

Respiratory Function Testing in Early Childhood: Where Have We Come From and Where Are We Going?

Janet Stocks

INTRODUCTION

During recent years, the extraordinary advances that have been made in the fields of molecular genetics, cell biology and biochemistry have at times seemed to overshadow the study of «whole organ physiology», including that of the respiratory system. However, it is becoming increasingly evident that the effects of the new diagnostic and therapeutic advances will still need to be evaluated *in vivo* by employing objective outcome measures in the form of respiratory function tests. This holds true just as much for the infant and young child as for the older subject. Indeed, the assessment of respiratory function in the very young has major implications for our understanding of respiratory health and disease, not just during childhood but throughout life, particularly in view of the growing awareness of the association between respiratory function in early life and chronic lung disease in adulthood.^{1,2} It is therefore appropriate to review recent progress in this field and to identify the various challenges that must be met in the near future if we are to optimize the application and interpretation of respiratory function tests in the infant and young child.

EQUIPMENT

In addition to various physiological differences between infants and adults,³⁻⁵ one of the greatest difficulties in assessing respiratory function in early childhood has been that of obtaining suitable equipment. Because of the general lack of commercially available, well validated systems, most research establishments have been using their own home made equipment and software, which has impeded training, attempts to establish multicentre trials, and any meaningful comparison of results between different centres.⁶ One of the greatest challenges in this field is therefore to increase the links between scientists, clinicians and industry so that properly validated, standardized and commercially available

equipment can be developed for use in infants and young children. This will require close international collaboration and is currently being addressed by a joint Task Force from the European Respiratory Society/American Thoracic Society (ERS/ATS).

AVAILABILITY OF TECHNIQUES

Until recently, the lack of suitable equipment and the complexity of measuring small uncooperative subjects limited infant RFTs to specialized research establishments. Although the first descriptions of respiratory measurements in infants were made in the late 19th century⁷ relatively little progress was made until 30 years ago when the classical techniques, originally developed for use in adults, began to be adapted for use in infants.⁸⁻¹²

Such techniques were further developed and validated during the 1970s and 1980s¹³⁻¹⁵ but at this stage there was also a change in emphasis as new and less complex techniques, specifically designed for use in infants began to be developed.¹⁶⁻¹⁸ This, together with the increasing computerization of techniques and commercial availability of equipment, meant that for the first time, infant lung function tests were no longer limited to specialized laboratories, but became accessible to clinicians caring for infants with respiratory problems. Despite the obvious advantages of such increased availability, these advances have been accompanied by an increased risk of misuse of such tests by those without specialist training, especially if inappropriate or poorly validated equipment had been purchased. This in turn has

Portex Anaesthesia, Intensive Therapy & Respiratory Medicine Unit,
Institute of Child Health, London.

Address correspondence and reprint requests to Dr. Janet Stocks, Portex
Anaesthesia, Intensive Therapy & Respiratory Medicine Unit,
Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.
E-mail: j.stocks@ich.ucl.ac.uk

led to the need for concerted efforts to standardize infant respiratory function measurements,^{4,19,20} in a manner similar to that previously undertaken for measurements in older subjects.

Since the rate at which various tests will be developed, validated and standardized for routine use in infants and young children will vary, it is essential that future equipment and software is developed in modular form, thereby facilitating rapid modification and expansion as and when new techniques are introduced.

WHICH TEST IS BEST?

An ideal lung function test for infants and young children would be one that was:

- applicable to any age and arousal state
- simple and involve no risk
- reproducible
- sensitive enough to distinguish between health and disease and
- able to reflect the clinical situation

No such test currently exists, and even if it did, no single test is ever likely to provide all the necessary information.

While it is impossible to recommend the best combination of tests - particularly without knowledge of the underlying question, evidence is accumulating that if, for example, airway function is to be assessed, results will need to be interpreted with respect to lung volume, and that some combination of tests to allow an assessment of dynamic airway resistance over the tidal range, flow limitation during forced expiratory maneuvers, and airway wall mechanics might be the ideal. By contrast when studying intubated newborns with respiratory distress, assessment of compliance, gas mixing and lung volume might be the preferred option. Techniques for measuring high-frequency input or transfer impedance in conjunction with sophisticated computer modeling,^{19,21,22} may combine the advantages of miniaturized equipment with the sophistication of detailed information about the mechanical properties of the lungs, with relative immunity to the potentially confounding effects of upper airway compliance. The validation and assessment of the clinical application of such tests in young children remains a major challenge. Since, for many respiratory diseases, the lung cannot be described as a single compartment, integrative measures of lung function may at times prove more useful than assessment of mechanical parameters.

Lung function measurements in infants and pre-school

children always present a challenge, and it is therefore vital that the purpose of any test session is clearly defined before starting. The clinical applications of LFTs in individual infants remain controversial. Investigations are rarely performed for diagnostic purposes, but rather to monitor severity or to assess the response to treatment (both physical, such as mechanical ventilation, and pharmacological). It should also be remembered that reference data are limited (see below), serial tests are more valuable than single assessments, and results must be interpreted in the light of all other clinical information. Most importantly, clinical reasoning and an understanding of the clinical questions being posed, rather than simply availability of equipment and expertise, should determine the choice of technique. Similarly, the integration of results and the actions arising from lung function measurement in children requires close communication between those requesting and those performing the measurements.

REFERENCE VALUES

Reference data are needed for several reasons, one of the most important being the means by which comparisons can be made between different laboratories.²³ Deviation from normality and determination of pathophysiology are also based on reference data. While the response to treatment can be determined by internal reference, completeness of recovery requires data from a reference population. Longitudinal reference data are important in the evaluation of the growth of lung function and for epidemiological studies. Reference ranges should always be provided and, wherever possible, instead of expressing results as « % predicted » a standard deviation score should be given.²³ Unfortunately, there is currently a dearth of reliable reference data for any of the respiratory parameters during the first 5 years of life, such that an appropriate, prospectively studied control group is often essential (but rarely available!) for meaningful interpretation of studies.⁴ The use of inappropriate reference data has resulted in serious misinterpretation of many published papers in this field, and can lead to false clinical judgements in individual patients. Establishment of reliable reference data remains a major challenge that can only be addressed by collaborative studies subsequent to the standardization of equipment and software for use in this age range.

APPLICATIONS OF RESPIRATORY FUNCTION TESTS IN EARLY CHILDHOOD

The increased availability of techniques and equipment during recent years has been accompanied by a dramatic increase in both the number of centres assessing respiratory function tests in infants and young children, and the applications to which these tests are now put. This has largely resulted from an increasing awareness of the potential relevance and significance of such assessments in early life. Respiratory functions have found wide application as measures of outcome in therapeutic trials in children of all ages. As prospects for early intervention based on antenatal diagnosis or on gene therapy for specific defects become more widespread, the contribution of measurements of lung mechanics to outcome measurement will increase.

However, while providing valuable information regarding type and severity of functional disorders, poor specificity and sensitivity of most tests of pulmonary physiology currently limit their use in diagnosis. In addition, respiratory function testing has not achieved the widespread clinical application in individual infants and pre-school children that it has in older subjects. A major challenge for the future is thus to increase the clinical applicability of pulmonary function testing in early life by:

- minimizing inter and intra-subject variability
- standardizing equipment and methodology
- improving training facilities
- developing appropriate reference data and
- establishing sensitivity and specificity of appropriate tests.

This will only be achieved by increasing links between industry, clinicians and scientists, international collaboration and standardization, and the establishment of well designed multicentre trials. Nevertheless, it must be appreciated that the complexity of measurements in these small uncooperative subjects, combined with the need for sedation in most infants above one month of age, makes it unlikely that these tests will ever be used as widely in the very young as in older children and adults.

WHAT CAN RESPIRATORY PHYSIOLOGY CONTRIBUTE TO OUR KNOWLEDGE OF RESPIRATORY ILLNESSES IN EARLY LIFE?

During recent years, understanding of respiratory physiology of the infant and young child has been

advanced by the development and application of new and simpler techniques to assess respiratory function in the very young. However, it is not simply the availability of new methods that has focused so much attention on this age group. The development of more objective measurements of airway function and airway responsiveness in infancy are contributing to a better understanding of the pathophysiology of wheezing disorders, chronic lung disease and other respiratory illnesses during early life. In addition, awareness that the foundations of chronic airway obstruction may be laid not so much during childhood as during fetal development and the first year of life, when the lungs and airways are developing so rapidly, has focused renewed attention on early pulmonary development.

Numerous factors are known to influence intra-uterine and perinatal lung growth, including a complex interaction of hormones, growth factors and physical constraints. In addition it is now recognized that numerous genetic and environmental factors will influence the normal growth and development of the lungs. These include maternal smoking during pregnancy, maternal malnutrition, genetic factors such as gender, ethnicity, family history of asthma and atopy, together with factors such as preterm delivery, mechanical ventilation and oxygen therapy.^{2,3,18,24-28} Although some remodeling for lung may occur during the first year of life, those born with suboptimal lung function tend to remain on the lower centiles thereafter. This suggests that the level of lung and airway function may be determined for life during fetal and early postnatal development. Indeed it is now recognized that adverse events occurring during the period of rapid growth and development in early life may have long term and irreversible effects.^{1,2,29}

Further insights into the mechanisms underlying the relationship between childhood respiratory problems and adult lung disease require carefully designed longitudinal studies. The ultimate aim would be for a life long continuum of assessments of the human respiratory system ranging from the fetus to old age. Much is still required to achieve such a goal, including the development of quantitatively accurate methods of determining fetal lung growth and development, together with more objective respiratory function tests for use not only during infancy but during the so called « dark ages » of pediatric pulmonology, i.e. between the ages of 2 to 5 years when a child is generally too young to co-operate but too old to sedate. In view of the number of infants who suffer from respiratory illness every year, future challenges include the design and execution of multi-centre studies using

standardized objective measures of lung and airway function during early childhood in an attempt to:

- minimize the morbidity and mortality associated with inherited, congenital, developmental, acquired and infectious respiratory illnesses during early life.
- determine the most beneficial therapeutic interventions for treating neonatal lung disease.
- prevent the development of chronic lung disease.
- prevent deterioration of pulmonary function and optimize quality of life in infants and young children with cystic fibrosis. This will require identification and evaluation of effective treatments of pulmonary disease during early life.
- predict whom, of those who wheeze during the first year of life, will subsequently develop asthma.
- determine the origin and evolution of airway hyper-reactivity during the first year of life.
- establish whether early therapeutic interventions can prevent or delay the development of asthma
- determine the mechanisms by which passive smoke exposure, malnutrition, infections and other insults to the developing lung, contribute to the development of acute and chronic lung disease.
- treat viral induced acute respiratory illness in the first year of life more effectively.

SUMMARY

After an initially slow beginning, we are currently witnessing something of a revolution in the field of respiratory function testing during early childhood, both with respect to the number of techniques available and the applications to which they are being put. There is now an urgent need for international, collaborative efforts to develop more objective, standardized methods of assessment (including improved, properly validated equipment and software) and reliable reference data for this age group. This would improve our understanding of exactly what these tests are measuring, and facilitate the development of effective therapeutic and preventive strategies to minimize suffering from respiratory illness not only during early childhood but, hopefully, throughout life.

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