

This article has been modified from an ERS School Course held in Nice, France, in 2007 on the assessment and interpretation of lung function in the first years of life. The original slides, webcast and material can be found online at www.ers-education-org

Early determinants of airway function: epidemiological evidence



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Educational aims

- › To review published epidemiological studies describing early determinants of airway function in early life.
- › To summarise the influence of sex, ethnic group, socio-economic factors, prematurity, intrauterine growth retardation and pre- and post-natal smoke exposure as determinants of airway function in infants.
- › To describe the association between premorbid lung function and subsequent wheezing during the first few years of life.

Summary

Since the late 1980s there has been an increasing number of epidemiological studies designed to investigate the early determinants of airway function and wheezing illnesses in infants. Most, but by no means all, of these studies have commenced in the first month of life and some cohorts have now been followed up for at least 20 years.

Educational questions

1. List five factors that are known early determinants of airway function in infants.
2. Why are sex-specific reference equations often necessary?
3. What is the magnitude of change in airway function in infants exposed to maternal smoking?
4. What do you understand by the term "tracking of lung function"?
5. True or false? Maximal expiratory flows are lower in a) infant females compared with infant males b) white compared with black infants.

Factors that may influence lung and airway growth and development include effects of both intra- and extra-uterine environment, including factors such as pre- and postnatal smoking exposure and nutrition, as well as genetic predisposition, sex and ethnic group and the effects of preterm delivery, intrauterine growth retardation (IUGR), respiratory disease and the effects of treatment.

Major longitudinal studies

The Tucson Children Respiratory Study [1] was the first longitudinal assessment of the natural history of asthma that included infant lung function tests. Over 1,200 children were involved at birth and 600 of these were still participating at age 22 years. However, infant lung function testing was included relatively late in this study and only 124 infants actually had lung function tests within the first 3 months of life. One of the major outcomes from this study, which has been confirmed by many others since, was the concept of different wheezing phenotypes including the transient early wheezer, where initial wheezing commences before 3 years of life; nonatopic wheezing, which tends to reach a peak during the preschool years; and asthma or immunoglobulin E-associated wheeze, which increases in prevalence as the child approaches school age. Similar large longitudinal studies that have included infant lung function tests have been undertaken in Boston, Perth and London [2-5].

Gender differences

Numerous studies have shown that airway function, as reflected by maximal expiratory flows at low lung volume, is significantly lower in boys than girls during infancy. Important sex differences in vulnerability to respiratory disease in early life have also been reported, with respiratory distress syndrome being more prevalent and severe in boys and in white babies for any given gestational age and with asthma and wheezing being more prevalent in boys. This difference in airway function in early life is such that sex-specific reference data are required in order to avoid missing significant reductions in airway functions in girls or overestimating the degree of any dysfunction among boys.

Birth weight

Despite the known association between



intrauterine growth retardation and subsequent airway function and morbidity in later life, there have been relatively few studies investigating the impact of IUGR on lung function during infancy. A recent study at the Institute of Child Health, London, UK, demonstrated that after adjusting for all known confounders, timed forced expiratory volumes are significantly lower in infants small for gestational age (SGA) than in appropriately grown controls, with a similar tendency for forced expired flows as recorded using the raised volume technique [4]. This study also showed that airway function was significantly reduced in infants born to mothers with manual occupation or lower education [6]. The complex interactions that were detected emphasise the need for recruitment of very large numbers of infants into studies such as these in order to tease out interactions between birth weight, socio-economic status, smoking and airway function.

Maternal smoking

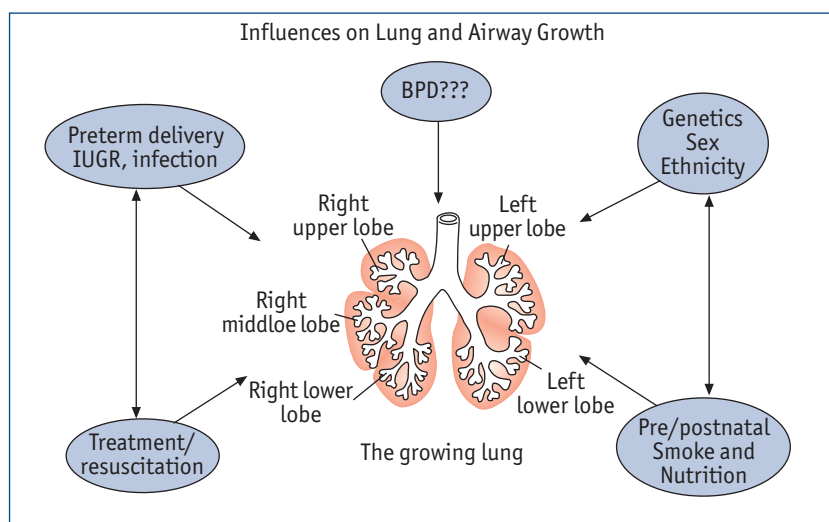
It is known that maternal smoking may influence lung growth and development by interference with the immune system and respiratory control as well as by damage to the developing respiratory system. There is considerable evidence that airway function is significantly impaired through at least the first 18 months of life if mothers smoke during pregnancy and that this persists through to childhood and adulthood [7]. The effect during infancy is apparent at least 7 weeks prior to the expected date of delivery and is independent of any postnatal exposure as demonstrated by Hoo *et al.* [8], who evaluated the effect in healthy preterm infants prior to discharge from the neonatal unit. The magnitude of changes in airway function, following exposure to maternal smoking is considerably greater in infancy (with ~15-20% reduction in flows) than that reported in later childhood. The main changes that have been reported include reduction in respiratory flows and increase in both airway and total resistance. Interpreting the results of such studies is

always complicated by the association of maternal smoking with poor socio-economic status, lower education, poor nutrition, *etc.* However, recent work using animal models by SEKHON *et al.* [9], who investigated the effect of prenatal nicotine exposure by infusion to the mother, showed similar reductions in airway function to that observed among human infants. The effect of maternal smoking is, of course, not limited to healthy infants but equally affects those with lung disease and this must be taken into account when interpreting lung function results from infants in young children with lung disease [10]. Parental smoking status, including prenatal exposures, should always be recorded in infant lung function studies ideally with biochemical validation.

Tracking of lung function

It is known that there is an increased prevalence and severity of respiratory disease during infancy, which may be attributable to developmental differences in respiratory structure and function, genetics or lung immaturity. There are also known to be strong associations between respiratory disease in early childhood and later life. However, until very recently there was ongoing debate as to whether this represented a causal association or predisposition. Despite using a wide variety of techniques and recruiting healthy children from a wide range of environments, all the major epidemiological studies have now provided evidence that airway function is indeed diminished prior to, and is predictive of, subsequent wheezing illnesses.

One of the major aims of these epidemiological studies has been to predict which of the many infants who wheeze are likely to progress to asthma in later life. To date, this has not been realised, but considerable light has been shed on the many wheezing phenotypes. While it is still not possible to predict at the individual level which infants will out-grow their wheeze as compared with those who will develop asthma, various risk factors have now been identified. Those with a very early onset of wheeze (first year of life), whose mothers smoke and where there is no family history of asthma tend to have a low risk for subsequent asthma, whereas those with a late onset of wheeze, in whom there is a maternal history of asthma, maternal exposure to environmental tobacco smoke, personal atopy



(initially to food and later to inhaled allergens) and/or increased bronchial responsiveness (with or without diminished flows) in infancy have a high risk for subsequent asthma.

Although some remodelling of the lung occurs during the first year of life there is remarkable tracking of lung function throughout childhood and into early adulthood (*i.e.* those with the lowest levels of airway function initially tend to retain this position throughout life) [11]. This suggests that life-long levels of lung and airway function may be determined during foetal development and the first months of postnatal life. This tracking of lung function has been demonstrated in healthy term infants, in healthy preterm infants, in infants and young children with cystic fibrosis and between infancy and school age in those with bronchopulmonary dysplasia.

Figure 1
Influences on lung function and early growth. BPD: bronchopulmonary dysplasia; IUGR: intrauterine growth retardation.

Conclusions

Diminished airway function in early life has been observed in infants who are male, have a maternal history of asthma, who have been exposed to maternal smoking, who have been delivered prematurely or who were SGA. An increased vulnerability to respiratory disease has also been found in all of these groups.

Infant lung function tests have an important role as outcome measures in epidemiological studies to investigate the early determinants of airway function. Despite the complexity of recruitment, follow-up, data analysis and interpretation of results, there is conclusive evidence that some infants are born more susceptible to respiratory problems and that there is considerable continuity in aspects of lung function from birth into childhood and beyond.

Suggested answers

1. Sex, ethnic group, exposure to maternal smoking, pre-mature delivery, SGA or first-degree family history of asthma
2. To avoid missing significant reductions in airway function in girls or overestimating dysfunction in boys during early life.
3. Approximately 15–20% reduction in expiratory flow.
4. Those with lower lung function tend to retain this throughout life.
5. a) False.
b) True.

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