Impact of IgE-Mediated Hypersensitivity on Nasal Mucociliary Clearance

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Objective: To evaluate the effect of IgE-mediated hypersensitivity on mucociliary clearance time (MCCT) and clinical severity, as indicated by total nasal symptoms score (TNSS) and peak expiratory flow index (PEFI).

Design: A prospective cross-sectional study.

Setting: Tertiary medical center.

Participants: One hundred twenty-nine patients with rhinitis and 48 healthy control subjects.

Main Outcome Measures: Results of an allergy skin prick test in the patients with rhinitis categorized them as allergic (AR) or nonallergic (non-AR). We evaluated TNSS and PEFI in the patient group and assessed MCCTs from the patients in the rhinitis groups and the healthy controls.

Results: The AR group patients had the longest MCCT, followed by patients in the non-AR group and the healthy controls (mean MCCTs, 14.36, 10.87, and 6.55 minutes, respectively). The AR group patients had significantly higher TNSS and worse PEFI compared with patients in the non-AR group (P = .002 and P = .03, respectively). We found a significant positive correlation of MCCTs with TNSS, and MCCTs showed a tendency to be inversely correlated with PEFI (r = 0.43 [P < .001] and r = −0.22 [P = .05], respectively). In AR group patients, the wheal responses to Dermatophagoides pteronyssinus, Dermatophagoides farinae, American cockroach, and Bermuda grass were fairly correlated with the MCCTs (r = 0.39 [P = .001], r = 0.40 [P = .001], r = 0.34 [P = .01], and r = 0.36 [P = .02], respectively). The maximal wheal response among various positive allergen responses was well correlated with the MCCTs (r = 0.54 [P < .001]).

Conclusion: A prolonged MCCT, significant correlation between MCCTs and the magnitude of allergen reactivity, and clinical severity suggest an impact of IgE-mediated hypersensitivity on mucociliary clearance function.


Allergic rhinitis (AR) is classically considered to result from an IgE-mediated allergy associated with a nasal inflammation of variable intensity. Epidemiological data have shown a high association between allergies and long-term respiratory disease, nasal infection, sinusitis, and otitis media, but the mechanism of how IgE-mediated hypersensitivity predisposes to these comorbidities remains unclear. Filtration of inspired air is one of the major functions of the nose. Nasal mucociliary clearance (MCC), an important host defense of the ciliated epithelium of the upper respiratory tract against foreign particles, including bacteria, has been found to be altered in several respiratory diseases. The impaired ciliary and/or secretory components of the MCC system caused by allergic inflammation might interfere with the normal mechanical, physiological, and biological protective functions of the airway mucosa and predispose to these respiratory comorbidities.

The relationship between allergy and nasal MCC function has been evaluated in various studies, but a consensus has not been reached. These studies may be criticized because the control groups consisted of healthy subjects, but of course a disturbance of the MCC function in any patient with rhinitis and mucosal inflammation compared with healthy subjects would not be unexpected. To study the association, we first compared the differences in MCC times (MCCTs) in patients with AR, in patients with nonallergic rhinitis (non-AR), and in healthy control subjects and the difference in total nasal symptoms score (TNSS) and peak expiratory flow index (PEFI) between AR and non-AR patient groups to explore the role of IgE-mediated hypersensitivity in MCC and clinical disease severity. We examined the
correlation between MCCTs and TNSS/PEFI for exploring the clinical relevance of MCC dysfunction and clinical disease severity. We then evaluated the correlation between magnitude and total number of the allergen sensitivities and MCCTs for better understanding of the effect of IgE-mediated hypersensitivity on MCC function.

METHODS

A prospective cross-sectional study was conducted on 129 patients with rhinitis and 48 healthy volunteers at the Allergy and Rhinology Clinic, Department of Otolaryngology, Faculty of Medicine, Songklanagarind Hospital, from January 1, 2007, through September 30, 2008. Patients with non-AR were used as an active control group with the aim of excluding other nonallergic risk factors that might affect non-specific mucosal inflammation. Healthy volunteers were also recruited to serve as a baseline control group. Measurements of MCCT, an overall integrated measurement of ciliary function, were used as objective data in relation to underlying mucosal inflammation to provide an assessment of the net effect of disease processes. Measurements of the TNSS, a subjective disease severity rating method, and nasal and oral PEFI, an objective assessment of nasal patency, were used to evaluate clinical disease severity.

The protocol was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. All patients and healthy volunteers gave their signed, informed consent before being recruited into the study. Subjects with a history of current or recent smoking, those with a smoking history of more than 10 pack-years, or those who had used intranasal, inhaled, or systemic corticosteroids during the previous 2 months, a first-generation antihistamine within the previous 2 days, a non-sedating antihistamine within the previous 1 week, or a decongestant within the previous 2 days were excluded from the study. Healthy controls were recruited from volunteers in the local community. Volunteers were not accepted if they had health care-associated risk factors, that is, if they were members of the hospital staff or other medical personnel, had a cold or a sinonasal infection in the past 8 weeks, had signs or symptoms suggestive of sinonasal disease, had a known systemic disease, or had had previous sinus or nose surgery. All healthy volunteers were given a prestudy examination and had normal findings.

DATA COLLECTION PROCEDURES

For the rhinitis groups, medical history, including age, sex, nasal symptoms, concomitant diseases, and medications, was recorded. Asthma was noted if the patient had a history of recurrent wheezing, dyspnea, chest tightness, or cough (particularly at night) but normal findings on a chest radiograph. Patients with rhinitis were excluded if they had symptoms or nasal endoscopic or sinus radiographic (Caldwell and Waters positions) findings suggestive of drug-induced rhinitis, occupational rhinitis, rhinosinusitis, nasal polyposis, neoplasm, or severe septal deviation. After excluding these known causes of nonallergic sinonasal diseases, an allergy skin prick test was performed with 18 common aeroallergens (Bermuda grass, Johnson grass, acacia, careless weed, Alternaria species, Aspergillus mix, Candida albicans, Penicillium mix, fusarium, cat pelt, dog epithelium, mixed feathers, kapok, Dermatophagoides pteronyssinus, Dermatophagoides farinae, American cockroach, pythrum, and Cladosporium sphaerospermum; Al-lertechn Co, Ltd, Bangkok, Thailand). Histamine phosphate was used as a positive control and glycerin saline as a negative control. Skin wheal diameter was determined at 20 minutes using the mean of the longest diameter and the perpendicular midpoint diameter. A positive reaction was defined as a skin wheal diameter of at least 3 mm greater than the negative control skin wheal. These results were used to divide the patients into 2 groups: the AR group (patients who had a positive skin reaction to at least 1 aeroallergen) and the non-AR group (patients whose skin reactions were all negative).

Evaluation of the nasal symptoms of each patient with rhinitis was based on a compilation score assessing blocked nose, rhinorrhea, sneezing, nasal itching, and postnasal drip, scored as follows: 0 indicates no symptoms; 1, mild symptoms (present but not troublesome); 2, moderate symptoms (troublesome symptoms but not sufficient to interfere with sleep, daily activities/sport, and/or work/school); and 3, severe symptoms (symptoms interfere with ≥1 of the items listed in 2). The sum of the individual scores for nasal blockage, rhinorrhea, sneezing, nasal itching, and postnasal drip produced the TNSS.

Nasal patency was assessed for each patient with rhinitis by using the nasal and oral PEFI. A peak flowmeter (Mini-Wright; Clement Clarke International Ltd, London, England) connected to an anesthetic face mask covering the nose and mouth was used instead of a mouthpiece for nasal peak expiratory flow measurements. The patients were instructed to keep their lips tightly closed while performing the maximal total expiratory effort through the nose after a maximal inspiration. Peak flow rate was read from a cursor in liters per minute. The best of 3 readings with a variation of less than 10% was considered to be the true peak flow, which was given as the result. The PEFI was calculated as the nasal peak expiratory flow divided by the oral peak expiratory flow to compensate for changes in lung function.

MCCTs were measured in the healthy control and rhinitis groups with the use of a mixture of charcoal and saccharin powder in all subjects, following the method described by Rutland and Cole, which is a modification of Andersen’s original description of the test. A 1- to 2-mm patch of charcoal-saccharin powder was placed on the anterior end of the inferior turbinate, behind the area of slow anterior clearance, 1 cm below the top of the concha. The subject was asked to sit quietly with head forward and not to sniff or sneeze. The subjects were asked to note their first sensation of a sweet taste, at which time the pharyngeal wall was examined for a charcoal-like appearance. Repeated inspections were made at 15-second intervals until the charcoal appearance was observed to establish the MCCT. The patients were asked to wait until the sweet taste was gone and no charcoal was seen in the nasopharynx and oropharynx. The test was repeated in the other nasal passage, and the average of the 2 times was taken as the MCCT for the subject. This was done to exclude a potential effect of nasal cycle on MCCT. The charcoal-saccharin tests were performed from 1 to 3 PM to eliminate the influence of circadian and nasal rhythms.

STATISTICAL ANALYSIS

Demographic data were summarized as number, mean, and range; and each nasal symptom score and MCCT was analyzed as mean (SD). The MCCTs were then compared among the AR, non-AR, and healthy control groups. Because the normality and homogeneity assumptions were satisfied, 1-way analysis of variance was used first to ascertain whether significant variance existed among the groups, and, if a significant difference was apparent, post hoc multiple comparisons using the Tukey test were then used to test the significance of the differences between the groups. We compared the TNSS and PEFI between the AR and non-AR groups using the Mann-Whitney test and unpaired t test, respectively. Comparison of MCCTs
between the AR and non-AR groups at each TNSS used the unpaired t test. Correlations among the PEFI, maximal wheal responses of allergen reactivities or total number of allergen reactions, and MCCT were analyzed by Pearson correlation coefficients. Correlations between TNSS and MCCT or maximal wheal response among various positive allergen responses were analyzed using Spearman rank correlation coefficients. The associations between MCCT as a dependent variable and wheal responses to *D pteronyssinus*, *D farinae*, American cockroach, and Bermuda grass as independent variables were tested using multiple regression analysis. In all tests of significance, 2-tailed alternatives were used. \(P < .05\) was considered statistically significant.

### RESULTS

We enrolled 81 patients in the AR group, 48 in the non-AR group, and 48 healthy controls. Their characteristics are presented in the Table. There were no statistically significant differences in demographic data among the 3 groups. All patients had had nasal symptoms for at least 6 months. There was no significant difference in duration of symptoms between the AR and non-AR groups. The patients in the AR group had a significantly higher rate of concomitant asthma than did those in the non-AR group (\(P = .001\)) and significantly more rhinorrhea, sneezing, and nasal itching (\(P = .006, P = .01,\) and \(P = .002\), respectively) but not nasal blockage or postnasal drip (\(P = .14\) and \(P = .23\), respectively).

**COMPARISONS OF MCCTS AMONG GROUPS**

The MCCTs of the AR and non-AR groups and healthy controls are also presented in the Table. In comparisons of MCCTs among the groups, the patients in the AR group had the worst MCCTs, followed by those in the non-AR group and the healthy controls (mean MCCTs, 14.36 [4.54], 10.87 [3.43], and 6.55 [1.91] minutes, respectively). The MCCTs of the AR and non-AR groups were significantly longer than those of the healthy controls (\(P < .001\)), and the MCCTs of the AR group were significantly longer than those of the non-AR group (\(P < .001\)) (Figure 1).

**EFFECT OF IgE-MEDIATED HYPERSENSITIVITY ON TNSS AND PEFI**

The TNSS and PEFI of the AR and non-AR group patients are presented in the Table. The patients in the AR group had significantly higher TNSSs and worse PEFIs compared with those in the non-AR group (\(P = .002\) and \(P = .03\), respectively) (Figure 2). The TNSSs demonstrated a significant positive correlation with MCCTs (\(r = 0.43\) [\(P < .001\)]), and PEFIs showed a tendency to be inversely correlated with MCCTs (\(r = -0.22\) [\(P = .05\)]. The TNSSs tended to be correlated with maximal wheal response among various positive allergen responses (\(r = 0.23\) [\(P = .05\)]. With the same TNSS severity, patients in the AR group showed longer MCCTs compared with patients in the non-AR group and reached statistical significance in several TNSS comparisons (Figure 3).

**RELATIONSHIPS BETWEEN MCCTS AND ALLERGEN REACTIVITY**

The most frequently demonstrated sensitivity reaction was to *D pteronyssinus*, followed by *D farinae*, American cockroach, and Bermuda grass (80.2%, 77.8%, 56.8%, and 14.8%, respectively). A few subjects reacted to the other allergens (Johnson grass, cat pelt, kapok, acacia, dog epithelium, *Aspergillus* mix, mixed feather, pyrethrum, *C sphaerospermum*, and *Alternaria* species). Wheal responses to *D pteronyssinus*, *D farinae*, American cockroach, and Bermuda grass were fairly correlated with...
Nasal MCC, an important host defense of the ciliated epithelium of the upper respiratory tract against foreign particles, including bacteria, has been found to be altered in various rhinopathic conditions. It is possible that the nasal MCC function could be severely injured by allergic inflammation and lead to respiratory comorbidities. Our study found that MCC functions were impaired in both the AR and non-AR groups but more severely in the AR group. This more severe mucociliary dysfunction in AR suggests an add-on effect of an IgE-mediated allergy on the nonallergic mucosal inflammation background. Inflammation of the nasal mucosa in AR is triggered by the interaction of mediators released by cells that are implicated in both allergic and nonspecific inflammations.18 Allergic inflammatory mediators influence MCC function, ciliary structure and function, and mucus production.19 Damage to nasal cilia includes absence of dynein arms and radial spokes, ciliary membrane injury, and disorientation of central tubules.20 This advanced allergic mucociliary dysfunction could interfere with the normal protective functions of the respiratory mucosa and cause the comorbidities.

Most studies of AR have also found prolonged nasal MCCT compared with healthy controls4-8; however, a few studies have reported opposite results.9,10 The discrep-
ances between the studies are probably the result of different techniques and different clinical stages of the disease. There is considerable variation between individuals in measurements of MCC function. Traceable particles that may be soluble, insoluble, or radioisotopes are placed on different areas of the nasal mucosa, and MCCCTs are obtained by recording the time until the tracer can be tasted (saccharin) or visually observed in the pharynx (charcoal). The transport rate of radioactive particles can be calculated by following them over a certain distance for a certain period. We used saccharin clearance time, following the method described by Rutland and Cole, which has been established as a valid and reliable measure of MCC function. The addition of a small amount of charcoal to the saccharin provides an objective variable and improves reproducibility. The efficiency of MCC depends on ciliary activity and the rheological characteristics of the mucus. Mucociliary transport may be increased or decreased depending on disease severity. In mild allergic inflammation, defects in the cilium might be small and transient and the mucociliary transport rate might increase owing to alterations in the rheological properties of the mucus and ciliary beat frequency. Damage to the ciliary structure in patients with long-standing AR can cause permanent impairment to mucociliary function.

We further evaluated whether IgE-mediated hypersensitivity had any effect on clinical disease severity, as indicated by TNSSs and PEFIs. Patients in the AR group had significantly higher TNSSs and worse PEFIs compared with those in the non-AR group. Higher TNSSs and PEFIs were found to be associated with longer MCCCTs. The findings suggest that MCC could represent a net effect of the clinical disease processes that are associated with underlying allergic inflammation, in support of the theory that IgE-mediated hypersensitivity has a clinical effect on mucosal inflammation.

We then explored whether the degree of response of the allergy skin test reactions, an immunologic status representing the level of IgE on inflammatory cells, was related to the degree of allergic mucociliary dysfunction. Although allergy skin tests are only an indirect method for detecting allergens relevant to respiratory mucosal inflammation, the prevalence of IgE sensitization to indoor allergens (house dust mite and cat allergen) has been positively correlated with the frequency of asthma and its severity, and other studies have suggested a correlation between the degree of cutaneous reactivity and airway responses in asthmatic subjects. Different allergen sensitivities might interact to increase their association with atopic comorbidities. Our findings showed a positive correlation between wheal response to D pteronyssinus, D farinae, American cockroach, or Bermuda grass and MCCCT. The longer the wheal response to one of these allergens, the more likely the patient was to have a longer MCCCT. The prolonged MCCCT in the AR group could be influenced in part by the severity of nasal symptoms. However, the IgE-mediated hypersensitivity still showed a significant effect on MCC function. The data support the theory that the degree of cutaneous reactivity may determine the severity of underlying allergic mucosal inflammation. Although previous asthma studies have suggested that sensitization to some allergen types (ie, house dust mite, cat, or cockroach allergens) is a risk factor for more severe asthmatic disease, we did not find any notable differences in the correlation coefficients between allergen types and MCCCT in AR (data not shown).

In our study, we did not find a significant correlation between the total number of allergen reactions and MCCCTs. Multiple different allergens appeared to have little synergistic effect on allergic mucociliary dysfunction. However, we observed higher positive correlation coefficients of maximal wheal response among various positive allergen responses compared with allergen type. These findings showed that the maximum allergen cutaneous reactions showed more of an effect on MCC functions than the type of reactivity or multiple reactivities. The skin test reaction might thus provide an indirect, noninvasive method for predicting the severity of underlying nasal inflammation and provide a guide to appropriate stepwise management in AR.

In conclusion, the present study has 4 main findings. (1) Nasal MCC function is impaired in AR and non-AR, but the impairment is more severe in the allergic form. (2) The magnitude of allergen reactivity as indicated by maximal wheal response among various positive allergen responses, but not the type and total number of allergen reactions, has an effect on MCC function. (3) Mucociliary clearance dysfunction is associated with worse TNSS and PEFI. (4) The elaboration of the magnitude of allergen reactivity is responsible, at least in part, for underlying mucosal inflammation and could be a guide to devising effective stepwise management plans in AR.

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