



## The relation between nonspecific hyperreactivity of the airways and atopic constitution in asthmatics

Odnos između nespecifične hiperreaktivnosti disajnih puteva i atopijske konstitucije kod astmatičara

Dobrivoje Novković\*, Marina Petrović†, Vladan Živković\*, Nenad Baletić‡§

\*Clinic for Pulmonary Diseases, ‡Clinic for Ear, Nose and Throat, Military Medical Academy, Belgrade, Serbia; †Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; §Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia

### Abstract

**Background/Aim.** Hyperreactivity of the airways caused by inflammation in asthmatics is the most important pathophysiological change. It represents a suitable ground that in the presence of risk factors and the drivers of asthma, asthmatic attack occurs. Atopic constitution is one of the most important risk factors for the development and expression of asthma. The aim of our study was to investigate the relationship between nonspecific airway hyperreactivity and atopic constitution in asthmatics. **Methods.** This retrospective analysis was conducted considering the results of nonspecific bronchoprovocative test with histamine, skin tests to inhalant allergens and total IgE levels in the serum of asthmatic patients with controlled bronchial asthma. The sample consisted of 162 asthmatics examined during one-year period. **Results.** The examinees were male asthmatic patients, aged between 18 and 30 years. We found that the examinees with a pronounced non-specific hyperreactivity had more significant skin reaction to inhaled allergens and higher levels of total IgE in serum. **Conclusion.** The results of our study show that the intensity of airway hyperresponsiveness to histamine in asthmatics is directly related to atopic constitution.

### Key words:

asthma; respiratory hypersensitivity; immunoglobulin e; hypersensitivity, immediate; histamine; skin test.

### Apstrakt

**Uvod/Cilj.** Hiperreaktivnost disajnih puteva uzrokovana inflamacijom kod astmatičara je najznačajnija patofiziološka promena. Ona predstavlja pogodan teren da se u prisustvu faktora rizika i pokretača astme ispolji astmatični napad. Atopijska konstitucija je jedan od najznačajnijih faktora rizika od nastanka i ispoljavanja astme. Cilj našeg rada bio je da se ispita odnos između nespecifične hiperreaktivnosti disajnih puteva i atopijske konstitucije kod astmatičara. **Metode.** Izvršena je retrospektivna analiza rezultata nespecifičnog bronhoprovokacijskog testa sa histaminom, kožnih proba na inhalacione alergene i nivoa ukupnih IgE u serumu bolesnika sa kontrolisanom bronhijalnom astmom. U analizu su bila uključena 162 astmatičara, ispitivana tokom jednogodišnjeg perioda. **Rezultati.** Svi bolesnici su bili muškarci, starosti od 18 do 30 godina. Utvrđeno je da su ispitanici sa izraženijom nespecifičnom hiperreaktivnošću imali izraženiju kožnu reakciju na inhalacione alergene i viši nivo ukupnih IgE u serumu. **Zaključak.** Rezultati našeg istraživanja ukazuju na to da je intenzitet hiperreaktivnosti disajnih puteva na histamin kod astmatičara u direktnoj vezi sa atopijskom konstitucijom.

### Ključne reči:

astma; hipersenzibilnost, respiratorna; ige; hipersenzibilnost, rana; histamin; koža, testovi.

### Introduction

As a consequence of chronic inflammation, enhanced bronchoconstriction occurs in bronchial asthma as a response of the airways to many endogenous and exogenous factors. That amplified response of the airways to a variety of stimuli that elicit the bronchoconstriction represents the bronchial hyperreactivity (BHR) <sup>1</sup>.

BHR is variable and dependent upon the nature of the inflammatory processes whose intensity varies with asthma and is influenced by numerous factors such as allergens, respiratory infection, and certain medications <sup>2</sup>. Considering that a certain degree of reactivity of the airways in asthmatic patients is always present, BHR can be referred to as variable or constant phenomenon. Strict division of the mentioned components is not possible because the processes that influ-

ence BHR are interdependent. Such is the case with inflammation in chronic form which can lead to cell changes that can cause permanent BHR<sup>3</sup>.

BHR can also be divided to the direct or indirect depending on the mechanisms of action and the stimuli which caused it. At the same time, some of them influence more permanent and the others variable components. Histamine acts directly on the receptor in the airway smooth muscle leading to their contractions and bronchoconstriction.

On the other hand, indirect stimuli, which include physical exertion, hyperventilation, hypertonic solution, cause the release of mediators (prostaglandins, leukotrienes and histamine), which act on receptors in the smooth muscle of the respiratory tract, leading to the same effect – bronchospasm<sup>4</sup>.

Histamine with its direct influence amplifies the effect of permanent BHR. However, histamine achieves the effect of histamine on the reflex mechanisms of bronchoconstriction and contributes to the manifestation of the effects of indirect stimulus to the airways. Although the mechanism of effects of histamine is not clear enough, nor investigated in detail, it is known that it depends on the preexisting inflammation and other bronchoconstrictor stimuli<sup>1,3</sup>.

Viewed from the aspect of pathophysiology, hyperreactivity is a complex process associated with a series of immunological, neurological, and structural changes that lead to bronchial obstruction which is manifested by characteristic symptoms and signs of an asthma attack.

The occurrence and expression of bronchial asthma is affected by multiple risk factors for worsening of preexisting asthma or asthma exacerbation factors, provocative factors or triggers of asthma. Among these the most common are allergens, respiratory infections, physical exertion, hyperventilation, emotional stress, respiratory irritants that directly or indirectly trigger bronchoconstriction receptors in the airways.

The existence of hyperreactivity of the airways can be determined and measured by laboratory tests that involve controlled exposure to direct or indirect stimuli. These tests contribute significantly to the precise diagnosis of asthma or reduce the risk of wrong diagnosis of the disease based only on asthma symptoms<sup>5,6</sup>.

Atopic constitution is the tendency of the body to react to a contact with allergens with increasing production of immunoglobulin E (IgE). Atopic constitution and bronchial hyperresponsiveness are tightly linked characteristics of bronchial asthma<sup>7</sup>. Atopy affects the hyperreactivity of the airways in a manner that it induces and promotes inflammation in the airways and thereby increases BHR<sup>8</sup>.

Although there are various indicators of the degree of atopy, there is no complete consensus in the scientific community concerning this issue. The most frequently used are total IgE, specific IgE, the number of positive intracutaneous tests or sum of several indicators<sup>7</sup>.

Recent evidences suggest that the increase of IgE serum levels to dust mites is a reliable indicator of worsening asthma<sup>9</sup>.

The aim of this study was to investigate the relationship between nonspecific airway hyperreactivity and atopic constitution in asthmatics.

## Methods

We retrospectively analyzed the results of bronchoprovocation test with histamine on 162 asthmatics with controlled bronchial asthma who were examined during the one-year period in the functional diagnostics of the lung in the Military Medical Academy in Belgrade, Serbia. The examinees were male, aged between 18 and 30 years. They all underwent bronchoprovocation test with histamine. The assay started with a minimal concentration of 0.03 mg/mL and each next concentration was twice the previous. They all had a positive bronchoprovocation histamine test. All of them had a decrease in forced expiratory volume in the first second (FEV1) compared to baseline value of at least 20% with inhaled histamine concentrations up to 4 mg/mL. In addition, all the subjects underwent skin prick-tests with inhaled allergens. The diameter of changes on the skin at the site of application of allergens was measured in mm. Test was considered positive if there was the appearance of skin lesions of the diameter at least 50% of the diameter of the skin change on the site of histamine administration, which was used as a positive control. The level of total IgE in the serum was determined in all patients using nephelometric method. The examinees were divided into two equal experimental groups *per* 81 patients each. The first group consisted of the patient with positive histamine test at the concentration of histamine up to 2 mg/mL and the second group of the patients had positive histamine test at the concentration of 2–4 mg/mL.

## Statistical analysis

Complete statistical analysis was performed using a commercial statistical software SPSS Statistics 17. A certain number of variables was incorporated in the form of the frequency of certain features (categories) and the statistical significance of differences between the groups was evaluated using the  $\chi^2$  test.

In the case of continuous variables, the data were presented as the mean  $\pm$  standard deviation (SD). Normal distribution of the data was checked using the Kolmogorov-Smirnov test. In case of fulfillment of the conditions of normality, statistical significance within and between the groups was checked using the *t*-test for dependent and independent features. Otherwise, for the estimation of significance between the groups, the Mann-Whitney U-test was used. A statistically significant difference was estimated at the minimum level of  $p < 0.05$ .

## Results

All the participants were male, asthmatics. There was no significant difference in age or in the baseline FEV1 between two groups of patients (Table 1).

The examination of atopic constitution showed some characteristics. All the subjects had positive skin tests to most standard inhaled allergens. However, the intensity of skin reactions to certain allergens, expressed as atopic index,

**Table 1**  
**Characteristics of the patients (n = 62) with asthma according to the groups**

Characteristics	Group I (n = 81)	Group II (n = 81)
Age (years), $\bar{x} \pm SD$	23.98 $\pm$ 0.22	23.62 $\pm$ 0.30
Men/women, n	81/0	81/0
FEV1 (l) basal (%), $\bar{x} \pm SD$	4310 $\pm$ 1.50	4653 $\pm$ 1.20
Histamine PC20 (mg/mL), $\bar{x} \pm SD$	0.60 $\pm$ 0.07	1.25 $\pm$ 0.10

**FEV1 – forced expiratory volume in 1 s; Histamine PC20 – the concentration causing a 20% fall of the FEV1.**

**Group I: positive histamine test at a concentration of histamine up to 2 mg/mL;**

**Group II: positive histamine test at a concentration of histamine 2–4 mg/mL.**

which represents the mean maximum diameter of skin lesions, was not the same by the groups. The patients from the first group had a more intense, statistically important, skin reaction to dermatophagus and grass pollen (Figure 1). By analysing the levels of total IgE in the serum as another indicator of atopic constitution, we obtained the results that confirmed the previous ones, related to skin tests. Respectively, the first group of our examinees with more intense skin reaction, also had significantly higher levels of total IgE in the serum (Table 2).

When examining of nonspecific airway hyperresponsiveness to histamine it was found more pronounced hypersensitivity and airway hyperresponsiveness in the subjects of the first group. They reacted to a much lower concentration of histamine, on the average of about 0.6 mg/mL (Table 2).

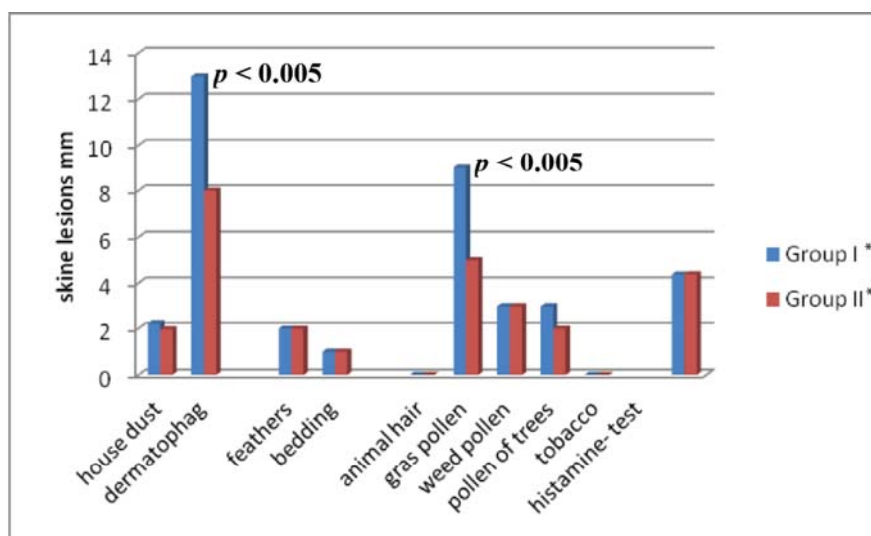
With regard to hyperreactivity, or the degree of FEV 1

decrease after histamine test, subjects of the first group also showed a higher degree of reduction of this parameter. The patients in the first group had an average decline in FEV1 of 33.5%, whereas the respondents in the second group had a decline in FEV1 of 29.8% (Table 2).

**Discussion**

BHR and atopy are two characteristic features of bronchial asthma. Their association contributes to complex pathophysiological events and clinical manifestations of bronchial asthma.

In our study, we aimed to investigate the relationship between nonspecific airway hyperreactivity and the atopic constitution of asthmatics.



**Fig. 1 – Skin reactions to inhaled allergens according to the groups of the patients with asthma (\*For explanation see under Table 1).**

**Table 2**  
**Average values of the serum level of IgE, concentration of histamine causing the decrease in FEV1 of 20% and percentage of decrease in FEV1 after histamine test in asthmatic patients**

Parameters	Group I*	Group II*	p
Average level of IgE in the serum (U/mL)	354	225.87	< 0.05
Average concentration of histamine causing the decline in FEV1 of 20% (mg/mL)	0.6	1.3	< 0.05
Average decrease in FEV1 after histamine test (%)	33.5	29.8	< 0.05

**FEV1 – forced expiratory volume in 1 s.**

(\*For explanation see under Table 1).

Although all the respondents were sensitive to most of inhaled allergens, we observed a significantly higher response to dermatophagus and grass pollen consistent with the climate they lived in. The intensity of skin reactions to inhaled allergens is also positively correlated with the level of total IgE in the serum as another indicator of atopic constitution. Backer et al.<sup>10</sup> got similar results in the Australian study conducted on a population of 527 children and adolescents, where they had proven that atopic index and BHR are closely related.

Results of other studies confirm that atopy promotes otherwise already present chronic inflammation in the airways of asthmatics, which leads to increased BHR<sup>8</sup>.

The association of allergy and atopic constitution and bronchial asthma is characteristic of allergic asthma, generally among younger population of asthmatics.

However, the effect of atopy on asthma is significant and in later life to which, among others, pointed Plaschke et al.<sup>11</sup> in their research.

The specificity of our research was in the fact that we tested the older population than it was the case with other authors and that all of our respondents had clearly manifested bronchial asthma. This research confirms the previously

stated fact that atopic constitution remains an important factor not only in adolescents but also in adults.

Kim et al.<sup>7</sup>, have demonstrate that the relation between atopy and asthma is positive, *ie* BHR increases with increasing levels of total IgE in serum.

The results that we obtained, lead us to a similar conclusion. A group of our patients with pronounced BHR also had a pronounced atopic constitution or higher levels of total IgE in the serum and intense skin reaction to inhaled allergens.

### Conclusion

Based on the results of this study, we can conclude that the asthmatic's bronchial hyperreactivity depends on atopic constitution.

Atopic constitution represents the most important event in the development of bronchial hyperreactivity in asthmatics. The intensity of bronchial hyperreactivity in asthmatics is directly related to the intensity of atopic constitution manifested by the increased formation of IgE in the serum and skin hypersensitivity to inhaled allergens.

### R E F E R E N C E S

1. *Cockcroft D, Davis B.* Direct and indirect challenges in the clinical assessment of asthma. *Ann Allergy Asthma Immunol* 2009; 103(5): 363–9.
2. *Brannan JD, Turton JA.* The Inflammatory Basis of Exercise Induced Bronchoconstriction. *Phys Sportsmed* 2010; 38(4): 67–73.
3. *Busse WW.* The relationship of airway hyperresponsiveness and airway inflammation: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010; 138(2 Suppl): 4s–10s.
4. *Anderson SD, Brannan JD.* Bronchial Provocation Testing: The Future. *Curr Opin Allergy Clin Immunol* 2011; 11(1): 46–52.
5. *Maurer M, Simonett D, Brutsche MH.* Challenge of exercise-induced asthma and exercise-induced bronchoconstriction. *Expert Rev Respir Med* 2009; 3(1): 13–9.
6. *McGrath KW1, Faby JV.* Negative methacholine challenge tests in subjects who report physician-diagnosed asthma. *Clin Exp Allergy* 2011; 41(1): 46–51.
7. *Kim BS, Jin HS, Kim HB, Lee SY, Kim JH, Kwon JW, et al.* Airway hyperresponsiveness is associated with total serum immunoglobulin E and sensitization to aeroallergens in Korean adolescents. *Pediatr Pulmonol* 2010; 45(12): 1220–7.
8. *Kim YM, Kim YS, Jeon SG, Kim YK.* Immunopathogenesis of Allergic Asthma: More Than the Th2 Hypothesis. *Allergy Asthma Immunol Res* 2013; 5(4): 189–96.
9. *Kennedy JL, Heymann PW, Platts-Mills TA.* The role of allergy in severe asthma. *Clin Exp Allergy* 2012; 42(5): 659–69.
10. *Backer V, Ulrik CS, Hansen KK, Laursen EM, Dirksen A, Bach-Mortensen N.* Atopy and bronchial responsiveness in random population sample of 527 children and adolescents. *Ann Allergy* 1992; 69(2): 116–22.
11. *Plaschke P, Janson C, Norrman E, Björnsson E, Ellbjär S, Järnholm B.* Association between atopic sensitization and asthma and bronchial hyperresponsiveness in swedish adults: pets, and not mites, are the most important allergens. *J Allergy Clin Immunol* 1999; 104(1): 58–65.

Received on October 29, 2014.

Revised on May, 2015.

Accepted on June 30, 2015.

Online First May, 2016.