Exercise-induced bronchoconstriction and non-specific airway hyperreactivity in patients suffering from bronchial asthma

Bronhokonstrikcija izazvana naporom i nespecifična hiperreaktivnost disajnih puteva kod oboljelih od bronhijalne astme

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Abstract

Background/Aim. Physical activity is a common stimulus of asthmatic symptoms manifestation. Airway hyperreactivity is a predisposing cause of exercise induced bronchial obstruction, diagnosed by histamine inhalation. The aim of this study was to determine the relation between the amounts of histamine needed to induce non-specific airway hyperreactivity and exercise-induced bronchial obstruction.

Methods. This randomized cross-over study included 160 male patients (age 19–27 years) suffering from bronchial asthma who showed positive results as the reaction after the histamine bronchial provocation test. Histamine concentrations were in a range of 0.03 to 4 mg/mL. Each patient participated in the exercise stress test conducted on a conveyor belt. The results of the exercise stress test were considered positive if the FEV1 level dropped by at least 15% from its initial value, 5–10 minutes after the test. Results. All the patients showed positive results as the reaction after the histamine bronchial provocation test, while 50 of them showed positive results after the exercise-induced stress test. There was a statistically highly significant difference in administered histamine concentrations between the group of patients that had positive results on exercise stress test and those who did not (1mg/mL vs 0.5mg/mL; U = 1678; p < 0.01). Also, there was a statistically significant difference concerning the frequency of the positive results regarding histamine concentration after induced stress test (x2 = 10.885; p = 0.001). Among the patients with positive results, there was a statistically highly significant number of patients with bronchial obstruction induced by less than 2 mg/mL of histamine (p < 0.01). A statistically significant relation between the amount of histamine needed to induce bronchial obstruction and the results of the exercise stress test (p < 0.01) was also observed after the testing. Conclusion. In the group of patients with positive results after the exercise-induced stress test, there were significantly more patients with positive results to non-specific bronchial provocation test with lower histamine concentrations. Histamine concentrations needed to induce non-specific hyperreactivity of asthmatic airway were shown to be related to the reactivity to physical effort.

Key words: asthma; histamine; diagnosis; exercise test; respiratory function tests.

Apstrakt

Uvod/Cilj. Fizički napor je čest stimulus-uzročnik ispočevanja astmatičnih simptoma. Hiperreaktivnost disajnih puteva je predisponirajuči faktor za nastanak bronhospresktrukcije na napor i ona se dokazuje inhalacijom histamina ali sličnih materija. Cilj ove studije bio je da se ispita odnos između doze histamina potrebne za izazivanje nespecifične hiperreaktivnosti disajnih puteva i bronhospresktrukcije izazvane naporom. Metode. Ova studija preseka obuhvatila je 160 astmatičara, muškaraca, starih 19–27 godina, koji su imali pozitivan bronhovrakafcijski test na histamin. Koncentracija histamina kretala se od 0,03 do 4 mg/mL. Svim bolesnicima urađen je test opterećenja na pokretnoj traci. Test opterećenja smatran je pozitivnim ukoliko bi 5–10 minuta po završetku testa došlo do pada FEV1 za najmanje 15% od početnih vrednosti. Rezultati. Svi ispitanimi imali su pozitivan histaminski test, a njih 50 i pozitivan test opterećenja. Postoji statistički visokoznačajna razlika u datim koncentracijama histamina između bolesnika koji su imali pozitivan test opterećenja i drugih kod kojih je test opterećenja bio negativan (1 mg/mL vs 0,5 mg/mL; U = 1678; p < 0.01). U grupi bolesnika sa pozitivnim testom opterećenja, postoji statistički visoko značajno više onih...
Introduction

The main pathophysiological characteristic of bronchial asthma is a reversible bronchial obstruction. Bronchial obstruction is caused by inflammation, which is, to some extent, constantly present in asthmatic airway mucosa. Chronic inflammation causes airway hyperreactivity, which leads to bronchial obstruction, i.e., asthmatic symptom manifestation.

Each of these processes (inflammation, hyperreactivity and bronchial obstruction) is variable and can be amplified by certain factors. Thus, the stimulus (inhaled or, in some cases, produced by the body itself), will trigger the manifestation of bronchial obstruction. There are many substances and states which can induce an asthma attack. The most common stimuli are inhaled allergens, airway infections and increased physical activity, which can induce an asthma attack. The most common stimuli are inhaled allergens, airway infections and increased physical activity, which can induce an asthma attack. The most common stimuli are inhaled allergens, airway infections and increased physical activity, which can induce an asthma attack. The most common stimuli are inhaled allergens, airway infections and increased physical activity, which can induce an asthma attack. The most common stimuli are inhaled allergens, airway infections and increased physical activity, which can induce an asthma attack. The last-acting bronchodilators. Apart from this early reaction to physical effort, in rare cases, there can also be a late reaction to physical activity, even 6–8 hours after the exercise. Considering its specific nature and the pathophysiological mechanism of formation, exercise-induced bronchospasm is sometimes considered as a separate entity, as "exercise-induced bronchoconstriction" (EIB).

It is estimated that the prevalence of EIB in general population varies from 7% to 20%, while in asthmatic population, more than 90% of patients show the symptoms of EIB. In certain cases, especially in children and young people, exercise can be the only cause of asthma attacks and coughing during physical effort, as the only symptom of bronchial asthma. The manifestation of EIB is tightly related to the level of bronchial reactivity. This is also confirmed by the fact that the level of asthmatic symptom manifestation is tightly related to the level of bronchial reactivity. 

During exercise, the respiratory tract gets partially inflamed (this is confirmed by bronchoalveolar lavage cell structure, as well as through the reduction in proinflammatory effect on people who use inhalatory corticosteroids). A potential proinflammatory effect of exercise on respiratory system increases chronic inflammation that induces the process of bronchial obstruction in asthmatics.

after the test the FEV1 level was reduced by at least 15% percent from its initial value.

Spirometry test and exercise stress test were conducted on pneumoscrin and a Jaeger conveyor belt.

Statistic data processing was performed with probability distributions tests (such as Kolmogorov–Smirnov test), non-parametric significance tests, such as Mann-Whitney and chi-squared test (goodness-of-fit test or chi-squared test for independence), as well as the binary dependent variable test (logistic regression).

**Results**

Positive results at the exercise stress test were obtained in 50 (31.3%) of the patients. In 105 (65.6%) patients bronchial obstruction was induced with less than 2 mg/mL of histamine inhaled. The median histamine concentration needed to induce bronchial obstruction in the group of patients with positive result on the exercise stress test was 1 mg/mL, and in the group with negative results it was 0.5 mg/mL ($U = 1678; p < 0.01$) (Figure 1).

**Discussion**

Triggering asthma attack was shown to be a complex process which included an interaction between multiple factors and the processes in the respiratory tract. Speaking of exercise as a factor which could trigger asthma, the key factor was the ventilation volume increase, which was necessary to satisfy the increased need for oxygen.

The main bronchoconstrictive stimuli of EIB were: increased ventilation and inhalation of increased volume of cold air, change in airway surface liquid osmolality (the layer coating the airway mucosal surface), as well as increased disposition of allergens into respiratory tract. The above mentioned changes could have been categorized into two groups, based on two theories of EIB origin: heating and hyperosmolarity theory.

The theory is based on the assumption that temperature variations in the respiratory tract (sudden cooling at the beginning of exercise and subsequent warming during exercise) are the main reasons for the bronchoconstricting substances release and the airway smooth muscle irritation.

According to the second, hyperosmolarity theory, hyperventilation that takes place during exercise, dries the airway tract, thus increasing the mineral concentration of the liquid surface layer which cools the airway mucus tissue. The increase in osmolarity dries out the water from mast cells and eosinophils, which releases vasoactive amines (histamine, prostaglandins and leukotrienes) that directly irritate nerve endings and increase blood vessels permeability leading to edema and bronchospasm.

The mechanisms used to explain the above mentioned theories were not sufficient enough to cause bronchospasm all by themselves, because increased physical effort did not induce such dramatic changes in a healthy person’s respiratory tract. Asthmatics, however, were more prone to bronchoconstriction due to the chronic respiratory tract inflammation, because, in many cases, physical effort could not induce it by itself. Healthy persons who took deep breaths during the exercise even experienced lower level of airway reactivity to methacholine. In other words, the exercise combined with deep breathing demonstrated some sort of protective role

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against bronchoconstriction. This type of bronchodilatative condition after exercise probably occurred due to the reduction in parasympathetic-induced bronchoconstriction 3.

Apart from the above mentioned factors, other relevant factors which can cause EIB were present: the increase in inflammatory and bronchoconstrictive mediators, especially LTC4 and LTD4 histamine and interleukine-IL-8; activation of TH2 lymphocytes with the increase in T cell expression CD25 and B cell expression CD23; eosinophilic influx and airway activation 1.

The goal of pharmacodynamic or bronchoprovocation tests, conducted in laboratory conditions, was to induce a process similar to real asthma attack in the lungs. This included bronchoprovocation tests with histamine, as well as exercise. They had an important role in the bronchial asthma diagnostics. Considering their somewhat different pathophysiologic mechanisms of action, they enabled more complete and precise insight into bronchial obstruction origin in asthmatics 1, 12.

By inhaling certain dosages and monitoring the respiratory tract response, it was possible not only to determine the reactivity but also to quantify the response value. Non-specificity of this kind of bronchial asthma test was reflected by its positive response in other inflammatory and allergic respiratory tract diseases, such as allergic rhinitis, chronic bronchitis and bronchiectasis 11.

Our goal was to determine whether there was or there was not a non-specific reactivity to histamine in asthmatics. We concluded that each examinee showed positive result (because they had experienced the expected FEV1 level reduction from its initial value with histamine concentration of up to 4 mg/mL). Due to different extent of respiratory tract inflammation, as well as the number of other factors, the examinees reacted to different dosages of histamine, which confirmed earlier data about the variability of inflammation and lack of stable correlation with the symptoms of bronchial asthma 1.

By participating in the exercise stress test, the group of examinees with positive results on histamine test helped us to ascertain that the test results were more frequently positive in the group of examinees that reacted to lower levels of histamine. In other words, 84% of examinees with positive exercise stress test results also showed positive results on the bronchoprovocation test with histamine dosages of up to 2 mg/mL. These results clearly speak in favor similarity in the origin of mechanisms of these two types of reactivity, ie the same preconditions needed for their formation.

On the other hand, a medium histamine concentration in the examinees that were positive only to histamine test was lower than the concentration in the examinees that had shown positive results on both tests, which, on the other hand, indicated a difference between them. The above mentioned characteristics of the reactivity that manifested them through our research were also noted by Dor et al. 13.

Our study proved that bronchial response in asthmatics is related to the intensity of non-specific hyperreactivity to histamine.

Many other authors studying these questions came to similar results, thus confirm the previous statement about pathophysiologic processes in asthma 8, 10.

Conclusion

In the group of examinees with positive results on the exercise stress test, there were more those who reacted to a lower histamine concentration, while the frequency of those with positive results on the exercise stress test was lower in the patients with positive bronchoprovocation test with a higher histamine concentration.

Thus, histamine concentrations needed to induce non-specific hyperreactivity of asthmatic respiratory tract, as a factor of their tendency to asthma attacks in the presence of a trigger, were related to the reactivity to physical effort.

REFERENCES


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