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Bronchial challenges in children

Testy prowokacyjne oskrzeli u dzieci

Bronchial hyperresponsiveness (BHR) is a characteristic feature of asthma. Its presence, together with persistent allergic inflammation and bronchial obstruction, allow diagnosing of asthma. In the simplest definition, BHR is described as an excessive response of bronchi to stimuli that do not induce such reaction in healthy people. There is general agreement that is no asthma without BHR. However most of researchers show small but significant group of asthmatic patients with results of nonspecific bronchial challenges within normal limits. The explanation of this phenomenon is probably limited sensitivity of bronchial challenges, its inappropriate technique, or temporary remission of hyperresponsiveness that occurred after long period without exposure to allergens and irritants or after treatment. Moreover BHR is not exclusive feature of asthma. In many clinical situations increased responsiveness is observed temporarily or constantly. Patients with COPD, congestive heart failure, acute respiratory tract infections, cystic fibrosis and allergic rhinitis in significant percentage may present BHR. As the nonspecific bronchial provocation tests still remain widely used in a diagnosing of asthma it is necessary to valuate its importance in the clinical practice nowadays. Because the indications for specific bronchial challenge are strictly defined and they are not very often performed, especially in children, most of interest is directed to non-specific BHR. There are still many questions particularly in the fields of specificity, sensitivity and technique of bronchial challenges.

History of a bronchial responsiveness testing starts in 1910 with the Dale and Laidlaw's discovery of constricting action of histamine on smooth muscles *in vitro*. Eleven years later Alexander and Paddock observed bronchial constriction *in vivo* in patients with asthma, after subcutaneous administration of pilocarpine, and the similar observation was done by Weiss in 1929 after intravenous histamine. But Tiffenau using acetylcholine as a provoking agent and spirography to control reaction of bronchi performed the first really controlled bronchial challenge. In Poland pioneers of research on BHR were Droszcz and Ajewski.

Tab. I. The division of factors causing bronchial constriction regarding their action [1]

Direct stimuli	Indirect stimuli
➢ acetylcholine (methacholine, carbachol) ➢ histamine ➢ PGD_2 ➢ Leukotrienes $C_4/D_4/E_4$	➢ AMP ➢ Tachykinins (SP, NKA) ➢ Bradykinin ➢ SO_2 and sodium metabisulphite ➢ Exercise ➢ Hypo- and hypertonic solution ➢ Isocapnic hyperventilation

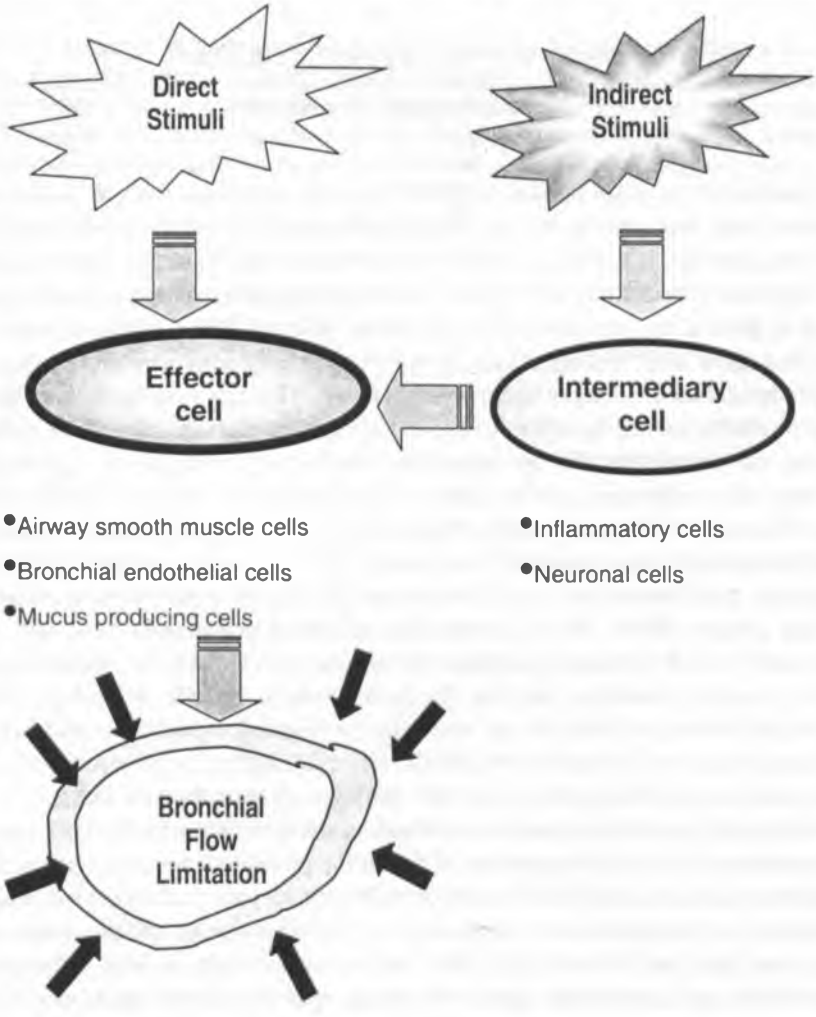

Fig. 1. Mechanisms of action — direct and indirect stimuli (modified after Van Schoor J., Joos G.F., Pauwels R.A., *Eur. Respir. J.*, 2000 [1])

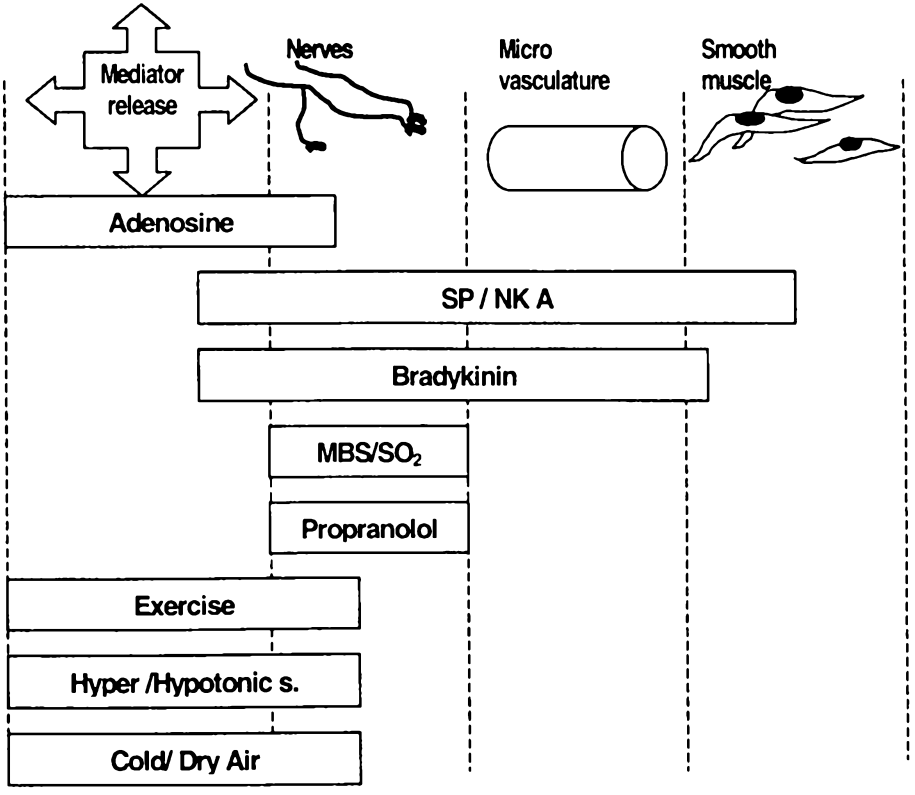

Fig. 2. Mechanisms of action of indirect stimuli during bronchial challenge (acc. to Van Schoor J., Joos G.F., Pauwels RA, *Eur. Respir. J.*, 2000 [1])

The aims of bronchial responsiveness testing include:
1) disease diagnosis,
2) identification of factors responsible for bronchial constriction,
3) research on mechanisms of BHR,
4) control of asthma treatment,
5) epidemiological studies.

Many factors are responsible for inducing of bronchial obstruction. They can be divided into two groups: direct and indirect stimuli [1] (Tab. I). Direct stimuli act through the immediate action on effector cells such as: smooth muscle cells, endothelial cells and mucus producing cells. It results in bronchial smooth muscle constriction, mucosal swelling and oedema, and flow limitation by mucus overproduction. Intermediary cells as inflammatory cells and neuronal cells mediate action of indirect stimuli. They interact with effector cells to produce similar effect as direct stimuli. (Fig. 1). Some stimuli have both a direct and an indirect activity. Methodology of direct bronchial challenges seems to be better standardized and for years these tests

have been more popular [2, 3]. The technique is relatively uncomplicated and they are not very expensive. The most commonly used substances in non-specific BHR testing are histamine and derivatives of acetylcholine, mainly methacholine. They seems to be more useful in excluding a diagnosis of asthma than establishing one, because their negative predictive power is greater than their positive predictive power. In the group of indirect challenges only exercise challenge is widely performed, although others have recently become more popular. Increasing interest with indirect stimuli as adenosine, tachykinins, hyper- and hypotonic solutions, isocapnic hyperventilation and exercise, is supported by many experimental data showing higher specificity of such challenges for bronchial asthma [4]. Moreover these tests are considered to provide additional information about mechanisms of development of BHR (Fig. 2.). Because the results of different bronchial tests are not interchangeable, they indirectly confirm that pathways leading to airway narrowing are more complex than it has been thought previously [2].

BHR testing in children is not fully standardized. There are many general recommendations both for adults and children, but at the moment no particular method has been adopted as a universal protocol. Similarly as in adults, even the terminology lacks uniformity. Responsiveness is now considered to be a general term describing reaction of bronchi to various stimuli. Two other terms commonly used for challenges with pharmacological agents are based on the dose-response curve. Sensitivity means a leftward shift of this curve, whereas reactivity implies the dose-response slope. Previously all three words were used interchangeable.

Protocol of responsiveness testing is modified accordingly to the provoking agent, dosing method, lung function used to control its course, and a way of result calculation. In inhalation challenges three methods are accepted:

1) Yan technique [5],
2) five-breath technique described initially by Sears et al. [6],
3) the tidal breathing technique [7].

The proper selection is determined mainly by the age of children and available equipment. The most difficult to perform are tests in small children not cooperating during challenge. There is still lack of good, non-invasive, cheap and reliable method of lung function control for this age group. Body plethysmography seems to be the most accurate one. Others as forced oscillation technique, transcutaneous oxygen monitoring and auscultation are not properly standardized. The most important demand of all bronchial provocation tests is a safety of the procedure. Direct stimuli do not cause delayed or prolonged response when used in conventional doses on the contrary to specific challenges. Safety and reproducibility measures in children similarly as in adults require appropriate patient preparation to the test. Factors changing bronchial responsiveness as respiratory infection, exposure to allergens and irritants have to be avoided to diminish the possibility of interference with the test results. Besides the baseline lung function has to be properly standardized and concomitant treatment, which might influence on the test result, has to be temporarily discontinued [3]. The recommended minimal intervals from the last dose to the study vary

from several hours to 1 week, depending on the drug. Routine withholding oral or inhaled corticosteroids is not generally recommended but their anti-inflammatory effect may possibly decrease bronchial responsiveness. However the individual decision has to be made, depending on the information requested by investigator. If the effectiveness of the treatment is studied, it is not necessary stop it.

In order to interpret the challenge result properly the correct choice of cut-off point is required. Review of the literature shows that in many studies such decision has been made on a purely arbitrary basis. Godfrey et al. [8] performed systematic review of bronchial challenges with two pharmacological stimuli — histamine and methacholine — and with exercise. The study comprised data from the literature between 1962 and 1998. According to authors that provided enough information to enable the calculation of optimal cut-off points between normal and asthmatic children. For exercise 13% fall in forced expiratory volume in one second (FEV_1), and for inhalation challenges provocative dose of histamine or methacholine causing 20% fall in FEV_1 (PD_{20}) between 6.6 and 7.2 mmol have been postulated.

Standardized methodology will help to compare epidemiological data worldwide. In such studies prevalence of bronchial hyperresponsiveness is much higher than bronchial asthma. According to Martinez et al. [9], 50% of children up to 6 years of age have constant or transient BHR. Warner [10] estimates that one third of them has asthma. Own studies proved almost 26% prevalence of asymptomatic BHR in school children in Warsaw [11]. It has been also shown that many diseases of the respiratory tract may increase bronchial responsiveness. Six weeks post acute airway viral infection 40% of children still presented their enhanced reactivity. Significance of this and similar studies remain under discussion. Some authors show correlation between asymptomatic bronchial hyperresponsiveness and a risk of asthma. In Jones et al studies [12] long-term observation demonstrated as high as 58% manifestation of asthma symptoms in a group of asymptomatic subjects with BHR. Other studies show appearance of asthma in 11% to 39.5% observed patients. However according to Ulrik and Backer [13] the prevalence of BHR declines from childhood to early adulthood (25% and 6%, respectively) and its presence in children has limited value for prediction of asthma in the future.

In conclusion, BHR is one of major features of asthma, but to establish the diagnosis it is necessary to confirm two other parts of the definition — chronic inflammatory process and reversible bronchial obstruction. Use of bronchial challenge as a diagnostic tool is only a part of its wider application. Many questions about patomechanizm and epidemiology of BHR remain unanswered. More discussion is still necessary to uniform methodology of bronchial challenges, especially in children.

REFERENCES

1. *Van Schoor J., Joos G.F., Pauwels R.A.*: Indirect bronchial hyperresponsiveness in asthma: mechanisms, pharmacology and implications for clinical research. Eur. Respir. J., 2000; 16: 514-533.

2. *Sterk P.J., Fabbri L.M., Quanjer Ph.H., et al.*: Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur. Respir. J., 1993; 6 Suppl.: 16, 53-83.
3. American Thoracic Society.: Guidelines for methacholine and exercise challenge testing – 1999. Am. J. Respir. Crit. Care Med., 2000; 161: 309-329.
4. *Rogers D.F., O'Connor B.J.*: Airway hyperresponsiveness: relation to asthma and inflammation? Thorax, 1993; 48: 1095-1096.
5. *Yan K., Salome C., Woolcock A.J.*: Rapid method for measurement of bronchial responsiveness. Thorax, 1983; 38: 760-765.
6. *Sears R.M., Jones D.T., Holdway M.D. et al.*: Prevalence of bronchial reactivity to inhaled methacholine in New Zealand in children. Thorax, 1986; 41: 283-289.
7. *Cockcroft D.W., Killian D.M., Mellon J.J.A., Hargreave F.E.*: Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin. Allergy, 1977; 7: 235-243.
8. *Godfrey S., Springer C., Bar-Yishay E., Avital A.*: Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. Eur. Respir. J., 1999; 14: 659-668.
9. *Martinez FD, Wright AL, Taussig LM, et al.*: Asthma and wheezing in the first six years of life. N. Engl. J. Med., 1995; 332: 133-138.
10. *Warner J. O., Warner J.A., Miles E.A., Jones A.C.*: Reduced interferon-gamma secretion in neonates and subsequent atopy. Lancet, 1994; 344: 1516.
11. *Kulus M.*: Non-specific bronchial reactivity in selected disorders of the respiratory tract and in healthy children. Ed. Medical University of Warsaw, 2000.
12. *Jones A.*: Asymptomatic bronchial hyperreactivity and the development of asthma and other respiratory tract illnesses in children. Thorax, 1994; 49: 757-61.
13. *Ulrik C.S., Backer V.*: Longitudinal determinants of bronchial responsiveness to inhaled histamine. Chest, 1998; 113: 973-979.

STRESZCZENIE

Testy prowokacyjne oskrzeli w wieku dziecięcym służą pomocą w różnicowaniu niektórych przewlekłych chorób układu oddechowego przebiegających z nadreaktywnością oskrzeli, identyfikacji czynników powodujących skurcz oskrzeli, kontroli przebiegu choroby, badaniom nad etiopatogenezą nadreaktywności oskrzeli (BHR) oraz badaniom epidemiologicznym. W artykule omówiono mechanizmy reakcji oskrzeli na bezpośrednie i pośrednie czynniki stymulujące skurcz oskrzeli, a także ich praktyczną przydatność w wykrywaniu nadreaktywności oskrzeli. Przedstawiono także techniki badania BHR u dzieci oraz metody interpretacji tych danych.