Dysfunction of upper and lower airways frequently coexists, and they appear to share key elements of pathogenesis. The interrelationship between upper and lower airway manifestations of allergy remains still incompletely investigated. Little is known about the critical factors that determine airway afferent nerve endings reactivity (cough sensitivity) in patients with allergic rhinitis. Subclinical inflammatory changes within the lower airways and/or chronic upper airway cough syndrome (previously referred to as postnasal drip syndrome) are probably responsible for this effect. The aim of this study was to evaluate capsaicin cough sensitivity in pollen sensitive patients with seasonal allergic rhinitis without treatment out of a grass pollen season time using the European Respiratory Society (ERS) guidelines on the assessment of cough. Cough sensitivity was defined as the lowest capsaicin concentration which evoked two (C2) or five (C5) coughs. Capsaicin aerosol in doubling concentrations (from 0.49 to 1000 µmol/l) was inhaled by a single breath method (KoKo DigiDoser; nSpire heath Inc, Louisville, CO), modified by the addition of an inspiratory flow regulator valve (RIFR; nSpire heath Inc, Louisville, CO). The seasonal rhinitis subjects (5M, 7F; mean age 23 yr) had not been complaining primarily about coughing. Their pulmonary function was within normal range. Concentrations of capsaicin causing two (C2) and five coughs (C5) were reported. Volunteers’ (5M, 7F, mean age 23 yr) cough sensitivity (geometric mean and 95 % CI) for C2 was 16.5 (4.1-67.0) µmol/l vs. allergic rhinitis patients’ C2 3.5 (1.9 - 6.4) (P= 0.018). Volunteers’ C5 was 132.4 (41.3 – 424.5) µmol/l vs. allergic rhinitis patients’ C5 13.1 (6.0 – 28.6) µmol/l (P= 0.013). We conclude that airway afferent nerve endings reactivity in pollen sensitive subjects suffering from seasonal allergic rhinitis was significantly increased out of pollen season compared with healthy volunteers.

Key words: capsaicin, cough, cough challenges, cough reflex sensitivity, seasonal allergic rhinitis
INTRODUCTION

Epidemiologic surveys and clinical reports have documented that allergic rhinitis coexists with asthma in many patients. Provocative bronchial methacholine challenge in allergic rhinitis patients demonstrate increased airway responsiveness to the bronchial challenge in 30% of those allergic rhinitis patients who have no past history of asthma. These data suggest that subclinical asthma may be present in certain patients with allergic rhinitis (1). Dysfunction of upper and lower airways frequently coexists, and they appear to share key elements of pathogenesis. Epidemiological studies have identified a temporal relation between the onset of rhinitis and asthma, with rhinitis frequently preceding the development of asthma. The observation that management of allergic rhinitis also relieves symptoms of asthma has heightened interest in the link between these diseases. A link between allergic rhinitis and asthma is evident from epidemiologic, pathophysiologic, and clinical studies (2).

Allergic rhinitis, rhinosinusitis, and asthma are frequently comorbid conditions, and this association has been recognized since the early 1900s. Recent studies have strengthened the concept that allergic rhinitis, rhinosinusitis, and asthma are manifestations of an inflammatory process within a continuous airway. Although the key component of this concept is inflammation, various additional mechanisms that link the upper (nose, sinuses, larynx, pharynx, and trachea) and lower (bronchi and lungs) airway segments are possible and not yet completely understood. Still, the integrated airway hypothesis – often referred to as the united airway disease, the chronic respiratory inflammation syndrome (3), or rhinosinobronchitis – is widely appreciated and is supported by findings from numerous studies (3-6). If validated, the integrated airway hypothesis may have significant clinical implications for the management of patients with allergic rhinitis or asthma (7).

Since the mid 1960s, there has been a sharp increase in the number of published manuscripts concerned with various aspects of cough in human and animal studies. Standardisation of cough challenge methodology is required if reliable comparison of experimental results between laboratories are to be made. Inhalation cough challenge methodology was recommended by the European Respiratory Society Task Force (8). Cough sensitivity in patients suffering from allergic rhinitis was significantly increased during the pollen season in our study (9), regardless of whether the patients were treated with antihistamines. This results finds support in the increased cough sensitivity in awake guinea-pigs with ovalbumin-induced allergic rhinitis (10).

The aim of this study was to evaluate capsaicin cough sensitivity in pollen sensitive patients with seasonal allergic rhinitis without treatment out of a grass pollen season time using the current European Respiratory Society guidelines (8) on the assessment of cough.
MATERIAL AND METHODS

The study was approved by Ethics Committee of Jessenius Faculty of Medicine and informed consent was obtained from all subjects after the purpose of the test had been explained.

Nonallergic control subjects

The study was carried out on 12 healthy volunteers (5 males, 7 females; mean age 23 years). They had no history of asthma, chronic rhinitis, atopic eczema, or other relevant diseases. They were nonsmokers and their baseline FEV1 was >85% of the predicted value. None of the subjects experienced a respiratory tract infection for >3 weeks before or during the study.

Seasonal allergic rhinitis patients

Twelve patients with seasonal allergic rhinitis (5 males, 7 females; mean age 23 years) had a characteristic history of seasonal allergic rhinitis (rhinorrhoea, nasal itching, sneezing, nasal obstruction) and positive skin prick tests results (>3 mm weal response) to grass pollen. None of them had a present or past history of asthma (wheezing, dyspnea, chest tightness, chronic cough). They were nonsmokers and their baseline forced expiratory volume in one second (FEV1) was >85% of the predicted value. None of the studied subjects experienced a respiratory tract infection for >3 weeks before or during the study. They were free of lower airway respiratory symptoms. They were not treated with antihistamines at the time of examination.

Study design

Based on a structured, interviewer-led questionnaire, each subject was asked about respiratory symptoms and a past and family history of bronchial asthma, allergic rhinitis, gastroesophageal reflux, cardiovascular diseases, metabolic diseases, ACE inhibitor treatment. Subjects attended the laboratory to undergo a cough reflex sensitivity test and spirometry before and after the test. All volunteers and patients were examined at the same time of the day (capsaicin cough sensitivity testing) out of pollen season. Subjects reported subjective feeling during cough challenge testing.

Assessment of cough reflex sensitivity

Measurement of cough threshold to inhaled tussigenic agent was carried out using a single breath method (8). Solutions of capsaicin (Sigma Chemicals, St. Louis, MO) were prepared to make a stock solution of 0.01 mol, and subsequently further diluted with physiologic saline solution to yield serial doubling concentrations ranging from 0.49 to 1000 µmol/l. Inhalations of 0.9% saline solution were randomly interspersed to increase challenge blindness (8, 11).

Subjects inhaled single breaths of capsaicin aerosol administered via a nebulizer (KoKo DigiDoser; nSpire heath Inc, Louisville, CO) that was equipped with an inspiratory flow regulator valve (RIFR; nSpire heath Inc, Louisville, CO). The duration of aerosol delivery was programmed at 0.5 s. Single breaths of capsaicin aerosols were administered in ascending order, with inhalations of saline solution randomly interspersed to increase challenge blindness, until the concentration including two or more coughs (C2) and five or more coughs (C5) were reached. Breaths were delivered at 1-min intervals. Subjects were unaware that the end point of the study was the number of coughs induced. The number of coughs in the first 15 s after each inhalation were counted by two experienced observers. Each concentration of tussigenic agent was inhaled once. The challenge was terminated at the concentration of tussigenic agent that resulted in 5 consecutive coughs (C5). If
subject did not reach C2 and/or C5 during the capsaicin cough challenge, the subject was considered to be a non-responder.

Cough reflex sensitivity was defined as the lowest concentration of capsaicin that elicited 2 and 5 coughs (C2 = concentration of capsaicin inducing two or more coughs; C5 = concentration of capsaicin inducing five or more coughs).

**Data analysis**

The C2 and C5 were expressed as a geometric mean value with 95% confidence intervals (CI) and was calculated for each group. Data were analysed by a non-parametric Mann-Whitney-Wilcoxon test. A value of \( P < 0.05 \) was considered to show a significant difference.

**RESULTS**

The C2 capsaicin concentration was 3.5 (1.9-6.4) \( \mu \text{mol/l} \) in seasonal allergic rhinitis patients evaluated out of pollen season, which was significantly less than 16.5 (4.1-67.0) \( \mu \text{mol/l} \) in healthy subjects (\( P= 0.018 \)). Cough reflex sensitivity, expressed as the C2 capsaicin concentration was thus significantly increased in the patients with seasonal allergic rhinitis out of pollen season (Fig. 1). The C5 capsaicin concentration was 13.1 (6.0–28.6) \( \mu \text{mol/l} \) in seasonal allergic rhinitis patients, which was significantly less than 132.4 (41.3–424.5) \( \mu \text{mol/l} \) in healthy volunteers (\( P= 0.013 \)). Cough reflex sensitivity, expressed as the C5 capsaicin concentration also was significantly increased in the patients with seasonal allergic rhinitis out of pollen season (Fig. 2). No serious adverse reactions to capsaicin inhalation challenge were reported (12).

**DISCUSSION**

Here we report that cough reflex sensitivity is significantly increased in non-treated seasonal allergic rhinitis patients out of pollen season.

On review of the existing literature, different methods of cough challenge have been identified, with wide variation on the choice of tussive agents, delivery device and test end-point employed. Standardization of cough challenge methodology is required if reliable comparisons of experimental results between laboratories are to be made. In this study we used a standardized method of capsaicin inhalation cough challenge (8). The inhalation cough challenge permits the measurement of sensitivity of the cough reflex and the assessment of the antitussive effects of specific therapies. Capsaicin, the most commonly used non-acid tussive to experimentally induce cough in humans, was first described in 1984 (13). Because of the lack of standardization of cough challenge methodology in terms of equipment, preparation of solutions, method of administration, nebuliser output, inspiratory flow rate and dose of aerosol per
**Fig. 1.** Standardized cough reflex sensitivity to capsaicin in seasonal allergic rhinitis patients out of pollen season – C2 value (capsaicin concentration that results in two or more coughs).

**Fig. 2.** Standardized cough reflex sensitivity to capsaicin in seasonal allergic rhinitis patients out of pollen season – C5 value (capsaicin concentration that results in five or more coughs).
breath, comparisons of cough sensitivity data currently in the literature from different institutions are not valid (8).

In most experimental circumstances, the single-breath dose-response method is preferred because of the accuracy and reproducibility of the dose delivered and the ease with which a tussive response can be determined (8). The rate of inspiratory flow affects the pattern of deposition of aerosol within the airways. Variations in inspiratory flow rate have been demonstrated to affect the results of capsaicin (14). Therefore, the flow rate needs to be constant (8). Standardized methodology was one of the reasons why we have performed this study.

We have recently published (9) that cough sensitivity is significantly increased in pollen sensitive subjects who suffer from seasonal allergic rhinitis during both the pollen season and out of it (9). In this study we report that cough sensitivity is significantly increased in non-treated seasonal allergic rhinitis patients out of pollen season using standardized cough sensitivity testing methodology (8). Control group and seasonal rhinitis patients were sex and age-matched.

There are many common anatomic pathophysiologic features between upper and lower airway disorders, primarily in histology and immunology. Examples of common anatomic features include ciliated columnar cell epithelial lining, mucinous glands, vasculature, and innervation. Regarding pathophysiology, both asthma and allergic rhinitis exhibit a similar early allergic response characterized by vasodilation and increased vascular permeability and mucus production. Upper and lower airway disorders also exhibit similar characteristics of chronic inflammation, including infiltrations of leukocytes, and the involvement of eosinophils, lymphocytes, macrophages, mast cells, cytokines, leukotrienes, and other inflammatory mediators (15).

The anatomic connection between the upper and lower airways suggest a possible role of nasal drippings in eliciting bronchial hyperreactivity in patients with allergic rhinitis or rhinosinusitis (7). Despite the strong correlation between allergic rhinitis and asthma, some patients with allergic rhinitis never develop asthma (and vice versa), and the reasons for this are still unclear. Although nonspecific subclinical bronchial hyperreactivity is common in many patients with allergic rhinitis (16-19), it is unknown what causes certain patients to progress to clinically apparent asthma over time. Further clarifying and understanding the relationship between disease of the upper and lower respiratory tracts is important because of the prevalence of allergic rhinitis, rhinosinusitis, and asthma. Recent progress in understanding the biology of airway disease has identified that systemic inflammatory responses play critical and integrating role in these diseases (7).

Capsaicin cough sensitivity in allergic asthmatic patients increases during the birch pollen season. Sensory reactivity in allergic asthmatic patients may be increased during prolonged allergen exposure, such as during a pollen season. These findings suggest that allergic inflammation in the lower and/or upper airways triggers neurogenic mechanisms of significant clinical importance (20).
No difference was found in capsaicin sensitivity between patients sensitive or insensitive to methacholine who underwent a bronchial methacholine test, primarily because of suspected asthma (21).

Cough sensitivity is influenced by allergic process localized beyond the lower airways. It is increased in patients with atopic dermatitis who do not complain about cough and other respiratory symptoms. One may suppose that atopic dermatitis is accompanied by „subclinical“ inflammation of the airways (22). Skin allergy could have a reflection in the airways. There are, however, no significant changes of cough reflex sensitivity between healthy subjects and patients suffering from psoriasis vulgaris who have no respiratory symptoms.

Cough reflex sensitivity in non-treated patients suffering from seasonal allergic rhinitis was significantly increased out of pollen season in the present study. This result finds support in the increased cough intensity in awake guinea-pigs with ovalbumine-induced allergic rhinitis (10).

Our data suggest that the capsaicin cough reflex sensitivity testing can reflect functional changes in the airway afferent nerve-endings mediating cough during allergic atopic process with clinical inflammatory symptomatology in the nose. Although little is known about allergic atopic process „spreading“ to the airways and its detection by the capsaicin cough reflex sensitivity testing, this observation is of interest and merits further investigation.

Acknowledgments: This study was supported by Ministry of Health of Slovak Republic grants 2005/13-MFN-05 and 2007/50-UK-14.

REFERENCES


*Received*: June 16, 2008  
*Accepted*: August 22, 2008

Author’s address: Renata Pecova, Department of Pathological Physiology, Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Sklabinska 26 St., 037 53 Martin, Slovakia; phone +421 43 4238213; fax +421 43 4134807; e-mail: pecova@jfmed.uniba.sk