

Lung Function Testing in Infants

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INTRODUCTION

Respiratory disease is the major cause of morbidity in infants and young children, with up to 40% of infants wheezing during the first two years of life. Disturbances of the mechanical function of the respiratory system are central to many disorders in newborns and infants^{1,4} and may be the direct result of lung disease, for instance in infantile asthma, pulmonary hypoplasia or neonatal hyaline membrane disease, or result indirectly from cardiovascular or neuromuscular disorders.

DEVELOPMENTAL PHYSIOLOGY

An understanding of developmental anatomy and physiology is essential for clinical measurement and interpretation of pulmonary function tests in infants and young children.^{2,3,5} In healthy individuals, most parameters of respiratory function remain remarkably constant when related to either surface area or body size, reflecting the fact that respiration is closely attuned to the metabolic requirements of the body (Table 1). However the underlying factors determining these parameters may vary considerably according to age.^{2,4,6}

Infants are preferential nose breathers with nasal resistance representing approximately 50% of total airways resistance. Consequently changes in lower airway resistance with disease or therapeutic interventions may be masked, especially if there has been a recent upper respiratory infection. The highly compliant chest wall means that there is relatively little outward recoil with which to distend the lungs and airways, resulting in a low and unstable FRC, and the tendency to airway closure during tidal breathing. However, the difficulties imposed by the compliant chest wall are at least partially compensated for by the tendency of infants to breathe in before they reach the lung volume determined by the passive mechanics of their respiratory system.

Airway responsiveness to histamine and methacholine can be measured from early infancy. However, its role in

wheezing lower respiratory illnesses in young infants may be over-shadowed by other factors such as congenital differences in airway geometry and lung mechanics or by pathological changes such as airway edema and mucous hypersecretion.^{3,5}

WHY MEASURE RESPIRATORY FUNCTION IN INFANTS?

Reasons for assessing respiratory function in infants are summarized in Table 2.^{6,8} The clinical applications of infant LFTs in individual patients remain controversial. In particular, it should be remembered that the tests are rarely diagnostic, reference data are limited, serial tests are more valuable than single assessments, and results must be interpreted in the light of all other clinical information.

DIFFERENCES IN ASSESSMENT OF INFANTS COMPARED WITH ADULTS OR OLDER CHILDREN

Measurements in infants and young children under two years are usually made in the supine position while breathing through a face mask. Since infants are unable to cooperate, most measurements must be made during sleep which, in infants beyond four weeks postnatal age, frequently requires sedation. The inability of babies to perform special respiratory manoeuvres means that many of the measurements are limited to the tidal breathing range, although innovative techniques do now allow measurements at raised lung volumes.^{6,7}

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TABLE 1—Typical values of lung function in healthy individuals

Parameter	Preterm	Newborn	1 year	7 year	Adult
Body Weight (kg)	1	3	10	25	70
Crown-heel length (cm)	35	50	75	120	175
Respiratory rate (min ⁻¹)	60	45	30	20	15
Tidal volume (mL)	7	21	70	180	500
Anatomic dead space (mL)	3	6	20	50	150
Maximal flow at FRC (mL·s ⁻¹)	80	150	300	—	—
FRC (mL)	25	85	250	750	2100
Lung compliance (mL·kPa ⁻¹)	15	50	150	500	2000
Airway resistance (kPa·L ⁻¹ ·s)	8.0	4.0	1.5	0.4	0.2
Specific compliance (kPa ⁻¹)	0.6	0.6	0.6	0.7	0.8
Specific conductance (s ⁻¹ ·kPa ⁻¹)	5.0	2.9	2.7	2.7	2.3

Footnote: Divide compliance, and specific compliance by 10 to obtain values in cmH₂O, multiply resistance by 10 to obtain values as cmH₂O·L⁻¹·s; divide specific conductance by 10 to obtain values in s⁻¹·cmH₂O⁻¹.

TABLE 2 — Reasons for assessing respiratory function in infants

Research Applications	Clinical Applications in individuals
• Influence of early life events (e.g. passive tobacco smoke exposure, ventilator or oxygen therapy, air pollution, premature delivery) on lung development and on relative risk of developing respiratory disease • Determinants of lung function - body size, age, maturity, gender, ethnic group, family history of atopy • Evaluation of therapeutic interventions drug therapy (surfactant, steroids, bronchodilators), - mode of ventilatory support, - surgery, etc	• Early recognition of disease e.g. CF screening, effects of neuromuscular weakness • Identification of iatrogenic damage IPPV, O₂ therapy • Determination of type and severity of pulmonary defect • Efficacy of treatment - e.g. bronchodilator therapy, - steroids - surgical procedures on upper airway

EQUIPMENT REQUIREMENTS

Although a number of automated lung function carts are now available for use in infants, these tend to be less sophisticated and more inflexible than those available for adults, and many specialist laboratories still rely on home-made equipment. Full details of equipment requirements for infant respiratory function testing have been reported recently.⁶ The characteristics of all equipment must accommodate the rapid respiratory rate of infants, combined with the need to miniaturize equipment so that dead space is reduced without unduly increasing resistance.

MEASUREMENT CONDITIONS

When measuring young infants, standardisation of measurement conditions is crucial for the infant's safety, accuracy of the test and reproducibility of the data. Standardisation of measurement conditions must address both laboratory conditions and the infant's state, with respect to factors such as posture, sedation and sleep state. Recommendations have been published recently.⁶

TECHNIQUES AVAILABLE

Introduction

The connection with the recording instruments is usually made via a face mask in infants. This should fit snugly and not leak at the line of contact with the face. A leak free seal may be facilitated using therapeutic silicone putty or Vaseline (petroleum jelly). The connection should always be tested for leaks prior to commencing measurements.⁶ Tidal volume can be measured using a spirometer or reverse plethysmograph but is more commonly obtained by integration of a flow signal from a pneumotachograph (PNT).

Airway function

Assessment of airway function may be useful in infants with upper or lower airway obstruction, as a means of locating the site (upper, large or small airways) and severity. In wheezy infants measurements before and after therapeutic agents (e.g. bronchodilator aerosols) can

help to guide management. A number of techniques exist as described below.

Plethysmography

Airway resistance (R_{aw}) can be measured throughout the breathing cycle using a whole body plethysmograph.^{6,8} The technique is very similar to that described for adults with the exception that, as infants cannot be instructed to pant in order to minimize changes in temperature and humidity of the respired gas, they are allowed to breathe through a face mask connected via a pneumotachograph to a heated rebreathing bag containing saturated gas at body temperature and pressure (BTPS). The infant whole body plethysmograph is a valuable tool for obtaining simultaneous measurements of lung volume and airway resistance and may be particularly useful for discriminating between upper and lower airway disease. However it is technically demanding and its use is restricted to relatively few specialised laboratories.

Esophageal manometry

Dynamic lung resistance (R_L) (tissues plus airway) and compliance (C_L) can be measured in infants using esophageal manometry. Pleural pressure can be measured in the lower third of the esophagus as in adults using an esophageal balloon, fluid filled catheter or one of the recently introduced flexible catheter tipped microtransducers.⁶ Reliability of esophageal pressure measurement should always be checked by comparing pressure changes with those recorded at the airway opening (ΔP_{ao}) during respiratory efforts against a briefly occluded airway. With care, reliable measurements can be obtained even in small, sick preterm infants. Nevertheless this technique remains technically demanding and the need to pass an esophageal catheter (which is poorly tolerated by older infants and young children) has limited the application of this technique to early infancy.

Forced Oscillation Technique

Measurement of total respiratory resistance (R_{rs}) by the forced oscillation technique^{6,7} is potentially applicable to a wide age range. Again, the technique used in infants has been adapted from that developed for adults, wherein the impedance of the total respiratory system is determined by applying single or multiple frequency pressure oscillations to the respiratory system, usually

using a loudspeaker, via a mask or headbox, and measuring the resultant flow. When measuring input impedance, the applied pressure and resulting flow are measured at the airway opening. Alternatively, transfer impedance may be studied by measuring pressure and flow at two different points of the respiratory system, usually with pressure applied to the body surface and flow measured at the airway opening. Since oscillations are imposed on the subject's spontaneous breathing, the forced oscillation technique is non-invasive and does not require active cooperation. However, interpretation of results is limited by the wide range of values reported from healthy infants, the domination of upper airway resistance and, when using the simpler technique of input impedance, the compliance of the cheeks and pharynx.

Occlusion Techniques

Methods of measuring passive respiratory mechanics are simple and rapid to perform, requiring only a face mask, shutter and pneumotachograph (Fig. 1). If pressure changes are measured at the airway opening during relaxation against an end inspiratory airway occlusion, they represent the driving force across the chest wall, tissues and airways (i.e. the elastic recoil of the respiratory system) and can be used to measure passive respiratory mechanics.⁶

Currently, the most widely used techniques are the multiple occlusion (MOT) and single breath techniques (SBT), which can be applied to both spontaneously breathing and intubated ventilated infants. Both rely on the assumption that the Hering-Breuer inflation reflex can be elicited during brief airway occlusions. Provided the infant relaxes against the occlusion and complete equilibration of pressure occurs, pressure at the airway opening reflects the elastic recoil pressure of the respiratory system (Fig. 1).

The SBT also assumes that, on release of the occlusion, expiration remains entirely passive and that the respiratory system can be represented by a single time constant as shown by exponential decline of flow and volume on a time based trace and a linear descending portion of the expiratory flow volume curve.

While the assumption that the respiratory system can be regarded as a single compartment model is probably valid in most healthy infants, this is unlikely to be true in the presence of lung or airway disease. There is evidence that the SBT may under-estimate resistance in wheezy infants, and overestimate it in the presence of marked laryngeal braking.⁶ The latter is common in healthy babies

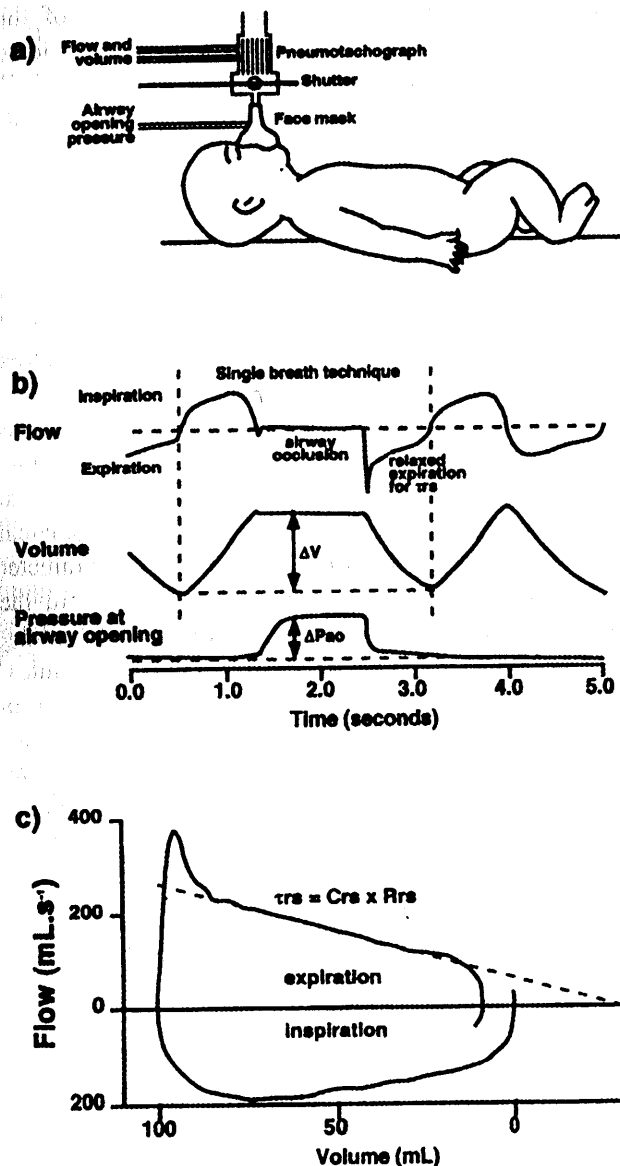
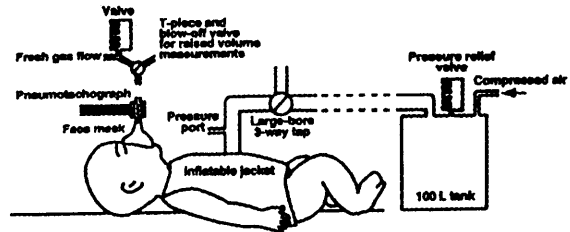


Fig 1. Measurement of passive respiratory mechanics using the single breath technique. (A) Equipment, (B) time-based trace, showing airway occlusion at end inspiration; (C) the reciprocal slope of the descending expiratory flow-volume curve (i.e. volume/flow) during muscle relaxation induced by brief airway occlusion, represents the time constant of the respiratory system ($\tau_{rs} = C_{rs} \times R_{rs}$). Measurement of the elastic recoil pressure of the respiratory system which develops during end inspiratory occlusion and which can be measured at the airway opening (ΔP_{ao}) enables compliance and resistance of the respiratory system to be assessed.

during the neonatal period. Again, nasal resistance is usually included in these measurements.

a) Equipment



b) Partial expiratory flow-volume curves

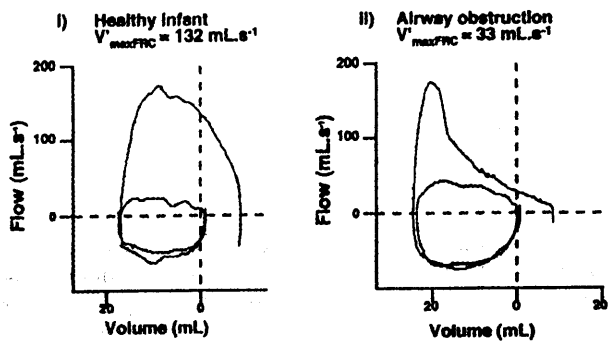


Fig. 2. Measurement of forced expiratory flow volume curves using the rapid thoraco-abdominal compression (RTC) technique. (A) Partial flow-volume curves are obtained by inflating the jacket at the end of tidal inspiration. If forced expirations from raised lung volumes are required (6), additional circuitry to enable lung inflation prior to jacket inflation must be included. (B) flow-volume curves recorded during application of the RTC technique and the preceding tidal breath, showing derivation of V'_{maxFRC} in a) a healthy preterm infant and b) an infant of similar age and weight with airway obstruction and marked flow limitation.

Indices of Forced Expiratory Flow

Although infants cannot be instructed to perform forced expiratory manoeuvres, partial expiratory flow-volume (PEFV) curves can be produced by wrapping an inflatable jacket around the child's thorax and abdomen and allowing them to breathe through a pneumotachograph attached to a face mask (Fig. 2). This technique is usually referred to as the "squeeze" or rapid thoraco-abdominal compression (RTC) technique.⁶⁻⁸ The jacket is connected via a tap to a reservoir which contains air at pressures up to 10 kPa (100 cmH₂O). At end inspiration, the tap is suddenly turned causing rapid inflation of the jacket which compresses the chest and

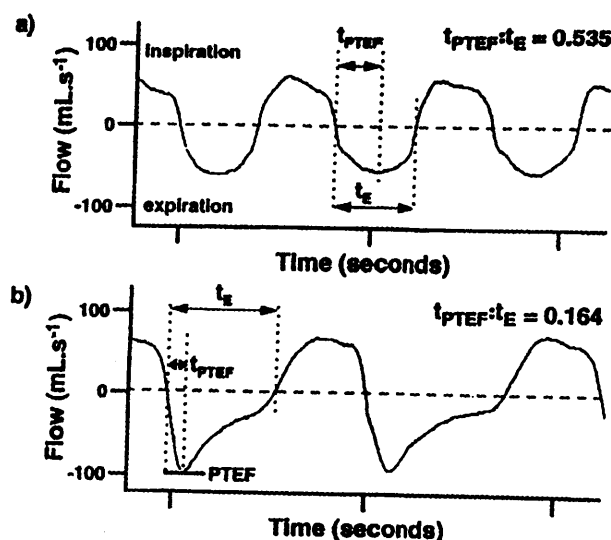


Fig. 3. Derivation of the tidal expiratory flow ratio. The time to peak tidal expiratory flow is calculated as a proportion of total expiratory time ($t_{PTEF}:t_E$). Beyond the first month of age, the average ratio is approximately 0.3 in healthy infants as in adults. Lower ratios are sometimes seen in infants with airway disease.

forces air out of the infant's lung to produce the PEFV curve. A reproducible end expiratory level must be established prior to performing the RTC manoeuvre. Jacket pressure is increased until evidence of flow limitation is achieved; i. e. here is no further increase in flow despite increases in jacket pressure. Measurements are standardised by measuring maximal flow at functional residual capacity (V'_{maxFRC}) from the PEFV curve (Fig. 2). Curves obtained from healthy infants usually have a convex shape whereas those from infants with airway obstruction, in whom there is marked reduction in V'_{maxFRC} , are usually associated with concavity of the flow volume curve. V'_{maxFRC} is thought to reflect primarily airway caliber upstream to the airway segment subjected to flow limitation and therefore give a measure of peripheral airway function that is relatively uninfluenced by the resistance of the upper airways. However, since the caliber of the small (intrathoracic) airways is determined not only by their anatomic dimensions but by the distending pressures surrounding them, full interpretation of results often requires simultaneous measurements of lung volume and elastic recoil of the respiratory system. Whether or not flow limitation can be reached in healthy infants using this technique remains controversial.^{6,8} Nevertheless it provides a useful forcing function which can provide a valuable measure of airway function in

infants. During the last few years, adaptations of this technique have been described wherein the infant's lungs are passively inflated towards total lung capacity (TLC) before applying the compression pressure.⁶ This enables full forced expiratory manoeuvres to be obtained in infants similar to those in adults.

Tidal breathing

The observation that the time to peak tidal expiratory flow as a proportion of total expiratory time ($t_{PTEF}:t_E$ - see Fig. 3) was less in adults with airway obstruction has aroused considerable interest in the field of infant lung function testing on account of its simplicity and potential applicability to both clinical and epidemiological studies.^{6,7} However, the extent to which this parameter reflects airway function remains controversial.^{9,10} In the presence of severe airflow limitation, the tidal breathing curve is defined by intra-thoracic airway mechanics, whereas in healthy subjects the shape of this curve and its derived parameters are an integrated response of the entire respiratory system, and reflect neural and laryngeal, as well as intra-thoracic, components. While remaining a useful epidemiological tool, its clinical value in individual infants is limited by the marked variability both within and between infants, especially during the first month of life.

Body Surface Measurements

The possibility of measuring respiratory function without attachments at the airway opening, has generated considerable interest in the use of body surface measurements such as impedance pneumography, magnetometry strain gauges and respiratory inductance plethysmography (RIP). Of the currently available methods, RIP is the most widely used in infants and has been shown to be a valid method of recording respiratory rate and changes in tidal volume, and of assessing the degree of thoraco-abdominal asynchrony.⁶ The main advantage of this technique is that it is totally non invasive and does not require sedation. However, interpretation of results is critically dependent on using a properly calibrated system, which may be difficult to achieve in infants. Furthermore recordings are invalidated by movement error and change in posture so that reliable recordings can only be obtained while the infant is sleeping quietly.

Lung volumes

The only lung volume that can be measured routinely and reliably in infants and young children under three years of age is FRC. Such measurements are obtained using either plethysmography or gas dilution (nitrogen washout or helium dilution) as in adults.^{6,8} Plethysmography requires expensive, complex equipment but provides rapid, reproducible results and can be used for simultaneous measures of both lung volume and airways resistance (see above). By contrast, gas dilution methods are simple, cheaper and more portable, but are relatively time-consuming due to the period of washout and wash-in required, especially in the presence of airway obstruction. Accurate measurements are dependent on adequate miniaturization and adaptation of equipment. Lung volume can be reduced by restrictive disorders of the lungs and chest wall, by collapse or consolidation or, in early infancy, as a result of impaired fetal lung growth. Hyper-inflation can be dynamic (as a result of airway obstruction) or fixed, as in the presence of lung cysts or congenital lobar emphysema.

Lung and chest wall elasticity

Newborn infants have a highly compliant chest wall so that measurements of total respiratory compliance (C_{rs}) generally give a reasonable estimate of lung compliance (C_L) especially in young and preterm infants with lung disease. A wide variety of techniques is available including the occlusion techniques, using single or multiple breath airway occlusions (see above), or weighted spirometry for the assessment of C_{rs} , and esophageal manometry for the measurement of dynamic lung compliance (see above). Respiratory diseases causing reductions in lung and respiratory compliance are most commonly encountered during the neonatal period, with airway disease predominating in older infants and young children. Nevertheless, there are certain situations when the assessment of compliance can be very useful in older babies (e.g. prognosis of infants with neuromuscular and skeletal abnormalities and follow up of those undergoing chemotherapy). In addition, knowledge of the elasticity of the lung and chest wall can be extremely helpful when interpreting measures of lung volume, airway resistance and V'_{maxFRC} .

Non-invasive determination of blood gases

Since achieving and maintaining gas exchange is the primary function of the lung, respiratory function testing

should include a determination not only of lung mechanics but of blood gases. A review of the technical aspects related to currently available methods for non-invasive determination of blood gases in infants and young children has been published recently.⁶

Distribution of ventilation

Gas distribution can be adversely affected by any focal or generalized disorder of the lungs. As in older subjects, regional lung function and ventilation/perfusion abnormalities can be assessed in infants and children, when clinically indicated, using radioisotopes such as krypton 81 and technetium 99. Increasing use is also being made of computerized tomography and MRI scans in the detection and diagnosis of respiratory disease in this age group.⁷ During recent years, there has also been a resurgence of interest in the assessment of indices of gas exchange and mixing using computerized analysis of wash in and wash out curves to calculate indices of efficiency such as pulmonary clearance delay, gas distribution index or distribution of moments.

SUMMARY

During recent years, there has been rapid development in the availability and application of pulmonary function tests in infants and young children. Whereas original methods were based on adaptations of classical techniques, over the past decade there has been an increasing trend towards developing less complex techniques specifically for use in infants and young children. Interpretation of these measurements requires a knowledge of respiratory physiology, and may be confounded by an unstable end expiratory level, compliant chest wall, dominance of the upper airways, difficulty in achieving flow limitation in healthy infants, and the variability of respiratory, lung or airway resistance which increases the difficulty of assessing the significance of changes in resistance as a result of treatment or challenge. Nevertheless, with care, the assessment of respiratory function during infancy and early childhood can increase knowledge of the growth and development of the respiratory system, and our understanding of the patho-physiological processes underlying respiratory diseases in early life. They also have the potential to provide valuable objective outcome measures in the quest for effective preventive and therapeutic strategies in respiratory medicine.