

Chapter 13

Latent Airway Hyperresponsiveness: A Phenomenon Bordering Bronchial Asthma Definition

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Abstract The basic features of bronchial asthma are dyspnea with wheezing and objectively confirmed obstructive respiratory disorder reversible after inhalation of bronchodilators. In stable intermittent bronchial asthma, these features are not present; therefore confirmation of asthma consists of the presence of bronchial hyperresponsiveness (BHR). In the present study, there were 902 bronchoprovocation tests performed for the verification of BHR. A significant criterium for BHR is a decrease of FEV_1 of 20% from the baseline level. Every test either positive or negative was finished with inhalation of four doses of salbutamol through a spacer. We obtained 675 bronchoprovocation tests negative and 227 positive. Among the 675 subjects with a negative test there were 49 subjects who after inhalation of salbutamol had an increase in FEV_1 of $\geq 20\%$ above baseline. The bronchodilatory response of these 49 subjects, makes one think about the so-called latent bronchospasm present already at baseline, limiting further constriction during bronchoprovocation tests. The detection of such latent bronchospasm in BHR increases the number of patients with an objectively confirmed bronchial asthma from 25.0% to 30.5%. Our results suggest that bronchodilation test be performed in all patients with suspected bronchial asthma to allow detecting latent bronchospasm as an initial stage of the disease.

Keywords Airway hyperresponsiveness • Bronchial asthma • Bronchoprovocation test • Bronchodilation • Latent bronchospasm

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13.1 Introduction

The basic features of bronchial asthma are dyspnea with wheezing and objectively confirmed obstructive respiratory disorder reversible after inhalation of bronchodilators. In stable intermittent asthma these symptoms are not present. Therefore, confirmation of asthma consists of the presence of bronchial hyperreactivity (BHR), which is connected with eosinophilic and mastocytes inflammation of airways. BHR is defined as excessive narrowing of airways resulting from a significantly increased bronchoconstrictive response to various inhalation stimuli (Trigg et al. 1994). Besides inflammation, BHR represents a key element of bronchial asthma which is associated with the severity of the disease and is the target of therapeutic interventions (Grootendorst and Rabe 2004). BHR can be recognized as a bronchospasm caused by physical triggers or by chemical substances affecting the respiratory system and the whole organism and can be verified by bronchoprovocation test. Execution and interpretation of the bronchoprovocation test are well defined by a consensus of the European and American Medical Societies (AARC 2001; ATS 2000; Sterk et al. 1993). The test most often consist of histamine and methacholine challenges to cause bronchoconstriction by a direct effect on the effector cells of smooth muscles. In contrast, indirect stimuli acting through release of mediators from inflammatory cells, mostly mastocytes, and through neurons in response to stimulation due to osmolality changes cause contraction of bronchial smooth muscles (Joos et al. 2003). Direct tests of bronchial hyperreactivity, based on inhalation of bronchoconstrictive agents, are used most commonly and have greater sensitivity for the diagnosis of bronchial asthma. Indirect tests, on the other hand, in which broad spectrum of mediators is released including histamine, leucotriens, prostaglandins, acetylcholine and neuropeptides, have greater specificity (NHLBI/WHO 2010).

13.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by a local Ethics Committee.

There were 902 bronchoprovocation tests performed for verification of bronchial hyperreactivity in the pulmonary function lab of the Department of Occupational Medicine and Clinical Toxicology at the University Hospital of L. Pasteur in Kosice, Slovakia. The group studied consisted of 360 men and 542 women, mean age 40 (range 16–77 years). Subjects with absolute or relative contraindications for performing a test were not included in the group.

For verification of bronchial hyperreactivity, aerosol was generated by a jet mechanism in a standardized bronchoprovocation unit, which allows powerful, fast and reproducible application of aerosol to the respiratory system without contamination of external environment. Airflow stream generated by a compressor creates a satisfactory amount of respirable fraction of aerosol (output 1 ml in 1–3 min). In 235 cases, aerosol of methacholine was generated (acetyl- β -methylcholine chloride) in sequentially doubled concentrations (0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 mg/cm³), with a total cumulative dose of 230.9 μ g. In 671 cases, aerosol of histamine (dichloride or biphosphate) was used in doubled concentrations (0.1, 0.2, 0.4, 0.8, 1.5, 3.0, 6.0, and 12.0 mg/cm³), with a total cumulative dose of 172.8 μ g. According to the international guidelines presented by ERS and ATS, a significant criterium for the verification of bronchial hyperreactivity is a decrease of FEV₁ (forced expiratory volume in 1 s) of 20% from the baseline level. An example of a positive bronchoprovocation test is shown in Fig. 13.1a. The test was terminated in case of both positive and negative reactions, i.e., after reaching the highest concentration of a provocation substance. Every test either positive or negative was finished with a so-called ‘lysis inhalation’ – of 2 or 4 doses of

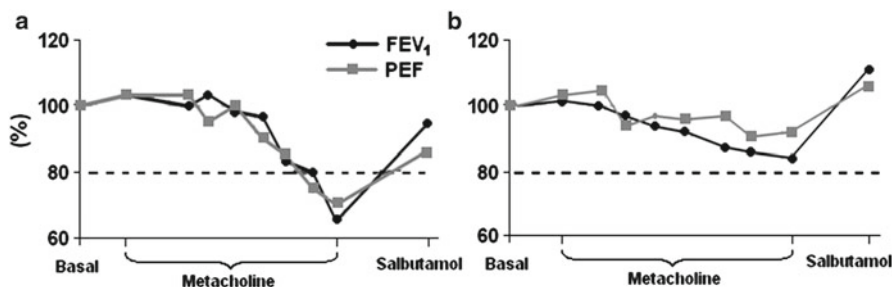


Fig. 13.1 A schematic display of a typical bronchoprovocative test. (a) Positive result – a decrease in FEV₁ and PEF of >20% off baseline in response to inhalation of a bronchoconstrictive mediator; the parameters remaining below baseline after a bronchodilator given at end-test; suggestive of the existence of asthma; (b) ‘spuriously’ negative result – less than 20% decrease in FEV₁ and PEF off baseline, but >20% bronchodilatory rebound overpassing baseline after a bronchodilator given at end-test; suggestive of a degree of pretest existing bronchospasm and thus of latent asthma

salbutamol through a spacer. We considered the tests as ‘truly’ positive and being suggestive of the existence of asthma, when there was a decrease in FEV₁ of >20% off baseline in response to a bronchoconstrictive mediator; which did not revert to the over-baseline-level after successive application of salbutamol at end-test.

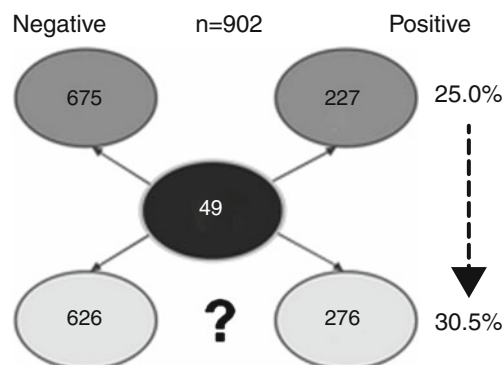
13.3 Results

We recorded 675 negative and 227 positive test results. In a group with negative results of the bronchoprovocation test, the curve of FEV₁ values did not decrease by >20% even after the highest cumulative doses of methacholine. However, FEV₁ tended to decrease continuously up the last points corresponding to the highest concentrations of the mediator. Administration of a β -adrenergic agent, in turn, led to an increase of FEV₁ which exceeded the baseline level (Fig. 13.1b). Such a curve represents a gradually decreasing downward trend in FEV₁ after administration of increasing doses of inhalant methacholine. In effect, dynamic pulmonary function parameters did not fall below the required 20% off baseline for a bronchoprovocation test to become positive. However, there was an apparent bronchodilating effect of a β -adrenergic mimetic.

For further analysis, from among the 675 subjects with negative tests results, we sorted out those who did not have a decrease of FEV₁ by $\geq 20\%$ of baseline after the highest concentrations of a mediator, but whose FEV₁ increased by $\geq 20\%$ after the subsequent inhalation of a β_2 -adrenergic mimetic. We found a group of 49 subjects, 17 men and 32 women, mean age 39 (range 18–68 years) who manifested this feature. Such a positive bronchodilatory effect, in otherwise negative bronchoprovocation test, allows assuming the presence of so-called latent hyperreactivity or latent readiness for bronchospasm. The acceptance of this seemingly reasonable assumption would increase the number of subjects with bronchial hyperreactivity from 25.0% to 30.5%, i.e., with objectively confirmed bronchial asthma in the cohort studied (Fig. 13.2).

As a typical example we can present a 50-year old non-smoker with a history of paroxysmal dyspnea at night, chest wheezing, and intermittent coughing with expectoration of mucoid sputum. At admission he complained of difficulty in breathing, but physical examination was unremarkable, with no spastic symptoms over the lungs. After inhalation of methacholine in gradually increasing concentrations from 0.125 to 16.0 mg/ml (highest concentration used) we did not observe a 20% decrease of FEV₁ off baseline. However, after inhalation of four doses of a β -adrenergic agent we

Fig. 13.2 Latent bronchospasm found in bronchoprovocation tests increases the true number of patients with bronchial hyperreactivity and thus with a suspicion of early stage of asthma



found an immediate significant increase of FEV_1 by 28%, i.e., which overpassed the baseline value; suggesting the elimination of bronchospasm provoked not only by inhalation of methacholine but also of its latent component present during the control conditions. In this patient, PEF was on the lower side of normal values, with occasional variable decreases below the normal level. Fiberoptic bronchoscopy was performed in the patient, with excision and subsequent histological examination. Severe inflammatory changes were found in histological specimens, with numerous eosinophilic leukocytes, focal signs of squamous metaplasia, and mild dysplasia, which all indicate the presence of chronic inflammation. In this patient, a history of dyspnea with chest wheezing and a negative bronchoprovocation test, with a decrease of FEV_1 only by 14%, indicate a preexisting latent bronchospasm. On the other hand, a positive bronchodilatory effect (increase of FEV_1 by 28%), significant variability in PEF monitoring, measured four times daily, the presence of eosinophils in induced sputum, and histological examinations of bronchial mucosa, confirmed the diagnosis of pesticide induced bronchial asthma.

13.4 Discussion

The major finding of the present study was that in a group of subjects with negative results of a bronchoprovocation test, there were a number of them with a significant bronchodilatory effect of a β -adrenergic agent, overshooting the baseline level of FEV_1 . This result points to the possible presence of a latent bronchospasm, which confirms bronchial hyperreactivity and supports the diagnosis of bronchial asthma despite the negative bronchoprovocation test. This reasoning was confirmed by a bronchoscopy and bronchial biopsy with eosinophilic infiltration in the presented patient case. Therefore, the authors of the present article submit that such latent bronchospasm, present already during the control conditions, causes that the bronchi are not no longer able to react in a constrictive way to subsequent bronchoconstrictor challenge. The observed reactions of FEV_1 consisting of a slight decrease at the highest concentrations of histamin or methacholine and then a bronchodilating effect of salbutamol after the end of a bronchoprovocation test may in fact detect the presence of a latent bronchial hyperreactivity. Such patients may have a high potential for later development of typical bronchial hyperreactivity with asthma and inflammation. Therefore, lung function in such deserves to be carefully followed.

We conclude that a low, gradual decrease of FEV_1 in response to bronchoprovocation with histamin or methacholine, and particularly an appreciable bronchodilatory rebound of FEV_1 of >20% after the use of a β_2 -adrenergic agent toward the end of a bronchoprovocation test, indicate a latent bronchospasm which is suggestive of an early stage of bronchial asthma. The results of this study

point to the importance of performing a bronchodilation trial at the end of bronchoprovocation test also in patients who have normal results of dynamic lung functional parameters. A bronchodilation trial in patients suspected of having asthma may allow detecting latent bronchospasm, a feature of early asthma, and may help manage the disease.

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