

Nasal conditioning in perennial allergic rhinitis after nasal allergen challenge

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Summary

Background Antigen challenge in seasonal allergic rhinitis is considered to be associated with an increased ability of the nose to condition inspired air. In contrast, little is known about air conditioning after antigen challenge in perennial allergic rhinitis (PAR).

Objective The aims of this study were to investigate whether antigen challenge in PAR changes nasal air conditioning and to assess the relationship between nasal conditioning and nasal patency and geometry.

Methods Nineteen subjects with PAR were enrolled into this study. Measurement of nasal conditioning, active anterior rhinomanometry (AAR), acoustic rhinometry (AR), and clinical symptom evaluation were performed before and after nasal allergen challenge with allergen extracts from house dust mites.

Results Ten and 20 min after nasal allergen challenge, the total water content of the air measured in the nasopharynx and the water gradient across the nose were significantly higher in the nasal cavity in which the allergen extract was sprayed. The temperature on both sides of the nose increased non-significantly after nasal allergen challenge. No correlation to data obtained by AAR, AR, and clinical symptom evaluation after nasal allergen challenge was found.

Conclusion We suggest that an increase in mucosal humidity due to the allergic provocation might be responsible for the increase in nasal conditioning capacity because no correlation to changes in nasal perimeter and patency was found.

Keywords allergic rhinitis, nasal air conditioning, nasal provocation

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Introduction

To date, the factors that influence nasal conditioning in subjects with allergic rhinitis have not yet been thoroughly investigated. However, investigations on nasal conditioning in allergic patients are necessary because of the important role of the nasal airways in conditioning and preparation of the inspired air before the inhaled air enters the lower respiratory tract [1–4]. Especially in allergic and asthmatic patients a reduced ability of the nose to condition inhaled air was suggested to be associated with an increased risk of pathologic disorders of the lower respiratory tract [5].

There are a few reports on nasal conditioning in patients suffering from seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and asthma [5–7]. Rouadi et al. [6] have found evidence that there are differences in nasal conditioning between patients with SAR out of season, PAR, and healthy volunteers. Patients with SAR were also studied in season and after antigen challenge [8]. In their study, both seasonal exposure and nasal challenge with antigen were

shown to increase the ability of the nasal airways to condition inhaled air [8]. The authors speculated that changes in the perimeter of the nasal cavity might be responsible for the increased nasal ability to condition the inspired air.

Nasal parameters such as nasal patency or nasal geometry have not been extensively examined *in vivo* to which extent they influence the ability of the nasal airways to condition air [5, 6, 8–11].

In a cast model of the upper respiratory tract, Hanna and Scherer [12] predicted that the blood temperature (TEMP) distribution along the airway wall and the cross-sectional area and perimeter of the nasal cavity are the most important parameters affecting nasal conditioning. We previously showed in patients after radical resection of the turbinates on one side of the nose that the increase in nasal airway volume and loss of nasal mucosa is associated with a reduced ability of the nose to warm and moisten air [10]. However, the impact of nasal airway parameters remains unclear in patients with complex nasal disorders such as allergic rhinitis.

The aim of the present study was to investigate nasal conditioning after nasal allergen challenge in subjects suffering solely from PAR. In addition, we examined parameters describing nasal patency and nasal geometry possibly influencing nasal conditioning and clinical symptoms before and after nasal allergen challenge and determined their relationship to nasal conditioning parameters.

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Materials and methods

Subjects

After receiving approval of the local ethical committee, 19 volunteers (median age, 24 years; range, 18–48 years; 10 females and nine males) with PAR were entered into the study. All subjects suffered from typical symptoms of house dust mite allergy and presented positive skin testing for *Dermatophagoides pteronyssinus* (Dpter) and/or *Dermatophagoides farinae* (Dfar). The subjects showed positive tests in serum-specific IgE determination either for Dpter and/or Dfar. They did not present a history of SAR complaints and did not react positively in skin testing. The volunteers had no history of nasal surgery or nasal trauma.

All study participants underwent an otorhinolaryngological examination including anterior rhinoscopy and endoscopy of the nasal cavity without application of decongestants or local anaesthetics.

Exclusion criteria were pregnancy, allergic asthma, SAR, considerable septal deviation, serious internal or neurological diseases, and patients under continuous steroid therapy. Anti-allergic treatment (i.e., treatment with oral or nasal antihistamines, cromolyn sodium, and nasal decongestants) had to be stopped at least 5 days prior to study participation.

Skin prick test (puncture) method

Skin testing was performed according to the guidelines of the Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology [13]. Seasonal allergens and perennial allergens in test solutions containing 10 000 AU/mL (Allergopharma J. Ganzer, Reinbek, Germany) were tested. The skin prick test battery consisted of inhalant allergens common in Central Europe. A positive test reaction was found if the weal reaction was at least 3 mm in diameter or at least 25% of the weal area following simultaneous pricking with 1 mg/mL histamine solution.

Active anterior rhinomanometry (AAR)

AAR (Rhinomanometer 300, Atmos, Lenzkirch, Germany; transnasal reference pressure, 150 Pa) was performed in all subjects according to current recommendations of the Committee Report on Standardization of Rhinomanometry [14].

Acoustic rhinometry (AR)

AR (SRE 2000, Rhinometrics, Lynge, Denmark) was used for evaluation of nasal geometry in both sides in all volunteers. The mean total volume of the anterior 22 mm (Vol22) and the mean total volume from 22 to 54 mm (Vol22–54) of the nasal cavity were calculated. The mean minimal cross-sectional area (MCA1) (0–22 mm from the nasal entrance) and MCA2 (22–54 mm from the nasal entrance) were calculated according to current recommendations [15].

Measurement of nasal conditioning

Nasopharyngeal measurements of TEMP and humidity before and after nasal allergen challenge were performed as described previously [9–11]. Humidity and TEMP of the air in the nasopharynx were detected and used for further calculation.

The TEMP of the nasal mucosa was not used to describe changes in nasal conditioning in this study.

Signals of an intranasally placed thermocouple that was connected to a relative humidity (RH) sensor (TEMP-2 and RH-2) were compared with TEMP and RH signals (TEMP-1 and RH-1) that were simultaneously recorded directly in front of the volunteer's nostrils (Fig. 1). The RH-2 sensor used was a capacitive thin-film humidity sensor (Humichip 17204 HM, Vaisala, Vantaa, Finland). It was incorporated in an acrylic glass box and connected to a suction system. With this equipment, RH between 0% and 100% could be measured. In high-velocity air it took less than 2 s to reach 90% of the steady state. A thermocouple device with an outer diameter of 0.34 mm (thermocouple type K, thermoelectric wire consisting of Chromel and Alumel, Thermocoax, Suresnes, France) was used for TEMP recording. Its actual response time in non-moving air was 0.4 s; the response time in high-velocity air was 0.1 s. The reference humidity and TEMP outside of the nose (TEMP-1 and RH-1) were obtained by a standardized reference TEMP and humidity indicator (HMI41 and HMP45, Vaisala). Continuous registration was achieved by using the computer program Visual Designer 4.0 (Intelligent Instrumentation, Tucson, AZ, USA).

The measurement system used was previously tested for accuracy, dynamic response, and long-term stability in our laboratory [9–11]. With this experimental set-up, we can generate reproducible well-defined step changes in TEMP and RH. An electronic compensation system to improve response time for humidity detection was integrated in the measurement system. Using this electronic system component, we have found that response time for humidity was accelerated by a factor of four. Thus, synchronization of both TEMP and humidity recording and real-time registration could be achieved. The practicality and applicability of the experimental system for *in vivo* measurements was extensively evaluated with human volunteers [9–11].

Calibration of the humidity sensor was regularly carried out against saturated calibration salt solutions (LiCl $11.3 \pm 0.3\%$, NaCl $75.5 \pm 0.1\%$; HMK15 humidity calibrator, Vaisala).

Nasal allergen challenge and experimental protocol

Initially the volunteers had to adapt, for 20–30 min, to the laboratory environment with a room temperature of $25 \pm 1^\circ\text{C}$ ($\pm$ SD), a RH of $30 \pm 4\%$ ($\pm$ SD), and an absolute humidity of 5.9 ± 0.8 g/kg air ($\pm$ SD), while breathing quietly through the nose in an upright position.

To study possible changes in nasal conditioning, AAR, AR, and clinical symptoms after nasal allergen challenge, a standardized nasal provocation test (NPT) with Dpter or Dfar was performed. The NPT was performed according to the guidelines of the German Society for Allergy and Clinical Immunology and the European Academy of Allergy and Clinical Immunology [16, 17]. Subjective clinical symptoms (nasal obstruction, secretion, nasal itching) were graded by the volunteers for each item on a scale as follows: 0 = no symptoms, 1 = mild symptoms, 2 = severe symptoms. Clinical symptom evaluation by the examiners (parameters: secretion, irritation, remote symptoms; feasible score points for each item: 0–2), which is part of the standard NPT was also performed.

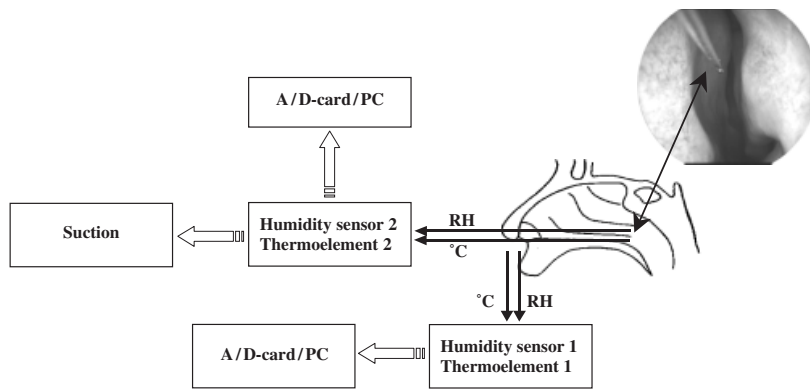


Fig. 1. Experimental set-up for nasal conditioning measurement. Two detectors, each of them consisting of a humidity sensor and a thermocouple, were measuring relative humidity (RH) and temperature in front of the nose and in the airstream in the nasopharynx simultaneously. After insertion through the nostril, the nasopharyngeal probe (the tip of the probe is shown in the right upper corner of the picture) was moved through the nasal airway and placed in the nasopharyngeal airstream. During recording the head of the volunteer was fixed in a head holder.

Prior to nasal allergen challenge with 5000 BU of Dpter or Dfar (i.e., 100 μ L of an allergen solution) 100 μ L of a control solution containing 0.4% phenol was applied to the less congested side of the nose to control for non-specific reactivity of the nasal mucosa. The allergen (Dpter or Dfar) with the highest reaction in skin prick testing was applied as test allergen for NPT in the individual case and sprayed into the less congested side of the nose. For intranasal application of the control solution and the allergen solution towards the head of the inferior turbinate, a commercially available nebulizer was used. To avoid bronchial provocation by the control solution and the test allergen, the spray was administered intranasally after prior deep inspiration and stoppage of breathing during nasal spray application. AAR, AR, clinical symptom evaluation, and measurements of nasal air conditioning were performed: (i) before, (ii) 10 min after application of the control solution, (iii) 10 min, and (iv) 20 min after application of the allergen solution. A 40% or greater decrease in the ipsilateral nasal airflow at a transnasal reference pressure of 150 Pa, an increase of four or more symptom score points (examiner's evaluation), or an increase of three symptom score points and a nasal flow reduction of 20% or more was considered a positive NPT reaction 10 or 20 min after allergen challenge. All volunteers fulfilled one of these criteria in NPT. No symptomatic anti-allergic treatment was allowed during the evaluation period after nasal allergen challenge.

Data processing and statistical analysis

The end-inspiratory nasopharyngeal RH and TEMP were detected in both sides of the nose separately. The mean end-inspiratory RH and TEMP of a respiratory cycle of 2 min were calculated. The mean RH and TEMP of the first five consecutive breaths were calculated and compared with the means recorded for the next five breaths. The measurement of RH and TEMP was accepted if the coefficient of variation between the two means was less than 10%. If the coefficient of variation did not become less than 10% in repeated measurements, the volunteer was excluded. Data of RH and TEMP obtained simultaneously in front of the nostrils and in the nasopharynx were used for calculation of the total water content (TWC) of the air in the nasopharynx and the water gradient (WG) across the nose (in milligrams per litre), analogous to calculation processes of other working groups [5, 6]. The WG was defined as $TWC_{\text{nasopharynx}}$ (measured in

the nasopharynx using sensor 2) minus TWC_{nostrils} (detected in front of the nostrils using sensor 1). WGs were established independently for both nasal airways.

Results are presented as a median $\pm$ 95% confidence interval. The non-parametric Wilcoxon signed-rank test was used to compare TEMP, TWC, and WG before and after nasal allergen challenge. To evaluate AAR and AR, the same statistical test was applied. Significance was accepted at the 95% confidence level ($P \leq 0.05$). To compare TEMP, TWC, and WG with data obtained by AAR, AR, and clinical symptom scoring, the Spearman rank correlation test was used [18]. Statistical analysis was performed using the statistical software WinSTAT[®] (Kalmia Inc., Cambridge, MA, USA).

Results

There were no individual or technical problems in performing the NPT and the measurements of nasal conditioning. While moving the measurement probe towards the nasopharynx, some discomfort appeared in a few volunteers without the need to interrupt the experiment. Endoscopic control and mucosal adaption prior to measurements were sufficient to avoid influences by mucosal irritation. In rare cases mucus was suctioned while moving the suction probe intranasally. This was indicated by permanently high humidity values ($\geq 93\%$ RH). In this case, the silicone probe was removed and a new probe was connected to the humidity detector and calibration was repeated.

The application of the control solution did not significantly change the TEMP, the TWC, and the WG across the nose detected in the nasopharynx in all volunteers (data not shown).

Before nasal provocation the end-inspiratory nasopharyngeal TEMP on the less congested side (T) of the nose was significantly lower than on the more congested control side (C) of the nose (median $TEMP_T$, 27.3 $^{\circ}$ C vs. median $TEMP_C$, 29.7 $^{\circ}$ C; Fig. 2). The TWC and the WG across the nose were not significantly different between the two sides of the nose before the allergen solution was sprayed into the nose (Figs 3 and 4).

Ten minutes after application of the allergen solution, there was a trend towards increasing TEMP on both sides, the side in which the allergen solution was sprayed and the side

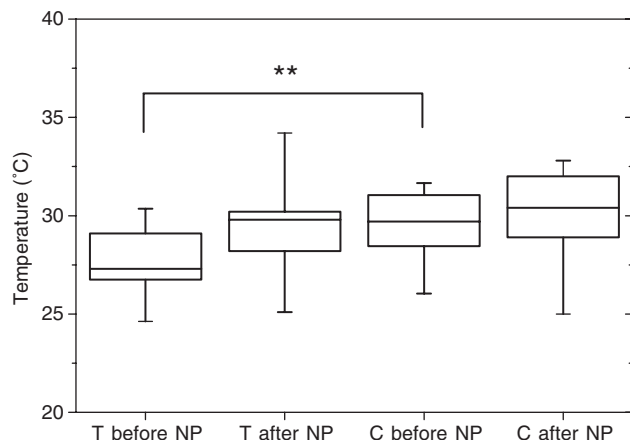


Fig. 2. End-inspiratory temperature (°C) in the nasopharynx. Data are median $\pm$ 95% confidence interval for 19 subjects with perennial allergic rhinitis. T, wider side of the nose in which the allergen solution was sprayed; C, narrower side of the nose without spray application; before NP, before nasal provocation; after NP, 10 min after nasal provocation. ** $P < 0.005$.

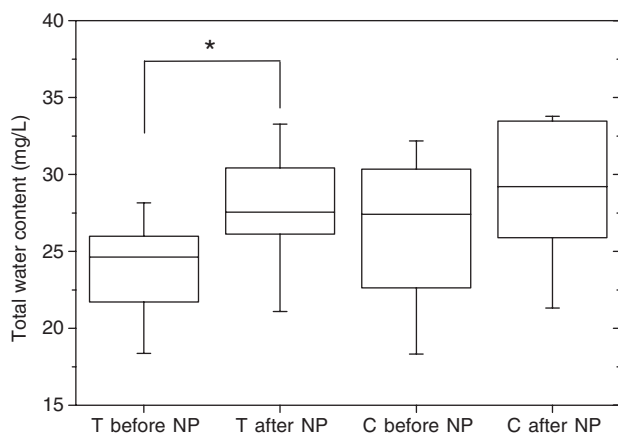


Fig. 3. End-inspiratory total water content (mg/L) in the nasopharynx. Data are median $\pm$ 95% confidence interval for 19 subjects with perennial allergic rhinitis. T, wider side of the nose in which the allergen solution was sprayed; C, narrower side of the nose without spray application; before NP, before nasal provocation; after NP, 10 min after nasal provocation. * $P < 0.05$.

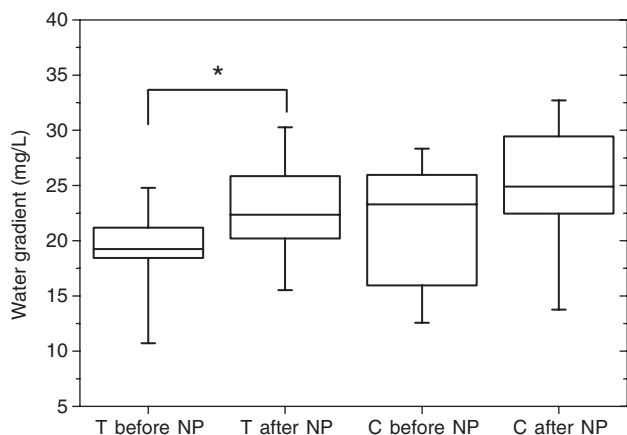


Fig. 4. End-inspiratory water gradient (mg/L) across the nose. Data are median $\pm$ 95% confidence interval for 19 subjects with perennial allergic rhinitis. T, wider side of the nose in which the allergen solution was sprayed; C, narrower side of the nose without spray application; before NP, before nasal provocation; after NP, 10 min after nasal provocation. * $P < 0.05$.

without allergen application. The TWC and the WG across the nose on the less congested side of the nose significantly increased after nasal provocation (median TWC before NP, 24.63 mg/L vs. median TWC after NP, 27.55 mg/L; median WG before NP, 19.24 mg/L vs. median WG after NP, 22.35 mg/L). The control side of the nose showed only a trend towards increased TWC and WG.

Twenty minutes after allergen provocation, the results for TEMP, TWC, and WG were similar to those obtained 10 min after allergen application (data not shown).

To investigate the relation of nasal patency and nasal geometric data (i.e., nasal volume and MCA) to TEMP, TWC, and WG, the Spearman rank correlation test was performed. Besides a slight positive correlation of TEMP of the control side and MCA1 and a positive correlation of WG on the control side and MCA1, no correlation between rhinomanometric and acoustic rhinometric data (Vol1, Vol2, MCA1, MCA2) and TEMP, TWC, and WG before and after nasal provocation was found at both times after NP (comparison of absolute values; Table 1). Comparing changes of rhinomanometrical and rhinometrical values with changes of TEMP, TWC, and WG before and after NP also did not show any correlation between the parameters tested (Table 2). Clinical symptom scores, evaluated by the volunteers as well as by the examiners, did not correlate to conditioning parameters (TEMP, TWC, WG) before and after nasal allergen challenge (data not shown).

Discussion

After nasal allergen challenge, the TWC and the WG across the nose on the less congested side of the nose significantly increased; whereas, the control sides only showed a trend

Table 1. Correlation matrix of absolute values of nasal perimeter and patency parameters and nasal conditioning data

	AR before NP	AR after NP	AAR before NP	AAR after NP
TEMP _T	0.19	-0.10	0.42	0.31
	0.335	0.409	0.168	0.268
TEMP _C	0.61	0.64	0.21	-0.2
	0.050	0.059	0.322	0.352
TWC _T	0.63	0.0	0.08	0.5
	0.183	0.5	0.435	0.195
TWC _C	-0.7	0.5	-0.08	0.14
	0.094	0.333	0.435	0.393
WG _T	0.19	-0.14	0.08	0.5
	0.335	0.393	0.435	0.195
WG _C	0.39	0.75	-0.08	0.31
	0.191	0.026	0.435	0.272

The correlation of acoustic rhinometric data (exemplary MCA1, cm²) and rhinomanometric data (cm³/s) with end-inspiratory TEMP (°C), TWC (mg/L), and WG (mg/L) on both sides of the nose before and 10 min after nasal provocation in 19 volunteers was tested. The correlation coefficients (r_s , upper value of each box) and the P -values (lower value of each box) of 24 consecutive executions of the Spearman rank correlation test are shown. MCA1, minimal cross-sectional area 1; AR, acoustic rhinometry; AAR, active anterior rhinomanometry; TEMP, temperature; TWC, total water content; WG, water gradient across the nose; NP, nasal provocation; r_s , correlation coefficient; T, nasal side with allergen application; C, control side without nasal allergen application.

Table 2. Correlation matrix of changes in nasal perimeter and patency parameters and nasal conditioning data

	Change in AR before and after NP	Change in AAR before and after NP
TEMP _T	0.22 0.423	0.46 0.220
TEMP _C	0.58 0.063	0.29 0.377
TWC _T	0.58 0.143	0.03 0.674
TWC _C	-0.6 0.128	-0.06 0.665
WG _T	0.23 0.174	0.04 0.848
WG _C	0.22 0.367	-0.06 0.442

The correlation of changes of acoustic rhinometric data (exemplary MCA1, cm²) and rhinomanometric data (cm³/s) with changes of end-inspiratory TEMP (°C), TWC (mg/L), and WG (mg/L) on both sides of the nose before and 10 min after nasal provocation in 19 volunteers was tested. The correlation coefficients (r_s , upper value of each box) and the *P*-values (lower value of each box) of 12 consecutive executions of the Spearman rank correlation test are shown. MCA1, minimal cross-sectional area 1; AR, acoustic rhinometry; AAR, active anterior rhinomanometry; TEMP, temperature; TWC, total water content; WG, water gradient across the nose; NP, nasal provocation; r_s , correlation coefficient; T, nasal side with allergen application; C, control side without nasal allergen application.

towards increased TWC and WG. The TEMP increased non-significantly on both sides after allergen challenge. These findings indicate that induction of an early response to nasal challenge with antigen and narrowing of the nasal airways leads to improved conditioning of the inspired air within the nasal airways. Both acoustic rhinometric and rhinomanometric parameters, describing nasal geometry and nasal patency, did not correlate to nasal conditioning in the study group examined in our investigation.

Our data supports the hypothesis that the nasal conditioning capacity after allergen challenge is elevated because of an increased water content in nasal secretions on the nasal mucosal surface due to the allergic reaction [19, 20]. The secretions may provide more water to the nasal mucosal surface that can be evaporated during nasal inspiration [4, 21].

Allergen challenge leads to an increase in the amount of secretion of nasal glands and an increase in blood flow through the subepithelial capillary plexus [22]. Thus, an increase in TWC of the inspired air may occur after antigenic stimulation on the side of the nose in which the antigen was administered.

An increase in humidity of the inhaled air after allergen challenge could be measured on both sides of the nose. It is well known that histamine is an important stimulator of blood vessels, nerves, and nasal glands [22]. An increase in histamine level in the nasal mucosa occurs within minutes of antigenic stimulation [22, 23]. We speculate that neurogenic reflexes are responsible not only for late-phase responses (late peak of histamine release) on the contralateral side of the nose after unilateral antigen stimulation [23], but also for changes in the complex system of subepithelial and glandular zones during early-phase responses.

Since it was previously shown in an evaluation of provocation thresholds of the NPT that 5000 BU allergen extract had led to a positive allergic reaction in all patients studied [24], this concentration was used in our investigation. Nevertheless, minor individual differences in the conditioning response to the allergen challenge have to be considered in our study.

Interestingly, the more congested side of the nose showed a trend towards higher TWC before antigenic stimulation, compared with the less congested side of the nose. The same constellation of higher TWC of the inspired air on the more congested side of the nose was found in the early phase after antigenic stimulation. We hypothesize that the humidity of the inhaled air on the more congested side of the nose is increased because the inspired air comes to a better and closer contact to the nasal mucosa if the nose is narrower. One important factor in improved conditioning is the congestion of the turbinate mucosa. Arteriovenous anastomoses in the cavernous plexus of the inferior and middle turbinates are mainly responsible for the congestion status of the turbinates [19, 21]. The cavernous plexus located in the turbinates has several functions. First, it is a potent regulator of the velocity of the inspired air because it can change the volume of the turbinates and the nasal airway volume. Second, it may provide heat to the cellular layer of secretory and ciliated cells [19, 21]. Because of the ability of the turbinates to change the speed and direction of the inspired air within the nasal cavity and to heat the epithelial layers of the mucosa, a higher increase in moisture transfer to the inhaled air may occur on the more congested side of the nose. The turbinates, acting as heating sources, warm the inhaled air sufficiently and, therefore, increase the capacity of the air to hold moisture.

The same phenomenon of higher values on the more congested sides of the nose could be observed for the TEMP of the respired air. The TEMP values on the more congested side of the nose were significantly higher than on the less congested side. However, only a trend towards increased TEMP of the respired air could be measured in both sides of the nose after nasal allergen challenge.

The observation that humidity rather than air TEMP was increased underlines the special relation of heat and moisture exchange on mucosal surfaces in the respiratory tract. The total energy content of air consists of sensible heat content (i.e., the TEMP of air) and latent heat content (i.e., the water content) [4]. The transfer of humidity from the mucosal surface to the respired air needs much more energy, provided by the epithelial and subepithelial structures of the mucosal surface, than heating of the air. Thus, an increased energy transfer after allergen stimulation of the nasal mucosa is mainly expressed rather by a significant increase in total water content of the air than by a significant increase in TEMP of the air. We therefore conclude that tremendous functional changes of epithelial and subepithelial structures of the nasal mucosa are responsible for the elevated nasal conditioning in the early response time after nasal allergen challenge. Although the complex mechanisms that are responsible for the fast increase in nasal conditioning on both the unilateral side and the contralateral side of the nose are not known yet, we speculate that reflexes (via trigeminal afferent nerves and parasympathetic nerves) leading to vasodilatation and mucus secretion in the nose may play an integral role in adjusting the

air conditioning function of the nose after allergen stimulation. Such reflexes altering sinus blood flow and nasal secretion from the submucosal nasal glands [25] may not only increase the air conditioning capacity of the nasal airways if challenged with antigen, but may also lead to improved protection of the epithelial surface. Immediate changes of the air in TEMP and water content after nasal allergen challenge, reflecting also significant changes in TEMP of the nasal mucosal surface [26], may also immediately compromise mucosal function. Thus, immediate neurogenic regulation resulting in increasing water and energy transfer to the mucosal surface may contribute to stabilization of mucosal function (i.e., mucociliary clearance and cleansing capacity, conditioning, heat and moisture recovery from the exhaled air, immunologic functions) after challenge with allergen. However, the mechanisms underlying this complex system of preservation and adjustment of conditioning function of the nasal airways are not fully understood yet.

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