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EDITORIAL

Can measurements of airway responsiveness be standardized in children?

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A great deal of interest has recently focused on the testing of airway responsiveness (AR) in children, particularly younger children and infants. Reasons for the current interest include the desire to perform investigations in several fields: normal physiology, particularly the natural history of AR in humans; aetiology of asthma - why some individuals get asthma and others do not; aetiology of respiratory disease - the relationship between airway and lung disease in AR; and therapeutics - the effect of drugs on AR. How valid are these tests and how can the associated problems be addressed?

Several approaches have been taken in detecting AR in infants and children. The most common of these is to use inhaled agonists, such as histamine or methacholine [1–5], but other approaches include the use of cold air [6, 7], osmotic challenge [8], or exercise challenge [9]. Recent investigation has shown that, in children, there are likely to be problems in the application of each of these approaches. At present, these problems appear to preclude any of the techniques being used to compare the level of responsiveness between different sized children.

Inhaled airway agonists

Provocation testing with inhaled airway agonists usually yields results of the concentration or dose of agonist required to reduce lung function by a given amount. In infants and young children, there are problems with both aspects of this. Firstly, there are no guidelines for standardizing the dose of agonist for the size of the child, and secondly, a given percentage change in lung function may not reflect a comparable change in airway calibre in children of different sizes.

Dosage considerations

The dose of nebulized agonist deposited in intrathoracic airways will vary considerably with inhalation route, and may vary with inhalational pattern, but appears to vary little with the age of the child [10, 11].

With regard to inhalational route, preliminary data strongly suggest that the dose of the aerosol deposited in children's lungs is between two and five times higher for inhalation *via* the oral route, compared with nasal inhalation [12]. Therefore, use of a mouthpiece will produce a lower provocation concentration (PC) than a face-mask with nasal inhalation. Since many studies in children have been performed with a face-mask, but no noseclip, the route of inhalation will not be known, and the PC will be inaccurate.

Age itself appears to have little effect on deposition, at least for orally inspired aerosols. Previous work in adults, has shown that the pattern of inhalation affects the lung deposition of aerosol: faster inhalation and smaller airways favour central deposition by impaction, and slower inhalation and increased residence time favours increased peripheral deposition by sedimentation [13]. Since younger children will have smaller airways, but slower inhalation rates and shorter residence times, predictions of the effect of age on deposition cannot be made with any accuracy, particularly as breathing pattern varies greatly with age during childhood. Therefore, although one might anticipate, from previous *in vitro* calculations based on morphometric data, that aerosol deposition would vary with age [14], recent *in vivo* experimental results do not show strong age effects. For children over the age of 6 yrs inhaling tidally through the mouth, nebulized aerosol dose to the lungs does not vary significantly with age [12]. These preliminary radioisotope aerosol deposition data are supported by measurements of aerosol delivery, based on comparisons of inspiratory flow *versus* nebulizer output [10]; in these flow-derived data, aerosol delivery to the airway opening was calculated to be similar for subjects between six months of age and adulthood. For nasally-inhaled aerosols, an age-effect does appear to be present, as lung deposition has been observed to be less in infants than in older children [12]. This may mean that the nose filters more aerosol in infants, due to its narrower calibre.

Given that infants and children of greatly differing size are likely to receive a similar dose of agonist for orally inspired agonists, and a not substantially different dose for nasally inspired agonists, clearly some form of dose standardization would be essential for comparisons between such individuals [11]. However, very large correction factors would be needed; the size of a one year old infant is only about 10% of that of an adolescent, and even a 10 year old is only about half the size of an adult [11]. A parameter which could be used for size-correction has not yet been established. Potential parameters include

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body weight, absolute lung volume and airway surface area, but at present, there are no data on how correction might be undertaken. Whichever way it was done, caution would be needed in interpreting the data, as there are many components contributing to an airway response. For example, there may be age-related differences in airway permeability and airway clearance of inhaled agonists, as well as in geometric factors such as smooth muscle *versus* airway cross-sectional area, and the tendency of agonists to occlude the airway by provoking oedema. The relevance of such variables to AR and asthma is difficult to estimate.

Respiratory function assessment

Does a given percentage change in a lung function parameter reflect a comparable change in airway calibre in children of different size? This is not known, and would be very difficult to investigate. Little is also known about physiological implications of a given percentage change in a respiratory parameter in children of greatly differing size. Additional problems exist for infants; respiratory function is currently assessed in the tidal volume range, and in older children the full lung volume range is used. Whether a given change in a parameter from the former volume range can be compared with a given change in a parameter from the latter has not yet been addressed.

AR testing in infants

Methodologies to test AR to inhaled agonists were designed for use in adults, and later adapted for use in infants. There are several important differences between methodologies used in the two different age ranges. Firstly, infants almost invariably require sedation, and the effect of this on AR is unclear. Secondly, methodologies used to test infant respiratory function are very different, as noted above. Thirdly, infants usually breathe through their noses, so that more agonist is likely to be deposited nasally than on intrathoracic airways. Nasal deposition of methacholine does not alter lung function in infants [15], but histamine has yet to be examined in this way. Fourthly, some investigators use changes in transcutaneous arterial oxygen level, measured as changes in tension or saturation [16–18], to judge response. In terms of oxygen levels, only infants of similar age should be studied, as younger infants have a smaller decrease in oxygen saturation than older infants for a given change in respiratory function [19]. However, transcutaneous oxygen tension (Po_2) may be more useful than saturation in detecting a response in infants [20]. Finally, interpretation of results in infants is further complicated by evidence that infants have different configuration of their airways, with more tissue on the lumen side of the band of smooth muscle, and the likelihood of greater decrease in airway calibre for a given percentage shortening of airway smooth muscle [21]. Again, these are preliminary results, but they add another note of caution for those attempting to interpret the level of response in infants, and particularly for attempts to compare AR between infants and older children.

Thus, the main message which can be derived from current knowledge of AR testing with inhaled agonists in children is that, provided care is taken to perform studies in infants or children of similar size and age, current techniques can provide useful information, but the tests are more qualitative than quantitative and cannot be used to compare AR between children of different size.

Other forms of bronchial provocation

For inhalational challenges using cold air, dry air, an osmotic load, or exercise, many of the problems described above would also apply. The route of inhalation will alter the effect of each of these challenges, breathing pattern may be important, and difficulty would be encountered in attempting to appropriately size-correct the challenge for the size of the child.

Cold air has been used in studies of AR in infants [6], and in several studies in children [7]. Adequate validation to allow comparison of the level of AR between children of different size has not been performed. Controlling the temperature of air at the airway opening may not be enough, as meaningful comparison would seem to be reasonable only if temperatures at each successive airway generation were matched. Predicting airway temperatures in different sized children would be very difficult. Given the shorter inhalation route and faster inhalation times encountered in smaller subjects, incoming air could be heated less in these subjects, so that for a given airway generation, the temperature might be lower than in older subjects. On the other hand, inspiratory volume is less in younger subjects, and their smaller airways could allow more rapid heat transfer than larger airways. The effect of the nose on inhalation temperature has apparently never been studied *in vivo* in children. Therefore, the effect of nasal inhalation, which is likely to be encountered more in infants, would need to be accounted for, and would also be difficult to predict. Presumably, airway temperature will be higher if the air is prewarmed by transit through the nose than by the more direct route through the mouth. Clearly, these problems could only begin to be resolved by actually measuring airway temperatures.

Similar arguments can be made for the effect of the upper airway on dry air. There are many age-related factors which could affect the degree of conditioning of the air by the upper airway, some may increase and others decrease it, and the route of inhalation should be an important variable.

A standardized osmotic load is useful for quantifying AR in adults [8]. For this approach to be meaningfully used in children, care would be needed to ensure that the osmotic change at the epithelium is the same at a given airway generation. Similar difficulties to those outlined above are likely to be encountered in adequately standardizing the osmotic dose and controlling the route of inhalation.

Exercise has been used to assess airway responsivness in children [9], but does it allow a standardized challenge to be applied in children of different size? How should the workload be graded for the size of the child?

Does increasing the heart rate by a given amount in children of different size mean that a similar degree of challenge is being applied? How can infants and very young children be exercised? Since exercise exerts much of its effect by changes in airway temperature, humidity and epithelial osmolality, theoretically, all of the variables mentioned in the three preceding paragraphs should also be standardized before meaningful comparisons could be made between individuals of different size.

Recommendations

1. At present, results from challenge testing can only be reliably compared between children of a similar age and size. This situation applies for challenges using inhaled airway agonists, and probably also applies for all other forms of airway challenge.
2. Since difficulties will invariably be encountered in attempting to size-correct the stimulus for size of the subject, future studies may need to be confined to age-specific cohorts.
3. For age-specific cohorts, longitudinal measurements can be made, and changes within the group can be assessed as changes in ranking within the cohort.
4. Over short periods, children can be used as their own controls.

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