The significance of bronchial responsiveness in children

M. Silverman*

On both the clinical and epidemiological level, there is extensive information about bronchial responsiveness (BR) in childhood [1]. For technical reasons, however, there is little data on infants and pre-school children, although new techniques for measuring changes in intrathoracic airway function have made this feasible, even in the youngest subjects.

Exercise tests were first used to provide a response in children, and recently there has been analogous work using hyperventilation challenge. However, most studies have used pharmacological, inhalation challenge with histamine or methacholine. Differences in the interpretation of results from these two types of challenge have been dealt with elsewhere.

The significance of bronchial responsiveness can be considered from the epidemiological or from the clinical viewpoint.

Epidemilogy of BR

The distribution of bronchial responsiveness in unselected populations of children appears to be unimodal. Several studies suggest that the measured response to a standardized challenge may be greater in children than in adults [2].

Such studies cannot take account of all variables such as: 1) the size of the stimulus, even if attempts are made at 'normalization'; 2) the population under study, which can be subjected to selection bias for instance by elimination of smokers or individuals with atopy; 3) variations in the ability to perform lung function tests with age.

Nevertheless, whether BR is measured by histamine or methacholine challenge, or by cold air inhalation, the data consistently show that children have greater BR than adults. Infants appear to have the greatest BR of any group [3]. Moreover, *in vitro* studies of guinea-pig airways are consistent, suggesting that the responsiveness of bronchial or tracheal muscle to a range of agonists, declines at the time of puberty.

A prospective study of a hospital-based population of asthmatics demonstrated a reduction in asthmatic symptoms before puberty, followed in early puberty by a sharp decline in the level of exercise-induced asthma. These observations, together with consistent but small sex differences in BR, point to a possible hormonal effect on BR, which remains to be elucidated.

There are significant familial (presumed hereditary) associations with childhood BR: atopy and parental asthma are the strongest. Environmental associations are also important: respiratory illness in infancy, prematurity and overall environment are all significant in population studies. On balance, it seems unlikely that recent upper respiratory tract infection has more than a marginal effect on BR in normal children.

The significance of epidemiological observations has to be interpreted cautiously. Technical factors clearly complicate comparison between groups of workers and between different age groups. Logistic regression analysis, which seems to provide 'explanations' for much of the variation in BR between individuals, only indicates association. Longitudinal studies, experimental manipulation of BR, or natural experiments provided by twins and by population movements, are needed to confirm causal hypotheses.

Clinical significance of BR

Suprisingly, there is no clear division into "normal" and "increased" BR. If, for example, there is an association between atopic status and increased BR, then assuming atopy is all-or-none (and not a continuum, like BR), there should be a bimodal population distribution of BR, with an excess at the hyperresponsive extreme.

Increased BR is clearly associated with the clinical diagnosis of asthma. However, the diagnostic significance of increased BR alters with degree: the specificity increases and the sensitivity declines as the cut-off level of BR increases. A test of BR can no longer be said to provide anything more than supportive, physiological information in diagnosis of asthma.

Among groups of asthmatic children, there is a correlation between the degree of BR and the severity of asthma, as judged by the level of treatment. The strength of the correlation provides little guidance in clinical management because there is so much scatter.

The fact that neither the diagnosis nor severity of asthma is strongly correlated with the level of BR, implies that factors other than the level of BR are important in the clinical manifestation of asthma in

*Royal Postgraduate Medical School, London W12 0HS, England.

individual subjects. The possibility remains to be tested, that BR is largely a secondary phenomenon! The symptoms of exercise-induced asthma, a significant problem in children and a measure of BR, provide the justification for thinking that BR has some primary significance in asthma.

Only about 10% of UK school children have clinical asthma. Many others have minor respiratory symptoms: cough after colds, night cough, mild wheeze. Population studies have shown that those children with greater levels of BR tend also to have more symptoms [4]. However, the pattern of symptoms in children with high levels of BR is not simply compatible with a diagnosis of 'mild asthma'.

We have compared two groups of 7-year-old children: 1) a cohort of about 150 children all of low birthweight (<2000 g and mainly pre-term); 2) a reference group of 125 local unselected school children [5]. There was a significant increase in BR to histamine among the low birthweight cohort, but no excess of atopy or asthma. The symptoms exhibited by the hyperresponsive children from the two groups differed: the low birthweight children had predominantly cough, whereas the reference children tended to wheeze. Histamine responsiveness failed to distinguish the two populations: perhaps isocapnic hyperventilation or exercise would have been more successful, as seems to be the case in distinguishing chronic bronchitis from asthma in adults.

Increased BR has been found in chronic airway diseases other than asthma in childhood. Some children undoubtedly also have asthma. But the significance of increased BR in these conditions is not in diagnosis but in its implications for a better understanding of airway pathophysiology and hence for rational therapy.

Conclusion

The real six significance of BR will only be apparent when its cellular basis is worked out. Until then, its clear association with symptoms and disease has lead to a better understanding of childhood respiratory illness. Longitudinal studies of BR may provide an answer to the question of its relevance, since we cannot easily manipulate BR experimentally in humans independently of asthma itself. Perhaps the answer will come from studies of normal newborn babies from asthmatic families: if increased BR pre-dates symptoms, then an innate, inherited disorder, of primary importance, would seem likely. This remains to be determined.

References

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