Measuring lung function in infancy

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Introduction

Respiratory function testing in adults and older children is used to aid diagnosis, evaluate severity of disease and monitor response to treatment. It is only in the past 15 years that an interest in infant lung function tests (ILFT) has developed, coincident with the advance of computer technology and the electronic engineering skills necessary to manufacture equipment of sufficient sensitivity and accuracy for assessing infants. Conventional methods, such as whole body plethysmography, require expensive and complicated equipment that is technically demanding to use. Recent interest has focused on developing simpler techniques that are more suitable for routine clinical assessment and research. Although many techniques are still undergoing evaluation and are restricted to a limited number of centres, information about the early growth and development of the lungs in health and disease is beginning to accumulate. In addition, ILFT may add to the clinician’s tools in characterizing the severity and type of respiratory illness in the very young, and also allow the assessment of response to therapeutic manoeuvres. With further developments and expansion of services it is possible that premorbid prediction of disease will enable the instigation of early intervention strategies, allowing disease prevention.

Difficulties in performing lung function tests in infants

Measurement of respiratory parameters in infants was attempted over 100 years ago using spirometry to assess tidal volume and respiratory rate. The large dead space of the equipment made readings inaccurate and it was not until the advent of plethysmography in the 1930s that reasonably reliable recordings of tidal breathing were made. Measurements of infant lung volume using gas dilution were described in the 1950s, and, by the 1960s, pneumotachographs with a suitably small dead space became available for studying infants. At the same time, plethysmography became established for measuring functional residual capacity (FRC), and later modifications of the technique allowed measurement of airway resistance (1). However, it is only in the past few decades that interest in the measurement of infant respiratory physiological parameters has really developed. There are a number of reasons for the relatively slow development of this discipline (Table 1). Infants are unable to cooperate with special respiratory manoeuvres and any measurements outside the tidal breathing range require innovative techniques to be used. Some techniques require the baby to be in quiet sleep, and because the duration of testing tends to be long, sleep needs to be augmented by sedative medication in all but the youngest of subjects. Equipment is often bulky and expensive. Interpretation of the data is time-consuming and can be tedious. Reference data remain limited because of the ethical issues surrounding the sedation of healthy infants for tests that will be of little benefit to the individual. Infants are preferentially nasal breathers, with nasal resistance accounting for 50% of total airway resistance. Nasal pathology, most commonly a recent viral infection, can therefore mask lower respiratory tract abnormalities. The chest wall is extremely compliant in babies and the low outward recoil results in a low and unstable FRC and the tendency to airway closure during tidal breathing. Difficulty in achieving flow limitation and the normal variability of airway resistance in this age group both hamper the assessment of changes in respiratory function in response to challenges or therapeutic interventions. Perhaps most importantly, the very infants in whom the disease process requires further definition and understanding are the ones whose illnesses make testing difficult.

Although measuring the respiratory function of infants remains more difficult than in adults, techniques continue to improve. Recent international collaborative effort between groups interested in this discipline have allowed the establishment of the European Respiratory Society Taskforce on the Standardization of Infant Respiratory Function Testing and the publication of a number of important documents (2–5).

Characteristics of a good respiratory function test

Lung function tests in infants should be performed under the direction of a clinician trained in the relevant techniques.
and aware of the limitations of the test. No single pulmonary function test provides a comprehensive range of the information likely to be required by the investigator, who should ensure that the tests chosen will provide the information required to answer the research or clinical question they are wishing to address.

When choosing an appropriate test the investigator will consider:

- Which test will provide the most useful information under conditions acceptable to both the patient and the investigator;
- the purpose of the test;
- the age of the infant.

In order to provide good quality data and to reduce both inter- and intra-laboratory variability, meticulous testing procedures need to be followed, and these should be supervised by operators who have undertaken the correct training and have obtained an appropriate level of expertise.

Multi-disciplinary working groups have attempted to identify the characteristics of the ideal ILFT (6).

The ideal infant lung function test should:

- be acceptable to the individual to be tested;
- not be an onerous time constraint for the individual being tested;
- be easy, rapid and safe to administer;
- be able to be completed in the field or outside of specialized laboratories;
- be sensitive and specific;
- be able to measure the different components of the respiratory system;
- have consistent and reproducible test results;
- be available at a relatively low cost.

The safety record of current test procedures is excellent, but caution is required as with all investigations. Infants should be assessed prior to testing, and tests should not proceed if the risks exceed the degree of benefit likely to be obtained from performing these tests. Guidelines to ensure safety of the infant have been published (7).

Many of the recommended ideals are not yet fulfilled by current methodologies, which are confined to use in specialized laboratories or intensive care settings. As further progress is made, and equipment suitable for wide scale manufacture is designed, infant lung function testing will move closer to these ideals.

**What can be measured and how?**

Tests of pulmonary function in infants can be used to explore the normal functional development of the lungs, understand their mechanical properties and assess both the effects of disease and responses to therapeutic interventions (Tables 2 and 3). It is vital that the clinician or researcher understands the application and limitations of the tests he performs.

## INDICES OF TIDAL BREATHING

Various measurements can be measured during tidal breathing. Respiratory rate and tidal volume are relatively easy to measure but are difficult to interpret because the process of measurement may influence the baby’s breathing pattern. Minute ventilation is measured to study control of breathing, particularly in response to carbon dioxide and hypoxia. Time to peak expiratory flow (t_PTEF) as a ratio of total expiratory time (t_E) is easily calculated from tidal breathing measurements. Studies have found $t_{PTEF}/t_E$ is reduced in male infants who subsequently progress to having wheezing illness (8) and infants whose mothers smoked during pregnancy. This would suggest an association between small calibre airways and reduced $t_{PTEF}/t_E$. However, a study in which airway obstruction was induced in infants using histamine failed to show a significant

### TABLE 1. Difficulties in performing ILFT

- Physiological problems
  - high upper airway resistance may mask lower airway abnormalities
  - unstable FRC
  - flow limitation is difficult to achieve
- Infants unable to cooperate
- Infant often required to be in quiet sleep
- Bulky, expensive equipment
- Data interpretation
- time consuming
- limited reference data

### TABLE 2. Research applications of ILFT

Current research applications include investigations of:

- The normal early growth and development of the lungs.
- Infant physiology in health and disease.
- Premorbid features of disease.
- The influence of environmental and genetic factors preconception, *in utero* and in early life on pulmonary development and disease.

### TABLE 3. Infant lung function tests as a clinical tool

The ideal test should answer the following questions:

- Does the infant have evidence for respiratory dysfunction? If so, what is the nature and severity of this dysfunction?
- What is the prognosis?
- Has the therapeutic intervention improved pulmonary function?
- Has the respiratory dysfunction worsened or resolved?
change in $t_{res}/t_e$ despite changes in other measurements (9). Thus, the significance of this measurement remains controversial and the reason for a relationship with obstructive airway disease remains speculative.

Measurement of tidal volume, rate, $t_{res}/t_e$, and minute ventilation in infants are usually made in the supine position during quiet sleep. The baby breathes spontaneously through a facemask with a leak-free seal. Inspired and expired gas flow can then be measured using a low dead-space pneumotachograph (PNT) at the airway opening. In ventilated infants the PNT is at the end of the tracheal tube. Flow is usually measured directly, and this is integrated to provide volume data. The differential pressure transducer used for the PNT can measure airway pressure. Because the PNT directly measures flow at the airway opening, it is the gold standard by which other methods are validated.

A thermistor can be used to detect flow-related temperature changes at the airway opening. The time of response to temperature change is such that the data produced does not accurately represent the true flow waveform, rendering them useful only for qualitative determination of airflow and timing respiratory rate. Alternatively, measurement of thoracic and abdominal movement can be used to sense respiratory effort even in the absence of airflow. Measurement of chest wall movements using strain gauges, impedance plethysmography and pressure capsules is easy and non-invasive. These methods have the advantage of not altering respiratory patterns. They are useful for measuring respiratory rate and detecting central apnoea, but with the exception of some types of strain gauge, these devices are not suitable for accurate determination of timing indices or volume change.

**LUNG VOLUMES**

Measurements of lung volumes are important for the understanding of pulmonary development, and can assist in interpreting measurements of lung mechanics that are volume dependent such as resistance and compliance. Functional residual capacity (FRC) is the only lung volume that can easily be measured repeatedly and reliably in infants. Total lung capacity (TLC) and residual volume (RV) can be estimated from forced inflation and deflation manoeuvres, but these measurements require tracheal intubation. TLC and RV have been estimated from measuring vital capacity during crying but these estimates have poor reproducibility and are not routinely used.

FRC is most commonly measured by body plethysmography or gas dilution. Measurement of FRC using body plethysmography is based on techniques used in adults. It has the advantage of measuring airway resistance simultaneously (1). Plethysmography measures the volume of all the gas in the lungs at the moment of occlusion, including any trapped behind narrow or closed airways. The major drawback is the complicated and expensive equipment, which has confined its use to a few specialized respiratory laboratories. Improvements in equipment and computer software are likely to make its use more widespread.

FRC can also be measured using helium dilution or nitrogen washout techniques in infants who are usually asleep and supine. Again, these methods are similar to those used in adults. Gas dilution techniques measure the lung volume that equilibrates with the inspired gas during tidal breathing, and therefore only measure areas of the lung in direct communication with the central airways. The measurements of FRC are consistently lower with gas dilution than plethysmography for reasons that are not fully understood, but include air trapping and poor gas mixing.

There is a growing interest in the use of imaging techniques for assessing lung volumes (10,11).

**FORCED EXPIRATORY MEASUREMENTS**

Measurements of peak expiratory flow and other forced expiratory flow indices have a central role in the diagnosis and management of adults and older children with intrathoracic airway disease. Although infants cannot comply with instructions to perform forced expiratory manoeuvres, the rapid thoraco-abdominal compression technique (RTC) allows study of forced expiratory flow in infants by creating partial expiratory flow-volume (PEFV) curves. Controversy exists regarding whether flow limitation is achieved using this method (4) and, without true flow limitation, comparisons between and within individuals are unreliable. RTC technique measurements made during tidal breathing use FRC as the volume landmark to calculate maximum flow at FRC ($V_{\text{max}, \text{FRC}}$). FRC can be unstable in infants and can be influenced by factors such as sleep state, addition of dead space and changes in airway calibre. This may explain the very high variability of $V_{\text{max}, \text{FRC}}$.

Adaptations of RTC involve increasing the lung volume immediately prior to the compression (see below). This technique allows measurement of timed expiratory volumes such as FEV$_{0.75}$ or FEV$_{0.5}$, thus avoiding the need for a volume landmark and providing data with much improved intra- and inter-subject variability. Non-quantitative data is also informative. The partial expiratory flow-volume curve in infants with obstructive airway disease shows significant concavity whereas the normal curve should be convex (Figs 1, 2 and 3).

Rapid thoraco-abdominal compressions (RTCs) require a fitted inflatable jacket to be wrapped around the sleeping infant’s abdomen and thorax. The jacket should be loose enough to allow the chest to fully expand. The infant breathes spontaneously through a facemask with PNT as described for measuring tidal breathing indices. The jacket is rapidly inflated at end-inspiration, producing a forced expiration. The RTC is repeated at increasing jacket pressures from 40 to a maximum of 100 cm H$_2$O until there is no further increase in flow despite increasing pressure. This is the pressure at which flow limitation occurs. Maximal flow at FRC is then calculated from the PEFV curve.

This technique has now been adapted with the RTC following passive inflation of the lungs to near total lung capacity (Fig. 4). The lung volume is raised by positive
pressure inflations from an external air source in synchronization with the infant’s breathing. This manoeuvre relaxes the respiratory muscles by invoking the Hering Breuer reflex. At the end of a relaxed inspiration the jacket is inflated to the pressure identified as being optimal for the collection of RTCs data, and timed expiratory flow is calculated made from the expiratory curve.

Fig. 1. Convex partial expiratory flow-volume curve. This little girl is 1 year old and had ILFT as part of her regular health check as she has cystic fibrosis. The curve suggests good pulmonary function at the time of testing.

Fig. 2. Concave partial expiratory flow-volume curve. This is the curve of an asymptomatic 6-week-old boy who has ILFT as part of an epidemiological study. His flow volume curve shows a slight concavity suggestive of mild obstructive airways disease. This finding is consistent with a slightly lower than predicted $V_{\text{max FRC}}$ result. He will be observed throughout his first year of life to see if he becomes symptomatic.

Fig. 3. Infant with severe obstructive airways disease. This infant has severe obstructive airways disease. There was a small degree of improvement of her $V_{\text{max FRC}}$ when a bronchodilator was administered and tests repeated.

Fig. 4. Raised volume RTC curve.
BRONCHIAL RESPONSIVENESS

Measurements of bronchial responsiveness are important as a research tool. Methacholine, histamine and cold air have all been used as provocative agents. Initial studies measured the fall in $V_{\text{max,FRC}}$ (12,13). More recently FEV$_1$ has been shown to decrease significantly in infants with a history of recurrent wheeze after provocation with histamine (14). As well as the technical problems of conducting the ILFT, the standardization of the dose of bronchodilator or bronchoconstrictor delivered from a nebulizer or spacer device must be considered.

RESISTANCE AND COMPLIANCE

Methods for measuring compliance and resistance can be classified as passive or dynamic. Dynamic mechanics are measured during spontaneous breathing or mechanically assisted respiration, and passive mechanics during manoeuvres that induce relaxation of the respiratory muscles. All techniques require the simultaneous measurement of flow, volume and pressure.

Passive mechanics measurements rely on eliciting the vagally-mediated Hering Breuer reflex by airway occlusion at volumes above FRC, causing complete relaxation of the inspiratory and expiratory muscles. The measurements can be performed in spontaneously breathing or mechanically ventilated infants, using a pneumotachograph and shutter. The most commonly used techniques are the multiple occlusion technique (MOT) for measurements of respiratory system compliance ($C_{rs}$) and the single breath technique (SBT) for respiratory system compliance ($C_{rs}$), resistance ($R_{rs}$) and time constant ($\tau_{rs}$). In the MOT, brief airway occlusions are performed at different levels above FRC during expiration, which cause the respiratory muscles to relax and airway pressure to equilibrate. The pressure at the airway outlet is measured and, assuming equilibrium with the pressure in the lungs, this reflects the elastic recoil pressure of the respiratory system. $C_{rs}$ is calculated from the volume-pressure plot. The SBT is performed by occluding the airway at end-inspiration to induce relaxation. $C_{rs}$, $R_{rs}$ and $\tau_{rs}$ are calculated from the passive flow-volume curve and the airway opening pressure measured during the occlusion. Multiple measurements are made and the mean value calculated.

Dynamic lung mechanics can be calculated in infants by accurately measuring airflow, tidal volume and transpulmonary pressure. These measurements can be performed in both spontaneously breathing and mechanically ventilated infants. Body plethysmography can also be used for measuring airway resistance ($R_{aw}$), but its use is limited by the technically demanding methodology and the need for complex, expensive equipment.

The measurements of dynamic lung resistance ($R_L$) and compliance ($C_L$) require the measurement of transpulmonary pressure, which is usually approximated by oesophageal manometry. An oesophageal balloon or flexible catheter tipped microtransducer is sited in the lower third of the oesophagus. A pneumotachograph measures flow, which is integrated to obtain volume. The measurements are technically demanding, and measured values may be affected by upper airway resistance or the resistance of the equipment. Also, oesophageal catheters are poorly tolerated in many infants.

Clinical and epidemiological applications

Although infant lung function tests were originally developed to aid in the assessment of the severity of a number of known obstructive respiratory disorders, in recent years these tests have developed more as a research tool with particular reference to normal growth and development of the respiratory system in late gestation and early life (Table 4).

Longitudinal epidemiological studies combining testing of premodal airway function in early life and subsequent clinical assessment of wheezing have led to a better understanding of the importance of early life events, and genetic and environmental factors (15–18). It is anticipated that increasingly it will be possible to identify those at greater risk of developing respiratory disease, such as asthma, by the use of these techniques.

Measurements of lung function are rarely diagnostic in themselves and there is much controversy regarding the value of pulmonary function testing as a clinical tool (19). The optimal clinical use of ILFTs at the present time is for repeated tests over a period of time, reviewing disease progression and resolution and examining an individual infant’s response to intervention therapies (Table 5). As yet, standardized reference data is not widely available, and without this it is difficult to assess objectively the value of any one individual infant’s results. More is needed to understand which lung function test will address specific clinical questions and will offer the best index to inform clinical management (Table 3).

Table 4. Specific clinical applications of infant lung function tests

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<th>Current clinical applications:</th>
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<td>- Evaluation of therapeutic interventions (surfactant, $\beta$-agonists, adrenergics, steroids).</td>
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<td>- To aid diagnosis of obstructive airway disease.</td>
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<td>- Evaluation of secondary lung involvement in congenital heart disease and neuromuscular disease.</td>
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<td>- To assess lung growth and development following the use of various types of ventilatory assistance (such as ECMO).</td>
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<td>- To optimise artificial ventilatory parameters thus decreasing the likelihood of the infant developing a pneumothorax or intraventricular hemorrhage.</td>
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<tr>
<td>- To make serial measurements to assess the severity and the progression of lung disease (as in chronic lung disease or bronchopulmonary dysplasia).</td>
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study demonstrated a significant rise in respiratory rate. Sedation is contraindicated in infants with known upper airway obstruction, and care should be taken in babies with a history of acute life-threatening events, in wheezy infants and in infants with hepatic, renal or cardiac disease. Continuous monitoring of vital signs and pulse oximetry are mandatory throughout the period of sedation in all infants.

If appropriate precautions are taken, chloral derivatives are safe and provide good testing conditions. A single dose of chloral hydrate, 50–100 mg kg$^{-1}$, effectively augments sleep but the baby will stir or wake to inappropriate stimuli. For each of the techniques mentioned above, full methodological details can be found in ‘Infant Respiratory Function Testing’ (2).

**Data analysis and interpretation**

Reference ranges taken from epidemiological studies are frequently used when interpreting data obtained from infants with clinical disease. This enables the clinician to establish whether the data falls within the range expected for a given age, gender and body size. The significance of data from an individual falling within or outside the given range depends on the quality of the normative data used and its appropriate application. If the scatter of the reference data is great due to wide biological variability or poor repeatability, a baby with disease may fall within the ‘normal’ range. The reference values should have been obtained under the same testing conditions as the laboratory using them, and the method of selection and size of the sample population should be known. Ideally, each ILFT laboratory should generate its own normative reference data. Realistically, few centres are likely to study sufficient numbers of healthy infants of each age, gender and ethnic group. However, published data from large studies of healthy infants or combined data from several laboratories that have a standardized testing procedure exist (5).

The need for standardization of both equipment and methodology, and an understanding of the limitation of tests is clear. Quality control of data, and the exclusion of inappropriate or inadequate data from analysis is also important. Although most of the analysis of data is aided by computer software, the visual inspection of each piece of data by an experienced individual is a vital part of the procedure. Only data that is technically acceptable by both visual and measured standards should be included for analysis. For example, features of glottic closure seen on a flow-volume loop may eliminate that breath from further analysis even if computer-generated analysis appears acceptable. Visually viewing the data also identifies qualitative abnormalities that may not be readily defined by quantitative analysis. For example, a concave partial expiratory flow-volume curve is suggestive of obstructive airway disease.

Test results are only meaningful if they are derived from testing procedures which follow established, standardized protocols. Every ILFT laboratory should have a carefully
documented protocol and inter-technician reproducibility should be assessed regularly (3). The final report of each test should contain information about testing conditions, reproducibility and quality of results.

Summary

Although the earliest reliable lung function tests in infants were performed as long as 40 years ago, there has only recently been a growth in this area, as simpler methods and better equipment and IT resources have been developed. Exciting information is accumulating about the normal physiology and pathology of the infant lung. Many basic questions are still unanswered and the ability to perform these tests remains confined to a few specialized centres. To co-ordinate the development of ILFT and establish standardization in a number of areas including measurement conditions, equipment specifications, methodology protocols and data analysis, international collaboration is necessary between the teams working in this field (Table 5). Collaborative groups are currently addressing these issues and are also developing recommendations regarding the design of randomized clinical trials, multi-centre studies and research agendas.

Infant lung function testing remains primarily a research tool. Our aim should be not only to refine and develop the techniques of physiological measurement but to apply ILFT to the objective study of respiratory illness in infants in the clinical setting so as to aid in the prevention and treatment of these common, debilitating and costly diseases.

References