Detecting asthma and bronchial hyperresponsiveness in children

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The prevalence of asthma in children is increasing worldwide. Although the features of asthma are well documented, defining asthma remains a problem. The clinical definition of asthma does not take into account the concept of airway inflammation. A broader definition that incorporates the inflammatory process, reversibility of airway obstruction, and airway responsiveness needs to be more widely adopted. Bronchial hyperresponsiveness is one of the key features in asthma and it can be documented by using pharmacological or non-pharmacological means. The latter appears to be a more physiological test and more acceptable to children. This article gives an overview of the features of asthma and bronchial hyperresponsiveness and shows how various non-pharmacological bronchial challenge tests can help identify bronchial hyperresponsiveness and thus help diagnose asthma in children.

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Introduction

Asthma in children is an important cause of chronic ill health and hospital admission. Over the past 15 to 20 years, there has been a significant increase in the prevalence of asthma among children in developed countries.[1,2] A similar increase is also occurring in Hong Kong[3]; the prevalence of asthma in 13- and 14-year-old Hong Kong children is 11.3%.[4] Significant aetiological factors are thought to include viral infections,[5] indoor allergens,[6] outdoor allergens,[7] overcrowding,[8] genetic predisposition,[9] maternal smoking,[10] airway hyperresponsiveness,[11,12] and psychosocial pressure.[13] Despite a greater awareness and better understanding of asthma among physicians, the problem of definition remains unresolved, and the diagnosis is often delayed or sometimes not made.[14]

Bronchial hyperresponsiveness (BHR) is a key pathophysiological feature of asthma. Even though there is no diagnostic test for asthma, bronchial provocation tests have been adopted to help confirm an asthma diagnosis. Drugs such as histamine and methacholine are commonly used for this purpose. There is increasing use, however, of non-pharmacological tests for BHR in Europe and North America.[15,16] At the Kwong Wah Hospital, hypertonic saline (HS) is routinely used as a non-pharmacological bronchial challenge agent in children. It is useful for physicians to have some knowledge of these tests and their mechanism of action.

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Asthma: definition and diagnosis

Characteristic features of asthma include wheeze, cough, nocturnal symptoms, reversibility of airway obstruction, airway hyperresponsiveness, positive skin-prick tests for different allergens, an elevated serum immunoglobulin (Ig) E level, sputum eosinophilia, and desquamative, eosinophilic airway inflammation. Children who have asthma sometimes present with recurrent cough but do not have wheeze or breathlessness. Chronic cough can be very distressing to a child and can also make the parents anxious. Persistent cough has been reported as the only manifestation of airway hyperresponsiveness (also called cough variant asthma).[17]

Currently, the clinical diagnosis of asthma in children is mainly made based on symptoms. In the United Kingdom, the working definition for childhood asthma during the past decade has been "[when] episodic wheeze and/or cough occur in a clinical setting where asthma is likely and other, rarer conditions have been excluded."[18] This definition relies heavily on history taking and physical examination, but it does not take airway inflammation into consideration. An early event in asthma is thought to be the release of inflammatory mediators such as histamine, prostaglandins, and leukotrienes from bronchial mast cells, T lymphocytes, alveolar macrophages, and epithelial cells. These mediators can cause bronchoconstriction directly. They can also activate eosinophils and neutrophils, and can induce the migration of these cells to airways to cause epithelial damage, mucous hypersecretion, airway oedema, and hyperresponsiveness.

The International Consensus Report on the diagnosis and treatment of asthma defines asthma as "a chronic inflammatory disorder of the airways in which many cells, including mast cells and eosinophils play a role. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and cause an associated increase in airway responsiveness to a variety of stimuli."[19] This definition incorporates both the inflammatory nature and potential reversibility of asthma, and thus suggests more appropriate forms of therapy. A problem, however, is that airway responsiveness is not usually investigated in clinical practice. This is particularly true for children younger than 6 years, because performing bronchial provocation tests at this age is not feasible. Nevertheless, this more detailed definition is widely adopted. It is expected that as research progresses, more attention will be focused on the biochemical and genetic aspects of asthma.[20]

Bronchial hyperresponsiveness: definition and diagnostic usefulness

Bronchial hyperresponsiveness is an exaggerated response to a variety of stimuli that lead to bronchoconstriction. While BHR is an essential feature of asthma, it is not exclusive to it.[21] Other conditions associated with BHR include viral respiratory infection,[22] bronchopulmonary dysplasia, tobacco smoking, smoke inhalation, atopy, bronchiectasis, cystic fibrosis, and near-drowning.

The association between BHR and adult asthma is quite strong (Fig), but its association with childhood asthma is less clear. Not all children with recurrent episodes of wheezing have increased BHR and some

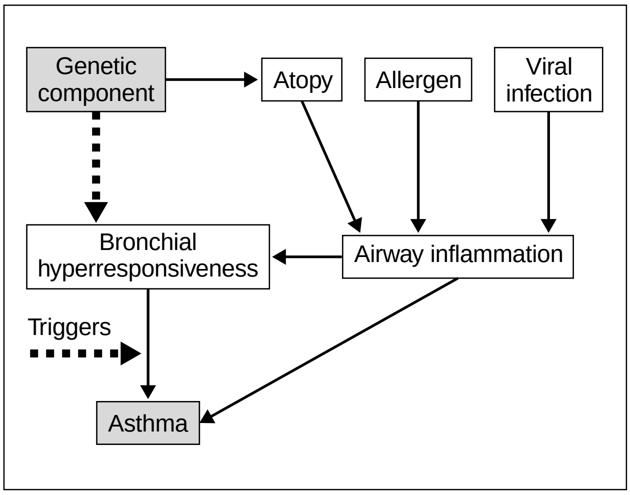

Fig. Role of bronchial hyperresponsiveness in asthma aetiology

children who do not have respiratory symptoms show signs of BHR.[23] Pronounced BHR in asymptomatic children is a positive and independent risk factor for wheezing attacks later in life.[24] The greater the degree of BHR, the more symptomatic is the individual. Persistence of BHR into adulthood is also common in children who have atopy. In addition, there are studies that show a correlation between the degree of BHR and serum IgE levels.[25] Hence, BHR may be a helpful in the diagnosis of asthma.

Generally speaking, BHR is referred to as non-specific hyperresponsiveness. Specific responsiveness relates to responses to allergens or occupational agents. The exact mechanisms that contribute to BHR are not fully understood. Proposed explanations include increased bronchial wall thickness internal to smooth muscle, enhanced muscle contractility, altered autonomic nervous control, and acute and chronic inflammatory processes in the airway that can lead to epithelial cell damage. All of these mechanisms may be the result of action by mediators released from the additional inflammatory cells present in asthmatic airways. There is the possibility that different mechanisms coexist in an individual patient and interact to cause airway narrowing.

The use of bronchial challenge tests to diagnose bronchial hyperresponsiveness

There are two ways to measure non-specific BHR: using pharmacological and non-pharmacological agents. The former group includes drugs such as methacholine, histamine, acetylcholine, prostaglandins, leukotrienes, adenosine, neuropeptides, and bradykinin. The following physical stimuli are examples of non-pharmacological challenges used: hyperventilation, exercise, cold dry air, HS, and distilled water. Non-pharmacological agents give an indirect challenge because they affect the osmotic or thermal properties of the airway surface while also releasing mediators from cells in the bronchial airway epithelium and muscle.

On the other hand, pharmacological agents can work directly or indirectly. Examples of indirectly acting agents are adenosine and bradykinin. Directly acting pharmacological agents such as methacholine and histamine act on specific airway receptors and cause the contraction of bronchial smooth muscle. With this method, patients breathe in escalating doses of either drug until a certain level of bronchoconstriction is achieved—usually a 20% reduction in the 1-second forced expiratory volume (FEV_1). Airway responsiveness is then taken as the provocative dose (PD_{20}) or concentration (PC_{20}) of the drug required to give this degree of bronchoconstriction. In the past, pharmacological bronchial challenges were considered to be more sensitive in the diagnosis of BHR than non-pharmacological challenges. This may not be entirely correct, as recent studies suggest that the sensitivity and specificity of these two tests are similar.[26,27]

No matter which stimulus is used, the end result is bronchoconstriction. However, both pharmacological and non-pharmacological challenges generate different types of bronchial responsiveness. The choice of test depends on the reason for measuring BHR. Drugs are expensive and not always available to a doctor. For example, methacholine is not readily available in Hong Kong. Parents may not readily accept that a pharmacological challenge for lung function test be given to their child. As the non-pharmacological challenge is more physiological in nature, it is more acceptable to parents.

Non-pharmacological bronchial challenge tests

Non-pharmacological bronchial challenges have been used to assess whether or not asthma is present in children who have persistent symptoms like a chronic cough. For children who are already receiving anti-asthmatic medication, these tests may help to evaluate the effectiveness of their treatment and the progress of their lung function. Exercise-induced asthma can be demonstrated by running an exercise challenge. From an epidemiological viewpoint, these tests help to assess the prevalence of BHR and exercise-induced asthma in a population. Examples of non-pharmacological agents that can be used in children include HS, distilled water, cold air and exercise.

Hypertonic saline challenge test

The HS challenge test was first reported in 1981 by Schoeffel et al[28] as being able to provoke an asthma attack in a patient. In 1994, Riedler[29] showed this to be a useful, simple, and safe test in children and one that enabled prevalence studies of BHR and asthma to be compared over time and between countries. The underlying mechanism of the test is not fully understood, but it has been suggested that the hypertonicity of the solution changes the osmolarity of airway surface fluid and causes the epithelial cells to release substances that lead to smooth muscle contraction and the increased permeability of blood vessels.[29] Histamine and prostagladin D_2 are examples of the mediators involved. Mast cells and the stimulation of bronchial neurogenic reflexes seem to play a key role in the change of bronchial calibre. As concurrent drug use can affect the test result, inhaled short-acting β_2–agonists and cromoglycate are withheld for 8 hours prior to the challenge, inhaled steroids for 12 hours, inhaled salmeterol for 24 hours, and antihistamines for 72 hours before testing.

In Riedler's study,[29] 4.5% HS was nebulised by using an ultrasonic nebuliser that had been connected to a corrugated aerosol tube and a valve. Saline was added to the nebuliser canister. The dose was increased successively by doubling the inhalation time from 0.5 minute up to 8 minutes with children breathing in tidal volumes. The FEV_1 was measured in duplicate, 1 minute after each challenge. The test was stopped when either the total inhalation time was 15.5 minutes or the FEV_1 had dropped by 15% or more. The nebuliser canister and the tubing were weighed on an electronic balance before and after the challenge, to enable the amount of aerosol nebulised to be calculated. A dose-response curve can be constructed by plotting the FEV_1 against the cumulative dose of aerosol delivered during each inhalation.

In the Department of Paediatrics at the Kwong Wah Hospital, a modified version of the HS challenge test is used, and we believe that it is more practical and user-friendly. The modified method, however, has not been validated against the published HS test and there are also no published reports of HS test results in Hong Kong Chinese children. An ultrasonic nebuliser (Comfort II Model 990 T; ITO Co. Ltd, Tokyo, Japan) is connected to an 80-cm corrugated tube and a mouthpiece. The aerosol particles made are from 2- to 5-µm in size and the nebulising output is 1.5 to 5 mL/min; 30 mL of 4.5% HS are added to the solution cup. A baseline FEV_1 (in duplicate) is measured before the test. During the challenge, the dose of saline is increased successively by doubling the inhalation time from 0.5 minute up to 8 minutes. A nose-clip is put on the child's nose so that the child breathes the aerosol at a normal rate and tidal volume through the mouth-piece. The FEV_1 is measured in duplicate, 60 seconds after each challenge. The test is terminated if the FEV_1 falls by more than 15% or if a cumulative inhalation time of 15.5 minutes has elapsed. As the tubing and medication cup are not weighed before and after the challenge, a dose response curve is not constructed. The response is expressed as either positive or negative to HS challenge. In other words, it is a semi-quantitative measure of airway response to HS.

A bronchodilator is given immediately through a spacer device or dry powder inhaler (eg Turbohaler; Astra, Stockholm, Sweden) to any child who has chest discomfort or whose test response is positive. Ten minutes after the child has inhaled the bronchodilator, the FEV_1 is again measured to show that the broncho-constriction is responsive to bronchodilator therapy. It is very important to bring the child's FEV_1 back to its prechallenge value after the test is finished. Some children complain of nausea, cough, and a salty taste during and after the challenge, but these side effects are not serious. A challenge test is not conducted if the baseline FEV_1 is less than 65% of the predicted value. Over 9 months, we performed 27 HS tests in children who had clinical asthma; 11 test results were positive (unpublished data, 1999). The sensitivity of the test was 41%; specificity could not be calculated, as all tested children had asthma. The published sensitivity and specificity of this test are 47% and 92%, respectively.[29]

Distilled water challenge

Hypotonic solutions such as distilled water[30] can also induce bronchoconstriction after being inhaled. The mechanism of action is similar to that of HS-induced bronchoconstriction; the procedures used are also similar. The main difference between the two tests is that HS increases the osmolarity of the bronchial lining fluid while hypotonic solution decreases osmolarity. The distilled water challenge is considered to be less sensitive than the saline test in identifying children with asthma.[31,32]

Cold air challenge

Cold air hyperventilation[33] has a powerful broncho-constricting effect. The cold air increases the osmolarity of the airway epithelial lining fluid. The underlying mechanism is similar to that which occurs with HS. The child breathes cold dry air for a fixed period from an apparatus that includes a compressed air cylinder, a carbon dioxide cylinder, a cooler, a heat exchanger, and a carbon dioxide analyser. The FEV_1 is measured before and after the challenge. The response is considered to be positive if the reduction in FEV_1 is more than 10%. This test is expensive because various pieces of equipment are required.

Exercise challenge

Exercise causes hyperventilation, which can induce bronchoconstriction.[34,35] Hence, exercise can be helpful in the diagnosis of BHR or asthma. However, a negative response does not rule out the possibility of asthma. The degree of response depends on the exercise type, duration, and intensity that is administered. An exercise challenge is usually performed as a free-running test on a treadmill or an exercise bicycle. The pre- and post-exercise values are measured and compared. A reduction in FEV_1 of more than 15% is considered a positive response. Standardisation of the procedure is extremely important, because without this, it is difficult to repeat and compare test results; this caveat is especially true for the free-running test. The air temperature and humidity should also be measured in a free-running exercise challenge. One disadvantage of the test is that older children may not be sufficiently motivated or cooperative enough to complete it.

Comparison of pharmacological and non-pharmacological bronchial challenge tests

The sensitivity and specificity of the various bronchial challenge tests used in children are shown in the

Table. Results of non-pharmacological and pharmacological bronchial challenge tests in children

Study	Challenge test		Mean age (years)	Sensitivity (%)	Specificity (%)
	Type	Test used			
Riedler et al[29]	NP*	Hypertonic saline	14.0	47	92
Riedler et al[29]	NP	Exercise	14.0	46	88
Frischer et al[36]	NP	Distilled water	85.0	36	92
Nicolai et al[37]	NP	Cold dry air	10.0	31	88
Salome et al[38]	P†	Histamine	9.5	53	90
Galdes Sebaldt et al[39]	P	Methacholine	11.5	95	83

* NP non-pharmacological
† P pharmacological

Table.[29,36-39] Methacholine has the highest sensitivity but is less specific compared with the other agents. Histamine has a similar sensitivity and specificity to the non-pharmacological agents used to identify asthma. A study has shown that the HS challenge has a closer relationship to the severity of exercise-induced symptoms than to BHR measured by histamine or methacholine reactivity.[40] Using a non-pharmacological bronchial challenge may thus offer a promising alternative to using pharmacological agents.

Conclusion

Bronchial hyperresponsiveness is a key indicator of asthma. As there is no single diagnostic test for asthma, bronchial challenge can serve as an aid in its diagnosis in difficult cases. However, it is very important not to rely solely on the results of a challenge when considering the diagnosis of asthma in a child. These results need to be interpreted as only part of the clinical picture. A negative challenge test result does not exclude asthma. A non-pharmacological bronchial challenge seems more natural to children than does the use of pharmacological agents; a test that does not need drugs is also more acceptable to parents. The HS challenge test is one such example. We found this test to be a useful tool in our management of cases of suspected or confirmed asthma. Further study is needed to validate our modified method against the standard published method before it can be recommended for use.

References

1. Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child 1989;64:1452-6.
2. Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ. Changing prevalence of asthma in Australian children. BMJ 1994; 308:1591-6.
3. Yeung CY. Childhood asthma: some local viewpoints. HK J Paediatr 1988; 5:95-104.
4. Leung R. International study of asthma and allergy in childhood (ISAAC): present and future. Respira 1996;3:1-8.
5. Martinez FD. Viral infections and the development of asthma. Am J Respir Crit Care Med 1995;151:1644-8.
6. Sporik R, Holgate S, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. A prospective study. N Engl J Med 1990; 323:502-7.
7. Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? Thorax 1994;49:171-4.
8. Newacheck PW. Poverty and childhood chronic illness. Arch Pediatr Adolesc Med 1994;148:1143-9.
9. Sandford A, P Pare, T Weir. The genetics of asthma. Am J Respir Crit Care Med 1996;153:1749-65.
10. Weitzman M, Gortmacher SL, Walker DK, Sobol A. Maternal smoking and childhood asthma. Paediatrics 1990;85:505-11.
11. Pattemore PK, Holgate ST. Bronchial hyperresponsiveness and its relationship to asthma in childhood. Clin Exp Allergy 1993;23:886-900.
12. Jones A. Asymptomatic bronchial hyperreactivity and the development of asthma and other respiratory tract illnesses in children. Thorax 1994;49:757-61.
13. Lask B. Psychological treatments for childhood asthma. Arch Dis Child 1992;67:891.
14. Joseph CL, Foxman B, Leickly FE, Peterson E, Ownby D. Prevalence of possible undiagnosed asthma and associated morbidity among urban schoolchildren. J Pediatr 1996;129: 735-42.
15. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J 1994; 6:53-83.
16. Smith CM, Anderson SD. Inhalation provocation tests using nonisotonic aerosols. J Allergy Clin Immuno 1989;84: 781-900.
17. Hannaway PJ, Hooper GD. Cough-variant asthma in children. JAMA 1982;247:206-8.
18. Warner JO. Asthma: a follow up statement from an international paediatric asthma consensus group. Arch Dis Child 1992; 67:240-8.
19. National Institutes of Health. International Consensus Report on Diagnosis and Treatment of Asthma. Eur Respir J 1992;5: 601-41.
20. Hall IP. The future of asthma. BMJ 1997;314:45-9.
21. Pattemore PK, Asher HI, Harrison AC, Mitchell EA, Rea HH, Steward AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma and asthma symptoms. Am Rev Respir Dis 1990;142:549-54.
22. Sterk P. Virus-induced airway hyperresponsiveness. Eur Respir J 1993;6:894-902.
23. Hopp RJ, Robert G, Townley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. Am Rev Respir Dis 1990;141:2-8.
24. Carey VJ, Weiss ST, Tager IB, Leeder SR, Speizer FE. Airways responsiveness, wheeze onset, and recurrent asthma episodes in young adolescents. Am J Respir Crit Care Med 1996;153:356-61.
25. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991;325:1067-71.
26. Wilson NM, Bridge P, Silverman M. Bronchial responsiveness and symptoms in 5-6 year old children: a comparison of a direct and indirect challenge. Thorax 1995;50:339-45.
27. Haby MM, Peat JK, Mellis CM, Anderson SD, WoolcockAJ. An exercise challenge for epidemiological studies of childhood asthma; validity and repeatability. Eur Respir J 1995;8: 729-36.
28. Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of distilled water and saline. Br Med J (Clin Res Ed) 1981;283:1285-7.
29. Riedler J, Reade T, Dalton M, Holst D, Robertson CF. Hypertonic saline challenge in an epidemiological survey of asthma in children. Am J Respir Crit Care Med 1994;150: 1632-9.
30. Eichler I, Götz M, Zarkovic J, Köflinger A. Distilled water challenges in asthmatic children. Chest 1992;102:753-8.
31. Obata T, Iikura Y. Comparison of bronchial reactivity to

ultrasonically nebulised distilled water, exercise and methacholine challenge test in asthmatic children. Ann Allergy 1994;72:162-72.
32. Wojnarowski C, Storm Van's Gravesande K, Riedler J, Eichler I, Gartner C, Frischer T. Comparison of bronchial challenge with ultrasonic nebulised distilled water and hypertonic saline in children with mild-to-moderate asthma. Eur Respir J 1996;9: 1896-1901.
33. Reisman J, Mappa L, De Benedictis F, McLaughlin J, Levison M. Cold air challenge in children with asthma. Pediatr Pulmonol 1987;3:251-4.
34. Williams D, Bruton J, Wilson I. Screening a state middle school for asthma using the free running asthma screening test. Arch Dis Child 1993;69:667-9.
35. Haby MM, Anderson SD, Peat JK, Mellis CM, Toelle BG, Woolcock AJ. An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. Eur Respir J 1994;7:43-9.
36. Frischer T, Studnicka M, Neumann M, Goetz M. Determinants of airway response to challenge with distilled water in a population sample of children aged 7 to 10 years old. Chest 1992; 102:764-70.
37. Nicolai T, Mitius EV, Reitmeir P, Wist M. Reactivity to cold air hyperventilation in normal and in asthmatic children in a survey of 5697 schoolchildren in Southern Bavaria. Am Rev Respir Dis 1993; 147: 565-72.
38. Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. I. Relation to respiratory symptoms and diagnosed asthma. Clin Allergy 1987;17:271-81.
39. Galdes Sebaldt M, McLaughlin FJ, Levison H. Comparison of cold air, ultrasonic mist, and methacholine inhalations as tests of bronchial reactivity in normal and asthmatic children. J Pediatr 1985;107:526-30.
40. Holgate ST, Makker HK. Relation of the hypertonic saline responsiveness of the airways to exercise induced asthma symptom severity and to histamine or methacholine reactivity. Thorax 1993;48:142-7.