How Nasal Function Influences the Eyes, Ears, Sinuses, and Lungs

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The nose is an integral part of the upper airway and the first contact of the body with inspired air. It is located in close proximity to several related airway structures that include the ears, paranasal sinuses, and eyes. It is also closely linked to the lower airway. Multiple lines of evidence support a close interaction and influence of the nose on these contiguous and distant organs via neural reflexes and systemic inflammatory processes. These interactions are reviewed in light of existing evidence.

Keywords: allergic rhinitis; asthma; rhinosinusitis; reflexes

The nose constitutes the first line of contact of the airway with inhaled air. It performs many important functions including that of filtering and humidifying inspired air, and it is primarily responsible for the sense of olfaction. Before discussing the relationship of the nose with other upper and lower airway organs such as the ears, sinuses, and lungs, a brief overview of its filtering and humidifying capacities is presented.

NASAL AIRFLOW

The nose provides the main pathway for inhaled air to the lower airways and offers two areas of resistance to airflow (provided there are no gross deviations of the nasal septum): the nasal valve and the state of mucosal swelling of the nasal airway. The cross-sectional area of the nasal airway decreases dramatically at each nasal valve, reaching 30 to 40 mm^2. This narrowed area separates the vestibules from the main airway and accounts for approximately half of the total resistance to respiratory airflow from ambient air to the alveoli. After bypassing this narrow area, inspired air flows into the main nasal airway, which is a broader tube bounded by the septal surface medially, and the irregular inferior and middle turbinates laterally. The variable caliber of the lumen of this portion of the airway is governed by changes in the blood content of the capillaries, capacitance vessels, and arteriovenous shunts of the lining mucosa and constitutes the second resistive segment that inspired air encounters on its way to the lungs. Changes in the blood content of these structures occur spontaneously and rhythmically, resulting in alternating volume reductions in the lumen of the two nasal cavities, a phenomenon referred to as the nasal cycle.

On inspiration, air first passes upward into the vestibules in a vertical direction at a velocity of 2 to 3 m/second, and then converges and changes its direction from vertical to horizontal just before the nasal valve, where, because of the narrowing of the airway, velocities reach their highest levels (up to 12 to 18 m/s). After passing the nasal valve, the cross-sectional area increases, and velocity decreases concomitantly to about 2 to 3 m/second. The nature of flow changes from laminar, before and at the nasal valve, to more turbulent posteriorly. As inspiratory flow increases beyond resting levels, turbulent characteristics commence at an increasingly anterior position and, with mild exercise, are found as early as the anterior ends of the turbinates. Turbulence of nasal airflow minimizes the presence of a boundary layer of air that would exist with laminar flow and maximizes interaction between the airstream and the nasal mucosa. This, in turn, allows the nose to perform its functions of heat and moisture exchange and of cleaning inspired air of suspended or soluble particles.

NASAL MUCUS AND MUCOCILIARY TRANSPORT

A 10- to 15-μm-deep layer of mucus covers the entire nasal cavity (1). It is slightly acidic, with a pH between 5.5 and 6.5. The mucous blanket consists of two layers: a thin, low-viscosity, periciliary layer (sol phase) that envelops the shafts of the cilia, and a thick, more viscous layer (gel phase) riding on the periciliary layer. The gel phase can also be envisioned as discontinuous plaques of mucus. The distal tips of the ciliary shafts contact these plaques when they are fully extended. Insoluble particles caught on the mucous plaques move with them as a consequence of ciliary beating. Soluble materials such as droplets, formaldehyde, and CO_2 dissolve in the periciliary layer. Thus nasal mucus effectively filters and removes nearly 100% of particles greater than 4 μm in diameter (2–4). An estimated 1 to 2 L of nasal mucus, composed of 2.5 to 3% glycoproteins, 1 to 2% salts, and 95% water, are produced per day. Mucin, one of the glycoproteins, gives mucus its unique attributes of protection and lubrication of mucosal surfaces.

The sources of nasal secretions are multiple and include anterior nasal glands, seromucous submucosal glands, epithelial secretory cells (of both mucous and serous types), tears, and transudation from blood vessels. Transudation increases in pathologic conditions as a result of the effects of inflammatory mediators that increase vascular permeability. In contrast to serum, immunoglobulins make up the bulk of the protein in mucus; other substances in nasal secretions include lactoferrin, lysozyme, antitrypsin, transferrin, lipids, histamine and other mediators, cytokines, antioxidants, ions (Cl, Na, Ca, K), cells, and bacteria. Mucus functions in mucociliary transport, and substances will not be cleared from the nose without it, despite adequate ciliary function. Furthermore, mucus provides immune and mechanical mucosal protection and its high water content plays a significant role in humidifying inspired air.

Mucociliary transport is unidirectional, based on the unique characteristics of cilia. Ciliary beating produces a current in the superficial layer of the periciliary fluid in the direction of the effective stroke. The mucous plaques move as a result of motion of the periciliary fluid layer and the movement of the extended tips of the cilia into the plaques. Mucociliary transport moves mucus and its contents toward the nasopharynx, with the exception of the anterior portion of the inferior turbinates,

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where transport is anterior. This anterior current prevents many of the particles deposited in this area from progressing further into the nasal cavity. The particles transported posteriorly toward the nasopharynx are periodically swallowed. Mucociliary transport, however, is not the only mechanism by which particles and secretions are cleared from the nose. Sniffing and nose blowing help in moving airway secretions backward and forward, respectively. Sneezing results in a burst of air, accompanied by an increase in watery nasal secretions that are then cleared by nose blowing and sniffing.

Respiratory cilia beat about 1,000 times per minute, which translates to surface materials being moved at a rate of 3 to 25 mm/minute. Both the beat rate and propelling speed vary. Several substances have been used to measure nasal mucociliary clearance, and the most often used are sodium saccharin, dyes, or tagged particles. Studies of several hundred healthy adult subjects by the tagged particle or saccharin method have consistently shown that 80% exhibit clearance rates of 3 to 25 mm/minute (average, 6 mm/min), with slower rates in the remaining 20% (5). In diseased subjects, slow clearance may be due to a variety of factors, including the immotility of cilia, transient or permanent injury to the mucociliary system by physical trauma, viral infection, dehydration, or excessively viscid secretions secondary to decreased ions and water in the mucus paired with increased amounts of DNA from dying cells, as in cystic fibrosis.

NASAL CONDITIONING OF TEMPERATURE AND HUMIDITY OF INSPIRED AIR

Inspiratory air is rapidly warmed and moistened mainly in the nasal cavities and, to a lesser extent, in the remainder of the upper airway down to the lungs (6). Inspired air is warmed from a temperature of about 20°C at the portal of entry to 31°C in the pharynx and 35°C in the trachea. This is facilitated by the turbulent characteristics of nasal airflow, which maximize the contact between inspired and expired air and the nasal mucosal surface (7). After inspiration ceases, warming of the nasal mucosa by the blood is such a relatively slow process that, at expiration, the temperature of the nasal mucosa remains lower than that of expired air. As expiratory air passes through the nose, it gives up heat to the cooler nasal mucosa. This cooling causes condensation of water vapor and, thus, a 33% return of both heat and moisture to the mucosal surface. Because recovery of heat from expiratory air occurs mainly in the region of the respiratory portal, blood flow changes that take place in the nasal mucosa affect respiratory air conditioning more markedly in this region (8).

Ingelstedt and Ivstam showed that the humidifying capacity of the nose is greatly impaired in healthy volunteers after a subcutaneous injection of atropine (6, 9). They thus concluded that atropine-inhibitable glandular secretion is a major source of water for humidification of inspired air. In addition to glandular secretions, other sources provide water for humidification of inspired air and these include water content of ambient air, lacrimation via the nasolacrimal duct, secretion from the paranasal sinuses, salivation (during oronasal breathing), secretions from goblet cells, and passive transport against an ionic gradient in the paracellular spaces (9, 10). Transudation of fluid from the blood vessels of the nose is also probably important as a source of water for humidification of inspired air. The ability to warm and humidify air has been investigated using a model system that involves measuring the amount of water delivered by the nose after inhaling cold dry air (11). This is calculated after measuring the temperature and humidity of air as it penetrates the nasal cavity and then again in the nasopharynx by using a specially designed probe. Using this model, the investigators were able to show that the ability to warm and humidify inhaled air is lower in subjects with allergic rhinitis out of season compared with normal control subjects. The effect of allergic inflammation on the nasal conditioning capacity of individuals with seasonal allergic rhinitis was then investigated by evaluating the ability of the nose to warm and humidify cold dry air in allergic subjects before and after the season as well as 24 hours after allergen challenge (12). These studies showed that allergic inflammation, induced by either the allergy season or an allergen challenge, increased the ability of the nose to warm and humidify inhaled air, and the authors speculated that this was related to a change in the nasal perimeter induced by allergic inflammation. In an interesting follow-up study, the same investigators compared the ability of the following groups of subjects to warm and humidify inhaled air: patients with perennial allergic rhinitis, patients with seasonal allergic rhinitis out of season, normal subjects, and subjects with bronchial asthma (13). They showed that subjects with perennial allergic rhinitis were comparable to normal subjects in their ability to condition air and that subjects with asthma had a reduced ability to perform this function compared with normal subjects. Furthermore, the total water gradient, a measure of the ability of the nose to condition air, correlated negatively with severity of asthma assessed by means of two different gradings, indicating that the ability to condition inspired air was worse in subjects with more severe asthma and suggesting that this reduced ability might contribute, at least in part, to the pathophysiology of asthma.

INTERACTIONS BETWEEN THE NOSE AND OTHER UPPER AND LOWER AIRWAY ORGANS

There is clinical and experimental evidence to support the importance of the nasal airway and its interaction with contiguous (ears, sinuses, eyes) and distant (lungs) airway organs. The best evidence centers around the effects of nasal allergic inflammation on these organs and is the focus of this section. Hypotheses as to these interactions are abundant but center around a few plausible explanations: (*1*) allergic inflammation leads to nasal mucosal edema, which in turn prevents drainage from the sinuses and ears and leads to symptoms in these organs; (*2*) nasal allergic inflammation stimulates nasal afferent nerves, which then generate efferent or axonal reflexes that could involve the contralateral nasal cavity, the eyes, and the paranasal sinuses; and (*3*) allergic inflammation of the nose leads to the priming of circulating leukocytes or the release into the circulation of inflammatory cytokines, which could then home in on other organs (eyes, sinuses, lungs, ears), creating inflammation within these organs as well, a phenomenon referred to as systemic allergic inflammation.

Nasonasal Interactions

Sneezing and itching during the early response to allergen provocation involve the nervous system. Unilateral intranasal antigen challenge experiments have supported the role of the nervous system in amplifying the allergic response as challenge not only leads to an increase in sneezes, rhinorrhea, nasal secretions, histamine, nasal airway resistance (14), and prostaglandin D_2 (PGD_2) (15, 16) on the side of challenge, but also to an increase in rhinorrhea, secretion weights, and PGD_2 contralateral to the challenge (16). The contralateral secretory response is rich in glandular markers (15) and is inhibited by atropine, an anticholinergic (14), suggesting that the efferent limb is cholinergically mediated. A similar nasonasal secretory reflex has been documented, not only after allergen challenge but also in

response to several stimuli including histamine, cold dry air, and capsaicin (14, 17–20). Several neuropeptides—in addition to sympathetic and parasympathetic nerves and their transmitters—are found in the nasal mucosa. These neuropeptides are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene–related peptide [CGRP], neurokinin, gastrin-releasing peptide), parasympathetic nerve endings (vasoactive intestinal peptide, peptide histidine methionine), and sympathetic nerve endings (neuropeptide Y). Substance P (SP), a member of the tachykinin family, is often found as a cotransmitter with neurokinin and CGRP; it has been found in high density in arterial vessels and, to some extent, in veins, gland acini, and epithelium (21). Several studies support the concept that neuronal mechanisms mediated by these peptides amplify the inflammatory allergic reaction (22–28). Mosimann and colleagues were able to demonstrate significant increases in the levels of SP, CGRP, and vasoactive intestinal peptide immediately after antigen challenge in allergic individuals, and in patients who experienced a late reaction only SP increased slightly (29). These experiments suggest that neuropeptides are released *in vivo* in humans after allergen challenge and might be partly responsible for symptoms of the allergic reaction. Repetitive application of capsaicin, the essence of chili peppers, releases SP and CGRP from sensory nerves and initiates both central and axonal reflexes (30). Capsaicin causes a burning sensation and profuse bilateral rhinorrhea when applied to one side of the nasal cavity, and repeated administration causes tachyphylaxis (31, 32). The capsaicin-induced nasal secretory response in humans is glandular and not caused by increased vascular permeability (20). Furthermore, capsaicin desensitization reduces sneezing in response to antigen and histamine challenges (33). All these findings point to the importance of the participation of neurogenic elements to the nasal response and their role in amplifying that response.

Nasal–Ocular Interactions

In patients with allergic rhinitis, eye symptoms including tearing, itching, and eye redness are an important part of the disease and the target of symptomatic therapy. The most logical and simple explanation of eye symptoms in allergic exposure is that pollen deposits on the conjunctiva and generates an allergic reaction similar to that produced in the nasal cavity after pollen exposure. Evidence, however, also supports the involvement of a nasal–ocular reflex in the genesis of eye symptoms in allergic rhinoconjunctivitis. In support of direct allergen deposition resulting in the symptoms is the fact that ocular allergen challenge leads to symptoms of watery and itchy eyes that are associated with the release of inflammatory mediators, including histamine, in ocular secretions (34, 35). In support of nasal–ocular reflexes is the existence of the nasonasal reflex as discussed previously, whereby allergen depositing on the nasal mucosa can trigger afferent reflexes that then propagate centrally. The efferent limbs of these reflexes could then be propagated not only to the contralateral nasal cavity but also to both conjunctivae. Other possible mechanisms to explain eye symptoms related to the nose is that the nasal allergic reaction leads to the release of mediators from the nose and upregulation of circulating cells, which, when attracted to the eye, are primed to release more mediators and cause more severe symptoms. Another possibility is direct propagation of allergen from the nose to the eye via the nasolacrimal duct. This is not a likely mechanism as the direction of flow of secretions within the nasolacrimal duct is usually from the eye to the nose and not in the opposite direction. Furthermore, the orifice of the nasolacrimal duct in the nasal cavity is in the inferior meatus, well shielded by the inferior turbinate from external penetration by allergen.

We have focused on attempting to explain the nasal–ocular reflex response. Prior studies of the nasal–ocular reflex after antigen stimulation have yielded mixed results. Lebel and colleagues, in a nasal challenge study, reported that approximately 20% of allergic rhinitis sufferers experienced ocular symptoms during nasal provocation with grass pollen, suggesting that allergic ocular symptoms can occur without direct exposure of the conjunctiva to allergen (36). Loth and Bende, on the other hand, concluded that nasal challenge with allergen does not increase lacrimal gland secretion, because inhibition of parasympathetic nerves by lidocaine did not reduce tears (37). The conclusions of their study can be questioned because the placebo arm failed to demonstrate any significant increase in lacrimation after nasal challenge with allergen, thus putting the value of the results obtained from the lidocaine arm of the study in doubt. Other studies using different forms of stimulation have supported the existence of a nasal–ocular reflex. Zilstorff-Pedersen reported bilateral lacrimation after unilateral irritation of the nasal mucosa (38). Using capsaicin as a stimulant and as a desensitizer, Philip and colleagues showed that unilateral nasal challenge with capsaicin produced ocular tearing and watering. This was reduced significantly after repeated capsaicin challenges that led to desensitization of the response (20).

To determine whether nasal challenge with antigen induces a nasal–ocular reflex, we performed a double-blind crossover trial in 20 subjects with seasonal allergic rhinitis (39). We speculated that histamine, released by mast cells on allergen deposition on the nasal mucosa, initiated the afferent limb of the reflex response, which resulted in contralateral nasal symptoms and also ocular symptoms within minutes of challenge. We therefore evaluated the effect of a topical antihistamine, azelastine, applied to the nasal cavity on the side of challenge on both the nasal and ocular reflex responses. Subjects were challenged with antigen in one nostril, using filter paper disks, and the response was monitored in both nostrils and in both eyes. Symptoms were recorded. Disks (intranasally) and Schirmer strips (intraocularly) were used to collect secretions in both nostrils and eyes and were weighed before and after collection, allowing us to calculate the weight of generated nasal and ocular secretions, objective measures of rhinorrhea and watery eyes, respectively. The disks and Schirmer strips were then placed in buffer to allow elution of collected secretions and the supernatants were measured for levels of histamine, an indicator of mast cell activation, and albumin, a marker of vascular permeability.

Subjects were treated once topically at the site of challenge with azelastine or placebo. After placebo treatment, ipsilateral nasal challenge caused nasal symptoms and an increase in bilateral nasal secretion weights, both of which were blocked by treatment with azelastine. Levels of histamine and albumin increased only at the site of nasal challenge and azelastine inhibited the increase in albumin, but not histamine. These findings are not new and have been demonstrated by our, and other, laboratories previously. They cement the existence of a nasonasal reflex and the important role of histamine in its generation. Concerning the ocular response, symptoms of itchy and watery eyes increased significantly after allergen challenge, compared with sham challenge, when the subjects were premedicated with placebo (Figure 1). This supports our hypothesis of the role of the nasoocular reflex in the generation of ocular symptoms after allergen deposition on the nasal mucosa. Furthermore, the eye symptoms were inhibited by premedication with azelastine, also suggesting that histamine, released by allergen challenge, was important in the genesis of ocular symptoms (Figure 1). Ocular secretion weights increased bilaterally after placebo and were not inhibited by azelastine.

Unfortunately, ocular secretion collection was technically difficult and ocular secretion weights are probably not as reliable an indicator of the ocular response as eye symptoms. This is related to the fact that the Schirmer strips led to irritation of the eyes and a high baseline of secretions even after the sham nasal challenge. In summary, the preceding data suggested that nasal allergen challenge induces histamine release at the site of the challenge, which causes both a nasonasal reflex and a nasal–ocular reflex. This antigen-induced reflex is blocked by an H_1 receptor antagonist applied at the site of the challenge. These observations support the hypothesis that eye symptoms associated with allergic rhinitis probably arise, at least in part, from a nasal–ocular reflex.

To follow up on this study and investigate the effects of intranasal steroids on the nasal–ocular reflex, we performed a double-blind, placebo-controlled, crossover experiment in 20 subjects who had seasonal allergic rhinitis (40). We hypothesized that repeated nasal allergen challenges would lead to priming and augmentation of nasonasal and nasal–ocular reflexes and that intranasal steroids would decrease inflammation and subsequently inhibit both nasonasal and nasal–ocular reflexes, thus resulting in reduction of eye symptoms. Nasal antigen challenge was performed consecutively for 3 days after 1 week of treatment with either placebo or fluticasone furoate nasal spray. Subjects recorded their nasal and ocular symptoms, and nasal secretions were quantified. Nasal scrapings for quantifying eosinophils were obtained before each antigen challenge. When subjects were receiving placebo, nasal challenge with antigen led to sneezing and to nasonasal and nasal–ocular reflexes. Priming in the number of sneezes, contralateral nasal secretion weights, and total eye symptoms was observed. Pretreatment with fluticasone furoate nasal spray reduced sneezing, the nasonasal and nasal–ocular reflexes, and the amount of eosinophils in nasal secretions (Figure 2). The results of this study helped confirm the existence of a nasal–ocular reflex after allergen challenge of the nose, and demonstrated the exaggeration, or priming, of this reflex by repeated exposure to allergen and thus supported the role of the nasal–ocular reflex in the genesis of at least part of the eye symptoms in patients with allergic rhinoconjunctivitis. This study also helped demonstrate the efficacy of an intranasal steroid (fluticasone furoate) in reducing allergic inflammation, priming, and subsequently the nasal–ocular reflex and ocular symptoms. Our results therefore support a mechanism that helps explain how control of eye symptoms can be achieved by the administration of an intranasal steroid in patients with seasonal allergic rhinitis.

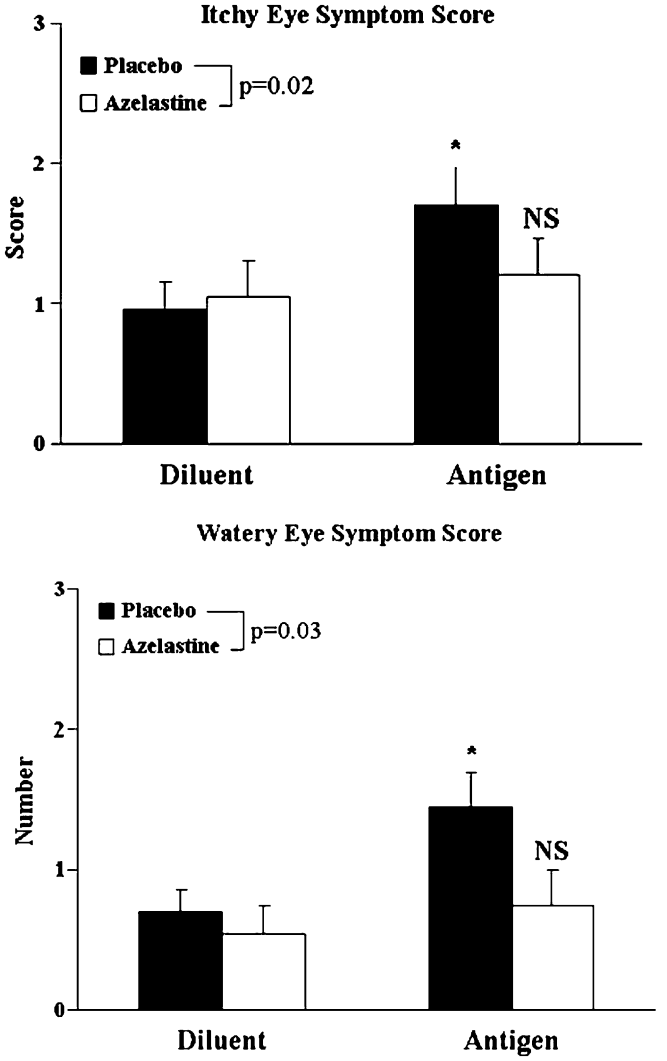

Figure 1. Itchy and watery eye symptom scores after challenge with either the diluent for the allergen extract or grass or ragweed allergen. *Solid columns,* responses after pretreatment with placebo; *open columns,* responses after pretreatment with azelastine. There was a significant increase in both itchy and watery eye symptoms after nasal allergen challenge compared with the diluent challenge with the patients receiving placebo. Pretreatment with azelastine intranasally resulted in inhibition of eye symptoms after nasal allergen challenge, or the nasal–ocular reflex response. *$P \leq 0.004$ versus respective diluent challenges (NS, not significant). Reprinted with permission from Reference 86.

Nose–Sinus Interactions

In close proximity to the nose are the paranasal sinuses, which include the frontal, anterior, and posterior ethmoid, maxillary, and sphenoid sinuses. These air-filled spaces are well known to cause disease manifested as inflammation and infection within them and referred to as rhinosinusitis (acute and chronic). Several clinical studies support the increased prevalence of sinusitis in subjects with allergic rhinitis. A good deal of evidence points away from a primary allergic reaction occurring in the sinuses. In one study, supraphysiological amounts of ^{99m}Tc-labeled ragweed pollen inhaled into the nose did not enter the paranasal sinuses (41). This finding is supported by histological studies showing that tissue-specific IgE antibodies to house dust mites were found in the nasal mucosa, but levels in the sinus mucosa of atopic patients with sinusitis were not significantly different from those of nonatopic patients with sinusitis (42). Imaging studies have been supportive of the preceding thesis. Although viral upper respiratory tract infections can result in marked abnormalities on sinus computed tomography (CT) (43), uncomplicated allergic rhinitis shows little or no change (44). In a later study, three other imaging techniques, single-photon emission computed tomography (SPECT) bone imaging, SPECT ^{111}In-labeled white blood cell uptake, and 2-18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography failed to show any changes in the sinuses in allergic rhinitis (45). In contrast, a study of CT scans performed on adults during the ragweed allergy season showed sinus changes (without clinical symptoms of sinusitis) in about 50% of these subjects (46). We have been interested in studying the relationship between sinusitis and allergic rhinitis in humans. To this end, we developed a model whereby human volunteers had a catheter inserted into their maxillary sinus under local anesthesia and this allowed us to repetitively sample the maxillary sinus by lavage. We then challenged the nasal

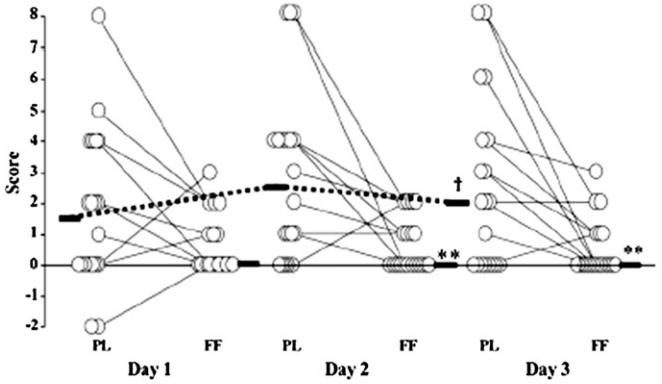

Figure 2. Effect of premedication with intranasal fluticasone furoate on total eye symptoms (itchy and watery) after nasal allergen challenge. Individual responses represent the net change from diluent challenge, with *solid bars* representing median values. Days 1, 2, and 3 are the consecutive days of challenge that were conducted to demonstrate a priming response. *PL* and *FF* represent pretreatment with either placebo or fluticasone furoate nasal spray. The *dotted line* connects the total eye symptom scores obtained with the patients receiving placebo during the consecutive day challenges and demonstrates an increase in symptoms on consecutive challenge, suggesting priming of the response ($^{\dagger}P \leq 0.04$ vs. Day 1). Premedication with FF resulted in a reduction in eye symptoms after nasal allergen challenge on Days 2 and 3 of the challenge protocol ($^{**}P \leq 0.01$ vs. placebo). Reprinted with permission from Reference 40.

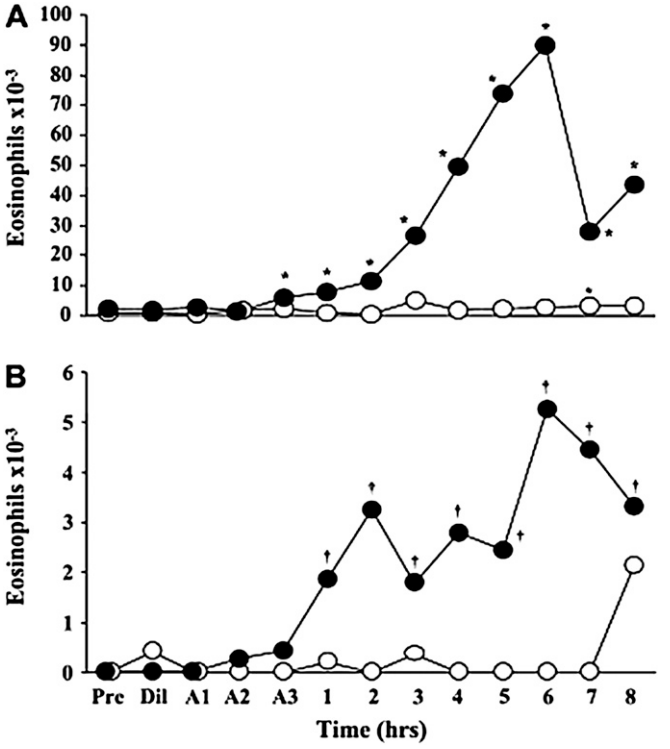

Figure 3. Influx of esoinophils into (*A*) nasal and (*B*) maxillary sinus secretions after either control (*open circles*, n = 11) or allergen (*solid circles*, n = 20) challenge. The x axis represents the challenge protocol: Pre, prechallenge baseline; Dil, diluent for the allergen extract; A1–A3, allergen challenge at three increasing doses; 1–8, sampling performed hourly for 8 hours after the challenge and representing the late-phase response. $^{*}P \leq 0.05$ and $^{\dagger}P < 0.01$ versus respective diluent challenges. There was a significant influx of eosinophils into both nasal and sinus secretions hours after allergen, but not control, challenges, with the nasal response almost 10 times higher in magnitude than the sinus response. Reprinted with permission from Reference 47.

cavity with allergen and sampled both the nasal cavity and the ipsilateral sinus cavity for 8 hours after allergen challenge (47). The most important finding from these studies is an eosinophil influx into the maxillary sinus during the late-phase response, which although smaller in magnitude compared with the nasal response was significantly increased over baseline (Figure 3). In another set of experiments, we challenged one nasal cavity with allergen and documented a similar influx of eosinophils not only in the ipsilateral maxillary sinus but also in the contralateral sinus. This suggests a possible systemic effect of nasal allergen provocation whereby nasal allergic inflammation induces a systemic response that is also manifest in both maxillary sinuses. These findings might explain the close relationship between allergic rhinitis and rhinosinusitis. Other studies of sinus lavage in patients with chronic rhinosinusitis have shown elevated levels of several mediators including histamine, prostaglandin D_2, and leukotrienes (48).

Nose–Ear Interactions

Acute otitis media, or infection of the middle ear, and otitis media with effusion (OME), fluid in the middle ear without symptoms of infection, are among the most common problems of childhood. A number of clinical studies have evaluated the association between allergic rhinitis and OME, with one series demonstrating a 21% prevalence of OME in unselected schoolchildren with allergic rhinitis (49) and another finding a 50% prevalence of allergic rhinitis in children with OME (50). In one study of 209 children with a history of chronic or recurrent otitis media who had been referred to a multidisciplinary "glue ear/allergy" clinic, allergic rhinitis was confirmed in 89%, asthma in 36%, and eczema in 24%. Rhinitis was diagnosed on the basis of a history of rhinorrhea and nasal obstruction and was classified as allergic if the child also had at least two of the following features: excessive sneezing, nasal itch, allergic crease/salute, pale and/or swollen turbinates, or one of these features plus a positive skin prick test or nasal eosinophilia. In addition, medical history and physical examination were performed in all children, and some were further evaluated for total IgE levels. Skin tests were positive to one or more of eight common inhalant allergens in 57% of children, and, among those undergoing serum testing, peripheral eosinophilia was documented in 40% and elevated serum IgE in 28%. Although there is a clear possibility of referral bias in this specialty population, the high frequency of allergy is notable (51).

The association between allergic rhinitis, recurrent otitis media, and OME is consistent with a unified airway model in atopic patients (52). The mucosa of the middle ear is an extension of the mucosa of the upper nasal passages, and the mucosa of the eustachian tube structurally resembles bronchial mucosa (49). Because the eustachian tube is contiguous with the nasopharynx, nasal allergic inflammation may contribute to edema and inflammation of the eustachian tube in the same manner as in the nasal mucosa, that is, through allergen-induced inflammatory mediators released by mucosal mast cells and other inflammatory cells (51, 53–55).

Analysis of middle ear effusions from atopic subjects with allergic rhinitis has demonstrated a pattern of inflammatory mediators not seen in nonatopic children, with significantly higher levels of eosinophil activity markers, mast cell products, and cytokines (49, 56, 57). Among atopic patients undergoing simultaneous tympanostomy tube placement for OME and adenoidectomy for adenoid hypertrophy, the middle ear fluid

had significantly higher levels of eosinophils, T lymphocytes, and IL-4 mRNA–positive cells and significantly lower levels of neutrophils and IFN-γ mRNA–positive cells compared with nonatopic patients. Similar cytokine and cellular profiles were noted in the excised adenoidal tissue, suggesting an allergic inflammatory response occurring on both sides of the eustachian tube (52). The linkage between inflammatory phenomena throughout the upper airways is further supported by results from Abdullah and colleagues (58), who reported that the population of mast cells in postoperative adenoid specimens from children with OME undergoing adenoidectomy was significantly greater than in children without OME. This suggests the presence of interwoven inflammatory processes between the upper airway and the ears.

Nose–Lung Interactions

The coexistence of allergic rhinitis and asthma has been extensively documented (59–61). Asthma is more common in patients with allergic rhinitis ("allergic march") (62, 63) than in those without, with as many as 50% of patients with allergic rhinitis having asthma (59–64). Furthermore, approximately 80 to 90% of patients with asthma have allergic rhinitis, with allergic rhinitis often preceding or occurring at the same time as asthma (62). Nonspecific bronchial hyperresponsiveness is also increased in patients with allergic rhinitis compared with nonrhinitic/nonasthmatic subjects, suggesting that patients with allergic rhinitis have an intermediate degree of bronchial hyperreactivity compared with nonallergic/nonasthmatic patients at one end of the spectrum and overt asthmatic patients at the other (60, 62, 65). Allergic rhinitis exacerbates asthma symptoms in patients with asthma and increases the risk of an acute attack, emergency treatment, and hospitalization (59). The association of asthma and allergic rhinitis is robust enough that atopic patients presenting with symptoms of either condition are usually evaluated for the presence of the other.

In patients with allergic rhinitis with a history of asthma exacerbations, bronchial hyperresponsiveness is increased after nasal allergen provocation (66). Consistent with bidirectional pathophysiological connections of the upper and lower tracts, bronchial challenge alone has also been shown to induce a nasal inflammatory reaction, and nasal challenge with allergen was also shown to lead to bronchial inflammatory changes (67). Moreover, challenge testing in patients with allergic rhinitis who do not have asthma has revealed abnormalities of lower airway function that are significantly different from those of nonallergic control subjects and that are comparable to changes in bronchial sensitivity observed in patients known to have asthma (68).

Although a review of the long-term and emergency management of asthma is beyond the scope of this discussion, it is well established that appropriate treatment of allergic rhinitis can improve asthma control and result in lower rates of hospitalization or emergency department visits due to asthma exacerbations (59). A retrospective cohort study enrolling 4,944 patients with both allergic rhinitis and asthma evaluated health care use by patients treated with intranasal steroids versus an untreated group. Asthma-related events occurred more often (7%) in the untreated group compared with the treated group (1%). Likewise, the risk of an asthma-related hospitalization or asthma-related emergency department visit among the group treated with intranasal steroids was about half that for untreated patients (69), suggesting that patients treated for allergic rhinitis have a significantly lower risk of asthma-related events than untreated subjects. A retrospective study evaluated claims data for 13,844 patients with asthma and determined that patients who received intranasal steroids for an associated upper airway condition (allergic rhinitis, rhinosinusitis, or otitis media) had a reduced risk of emergency department visits in comparison with patients receiving prescription antihistamines (70). In a case–control study, patients with allergic rhinitis and asthma who used intranasal steroids had a significantly lower risk of both asthma-related emergency room treatment and hospitalization compared with patients who used second-generation antihistamines. Furthermore, treatment with both medications was associated with an even further risk reduction (71).

Sinus–Lung Interactions

The association between sinusitis and asthma has long been appreciated. In one study, 100% of steroid-dependent patients with asthma had abnormal CT scans of the sinuses versus 77% of subjects with mild to moderate asthma (72). In another group of patients with severe asthma, 84% showed CT abnormalities. There was a significant correlation between CT scores, eosinophils in peripheral blood and induced sputum, and level of exhaled NO (73). The sinusitis typically associated with asthma has been termed chronic hyperplastic eosinophilic sinusitis, which is often associated with nasal polyps and has also been referred to as chronic rhinosinusitis with nasal polyposis. It has been suggested that this entity is best understood as "asthma of the upper airways" (74).

Although these studies strongly suggest that sinusitis triggers or worsens asthma, it could be argued that they merely coexist and represent different end products of the same inflammatory process occurring in different organ systems. Various mechanisms have been proposed to explain the relationship between sinusitis and asthma. In one intriguing study of 106 patients with chronic rhinosinusitis, histamine challenges to the lower airway before and after medical treatment of rhinosinusitis were performed. The FEV_1 was measured as an index of bronchial narrowing, and mid-inspiratory flow, as an index of extrabronchial airway narrowing (75). The intrabronchial and extrabronchial hyperreactivity decreased, with the reduction in extrabronchial hyperreactivity being more pronounced and preceding the intrabronchial hyperreactivity decline. The changes in intrabronchial and extrabronchial reactivity were strongly associated with pharyngitis as determined by history, physical examination, and nasal lavage. The authors propose that airway hyperresponsiveness in rhinosinusitis might depend on pharyngobronchial reflexes triggered by seeding of the inflammatory process into the pharynx through postnasal drip of mediators and infected material from affected sinuses. In a later study, these same authors demonstrated actual damage of the pharyngeal mucosa in patients with chronic rhinosinusitis, marked by epithelial thinning and a striking increase in pharyngeal nerve fiber density (76). This would favor increased access of irritants to submucosal nerve endings inducing the release of sensory neuropeptides via axon reflexes with activation of a neural arch, resulting in reflex airway constriction.

The linkage previously described between asthma and sinusitis severity, including eosinophils in the peripheral blood and sputum and NO levels in exhaled air, would support the concept that the influence of upper respiratory disease on asthma is mediated through the circulation. It has been hypothesized that inflamed sinus tissue not only releases mediators and cytokines into the circulation, thereby directly inducing inflammation of the upper airway, but also releases chemotactic factors that recruit eosinophils from the bone marrow and from the circulation into the upper and lower airways (77). In a comparative study, the histopathological markers of asthma were also present in sinonasal specimens from patients with chronic rhinosinusitis (78). This included eosinophilic inflammation and features of airway remodeling, such as erosion of the epithelium and basement membrane thickening. These

findings along with the high clinical overlap suggest that chronic rhinosinusitis and asthma are part of the same disease process; an eosinophilic inflammation of airway mucosa stretching from the nostril down to the alveoli.

Perhaps the most direct evidence of a cause-and-effect relationship of sinusitis to asthma is provided by studies that show significant improvement in asthma symptoms when sinusitis is appropriately treated. Although not completely controlled, several studies in children with combined sinusitis and asthma have demonstrated significant improvement in the asthmatic state when sinusitis was medically treated (79, 80). Sinus surgery has also been shown to result in improvement in lower airway disease. In a study of 15 adult patients with chronic rhinosinusitis who required inhaled corticosteroids and at least intermittent oral prednisone to control asthma, the authors report an improvement in symptoms and a decline in both total dosage and number of days of steroid use in the postoperative year (81). More objective findings were reported in a study on adult patients who not only showed improvement in symptoms, but also had a significant increase in peak expiratory flow after endoscopic sinus surgery (82). In another study, Dunlop and colleagues monitored 50 patients with asthma with chronic rhinosinusitis with or without nasal polyposis who had failed medical management (83). The patients underwent functional endoscopic sinus surgery (FESS) and were monitored for 12 months. Compared with their preoperative status, in the 12 months after FESS, 40% of patients noted that their asthma was easier to control, 54% stated that there was no difference, and 6% indicated that their asthma worsened. Peak flows were available for 23 of the 50 patients and of those 50, 28% were improved postoperatively, 6% were worse, 22% remained the same, and 44% did not submit peak flow measurements. There were significant reductions in oral steroid requirements and hospitalizations for asthma after FESS. There were no significant differences in outcome when the groups with and without polyposis were compared. Dejima and colleagues examined the outcomes of FESS prospectively in a population with chronic rhinosinusitis (84). They found that outcomes of FESS were significantly worse in the asthma group, especially when it came to endonasal findings. However, in the patients with asthma, there was significant improvement in asthma symptoms, peak flow, and medication scores after FESS, and the patients with a good FESS result tended to have the greatest improvement in their asthma outcomes. In one of the few negative studies reported, Goldstein and colleagues examined in a retrospective manner asthma outcomes after first-time FESS in 13 patients with chronic rhinosinusitis (85). They found no improvement in terms of asthma symptoms, medication use, pulmonary function test results, or the number of emergency department visits or hospital admissions. Notwithstanding that this study was retrospective and observational, and involved only 13 patients, the authors suggested revisiting the common belief that FESS benefits coexisting asthma in patients with chronic rhinosinusitis.

In summary, the majority of published reports suggest that ameliorating CRS by FESS improves asthma outcomes. Unfortunately, most of the studies are hampered by a myriad of limitations including small sample sizes, limited follow-up duration, retrospective designs, and lack of a control group in most cases.

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