³⁷⁾. We reduced the nasal volume without altering the mucosal

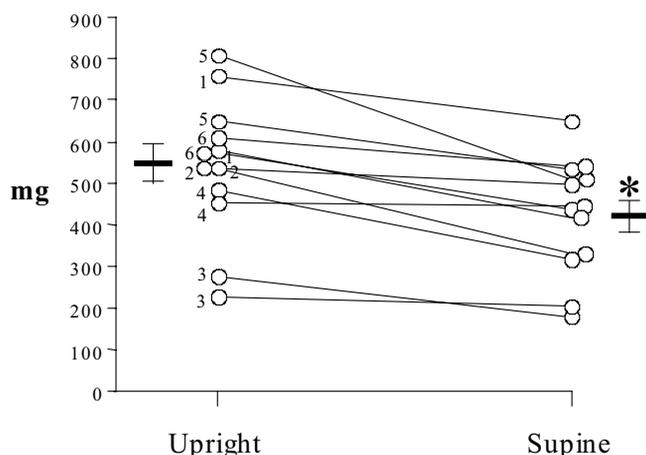


Figure 3. Individual data of total water gradient expressed in mg across the nose after placing subjects in 2 different positions as specified on the abscissa. The thick bars represent mean \pm SEM of the individual data points. Individual subjects have been numbered to show reproducibility of measurement. ****p < 0.001 vs. Upright.**

temperature by placing subjects in the supine position and studied this effect on the nasal conditioning capacity. Contrary to the theoretical model, subjects were less able to condition CDA in the supine position, compared with the upright position, demonstrating the need to test the theoretical models with human data, for the simple prediction from a theoretical model did not account for the complexity of the human situation. The study also supports the clinical practice of elevating the head of the bed of recovering head and neck surgery patients.

Temperature elevation

We have previously shown that raising the nasal mucosal temperature by immersing feet in warm water increases the amount of water evaporated by the nose as air passes through it (nasal conditioning capacity). To investigate further the effect of nasal mucosal temperature on the nasal conditioning capacity, we raised the temperature through α -adrenoreceptor blockade by intranasally administering phenoxybenzamine. We hypothesized that blocking α -adrenoreceptors during inhalation of CDA would lead to an increase in nasal blood flow, surface temperature, and nasal conditioning capacity, as measured by the WG. After appropriate pilot studies, we performed a double-blind, placebo-controlled, 2-way cross-over study on 9 non-atopic, healthy subjects by studying the effect of treatment with intranasal phenoxybenzamine⁽⁴⁰⁾. The nasal mucosal temperature increased significantly after administration of phenoxybenzamine. This increase was associated with a significantly smaller net decrease in nasal mucosal temperature after exposure to CDA ($p < 0.05$). However, there were no significant differences in nasal conditioning capacity between treatments ($p > 0.05$) (Figure 4). Phenoxybenzamine decreased the symptom of rhinorrhea after exposure to CDA ($p < 0.05$), but congestion did not differ between individuals given phe-

noxybenzamine and those given placebo ($p > 0.05$). Our data demonstrate that phenoxybenzamine, despite raising the mucosal temperature and not affecting the nasal volume, did not affect the ability of the nose to warm and humidify air.

Influence of glandular secretions

Major contributors to the volume of surface secretions are the parasympathetically driven glands in the nose⁽⁴¹⁾. Blocking of the parasympathetic system with anticholinergic agents reduces rhinorrhea^(42, 43). Ipratropium bromide is a commercially available anticholinergic agent for treatment for excessive rhinorrhea. Although ipratropium bromide treats the rhinorrhea appropriately, we were concerned that it might worsen the ability of the nose to condition air. To address this issue, we performed a double-blind, placebo-controlled study involving 15 normal subjects⁽⁴⁴⁾. The subjects were pretreated with either ipratropium bromide (0.06%) or normal saline sprayed into the nasal cavity and then underwent challenge with three increasing flows of CDA. We evaluated not only the effect of ipratropium on nasal conditioning, but also its effects on nasal

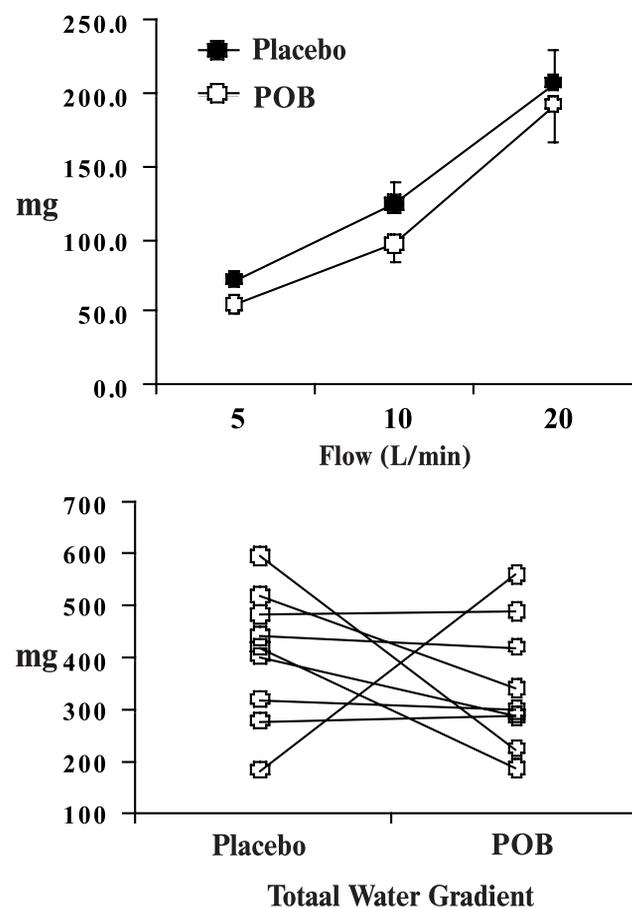


Figure 4. Effect of phenoxybenzamine on nasal conditioning capacity. Top panel: Water gradient (mg) across the nose at three flow rates (5, 10, 20 l/min). Data are mean \pm SEM for 9 subjects. There was increased conditioning with increasing flow rate. There were no differences between treatments. Bottom panel: Individual data of total water gradient (mg) across the nose. POB = phenoxybenzamine.

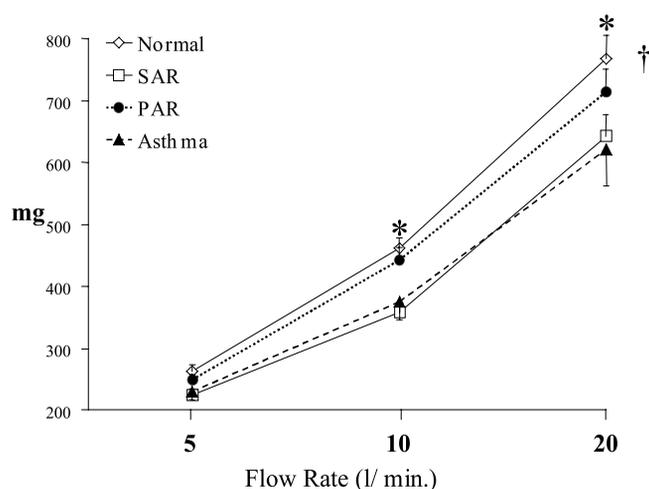


Figure 5. Water gradient across the nose in each group of subjects at 3 flow rates (5, 10, and 20 l/min.). Data are mean ± SEM for 15 subjects in each group as shown by symbols. SAR: seasonal allergic rhinitis. PAR: perennial allergic rhinitis. *p < 0.001 vs. respective 5 l/min in all groups, †p < 0.001 vs. respective 10 l/min in all groups.

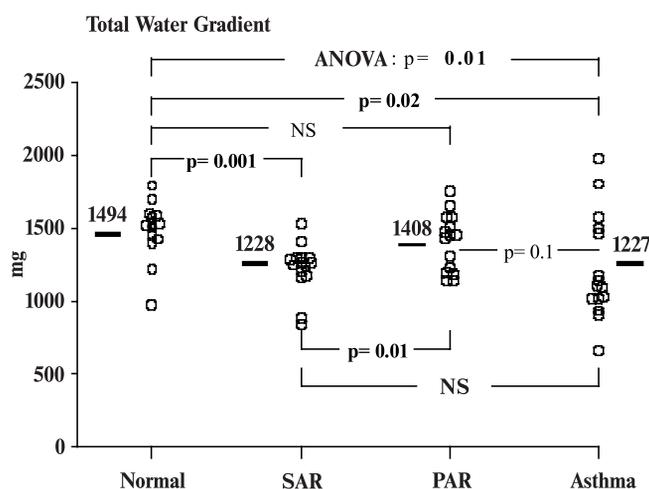


Figure 6. Individual data of total water gradient across the nose in each group of subjects specified on the abscissa. The solid bars with the numbers above them represent the mean of the individual data points; NS: not significant.

symptoms, nasal volume, and changes in the albumin and osmolality of the lavage fluid. Ipratropium bromide improved the conditioning of inspired air, as demonstrated by enhancement of the water supplied to the inhaled air during its passage across the nasal cavity. The TWG was 2432 ± 152 mg after placebo and 2926 ± 149 mg after ipratropium bromide ($p < 0.01$). The nasal volume decreased after exposure to CDA inhalation when the patients were pretreated with saline (7.85 to 4.29 cc, $p < 0.001$). The decrease after treatment with ipratropium bromide was also significant (from 6.89 to 3.88 cc), but the net decrease was significantly less after ipratropium bromide ($p = 0.01$) compared to saline premedication, although

the difference was small. The increase in secretions after exposure to cold, dry air compared to baseline was significantly less (7.1 to 21.2 mg vs 2.32 to 11.01 mg, $p < 0.05$) after ipratropium pretreatment than after pretreatment with saline. Albumin levels were greater on the days when the patients received ipratropium, suggesting increased vascular permeability.

The changes in the symptoms of rhinorrhea and nasal congestion paralleled the objective measurements. Nasal secretion osmolality increased following CDA exposure after both treatments, but the magnitude of the increase was reduced after ipratropium, a finding consistent with the observation by Mann et al. that glands induce hyperosmolar secretions⁽²⁶⁾.

To investigate whether the ipratropium-induced increased conditioning capacity of the nose was related to an effect on the nasal mucosal temperature, we conducted another series of experiments in which 7 normal subjects were premedicated in a double-blinded manner with either intranasal saline or ipratropium bromide (0.06%). The subjects were then exposed to CDA at 20 l/min. The nasal mucosal temperature was measured before application of the medication, after drug administration, and after 8 minutes of exposure to CDA at 20 l/min. Pretreatment with ipratropium did not lead to any changes in nasal mucosal temperature, and breathing CDA resulted in lowering of the nasal mucosal temperature to identical degrees after premedication with ipratropium and saline.

This study clearly demonstrates that blocking of the glands of normal individuals does not impair their ability to warm and humidify inspired air, a clinically useful observation. However, it points to the complexity of the nasal response in the face of altering of one parameter. We believe that the explanation for our data lies in the increased delivery of heat to the surface caused by an increase in blood flow secondary to the nasal mucosal response to conditioning air⁽⁴⁴⁾.

Our data on the allergic state may seem conflicting. First, atopy without inflammation is associated with a decreased ability to condition air. This suggests that either a primary or a secondary defect (associated with years of allergic inflammation) in water transport is associated with atopy. The second issue relates to the increased ability of atopic individuals to condition air when they have ongoing allergic inflammation. The precise reason for this increased ability to condition air is not apparent. It can relate to the effects of mediators released during allergic inflammation that have an impact on water transport mechanisms. Physiologic changes in blood flow and reactivity of nerves could also play a role.

Nasal conditioning in asthma

We showed above that seasonal allergic individuals had a reduced ability to condition air, which was improved by inflammation. We hypothesized that individuals with perennial

allergic rhinitis (PAR), who had ongoing inflammation, would condition air in the same way as do seasonal allergic subjects with inflammation. Because individuals with asthma usually have allergic inflammation in both the nose and the lungs, we hypothesized that they would have the ability to condition air nasally like individuals with PAR. We performed a prospective, parallel study in 15 normal subjects, 15 subjects with seasonal allergic rhinitis (SAR) outside their allergy season, 15 subjects with PAR, and 15 asthmatic subjects⁽⁴⁵⁾. We measured the ability of the noses of these subjects to humidify CDA. The TWG in the SAR group was significantly lower than that in normal subjects (Figures 5 and 6). There were no significant differences in TWG between the PAR and normal groups. Contrary to our hypothesis, asthmatic subjects had a significantly lower TWG than did normal subjects. There was a significant negative correlation between TWG and Aas score (which is a reflection of the severity of asthma) in the asthmatic group ($r_s = -0.8$, $p = 0.0007$).

Our data show that asthmatic subjects have a reduced ability of the nose to condition CDA. The mechanism underlying the observed differences in nasal conditioning among the groups above did not involve nasal volume, surface temperature, or glandular reactivity. We speculate that the reduced conditioning capacity of the nose may adversely affect the lower airway.

Because asthmatic subjects have inflamed airways that respond to steroids, we speculated that treating the inflammation would worsen their ability to condition inspired air. This speculation was based on our previous data showing that allergic inflammation improved the nasal conditioning of the nose. We performed a double-blind, placebo-controlled study investigating the effects of budesonide on nasal conditioning (Figure 7)⁽⁴⁶⁾. Consistent with our hypothesis, the intranasal steroid reduced the ability of 9 of 10 asthmatic subjects to condition air; i.e., reducing inflammation made the defect in water trans-

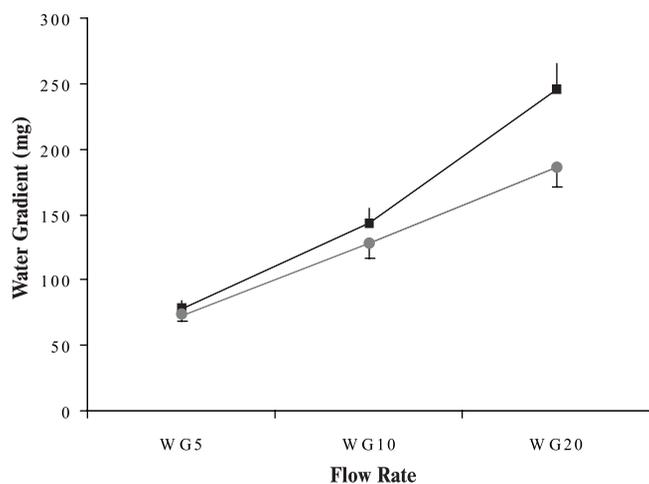


Figure 7. Response to nasal conditioning of 10 asthmatic subjects treated for 1 week with placebo (○) or budesonide (■).

port more apparent. This observation is consistent with our findings on the effects of natural and induced allergic inflammation on nasal air conditioning. This observation might explain some of the clinically observed, local adverse effects of intranasal steroids, drying, and local irritation.

Heredity and nasal conditioning capacity

In our previous studies on nasal conditioning, we observed a large variability among individuals in their ability to condition inspired air. Although we previously investigated different parameters such as age, sex, nasal mucosal temperature, pulse, blood pressure, and nasal volume, we have been unable to explain this variability. We hypothesized that heredity contributes to the differences in the nasal conditioning capacity of individuals. To address this hypothesis, we performed a prospective study on 47 sibling pairs. Cold, dry air was delivered to the nose, and we calculated the TWG to find the nasal conditioning capacity. We found a highly significant intraclass correlation of 0.53 ($p < 0.0001$) between sibling pairs for the TWG. These results suggest that there is a genetic basis for nasal conditioning, and they point to the possibility that a genetic variability in expression, or lack thereof, of one of the proteins described in the introduction of this review may be responsible for our observations.

CONCLUSION

In conclusion, our results over the years show the complex responses of a physiologic system such as the nose. The data presented support the notion of inflammation induced by hyperosmolar stimuli and also support the concept that patients with limited ability to condition inspired air are those who are subject to diseases of the airways, namely, allergic rhinitis and asthma. The interaction between allergic inflammation and water transport remains to be elucidated further.

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