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Bidirectional Link between Upper and Lower Airways in Patients with Allergic Rhinitis

A. Bencova[1], E. Rozborilova[1], M. Antosova[2]

[1]Clinic of Tuberculosis and Respiratory Diseases and [2]Institute of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia

Abstract

Objective: Exhaled nitric oxide has been proposed as a noninvasive marker of eosinophilic airway inflammation in lower airways. The aim of the study was to investigate the impact of atopy, pollen exposure, and pharmacological treatment on NO production in lower airways of patients with allergic rhinitis.

Subjects and methods: Measurements of exhaled NO were performed in 79 non-asthmatic subjects with seasonal allergic rhinitis outside and in pollen season, before and after pharmacological treatment, and in 54 healthy controls.

Results: Patients with allergic rhinitis had significantly higher levels of exhaled NO (18.3 ±11.0 ppb) than healthy controls (13.0 ±7.2 ppb) measured outside the pollen season (P=0.0024). Increased exhaled NO levels were also found in patients with allergic rhinitis in the pollen season (27.0 ±20.0 ppb) compared with the levels outside pollen season (P=0.0001), before pharmacological treatment. In rhinitic patients treated by nasal corticosteroids and antihistamines in the pollen season, the levels of exhaled NO were significantly lower (17.0 ±16.4 ppb; P=0.045) than those before treatment. No difference was found in NO levels in rhinitic patients outside and in pollen season after pharmacological treatment.

Conclusions: This study has shown the presence of eosinophilic airway inflammation in the lower airways in allergic rhinitis patients. A significant increase of exhaled NO after pollen exposure in rhinitic patients underlies the impact of inflammation on the upper respiratory tract. A bidirectional link between upper and lower airways is confirmed by a decrease in exhaled NO in the pollen season, almost to the starting levels, after application of topic corticosteroids and antihistamines.

Key words: exhaled nitric oxide, allergic rhinitis

Introduction

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose [1].

Allergic rhinitis represents a global health problem. It is an extremely common disease worldwide affecting 10 to 25 % of the population. However, this figure probably underestimates the prevalence of the disease, as many patients do not recognize rhinitis as a disease and therefore do not consult a physician [2]. Although allergic rhinitis is not usually a severe disease, it significantly alters the social life of patients [3] as well as work productivity [4].

Other conditions associated with allergic rhinitis are asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection and dental occlusion. The cost of treating these conditions should be considered when evaluating the socio-economic impact of allergic rhinitis [5].

Asthma and rhinitis are common co-morbidities suggesting the concept of 'one airway, one disease [6]'. Patients with persistent allergic rhinitis should therefore be evaluated for asthma, and patients with asthma should be evaluated for rhinitis. Epidemiological studies have demonstrated that about 60–80% of asthmatic individuals suffer from allergic rhinitis, and conversely approximately 20–40% of patients with allergic rhinitis suffer from asthma [7].

Pathophysiological studies have demonstrated several similarities in the nose and the bronchi, indicating that agents such as allergens and aspirin can trigger exacerbations of both asthma and rhinitis leading to inflammatory mucosal responses [8]. Allergen challenge leads to an increase in mast cells, eosinophils, lymphocytes, and the expression of Th2-profile proinflammatory cytokines in both allergic rhinitis and asthma [9], and additionally, challenge in either the upper or lower airways of patients with rhinitis has been shown to increase eosinophilia in both the upper and lower airways, suggesting a link between the upper and lower airways [10]. Polosa et al. showed that subjects with rhinitis alone have an increased number of eosinophils in the induced sputum during the grass pollen season [11]. Crimi et al. compared the bronchial inflammatory response following allergen-specific challenge in patients suffering from asthma alone or rhinitis alone. Utilizing bronchial biopsy and lavage, the authors found no morphological difference between the two groups: the bronchial inflammatory response (cell influx and basement membrane thickening) is the same regardless of which airway is affected by disease, confirming that atopic subjects have a common inflammatory response [12]. Techniques for evaluating inflammation in lower airways such as induced sputum, bronchial biopsy and lavage are invasive. Exhaled nitric oxide (eNO) has been proposed as a noninvasive marker of lower airway inflammation and its levels

correlate well with number of eosinophils in the induced sputum, bronchial biopsies and lavage [13].

To date, however, no study completely described influence of atopy, pollen season and used pharmacotherapy (intranasal corticosteroids, anihistamines) on nitric oxide levels in patients with allergic pollen-induced rhinitis alone. The aim of this study was to compare levels of exhaled nitric oxide in patients with allergic rhinitis and healthy subjects, to establish significancy of nitric oxide levels change during and outside the pollen season and to determine the effect of intranasal corticosteroids and antihistaminines on nitric oxide levels in exhaled air in pollen-induced rhinitis.

Material and Methods

Subjects

The study was approved by a local Ethics Committee and all subjects gave informed consent to study procedures. The population consisted of 79 non-asthmatic subjects (48 female and 31 male) with seasonal allergic rhinitis and 54 non-allergic control subjects (44 female and 10 male). The subjects with allergic rhinitis had a characteristic history of seasonal allergic rhinitis (rhinorhea, nasal itching, sneezing, and nasal obstruction) and a positive skin prick tests results (>3 mm weal response). They have never received immunotherapy or inhaled corticosteroids. Antihistamines were withheld at least for 7 days prior to each visit, but the patients were allowed to continue their nasal topical decongestants as usual. None of them had a present or past history of asthma (wheezing, dyspnea, chest tightness, or chronic cough). Non-allergic control subjects were free of any disease. All subjects were non-smokers. None of them had experienced a respiratory tract infection for 4 weeks before the study.

Study Design

The study consisted of three visits. At study entry, outside the pollen season (November-March), a detailed history was obtained and atopy was assessed by a skin prick test to common allergens. Then, the subjects underwent measurements of exhaled NO. The second visit was realized at the beginning of pollen season (end of April-June), after the first symptoms appeared and before the start of pharmacological treatment. The third visit was at least 3 weeks after the start of treatment with nasal corticosteroids and antihistamines.

Measurement of Exhaled Nitric Oxide

Exhaled NO was measured by a chemiluminiscence analyzer (NIOX-MINO®, Aerocrine, Sweden). Exhaled NO was determined during a single-breath exhalation. The recommended technique for adult patients involves inspiration of NO-free air via a mouthpiece to total lung capacity, followed immediately by 10 s exhalation against a constant, positive counter pressure of 10–20 cmH_2O to ensure an exhalation flow rate of 50 ml/s according to ATS guidelines. The pressure parameters are controlled by both visible and audible feedback in order to guide the subject in performing a valid exhalation maneuver. A valid breathing maneuver at a flow rate of 50 ml/s is considered if the mean exhalation rate is 50 ±5 ml/s. The results are processed using dedicated software, expressed as a mean of 3 acceptable measurements of NO concentration in ppb.

Statistical Analysis

Data of exhaled nitric oxide were expressed as means ±SE. The mean value of three measurements was calculated for each subject. Comparison of NO values in rhinitic patients was performed using the Kruskal-Wallis test. NO values between healthy individuals and rhinitic patients were compared by an unpaired t-test.

Results

The patients with allergic rhinitis had significantly higher levels of exhaled NO (18.3 ± 11.0 ppb) than healthy controls (13.0 ± 7.2 ppb; P = 0.002), measured outside the pollen season. Increased exhaled NO levels were also found in patients with allergic rhinitis during the pollen season (27.0 ± 20.0 ppb) compared with the levels outside the pollen season (14.5 ± 11.0 ppb; P = 0.0001), before pharmacological treatment. In rhinitic patients treated with nasal corticosteroids and antihistamines in the pollen season, the levels of exhaled NO were significantly lower (17.0 ± 16.4 ppb; P = 0.045) than those before treatment. There was no significant difference between the levels of exhaled

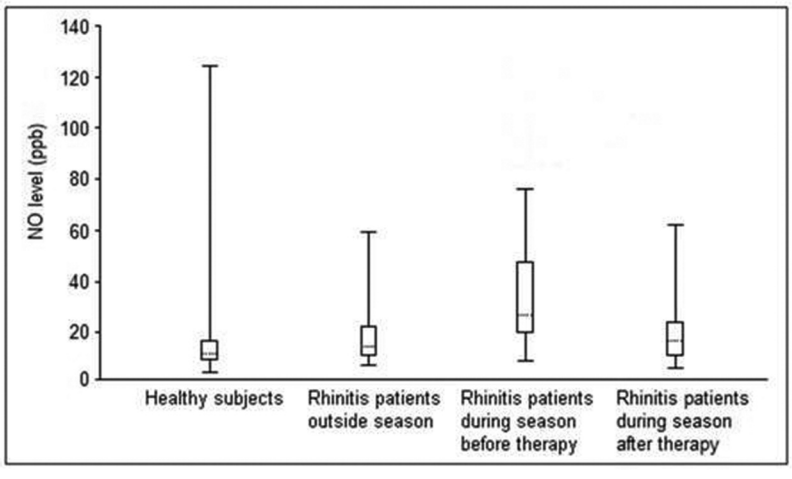

Fig. 1. Levels of exhaled nitric oxide in healthy subjects, and in patients with allergic rhinitis outside pollen season, in pollen season before treatment, and in pollen season after treatment.

NO in rhinitic patients outside and in pollen season after pharmacological treatment (Fig. 1).

Discussion

In the present study, we found significantly higher levels of exhaled NO in rhinitic patients outside the pollen season compared with healthy controls. There also were appreciable increases in exhaled NO in response to pollen exposure in patients with allergic rhinitis compared with NO levels outside pollen season. These findings are in agreement with those reported by Martin et al. [15] and Henriksen et al. [16], but in contrast that reported by Kharitonov et al. [17]. In the latter study, exhaled NO concentration during the pollen season in untreated subjects with seasonal allergic rhinitis, without asthma, did not differ significantly from that in control subjects. Increased concentration of exhaled NO in patients with allergic rhinitis suggests increased production of NO in lower airways. In the present study, common factors known to influence the concentration of exhaled NO, such as a history of asthma, asthma-like symptoms, acute upper or chronic lower respiratory tract infections, or smoking were absent in both our rhinitis patients and healthy controls. Contamination of the exhaled air by NO-rich air from the nasal cavity is unlikely, as the soft palate elevates when expiration is performed against a resistance. Furthermore, a bronchoscopic study in asthmatics has indicated that the exhaled NO concentration measured in the end-tidal phase of expiration is mainly derived from the lower respiratory tract [18].

In a study by Pipkorn et al. [19], topical intranasal corticosteroid treatment reduced the release of inflammatory mediators. In the present study, application of topical corticosteroids and antihistamines to rhinitic patients in pollen season decreased exhaled NO to the level present in the patients outside pollen season. The disappearance of the difference may be viewed as a sign of a bidirectional link between upper and lower airways.

Clinical significance of increased concentration of exhaled NO in the non-pollen season in allergic rhinitis remains to be clarified. It is tempting to speculate that sensitized subjects with elevated exhaled NO levels are at increased risk for the development of asthma. This hypothesis should be addressed in future prospective studies.

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Corresponding author:
Alica Bencova, MD
Clinic of Tuberculosis and Respiratory Diseases
Jessenius Faculty of Medicine
Kollarova 2 St,
Martin 03601, Slovakia
Phone: +421 907 641 810
Fax: +421 43 4133950
Bencova.alica@gmail.com