

Clinical relevance of bronchial hyperresponsiveness

Carlsen K-H. Clinical relevance of bronchial hyperresponsiveness.
Pediatr Allergy Immunol 1996; 7 (suppl 9): 34–38. © Munksgaard 1996.

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Key words: bronchial hyperresponsiveness; metacholine; histamine; exercise-induced bronchoconstriction; cold air inhalation; children; infants; environment

Bronchial hyperresponsiveness is recognised as an important characteristic of bronchial asthma. Already in 1959 Tiffenau described this property which is now recognised as an essential part of bronchial asthma, the non-specific hyperexcitability of the airways rendering them susceptible to many different stimuli (1).

“En dernier lieu entre en jeu l’hyperexcitabilité de l’appareil bronchovasomoteur. Ce processus essentiel est le substratum pathologique de l’asthme. Par l’intervention d’un mécanisme à seul, le degré de l’excitabilité bronchomotrice régit la quantité de médiateurs nécessaire (quantum critique) pour assurer l’effet ventilatoire asthmogène.”

R. Tiffenau 1959 (1).

Bronchial responsiveness may be described as subjective, as demonstrated by the symptoms experienced by the asthmatic child or adolescent, or objective, as can be measured by objective procedures in the pulmonary physiological laboratory or during daily life. The specific bronchial responsiveness, that is, the bronchial responsiveness to inhaled specific allergens, may be measured by the allergen bronchial provocation test (2). The non-specific bronchial hyperresponsiveness may be measured in several ways. According to the mechanisms of bringing about the bronchial response, the methods can be divided in direct and indirect (3). Typical examples of measurement of direct bronchial responsiveness are by bronchial provocation with the transmitter metacholine or the mediator histamine. The reaction is brought about by a direct effect upon the bronchial and vascular smooth muscle. Examples of indirect methods of measurement of the non-specific bronchial hyperresponsiveness are determination of exercise-induced bronchoconstriction (EIB), the re-

action brought about by inhalation of dry cold air, or by inhalation of nebulised hypo- or hyperosmolar solutions. The subsequent reduction in lung function is an indirect effect caused by mediator release. The use of these different methods has direct clinical significance, as their use as a diagnostic tool has different sensitivity and specificity (4–7), and they are influenced by anti-inflammatory treatment in different ways (8, 9).

Distribution of bronchial hyperresponsiveness within the population and according to age

The distribution of BHR in the population and within parts of the population gives a sound basis for evaluation of the methods of measurement, and how the different procedures of measuring non-specific bronchial responsiveness may be used to discriminate different bronchial and pulmonary disorders. Orehek & Gayraud suggested two possible different distributions within the population (10). Firstly, a possible bimodal distribution of non-specific BHR with the asthma population representing a separate subpopulation. Conditions under strong genetic control often demonstrate such a bimodal distribution of cases, whereas asthma recognised as a multifactorial condition, caused by the effect of several different environmental factors on a probable polygenic inheritance, ought to demonstrate a unimodal distribution (10). Depending on the selection of study population, different modes of distribution have been found. Townley et al studied metacholine responsiveness in two different groups without symptoms of asthma. In healthy subjects with a family history of asthma they found a bimodal distribution of BHR. In healthy subjects without a family history

Table 1. Classification of bronchial hyperresponsiveness

Classification	Measure
<i>Subjective</i>	Symptoms
<i>Objective</i>	
Specific	Allergen bronchial provocation test
Non-specific	
direct	Metacholine, histamine inhalation (PC ₂₀ , PD ₂₀)
indirect	Exercise test; cold air inhalation; inhalation of hypo- or hyper-osmolar solutions

of asthma, they found an unimodal distribution of BHR. This was interpreted as an increased occurrence of BHR in family members of asthmatic patients, even if they had no symptoms of asthma (11). Accordingly, in a population-based cross-sectional study of 2363 Australian schoolchildren 8–11 years old, Salome et al found a unimodal continuous distribution of BHR (PD₂₀-HISTAMINE). When BHR was defined by a PD₂₀ below 7.8 µmol histamine, 17.9% of the children had a positive reaction (12).

BHR varies according to age. Hopp et al found increased BHR among children and adolescents as well as elderly people compared to the middle ages (13). This has been confirmed by other groups (14). Also in infants and young children, BHR has been assessed, both by indirect methods as hypercapnic cold air provocation (15) and by direct means such as metacholine provocation (16). Increased occurrence of BHR among infants has been related to baseline lung function, small airway dimensions and dose relationship of the provoking agent (17–18). Also in older individuals BHR is influenced by baseline function (19).

Measurements of BHR have also been used as tools in epidemiological studies, especially in follow-up studies. Young et al reported increased levels of BHR at one year of age in infants found to have flow limitation at one month of age (20), whereas Korppi et al found that of children admitted to hospital during infancy due to acute bronchiolitis, 62% had BHR by metacholine provocation seven to eight years later, whereas only 15% had a diagnosis of asthma (21).

Effect of environmental conditions upon BHR

A number of environmental conditions has been found to influence BHR, thereby participating in establishing the clinical relevance of BHR. Several years ago a link to atopy and allergen exposure was reported. Cockcroft et al reported that the late allergic response after allergen bronchial provocation increased direct BHR, and that non-specific BHR increased during exposure to seasonal allergens, thereby increasing the bronchial sensitivity to both specific and non-specific stimuli also after the spe-

cific season. Thus, a seasonal allergy may contribute to a perennial asthma by increasing the non-specific BHR during allergen exposure (22–23). During school age a definite link between atopy and bronchial hyperresponsiveness has been established in asthmatic children (24).

Respiratory virus infections, particularly rhinovirus infections, are the main environmental provoking factor for acute asthma during childhood (25, 26). Respiratory virus infections have been found to increase bronchial responsiveness in healthy subjects, (27), in asthmatic and atopic individuals (28) and in animal studies (29). However, few studies on bronchial hyperresponsiveness with a punctilious virological diagnosis have been reported.

Also air pollution has been reported to increase BHR (30), although conflicting evidence has been reported also on this topic. However, a recent study demonstrates that living in an industrial polluted area during the first two years of life is related to bronchial hyperreactivity to metacholine during school age (31). Environmental tobacco smoke exposure is among the most important air pollutants, and an effect upon BHR in children has been reported, though the results are not unequivocal. Forastiere et al reported an effect upon metacholine bronchial responsiveness by passive tobacco smoke, most obvious among girls. They reported a dose-response relationship between the number of cigarettes smoked by the mother and BHR in the daughters (32).

Exercise and physical training have been reported to influence bronchial responsiveness. Short-term intensive exercise, as demonstrated by swimming, increased direct bronchial responsiveness both in asthmatic and healthy children (33). Intensive physical endurance training and competition increased bronchial responsiveness in young skiers (34, 35). A combination of respiratory virus infections and heavy training induced an increase in bronchial responsiveness for four to six weeks (36).

Thus, several environmental factors may increase BHR in susceptible subjects. On the other hand, asthmatic subjects staying in the mountains with low allergen exposure and low air pollution, improved both as regards respiratory symptoms and bronchial responsiveness as measured by metacholine provocation (37) and by exercise tests (37). The effect of environmental exposure upon respiratory health may thus be assessed by measuring bronchial responsiveness, either by direct or indirect means.

Relationship of BHR to respiratory symptoms

Tiffenau suggested that BHR was the most important characteristic of asthma (1). Later studies have shown that BHR is not obligatory for asthma, and

that different ways of measuring BHR may relate differently to asthma severity. Hargreave et al found a distinct relation to asthmatic symptoms and severity (38) in asthmatic subjects, whereas Salome et al in a population study found that a number of asthmatic children did not have BHR, and some children with BHR were not asthmatic (12). In a recent study of children with mild occasional wheezing, the latter finding was confirmed, as children with mild recurrent wheeze included children both with and without BHR (39).

Diagnostic significance of BHR

As BHR may be found both in children with and without asthma, and asthmatic children may or may not exhibit BHR, measurement of BHR cannot be a conclusive tool for the diagnosis of asthma. Although measurements of histamine, metacholine and by exercise tests in asthmatic children correlate well (40), studies comparing direct and indirect measurements of BHR in asthmatic children and children with other chronic lung diseases, show that direct measurements by histamine or metacholine provocation are sensitive tools in examining asthmatic children, but with a rather low specificity towards other lung diseases. Indirect measurements by exercise tests or by inhalation of cold, dry air, have low sensitivity, but high specificity (4, 41). A positive diagnosis by an exercise test thus favours the diagnosis of asthma. Furthermore, by use of exercise tests in children, a measure of their natural behaviour during daily play and during sports is assessed. Thus, a measure of their ability to master daily challenges is obtained, which is useful for planning the treatment.

Effect of therapy upon BHR

Anti-inflammatory therapy by inhaled steroids improve BHR in asthma. This may be assessed by repeated measurements of both direct and indirect measures of BHR. However, it has been demonstrated that inhaled steroids improve direct and indirect BHR to a different degree and with different speed. No effect upon BHR has been found by a single dose of inhaled steroid (42). Henriksen & Dahl reported a rapidly occurring improvement of exercise-induced asthma in children by inhaled budesonide (43), and this was confirmed by Waalkens et al (8), demonstrating a plateau effect within two months. A continuous improvement of BHR measured by metacholine provocation was demonstrated during a 22-month study by van Essen Zandlivet et al (9). Thus, the direct and the indirect tests of BHR may reflect different properties of non-specific bronchial responsiveness in asthmatic children.

BHR and airway inflammation

During later years, emphasis has been laid upon the role of airways inflammation in asthma. BHR has been taken as a sign of airway inflammation, and several studies have tried to assess the relationship between bronchial responsiveness and other measures of airway inflammation. BHR has been found to correlate with degree of epithelial damage in the bronchial mucosa (44, 45) and total number of cells in the respiratory epithelium. Recently, BHR measured by inhalation of nebulised distilled water and metacholine, was found to correlate with eosinophil infiltration in the epithelium, but not in the lamina propria. The thickness of the subepithelial layer correlated to baseline lung function, but only slightly to metacholine responsiveness, and not at all to inhalation of distilled water. No correlation was found between BHR and mast cell counts (46). Thus, the importance of the eosinophil cell was emphasised (46). In animal studies by instillation of IL-5, it has been demonstrated that airway inflammation as demonstrated by eosinophil infiltration precedes the development of BHR, measured by metacholine provocation (47). Virchow et al demonstrated a relationship between airway responsiveness and sputum eosinophil cationic protein (ECP) in patients without inhaled steroids, but not in patients with inhaled steroids (48). In a study of early infant wheezers, a correlation was found between the level of serum ECP and the lung function response to salbutamol, a measure of airway lability, but not of BHR (49). As markers of airway inflammation are evaluated, they will be assessed against measures of BHR, both by direct and indirect tests. Their usefulness will partly be evaluated by such studies.

Conclusions

Measurements of BHR are useful tools in assessing the severity of childhood asthma. However, the different methods of assessment differ to a certain extent in their ability to differentiate asthma from other chronic lung diseases, and they are influenced by therapy to a different degree. Measurements of BHR have given insight into pathophysiologic mechanisms of asthma, and they are frequently employed in epidemiological studies as objective measures. The tests of BHR are valuable tools in assessing, particularly severe asthma, but they cannot replace the careful clinical examination and assessment of children with asthma.

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