Pulmonary physiology, airway responsiveness and asthma

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ABSTRACT

What we know

- Tests that have allowed the measurement of lung function in infants have greatly enhanced our understanding of early pulmonary development and the pathophysiology of early respiratory disease.
- Airway responsiveness in infancy appears to be an independent determinant of symptoms and lung function later in childhood.
- New tests of airway responsiveness hold the promise of predicting, with increased specificity, infants at risk of developing asthma.

What we need to know

- What are the factors that determine airway responsiveness soon after birth?
- Why does airway responsiveness in the first weeks of life relate to lung function many years later?
- Do different challenge agents reflect different pathophysiological processes involved in the development of persistent asthma?

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THE PHYSIOLOGICAL CHARACTERISTICS of asthma include variable airway obstruction and increased airway responsiveness to chemical and physical stimuli. Measurements of airway responsiveness in infants have provided insight into the physiological basis and early risk factors for asthma.

Challenge tests for assessing airway responsiveness

A variety of methods have been used to assess airway responsiveness, including both direct and indirect stimuli to bronchoconstriction.[1,2] Examples of direct stimuli are inhaled methacholine or histamine, while exercise, voluntary hyperventilation, cold air, and inhalation of adenosine monophosphate, hypertonic saline or mannitol are indirect stimuli. Most challenge tests require an outcome measure that reflects airway function, although indirect outcome measures — transcutaneous oxygen levels and pulse oximetry — have been reported.

The ability to determine airway responsiveness in infants was made possible by advances in methods of testing lung function, most importantly forced expiratory flow rate. Early studies made use of the rapid thoracoabdominal compression technique for producing passive forced expiration — an inflatable jacket fitted around the thorax and abdomen, which was rapidly inflated at end-inspiration.[3] This technique was used to measure the maximum flow at functional residual capacity, at baseline and in response to cold air or to increasing concentrations of histamine or methacholine. More recently, the raised-volume rapid thoracoabdominal compression technique has been used during challenge tests[4] to obtain timed forced expiratory volumes (FEVt) as outcome variables (ie, measures analogous to forced expiratory volume in one second [FEV_1] in cooperative subjects).

A limitation of these types of studies in infants is the requirement for sedation. Clearly, exercise testing is not possible in infants and the hypersalivation that occurs with hypertonic saline challenges makes this type of challenge unsafe in sedated infants. The airway response to exercise appears to be mediated by changes in the tonicity of the airway lining fluid, and therefore a test in infants based on the inhalation of mannitol powder might be feasible and provide information similar to that from exercise challenges in cooperative older children.

There have been few reports of adenosine monophosphate challenges in infants or preschool children,[5] and none that have used direct measures of lung function to determine outcome. However, in cooperative older children and adults with asthma, adenosine monophosphate challenges appear to better reflect ongoing airway inflammation than histamine or methacholine challenges, and might be useful in identifying asthma in infants with wheeze.

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Airway responsiveness in asthma

The increased responsiveness to bronchoconstrictor challenges in asthma is thought to result from a combination of structural and physiological factors that include increased inner-wall thickness, increased smooth-muscle responsiveness and mucus secretion. These factors are also likely to determine a level of innate airway responsiveness that is genetically influenced. This baseline or innate responsiveness is thought to be modulated in asthma by chronic inflammation and airway remodelling.

About 90% of children with asthma with symptoms in the previous year will exhibit increased airway responsiveness to one or more challenge tests.[6] However, 10% of healthy children will also respond to one or other of the challenge tests.[6] Longitudinal studies in adults have shown that the development of airway responsiveness is associated with persistence of symptoms.[7] This has been interpreted as a reflection of airway remodelling, a hypothesis that is particularly attractive given the inconsistent relationship between airway responsiveness and markers of inflammation.

Airway responsiveness in infants

Most infants show a response to histamine[3] or methacholine challenge.[8] Although underlying physiological or structural factors may determine this relative increase in responsiveness in infants compared with older children, the most likely explanation is that infants receive a relatively larger dose of inhaled challenge agent than older children. Thus, when a correction is made for this dose effect, infants and older children appear to have a similar response to inhaled histamine.[9]

The importance of this observation is that absolute values of airway responsiveness cannot be used to compare airway responsiveness at different ages. However, airway responsiveness can be tracked over time within populations using z-scores, or, alternatively, by using non-parametric analyses based on ranking individuals at each time point. Such analyses have been used in birth-cohort studies to investigate the role of airway responsiveness in the early genesis of asthma.

A unique birth-cohort study has shown that airway responsiveness at one month is a predictor of lung function at six years.[10] Data from this study also show that the genetic determinants of atopy and airway responsiveness are independent.[11] In another study of infants with wheeze, persistence of airway responsiveness was associated with persistence of symptoms, although airway responsiveness at one month of age was neither a sensitive nor a specific predictor of outcome.[12]

These studies imply that airway responsiveness is a key factor in asthma, but it is not clear whether the factors that are important for the manifestation of airway responsiveness in early life are related to inflammation, structure or physiology of the airways. Furthermore, it is not clear how viruses, allergens and irritants in the environment modify innate airway responses.[13]

What we need to know

Observations of the importance of airway responsiveness in early life need to be extended to include investigations shedding light on the mechanisms involved. These should include an examination of possible genetic, immunological, infective and environmental influences. Observations that lung function in later life is predicted by early airway responsiveness, and that persistent airway responsiveness is associated with persistence of asthma symptoms, suggest that more information is required about the role of airway remodelling in the early stages of childhood asthma.

Evidence is emerging that various challenge agents can be used to provide different information about the processes taking place in airways that result in airway responsiveness.[14] However, very few data are available from infants exploiting these response differences. Therefore, further studies in infants are needed to investigate responses to the different challenges in relation to measurements of airway inflammation and the other physiological and structural factors known to contribute to airway responsiveness in older subjects.

A better understanding of the factors that underpin an individual's response to a given airway challenge could result in tests to predict outcomes at an early age and to monitor interventions.

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