

Bronchial hyperresponsiveness: definition and terminology

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During the last decade it has been realized that the key for the understanding, prevention and treatment of asthma lies in infancy and childhood. Recent progress in fundamental immunological research and molecular biology has opened a wide perspective of promising techniques to unravel the pathogenesis and, thereby, a potential cure for asthma.

It will be absolutely essential to bridge the gap to the functional and clinical abnormalities of patients *in vivo* in infancy and childhood. This integrated approach requires validated measurements of airway function *in vivo*. The bronchoconstrictive response to bronchoconstrictor agents is an important characteristic in adults with asthma. The current challenge in paediatrics is to translate this knowledge to infancy and childhood.

Few issues in asthma research have been investigated in more detail, whilst nevertheless leaving so many unanswered questions, as the phenomenon of "bronchial hyperresponsiveness". Even though clinicians and laboratory workers all consider hyperresponsiveness to bronchoconstrictor stimuli to be a major feature of the airways in asthma, its role in the pathogenesis and pathophysiology as well as in the diagnosis and treatment of asthma is far from being clear. This has encouraged some investigators to further explore the mechanisms of bronchial hyperresponsiveness, whereas it has discouraged many others who had hoped that bronchial hyperresponsiveness would provide the single best tool to investigate the cause, course and prognosis of asthma.

Following the decade that had peak expectations about the role of bronchial hyperresponsiveness in asthma research, it might be the right time for an attempt to provide a balanced view. Particularly, this refers to its role in paediatric asthma: e.g. how should it be measured in infancy and childhood,

what are its determinants in the various age groups, what is the clinical relevance of hyperresponsiveness at young age, and has it any prognostic implication in children? This will be addressed elsewhere in this supplement.

What is meant by bronchial hyperresponsiveness?

Already in 1859 Sir Henry Hyde Salter described the "bronchial sensibility" in patients with asthma (1). At present, this is referred to as bronchial hyperresponsiveness, which can be defined as an increase in the ease and degree of airway narrowing in response to bronchoconstrictor stimuli *in vivo*. It can be measured by challenge tests in the laboratory (2), which mimic the spontaneous variability in airways obstruction as observed in patients with asthma (3) or COPD (4). Usually, these challenges are performed in a dose-response way, by exposing the subject to increasing doses of the bronchoconstrictor stimulus, while measuring an index of lung function (2). The essential outcome of the challenge, therefore, is the bronchoconstrictor dose-response curve, which can be characterized by: *a*) the position (measuring *sensitivity*), *b*) the slope (measuring *reactivity*), and *c*) the plateau (measuring the *maximal response*) (5). It needs to be emphasised that these three characteristics of the dose-response curve need to be carefully distinguished, because they can vary independently (5).

It is mandatory to use strict terminology (2). The term "hyperresponsiveness" is recommended as a general description of the phenomenon. "Hypersensitivity" and "hyperreactivity" specifically refer to a leftward shift and an increase in slope, respectively, of the dose-response curve. Unfortunately, the term "hyperreactivity" is also often misused as being

synonymous to hypersensitivity. "Excessive airway narrowing" refers to an increase in maximal response, often leading to an unmeasurable plateau level. Because most investigators assume that the bronchi are the major component in these responses, the terms "airway hyperresponsiveness" and "bronchial hyperresponsiveness" are used interchangeably. Due to this confusing terminology it is mandatory to specifically indicate the outcome measurements when describing the results of challenge tests.

Bronchoconstrictors of choice

The bronchoconstrictor challenge tests require careful and detailed standardization. This has been accomplished in adulthood (2), but is still an on-going effort in infancy and childhood.

It is essential to specify the nature of the bronchoconstrictor (6). Acute airway obstruction can arise from smooth muscle contraction either with or without inflammatory changes in the airway wall. These inflammatory changes include hyperaemia, plasma exudate, oedema, or hypersecretion, which by themselves may not cause serious airway narrowing, but in combination with smooth muscle contraction will lead to severe, acute obstruction (7, 8, 9). These bronchoconstrictor mechanisms are involved to a various extent during different types of challenge tests (2, 6). Some bronchoconstrictors act directly and predominantly on airway smooth muscle itself (e.g.: methacholine, histamine), whereas other stimuli depend on the involvement of cellular or neurogenic mechanisms, indirectly leading to smooth muscle contraction and possibly to inflammatory changes in the airway wall (e.g.: non-isotonic aerosols, cold/dry air, exercise, adenosine 5'-monophosphate (AMP), bradykinin, tachykinins, leukotrienes, sodium metabisulphite, etc.) (2, 6). The inflammatory mechanisms predominate after challenge with sensitizing agents, particularly during late asthmatic reactions (e.g.: allergens, occupational sensitizers) (5). In addition, these challenges by themselves can also cause temporary increase in airway responsiveness to other, non-sensitizing stimuli (2, 5), which also occurs after respiratory virus infection (10).

Therefore, it is not surprising that the results of the various challenge tests are only weakly correlated, and thereby not being interchangeable, each test implicitly providing different and perhaps complementary information on the multiple pathways leading to airway narrowing.

Pathogenesis and pathophysiology

Epidemiological studies suggest that bronchial hyperresponsiveness has both a genetic and an envi-

ronmental background (11). In children from a general population, it appears to be associated with parental asthma, atopy and early respiratory illness (12). So far, the genetic predisposition of bronchial hyperresponsiveness is still unclear. Recent results in a clinical population indicate that hyperresponsiveness to histamine might be linked to loci on chromosome 5q, independently of linkage of serum IgE to the same chromosome (13). If these findings can be confirmed in other populations, it would definitely confirm that genetic predisposition is of importance in the development of bronchial hyperresponsiveness.

Environmental exposures, such as respiratory virus infections (12, 14, 15), allergens (16, 17), and parental smoking (18) might also induce bronchial hyperresponsiveness, presumably in interaction with genetic predisposition. Even though it is well established that respiratory virus infections can temporarily worsen the degree of bronchial hyperresponsiveness in asthma (10, 19, 20), it remains to be established as to whether virus infections are causally involved in the actual development of this abnormality (15, 21).

There is no doubt that the underlying mechanisms of bronchial hyperresponsiveness are multiple, being associated both with acute and chronic airways inflammation (22–25). The major determinants of bronchial hyperresponsiveness seem to be the mechanical consequences of (sub)mucosal as well as adventitial inflammation on airway luminal diameter during smooth muscle shortening. This is beyond the scope of the current paper, and has been reviewed elsewhere (9, 26).

Conclusions

During more than a century it has been realized that bronchial hyperresponsiveness comprises the common physiologic pathway of multiple (cellular and biochemical) abnormalities within the airways, leading to an increase in ease and degree of airway narrowing in response to bronchoconstrictor stimuli *in vivo*. The clinically most relevant component of bronchial hyperresponsiveness seems to be unlimited, potentially life-threatening airway narrowing, as shown by absence of a maximal response plateau on the *in vivo* dose-response curve.

The changes in airway mechanics are likely to be due to acute as well as chronic pro-inflammatory stimulation within the airways. Even though current asthma research is almost exclusively focused on the cells, cytokines and mediators in allergic inflammation, there is increasing evidence that non-allergic stimuli (such as virus infections) play an important role in the development of bronchial hyperresponsiveness. Prolonged exposure to a variety of

growth factors can potentially lead to structural changes of the tissue elements within the airway wall. The limited improvement of bronchial hyperresponsiveness by long-term treatment with inhaled glucocorticosteroids indicates that such chronic sequelae of inflammation might be important in maintenance of this functional disorder (27).

Bronchial hyperresponsiveness will be an essential part of research on the pathogenesis and treatment of asthma, as long as difficult breathing is considered to be the basic problem of this disease. It is now time to combine knowledge on the morphologic, physiologic and molecular basis of asthma to develop future prevention and therapy, along the lines already explored in more detail by our colleagues in cardiovascular research (28).

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