

CHAPTER 9

Respiratory function measurements in infants and children

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Most children above the age of 7–8 yrs can perform the full range of tests available for older individuals, using similar protocols to those described elsewhere in this Monograph. By contrast, assessments in young children and infants have generally been restricted to specialised research establishments, due to the lack of suitable equipment and the complexity of undertaking such measurements. The realisation that insults to the developing lung may have life-long effects and that much of the burden of respiratory disease in childhood and later life has its origins in infancy and early childhood has emphasised the need to develop and standardise sensitive methods of assessing respiratory function in infants and young children [1, 2]. During the past few years there have been concentrated efforts to improve the feasibility of assessing lung function in preschool children. With specially trained operators and a suitable environment, many pulmonary function tests (PFTs) now appear to be feasible in at least 50% of 3-yr-old children and in the majority of children aged >4 yrs.

The aims of this chapter are to provide an overview of:

- the differences in assessing lung function in infants and preschool children compared with older cooperative subjects;
- which tests are feasible in infants and young children;
- the limitations of applying these tests; and
- the problems associated with interpreting results in this age group.

Throughout this chapter, the focus will be on the most widely used pulmonary function tests for this age group. For simplicity, the term "infant PFTs" will refer to measurements in sleeping infants and young children (aged <2 yrs), whereas "preschool" will apply to those tests used in awake young children (aged 3–6 yrs).

Assessing lung function in different age groups

Infants and toddlers below 2 yrs of age

Marked developmental changes in respiratory physiology occur during the first years of life. The major issues in undertaking PFTs in children aged <2 yrs relate to sleep state, sedation, ethical issues, posture and the need to miniaturise and adapt equipment for measurements in small subjects who cannot cooperate actively and who are preferential nose breathers [3, 4].

Developmental changes

Developmental changes that influence the assessment of lung function in infants include: 1) the compliance of the chest wall; 2) dynamic elevation of functional residual capacity (FRC); and 3) the influence of the upper airways. During infancy, the highly compliant chest wall results in minimal outward elastic recoil such that, during passive expiration, the lungs recoil to a much lower volume in relation to total lung capacity (TLC) than in older subjects. The potential difficulties imposed by the compliant chest wall, including instability of FRC and a tendency for small airway closure during tidal breathing, are partially compensated by dynamic elevation of the end expiratory level. During the first months of life, infants modulate both expiratory time and flow to maintain an adequate FRC. In addition to changes in respiratory rate, babies often use laryngeal and post-inspiratory diaphragmatic activity to slow expiratory flow [4]. Unless care is taken to limit recordings to periods of quiet sleep, the variability of end expiratory level may impede assessment and interpretation both of lung volumes and of respiratory mechanics and forced expiratory flows, which are highly volume dependent. Changes in respiratory rate, expiratory time and the emptying time of the lung with growth may all have significant effects on the interpretation of changes in various indices with growth [5–7]. In infants, as in adults, nasal resistance represents ~50% of total airway resistance. In contrast to adults, however, infants are preferential nose breathers, with PFTs generally being performed using a mask rather than mouthpiece and noseclips. Changes in intrathoracic airway resistance as a result of disease or therapeutic interventions may therefore be masked, especially if there has been a recent upper respiratory infection. For this reason it is usually necessary to postpone PFTs in infants for at least 3 weeks following any respiratory infection.

Differences in measurement conditions

1) Sleep state, sedation and duration of testing procedure. Measurements in infants are normally limited to periods of sleep so that the infant will tolerate manoeuvres such as positioning of a face mask, brief airway occlusions and application of an inflatable jacket. It is essential that a stable end-expiratory level is established before measurements commence. To achieve this it is usually necessary for the child to be in quiet, rather than rapid eye movement, sleep. Since the duration of such epochs are inversely proportional to the post-conceptual (*i.e.* gestational + postnatal) age of the child [8], this presents a real challenge when undertaking measurements in very young or immature infants.

Successful measurements using a full range of tests can usually be achieved during natural sleep following a feed in all infants up to at least 1 month postnatal age (corrected for any prematurity). Sedation is usually achieved using oral chloral hydrate in a dose of 50–100 mg·kg⁻¹. With the exception of a small proportion of "high risk children" (such as those with known or suspected upper airway obstruction [8]), chloral hydrate has been shown to have an excellent safety record [9]. Nevertheless, its action can be unpredictable, with time taken to fall asleep after administration ranging from 15 min to >2 h, and duration of subsequent induced sleep can be equally variable. The relatively short time that an infant spends asleep, with or without sedation, means that important decisions have to be made regarding which respiratory function test(s) should be used.

2) Posture. During infancy, most PFTs are obtained in the supine position. This will influence the position of the diaphragm, efficiency of respiratory musculature, FRC, lung mechanics and the distribution of ventilation. Such changes must be taken into account when interpreting results, particularly when reporting longitudinal changes.

3) Safety issues. Despite the excellent safety record, strict safety precautions must be adhered to during all infant PFTs. Resuscitation equipment, including suction and oxygen, needs to be available and two skilled operators, fully trained in basic life support, one of whom has prime responsibility for monitoring the infant, must be present. Pulse oximetry is recommended throughout the entire session.

4) Equipment requirements. During recent years, close collaboration between scientists and manufacturers, guidelines published by a European Respiratory Society (ERS)/ American Thoracic Society (ATS) Task Force [1, 10–14], and technological advances have made it possible to perform standardised infant PFT in an increasing number of centres.

5) Leaks and deadspace. The use of a mask rather than a mouthpiece may introduce both physiological problems, due to the relatively large apparatus deadspace, and technical problems, in that it is difficult to estimate the "effective" dead space of the mask [15]. Leaks around the face mask, which occur frequently, can be difficult to identify. Many centres use therapeutic putty to facilitate an airtight seal between face and mask.

Preschool children

Preschool children are too old to sedate for lung function testing, and may lack the necessary coordination or concentration to perform some of the manoeuvres required for lung function tests designed for older subjects. They also have a short attention span and are easily distracted and thus need to be engaged and encouraged by the operator to participate in the test. Thus, while measurement conditions for testing preschool children are broadly similar to those required for older subjects, every effort should be made to make the environment as child-friendly (and safe) as possible. This includes provision of suitable furniture, games and wall coverings, as well as adaptation of the normal lung function terminology.

To this end the most important acquisition for any "preschool set up" is personnel with suitable temperaments, *i.e.* a love of children, infinite patience and stamina, and a good sense of humour. Adaptability, meticulous attention to detail and a thorough background in respiratory physiology are also essential requirements, since appropriate criteria for acceptable tests in the preschool child may differ markedly from those established for older subjects [16]. The criteria for a successful preschool session should not only be that valid respiratory function results are obtained, but also that the children and their parents want to return for subsequent visits. Because young children tire easily, visits should be timed carefully to maximise success. The emotional and developmental stage of the child are important determinants of success with preschool PFTs, and the child's past medical history may also be relevant. Those with extended hospital stays during the neonatal period may display considerable antipathy towards any electronic equipment or facial attachments. The need to gain the child's confidence, provide coaching in the various techniques and manoeuvres and accommodate a rest or games between the different PFTs when necessary, means that plenty of time should be set aside for preschool PFTs. The use of computer games and appropriate incentives to help the child understand what is required can be helpful [16] while encouragement to sit quietly during more prolonged periods of data collection (*e.g.* during multiple breath inert gas washouts) can be provided by the opportunity to watch a favourite video.

Commercial equipment is available for most preschool tests, albeit not specifically designed for this age group. The potential effects of using equipment that was developed for older and larger individuals, particularly with respect to deadspace and resistance,

need to be considered. These comments are equally relevant when assessing young school-age children.

Anthropometry and background details

Given the rapid growth during infancy and early childhood, accurate measurements of height and weight using a calibrated stadiometer and scales are essential. For accurate interpretations of the lung function tests it is also essential to record data on environmental, genetic and socioeconomic factors likely to impact on lung growth including: sex; ethnic group; family history of asthma and atopy; cigarette smoke exposure, both pre- and post-natal; allergen exposure, including pets; relevant current and past medical history and medication use.

Purpose of assessing lung function in infants and children

Lung function tests in the very young are rarely performed for diagnostic purposes, but rather to monitor the nature and severity of respiratory disease or to assess the response to treatment. As in adults, lung function measurements in older children can be used:

- as a diagnostic aid, to help determine the nature of the lung function disorder;
- to quantify the magnitude of the lung function disorder;
- to assist in determining prognosis or peri-operative risk;
- to assess the effects of medical interventions or diagnostic tests (such as the effects of bronchodilator and bronchoconstrictor stimuli);
- to evaluate innovative therapies aimed at improving prognosis, quality of life and lung function;
- to study the natural course of respiratory disease;
- to study the growth and development of the lungs and airways and evaluate early determinants of airway function.

Though there is little doubt about the value of infant and preschool PFTs in epidemiological and clinical research studies, their potential influence on individual clinical management is more debatable [17–19]. Within infants, the clinical utility of such tests will be limited by the time consuming nature of these tests and the need for sedation beyond the neonatal period, whereas the availability of "preschool tests" has been too recent for any reliable assessment of the potential value of such assessments within individuals. While highly reproducible measurements of lung function can be made in infants and young children during the same test occasion, little is yet known about the "between test repeatability".

During childhood, beyond the neonatal period, lung function disorders are usually of an obstructive nature, generally being confined to the intrathoracic, intrapulmonary airways. Hence, measurements of airway patency (maximal expiratory flow volume (MEFV) curves, spirometry, resistance measurements) are of most relevance for these patients. Restrictive lung diseases are less common in children than in adults, such that measurements of static lung volumes, maximal inspiratory or expiratory pressures, lung compliance and diffusion capacity are used less frequently. Such tests may however play a role in children suffering from cardiac diseases, systemic vasculitis, immunological disorders, neuromuscular and/or orthopaedic disease. Similarly, tests designed to assess parenchymal lung disease (lung compliance, lung volumes and partitioned respiratory mechanics) will be particularly pertinent in those delivered prematurely and/or suffering from the respiratory distress syndrome or chronic lung disease of infancy. During the

past decade, development of noninvasive methods, such as analysis of exhaled nitric oxide and breath condensates to assess the metabolic function of the lung, have begun to play a role in diagnosing and monitoring airway inflammation, especially in allergic asthma. The following section summarises the techniques currently available to study respiratory physiology and noninvasive inflammatory markers in children of various ages.

Methods of assessing pulmonary function in infants and young children

Details of most of the commonly used infant PFTs have been summarised previously [1, 3, 10–14, 20], whereas those relating to preschool tests have been emerging at an increasing rate during the past few years. Some of these tests can be applied throughout childhood, whereas others are specific to either a sleeping infant or cooperative preschool child. It is generally important to undertake tests based on tidal breathing recordings prior to any forced expiratory manoeuvres. It is also essential to consider what is feasible in the time available: while this is largely dictated by the duration of sleep in infants, and that of concentration and cooperation in preschoolers, it also dependent on the age and health of the subject and the expertise of the operators.

Even in older children, measurements may take considerably more time than in adults. The lung function technician should report the child's degree of cooperation. In young children, the chances of successful initial attempts at spirometry may increase if they have been introduced to the laboratory, and have practised blowing on a peak flow meter at home before their first testing session. Given the wide range of body size, several sizes of mouthpiece, and seats adjustable in height, should be available. Bacterial filters are mandatory. Unless otherwise specified, any medication should be discontinued for a prescribed period prior to testing; generally this would be 8 h for short-acting bronchodilators, 48 h for long acting bronchodilators and 72 h for any anti-histamines prior to a histamine provocation test.

Forced expiratory manoeuvres

While international guidelines are well established for spirometric measurements in adults [21], the extent to which these are appropriate for school-aged children remains questionable [22]. As discussed below, although major adaptations in terms of both data collection and analysis are required, similar information from "full" MEFV curves can now be obtained from both infants [20] and preschool children [16, 23–27].

The principles of paediatric spirometry in children aged >6–7 yrs are the same as in adults (see Chapter 1). When testing preschool children, specially adapted quality control criteria are required to allow for the fact that:

- Repeatability criteria need to be adjusted for the smaller absolute flows and volumes being measured.
- Young children may need more attempts when learning to produce an MEFV curve than are necessary in older subjects.
- Lung emptying occurs much faster than in older subjects. In preschool children expiration may be complete in <1 s, making the use of a forced expiratory volume in one second (FEV₁) an inappropriate outcome measure. Indeed, even when the child does produce a valid FEV₁, its value may approach forced vital capacity (FVC).

With appropriate training and encouragement, most children 3–6 yrs of age can achieve acceptable spirometry results. A variety of blowing games involving straws, bubbles and party whistles can facilitate this process, as can demonstrations from the operator and the use of carefully selected computer incentives [16, 28]. Considerable input is required from the investigator with respect to the targets that are set: too low and the child will not make a maximum effort, too high and they will become discouraged and stop trying [16].

Spirometry can be performed with the subject seated or standing, but posture should be reported. Most preschool children tolerate noseclips, although this is not mandatory for acceptable recordings [29]. For quality control reasons all loops should be saved for reviewing after the test. Three technically satisfactory curves can usually be obtained with persistence.

Potential guidelines for spirometric assessments in preschool children have been published recently [16]. Recommended criteria for acceptance of MEFV curves for school children [22], include:

- that the total duration of forced expiration can be much less than the 6 s recommended for adults (*e.g.* at least 2 s in children 8–19 yrs) provided there is a asymptotic approach of flow *versus* volume, or volume *versus* time;
- that the difference between the two best FEV₁s or FVCs should be based on a percentage (rather than absolute) difference of the highest value.

Preliminary reference values have also been published for preschool children, but have yet to be evaluated outside the centre where they were created [26–27].

Peak expiratory flow measurements

Widespread use of home peak flow monitoring has been considered a convenient and cheap way to assess the pulmonary condition of children with asthma in the home environment. More recent studies, however, seriously question the value and validity of such recordings. It appears that peak flow diaries are often made up [30], are unreliable and, most importantly, there is poor correlation between peak expiratory flow (PEF) and measures of peripheral airway function [31]. The contribution of home PEF recordings to better asthma management is unclear [32, 33]. The inter-subject variability for a specific age or height is huge, which implies that a "personal best" value is the only reliable anchor point. Peak flow diaries may still be of some use in isolated cases [34].

Forced expiratory manoeuvres in infants

By substituting an externally applied pressure to the chest and abdomen instead of voluntary effort to force expiration, it has been possible to obtain both partial and "full" forced expiratory manoeuvres in sleeping infants. Measurements of maximal flow at FRC ($V'_{\max\text{FRC}}$) have been used to help characterise the normal growth and development of the lungs during infancy and the pulmonary abnormalities associated with acute and chronic lung disorders during early childhood. Data derived from forced flows and volumes over an extended volume range have been found to discriminate clearly between those with and without respiratory disease, even in the absence of symptoms [19].

Tidal rapid thoracic compression technique

In infants, partial expiratory flow volume curves can be produced by a jacket around the chest and abdomen, which is inflated at the end of a tidal inspiration to force

expiration. The resultant flow is recorded through a flowmeter attached to a face mask (fig. 1). This technique is usually referred to as the "squeeze" or the tidal rapid thoraco-abdominal compression (RTC) technique. $V'_{\max\text{FRC}}$ is the most commonly reported parameter derived from this technique (fig. 2) and equates to forced flows at low lung volumes (e.g. MEF_{25%}FVC) in older children [5]. Guidelines regarding data collection and analysis for the tidal RTC have been published [11], as have sex-specific collated reference data [35].

$V'_{\max\text{FRC}}$ is thought to reflect primarily airway calibre upstream to the airway segment subjected to flow limitation and therefore to provide a measure of intrapulmonary airway function that is relatively uninfluenced by the resistance of the upper airways. This makes it a useful measure of intrathoracic airway function in infants, in whom nasal resistance comprises such a large proportion of total resistance. As in older subjects, the shape of the loop, as well as the derived numerical values, contribute to interpretation of results (fig. 2). The tidal RTC technique has been used widely in clinical and epidemiological research studies [19].

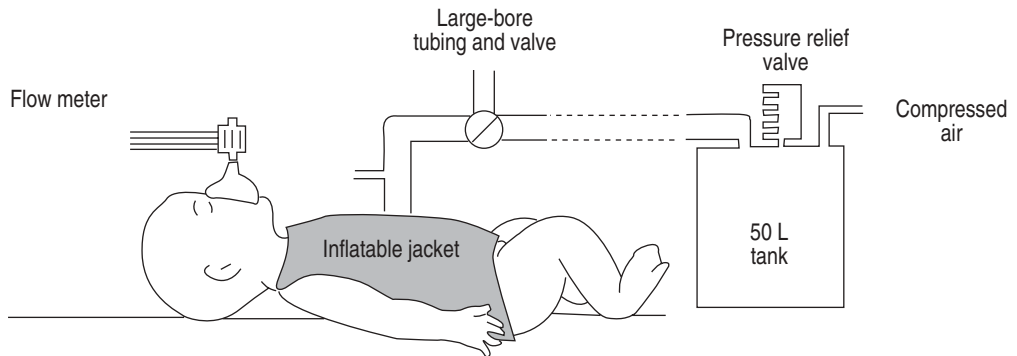


Fig. 1. – Equipment for partial forced expiratory manoeuvres using the tidal rapid thoraco-abdominal compression technique in infants.

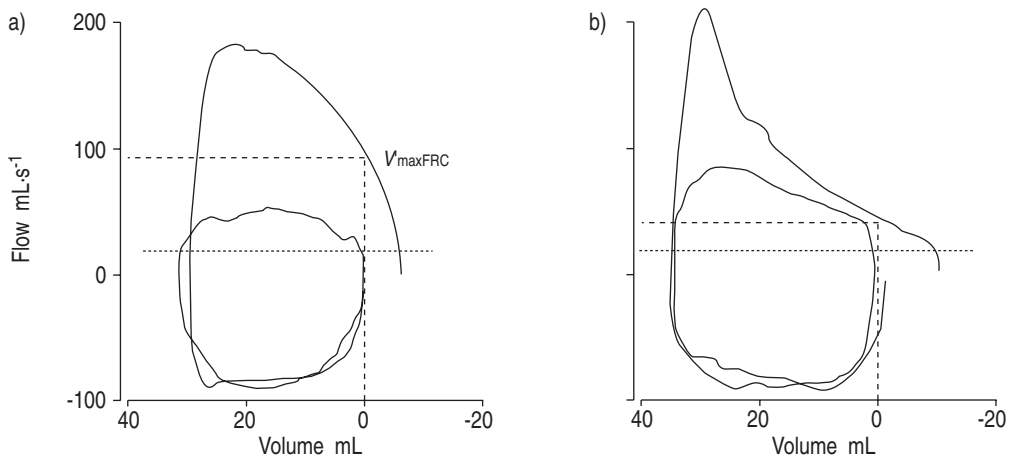


Fig. 2. – Partial flow–volume loops from a) a healthy newborn (maximal flow at functional residual capacity ($V'_{\max\text{FRC}}$)=92 mL·s⁻¹) and b) a newborn with evidence of airway obstruction ($V'_{\max\text{FRC}}$ =40 mL·s⁻¹).

Raised volume rapid thoraco-abdominal compression

The tidal RTC technique has been modified so that forced expiratory flows and volumes can be measured over an extended volume range, in what has become known as the "raised volume RTC or RVRTC technique". Similar to spirometric assessments in older subjects, the raised volume technique allows the infant to inhale towards total lung capacity before rapid inflation of the jacket initiates forced expiration from this elevated lung volume, the manoeuvre ending when the infant reaches residual volume (RV).

The airway pressure used to augment inspiration is most commonly 30 cmH₂O (2.94 kPa). Jacket inflation must be maintained until lung emptying is complete. This procedure is repeated until at least two technically satisfactory and repeatable manoeuvres have been recorded [20]. The relationship between a partial forced expiratory manoeuvre initiated from end tidal inspiration and that recorded from the same infant after raising lung volume with an inflation pressure of 30 cmH₂O is shown in figure 3.

Parameters commonly reported from the RVRTC include the "forced vital capacity from the applied inflation pressure", *e.g.* FVC₃₀, FEV after 0.4 or 0.5 s and maximum expiratory flow at 25% of forced vital capacity (MEF₂₅). Calculations of FEV₁ are rarely feasible in young infants, except in the presence of marked airway obstruction, due to the very rapid lung emptying and short forced expiratory time (FET) during early life [5, 6]. There is a marked age dependency of FEV₁/FVC ratios during infancy and early childhood and such ratios are poorly discriminative of changes in airway function due to disease [36, 37].

Raised lung volume flow-volume manoeuvres are more difficult to perform than partial flow-volume manoeuvres. Extensively trained personnel are needed to ensure accurate results. Potential advantages of the RVRTC technique include the fact that forced flows and volumes are measured from a reproducible, rather than a potentially variable, lung volume; flows can be assessed over an extended volume range from near TLC to RV; flow limitation should be easier to achieve; and longitudinal assessments of similar parameters are possible from infancy to adulthood.

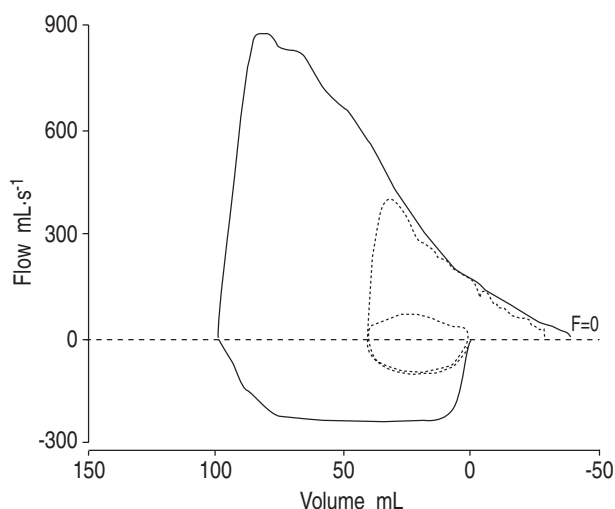


Fig. 3. – Overlay of forced expiratory flow–volume curves from the same infant obtained at the end of tidal inspiration (inner curve; ····) and after lung inflation to 30 cmH₂O (outer curve; —).

Several studies have indicated that RVRTC may be more discriminative than tidal RTC for distinguishing the effects of respiratory disease on airway function [38, 39]. This technique has the potential to quantify the degree of airway obstruction [38, 40], monitor changes in airway mechanics over time [36, 37] and evaluate bronchial responsiveness [40–42]. Measures of FEV_t are more reproducible than forced flows and have been found to be discriminative [36, 37, 43]. Forced flows may, however, be sensitive in wheezy infants during both baseline measurements and assessments of bronchial responsiveness [40, 41, 44].

Resistance and compliance measurements

Measurements of resistance reflect airway function during tidal breathing and are thus suitable for subjects who cannot actively participate in lung function tests. This section summarises special issues to consider when undertaking these measurements in infants and children, as well as providing an overview of techniques that have been developed specifically for use in younger subjects.

Plethysmographic assessments of airway resistance

Whole body plethysmography has been successfully adapted for measurements in both sleeping infants [3, 14] and awake preschool children [45]. Airway resistance (R_{aw}) has been used to study normal airway growth and development in relation to lung volume during the first year of life and has demonstrated the presence of "tracking" of airway function during this period [46, 47]. These measurements have also been used to discriminate between healthy infants and those with respiratory disease or prior wheezing [46, 48, 49]. Plethysmographic measurements of specific airway resistance (sR_{aw} : *i.e.* $R_{aw} \times FRC$) are becoming an increasingly popular method of assessing both baseline airway function and bronchial responsiveness in preschool children. Values of specific resistance remain relatively independent of changes in body size. This should facilitate attempts to distinguish changes in airway function due to disease from those resulting from growth and development. sR_{aw} has been used as an outcome measure in healthy young children [45, 50] and those with cystic fibrosis [51, 52], as well as being used to assess bronchial responsiveness or document the effect of anti-asthmatic therapies in preschool children [53–55].

The principles of plethysmographic assessments of airway resistance measurements are identical in infants and preschool children to those in older subjects [3, 14]. Most sleeping infants will readily tolerate an airway occlusion lasting 6–10 s, and will make respiratory efforts against the shutter, thereby generating the necessary pressure and volume changes to calculate FRC_{pleth} .

Most commercially available "adult" plethysmographs now rely on some form of electronic compensation, rather than a heated re-breathing system and/or the need for panting manoeuvres to minimise the influence of changes in humidity and temperature of the respired gas during these measurements. This method has been successfully adapted to measure sR_{aw} in preschool children [45], but has yet to be validated in infants, in whom published data has largely been obtained while breathing gas under body temperature, saturated (BTPS) conditions [3, 46, 48]. In preschool children, who are unlikely to tolerate the relatively prolonged airway occlusion required for measuring FRC_{pleth} , sR_{aw} is obtained simply by measuring changes in air flow relative to changes in plethysmographic volume during spontaneous breathing, *i.e.* as the slope of the specific resistance loop without simultaneous

measurement of FRC.

$$sR_{aw} = (\Delta V_{pleth} / \Delta \text{Flow}) \times (P_{amb} - P_{H_2O}) \quad (1)$$

Where P_{amb} is ambient pressure and P_{H_2O} is water vapour pressure. One of the shortcomings of plethysmographic measures of airway resistance is that there is no consensus regarding which parameters should be reported. Since resistance changes throughout the breathing cycle, there is no single value that can be considered truly representative. Most commercially available systems have several ways of calculating resistance and specific resistance including the pressure–flow relationship:

- between points of maximum pressure swing or maximum flows;
- throughout the entire breath (calculated by regression of $\Delta V_{pleth} / \Delta \text{Flow}$); and
- at a fixed flow during initial inspiration and/or expiration.

Possibly, the effective R_{aw} (R_{eff}) is the only objective and standardised way of calculating R_{aw} because it is representative for the entire breathing cycle and found by dividing two integrals. It is possible to separate into $R_{eff_{total}}$, $R_{eff_{in}}$ and $R_{eff_{ex}}$.

$$R_{eff} = \text{integral}(P_a \cdot V' \cdot dt) / \text{integral}((V')^2 \cdot dt) = \text{integral}(P_A \cdot dV) / \text{integral}(V' \cdot dV) \quad (2)$$

The interpretation is, however, difficult. The major advantages of plethysmographic R_{aw} are that it represents a direct reflection of airway calibre during tidal breathing and that a similar method can be used at all ages. Infant plethysmography, while providing valuable data in specialised centres, remains limited by the lack of any validated method of obtaining reliable results without reliance on a heated rebreathing bag, and the potential dominance of the upper airway in these nose breathing subjects. Preschool plethysmography has the advantage that the necessary equipment is available in most secondary hospitals, thereby simplifying a wide dissemination of this method, although its size precludes use in field studies and most primary care facilities. Improvements in commercially available software are required to facilitate both standardised data collection and quality control in this age group.

Passive respiratory mechanics

Measurements of passive respiratory mechanics (compliance, resistance, and expiratory time constant) are possible if a state of relaxation can be induced in the respiratory system. The vagally mediated Hering Breuer inflation reflex is active within the tidal volume range throughout the first year of life. The "occlusion technique" for measuring passive respiratory mechanics is based on the ability to invoke this reflex by performing brief intermittent post-inspiratory airway occlusions during spontaneous tidal breathing. This leads to inhibition of inspiration, and prolongation of expiratory time (fig. 4). Provided there is no respiratory muscle activity and that there is rapid equilibration of pressures across the respiratory system during the occlusion, alveolar pressure can be measured at the airway opening. By relating this recoil pressure either to the volume above the passively determined end expiratory volume at which the airway occlusion was performed or to the airflow occurring on release of the occlusion, the compliance and resistance of the respiratory system can be calculated [12]. A popular adaptation of this technique is the single occlusion technique (SOT). When using this technique, resistance, compliance and the passive expiratory time constant (τ_{rs}) of the respiratory system can be calculated from a single airway occlusion (fig. 5). Provided expiration is passive and there is no braking of expiratory flow following release of the airway occlusion, a plot of the flow-volume relationship can be used to calculate τ (since time constant=volume/flow). Compliance of the respiratory system (C_{rs}) is calculated by relating the volume above the passively determined lung volume at the moment of airway

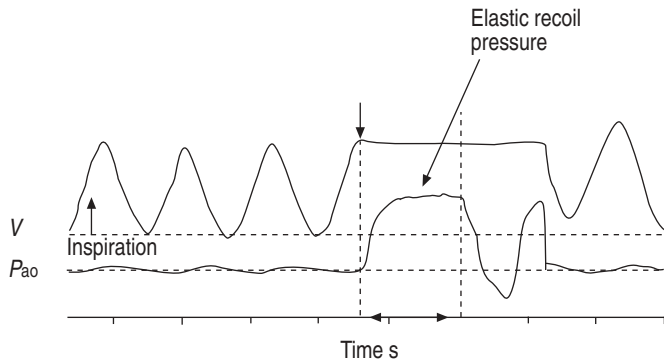


Fig. 4. – Assessment of passive mechanics using the occlusion technique, which is based on the ability to invoke Hering-Breuer inflation reflex. Airway occlusion at end tidal inspiration induces a respiratory pause (lengthening of expiratory time), during which the recoil pressure of the respiratory system can be measured at the airway opening. V : volume; P_{ao} : airway opening pressure.

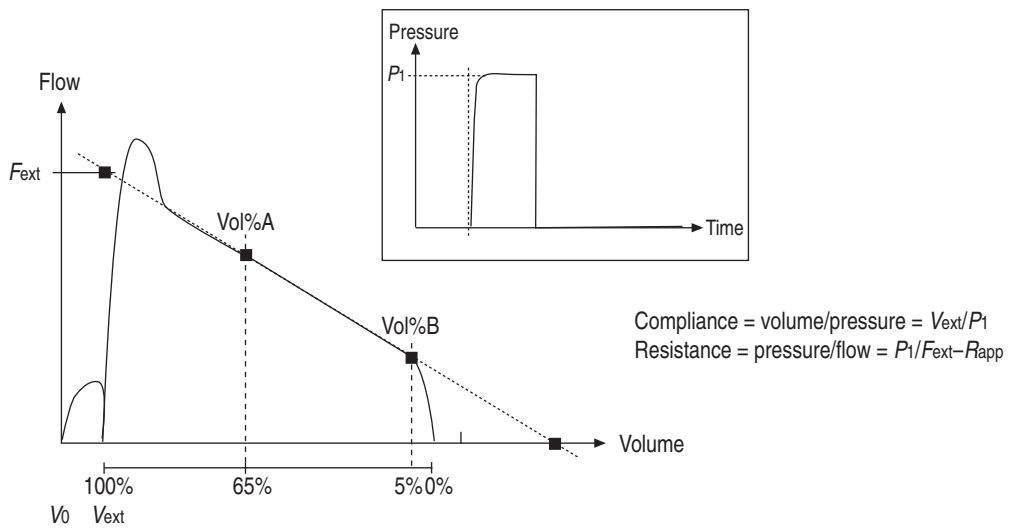


Fig. 5. – Assessment of passive respiratory mechanics using the single breath occlusion technique. Provided there is passive expiration, the time constant of the respiratory system can be measured by regression of volume/flow over the linear portion of the flow volume plot (*i.e.* between Vol%A and Vol%B) during expiration (a). Compliance is measured from the ratio of volume in the lung above the passively determined end expiratory level at time of occlusion (the "extrapolated volume" or V_{ext}), divided by the elastic recoil pressure at that volume ($P_1 - b$), whereas resistance is measured either from the pressure/flow relationship as shown or as: $resistance = time\ constant / compliance$ (for further details see [10]). F_{ext} : flow at V_{ext} .

occlusion to the elastic recoil pressure measured during the occlusion. The respiratory time constant represents the product of resistance and compliance. Respiratory resistance (R_{rs}) can thus simply be derived as C_{rs}/τ . An occlusion time of at least 400 ms (maximum 1.5 s) in which to attain a pressure plateau lasting at least 100 ms has been recommended [12].

The advantages of the SOT are that the equipment is relatively simple and cheap, consisting of a flowmeter and shutter attached to a face mask, and that measurements

can easily be made at the bedside. As with all infant PFTs, attainment of a stable respiratory pattern and leak free seal around the mask are mandatory. Valid measurements also depend on three vital assumptions, namely that:

- there is complete relaxation of the respiratory system not only during the occlusion, but during the subsequent expiration;
- pressure measured at the facemask equilibrates rapidly with alveolar pressure; and that;
- the lung can be treated as a single compartment, that can be described by a single time constant.

These conditions can be achieved in most healthy infants during quiet sleep but may be more difficult to satisfy in infants with severe airway disease. As with all measures of resistance during infancy, results may be dominated by the upper airways, particularly if there is any evidence of an upper respiratory tract infection. While significant changes in R_{rs} have been reported among groups of infants with airway disease [56], the major role for these measurements is to assess restrictive pulmonary changes in conditions, such as respiratory distress syndrome, chronic lung disease, pulmonary hypoplasia, interstitial lung disease and cardiac disease with pulmonary over perfusion [57–59].

Interrupter technique

Resistance of the respiratory system can be assessed in preschool children by using the interrupter technique, which relies on short interruptions to airflow. The interrupter technique was first reported in 1927 by von Neergaard and Wirz, who applied a sudden brief occlusion to the airways (100 ms) during a normal respiratory cycle while recording flow and mouth pressure (P_m). Based on the assumption that pressures equilibrate rapidly throughout the respiratory system during periods of no airflow, such that P_m will reflect alveolar pressure during the occlusion, the interrupter resistance (R_{int}) can be calculated by dividing the change in P_m after the occlusion by the flow immediately prior to the occlusion. Interest in the interrupter technique has been heightened during the past decade, as its potential use as a clinical tool for measuring lung function in young "noncollaborating" children has been appreciated [60].

Theoretically, when airflow at the mouth is suddenly interrupted, there will be a rapid initial change in P_m (P_{init}) followed by a slower change (P_{dif}) up to a plateau (P_{el}) (fig. 6). P_{init} is virtually instantaneous and reflects the pressure difference due to the airway resistance at the time of interruption. During tidal breathing, P_{init} , and thus R_{int} , will include a component of lung tissue and chest wall resistance, not just airway resistance. P_{dif} is due to the visco-elastic properties of the respiratory tissues and reflects stress adaptation (relaxation or recovery) within the tissues of the lung and chest wall, plus any gas redistribution (Pendelluft) between pulmonary units with different pressures at the time of interruption. The final plateau usually represents the pressure due to the elastic recoil of the respiratory system and may take several seconds to be reached, especially in the presence of any airway obstruction. In reality such a plateau is rarely observed during the interrupter technique due to the brevity of the shutter closure. The total time of interruption should be <100 ms, to prevent breathing against the occlusion [60]. The major advantage of the interrupter technique is its portability and the simplicity of data collection, which makes it suitable for use in field work.

Reference values for interrupter resistance in preschool children have been published [61–63], but methods and equipment used in different laboratories are not standardised. The definition of a clinically significant decrease in R_{int} in response to a bronchodilator [62, 64], the role of R_{int} in challenge tests and the usefulness of the interrupter technique in comparison with other techniques remain to be determined.

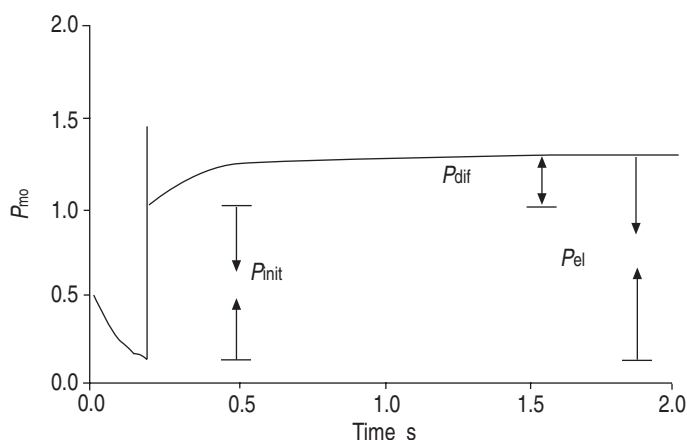


Fig. 6. – Schematic description of the pressure–time curve showing mouth pressure (P_{mo}) changes after a sudden interruption of airflow at mid expiration. P_{init} : rapid initial change in P_{mo} ; P_{dif} : secondary slower change in P_{mo} ; P_{el} : final plateau representing the pressure due to the elastic recoil of the respiratory system.

Forced oscillation technique

The forced oscillation technique (FOT), in which impedance of the respiratory system is measured by superimposing small amplitude pressure oscillations on the respiratory system and measuring the resultant oscillatory flow is another technique that has been successfully adapted for use in infants and preschool children, based on tidal breathing. A full description of data collection and analysis, together with guidelines for the application and interpretation of FOT have been provided [65], and are discussed further in Chapter 5 of this Monograph. The FOT can be used to define respiratory system impedance (Z_{rs}), if transrespiratory pressure is measured. Important limitations of the technique include the effects of upper airway compliance. This is particularly important in small children who have relatively low upper airway wall impedance relative to Z_{rs} , such that the latter may be underestimated.

Although some reference data have been reported [65], the wide degree of variability between healthy children limits the extent to which this technique can be used to assess either the presence or severity of airway disease within individuals. Nevertheless, in asthmatic children, parameters derived from the FOT may provide a more reliable evaluation of bronchial obstruction and its reversibility than R_{int} [66]. In addition, the FOT facilitates noninvasive assessments of the bronchomotor response to deep inhalation, as a reflection of the degree and nature of airway obstruction [67, 68]. These characteristics, together with the minimal requirement for the subject's cooperation, make FOT a suitable paediatric lung function test for epidemiological and field studies.

Assessment of lung volumes and ventilation

Tidal breathing parameters

Tidal breathing parameters have been used in both clinical and research settings to determine tidal volume, breathing frequency and minute ventilation, to investigate the

control of breathing, to trigger equipment and as an indirect measure of airway mechanics. Such measurements and their interpretation are in fact highly complex [10, 69] and it is therefore important to appreciate the numerous factors that may influence these recordings.

Patterns of tidal flow-volume loops can potentially yield important information about the likely site of obstruction (fig. 7). Attempts to quantify such patterns have resulted in numerical descriptors of the tidal flow pattern, such as the time to peak tidal expiratory flow as a ratio of total expiratory time (t_{PTEF}/t_E), which may be reduced in the presence of airway obstruction. t_{PTEF}/t_E has been shown to be a valuable outcome measure in epidemiological studies designed to investigate early determinants of airway function [47, 70–73]. However, this measurement is only distantly related to airway function and, as with most tidal breathing parameters, conveys mixed information on the interaction between control of breathing and airway mechanics [69, 74, 75].

The greatest advantage of undertaking these measurements is their noninvasive nature but it is difficult to record baseline values of tidal breathing when using any system that requires facial attachments. While attempts have been made to use body surface measurements, results have often been disappointing [76, 77]. In health, the pattern of tidal breathing is highly variable [75], and while assessments have been performed in awake newborn infants, repeatable measures normally require that the infants are in quiet sleep. In awake preschool children, such problems are even more marked. The clinical usefulness of tidal breathing measurements is limited by the marked within and between subject variability of breathing pattern. Within epidemiological studies, the discriminative ability of indices such as t_{PTEF}/t_E decreases with increasing age [3, 46, 73, 77].

Measurement of static lung volumes

Introduction. Measurement of static lung volumes may be essential for accurate interpretation of volume-dependent pulmonary mechanics, such as lung compliance, resistance or forced expiratory flows, as well as for defining normal lung growth. The most common abnormality of lung volume during infancy and early childhood is associated with airway obstruction, wherein both hyperinflation and/or gas trapping result in elevated values of FRC.

Lung volume measurements in this age group have primarily been undertaken during tidal breathing, *i.e.* FRC using either plethysmographic or gas dilution/washout techniques. With the raised volume technique it is now possible to calculate quasi-values of "TLC", "expiratory reserve volume" and "RV" [38].

Plethysmographic assessments of functional residual capacity. Assessment of static lung volumes in children aged 3–5 yrs are generally limited to those that can be obtained using one of the gas dilution or washout techniques, as they will rarely tolerate breathing against the shutter.

Plethysmographic assessments of FRC are, however, well established in children aged 0–2 yrs [14, 38] and have been used in both clinical [40, 48] and epidemiological research [46].

Functional residual capacity using gas dilution or washout techniques. Apart from the differing measurement conditions discussed above and the need to miniaturise the equipment, methods of assessing FRC by gas dilution or washout are much the same in infants as in older subjects. Details of equipment specifications and techniques for infants and preschool children have been published [13, 23].

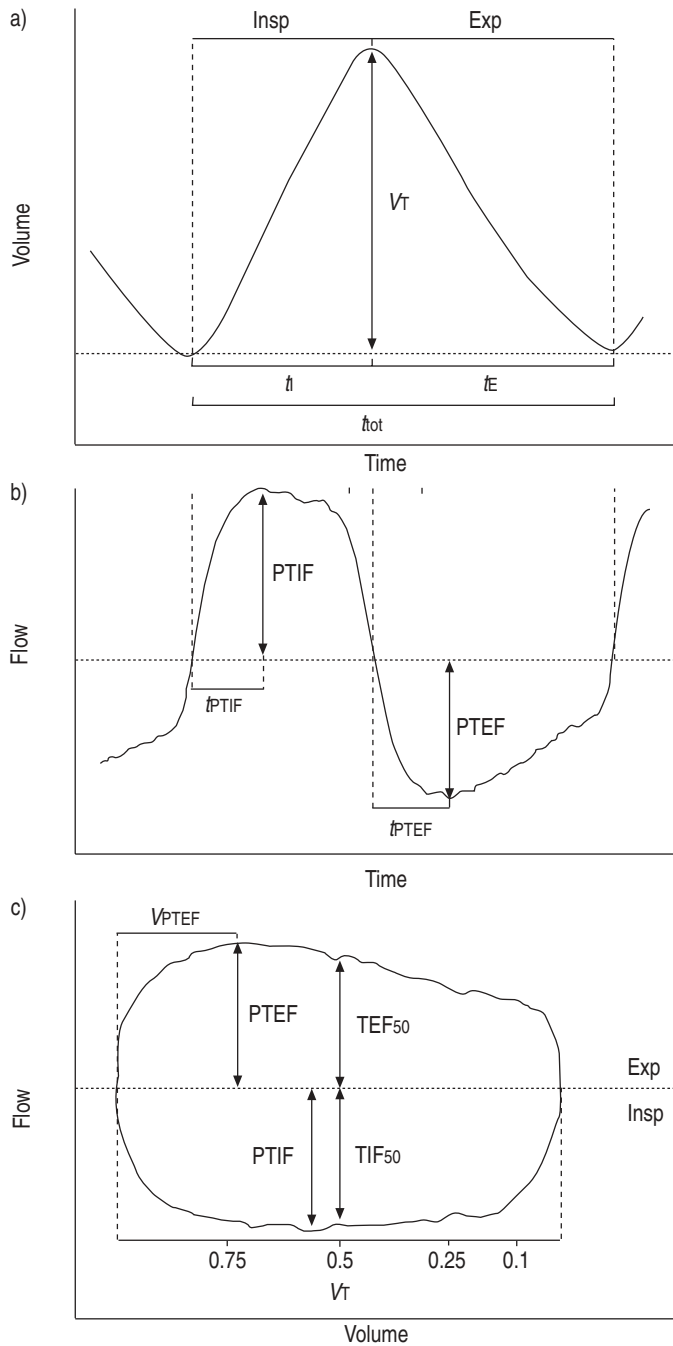


Fig. 7. – Graphical presentation of the relationship between a) tidal volume and time; b) tidal flow and time; and c) tidal flow and tidal volume. Insp: inspiration; Exp: expiration; V_T : tidal volume; t_I : inspiratory time; t_E : expiratory time; t_{tot} : total time of one breathing cycle; $PTIF$: peak tidal inspiratory flow; $PTEF$: peak tidal expiratory flow; t_{PTIF} : time to peak tidal inspiratory flow; t_{PTEF} : time to peak tidal expiratory flow; V_{PTEF} : volume to peak tidal expiratory flow; TEF_{50} : tidal expiratory flow at 50% of tidal volume; TIF_{50} : tidal inspiratory flow at 50% of tidal volume.

During recent years, there has been increasing emphasis on the use of washout techniques in infants and young children, using either the bias flow nitrogen washout technique, which is based on a mixing chamber technique [13] or the multiple breath gas washout (MBW) technique. The latter measures breath-to-breath changes in gas concentration during the washout of an inert gas and provides information on both lung volumes and ventilation distribution (see below) [78, 79]. Equipment designed for older subjects can often be adapted for use in children, provided care is taken to minimise deadspace of the circuitry.

Multiple-breath inert gas washout. The MBW test is performed during tidal breathing. The original test was the N₂ MBW test, using 100% O₂ for the washout, where washout of N₂ is monitored after inspiring 100% O₂. This is a valuable and simple technique for use in preschool and older children. The use of 100% O₂ may, however, alter tidal breathing patterns in young infants and is therefore less suitable in this age group, particularly if measures of ventilation inhomogeneity are required. A nonresident inert marker gas, such as Helium (He) or Sulfurhexafluoride (SF₆), may be used instead. The wash-in phase consists of the subject breathing a gas mixture containing the tracer gas through a facemask until equilibration is achieved throughout the lungs. The gas supply is then disconnected during an expiration so that "washout" can commence with the subject breathing room air until the end-tidal tracer gas concentration is <1/40th of the starting concentration. The gas concentration and flows are measured continuously at the airway opening. From such a washout, both the FRC and indices of ventilation inhomogeneity (see below) can be calculated [78, 79]. Since the MBW technique simply requires the child to breathe tidally through a facemask or mouthpiece attached to a flow meter and gas analyser, it is eminently suitable for subjects of all ages, from birth to old age.

With their rapid respiratory rate and higher ratio of tidal volume/FRC, wash-in and washouts are generally much faster in this age group, both phases of the technique being completed within 1–3 min in healthy subjects (the faster times being observed in infants) and within 5 min in those with airway disease.

Disadvantages of the MBW or gas dilution/washout techniques include the fact that they only measure the readily ventilated gas volume, and may require prolonged washout in those with severe disease, especially in older subjects. However, these techniques are suitable for bedside measurements, can be undertaken at all ages and can provide simultaneous assessments of gas mixing indices.

Gas mixing efficiency

The use of the MBW to assess gas mixing efficiency or ventilation inhomogeneity has only been used intermittently in infants and young children [80, 81]. Indices of ventilation inhomogeneity have been shown to be increased in patients of all ages with respiratory disease. MBW seems a more sensitive method of detecting early changes in lung function among infants and children with cystic fibrosis than conventional techniques [51, 79, 82]. A further advantage of this method is that gas mixing efficiency remains remarkably stable throughout life, facilitating improved discrimination between health and disease. There are as yet no guidelines for standardised measurements of ventilation inhomogeneity in infants, but the use of the technique in preschool [51] and school-aged [83, 84] children has recently been described in some detail.

Diffusion technique

The passage of gases across the blood-gas barrier in the alveoli can be described by the diffusion capacity [85]. Recommendations for standardised measurements in adults and older children have been published [86], but recent guidelines for younger children are lacking. Paediatric diffusion capacity measurements have been recently reviewed [87]. For children who cannot perform the single breath manoeuvre or who have a lung volume <1.5 L, a rebreathing method can be used where the decay of CO is monitored continuously in a closed system while the child breathes quietly (fig. 8, [88]).

Indications for assessment of diffusion capacity in children include monitoring during and after chemotherapy or irradiation, diagnosis and monitoring of interstitial lung disease, and monitoring for pulmonary bleeding disorders. One important limitation of diffusion measurement is unreliability in the case of severe airway obstruction due to inadequate time for equilibration of the gases in the airways. At reduced lung volume, diffusion per unit lung volume increases and this may lead to erroneous interpretation of data in children with restriction of chest movements. In that case, the use of appropriate reference values, obtained at the relevant lung volumes, is essential. Falsely high diffusion may be found due to the presence of blood in the airways and alveoli, or in the case of relative hyperperfusion.

Noninvasive monitoring of inflammatory markers

In the last decade new, rapid and simple techniques have been developed to assess inflammatory markers in exhaled air, which are especially attractive for paediatric pulmonology. The technique for measuring exhaled nitric oxide (eNO) in older children has been well standardised [89].

Measurement of exhaled nitric oxide

The most accessible and easy marker of airway inflammation in allergic asthma is the fractional concentration of Nitric Oxide (FE_{NO}) in a sample of exhaled gas. Practical



Fig. 8. – Rebreathing method in a closed system for measurements of diffusion capacity during quiet breathing.

recommendations and suggestions for measuring FE_{NO} in children are available [89], the choice of method depending on the age and cooperation of the child.

School age children

Single breath on-line measurement. The single breath on-line (SBOL) method is considered the preferred method for cooperative subjects, and is generally applicable in children aged >5 yrs. The child should be seated comfortably and encouraged to breathe quietly for ~ 5 min. The child inhales to near-TLC and immediately exhales at a constant flow of $50 \text{ mL}\cdot\text{s}^{-1}$ until an NO plateau of at least 2 s can be identified during an exhalation of at least 4 s. The exhalate is sampled continuously and fed into a chemiluminescence NO analyser. The inspired gas should contain minimal NO (<5 ppb). The expiratory pressure should be maintained between 5 and 20 cmH_2O to close the velum. This is necessary to avoid contamination with nasal gas, which has a high NO concentration. Repeated exhalations (three which agree within 10% or two within 5%) should be performed with at least 30 s intervals, and mean NO recorded [89]. A target expiratory flow of $50 \text{ mL}\cdot\text{s}^{-1}$ has a good reproducibility and discriminatory power in children [90, 91]. The SBOL technique may be difficult in preschool children who often have difficulties in maintaining flow or pressure within the required limits [92–94]. Audiovisual aids to facilitate inhalation to TLC and control of expiratory flow, together with the use of dynamic flow restrictors that allow the child to exhale with a variable mouth pressure while maintaining a constant expiratory flow, are helpful [94]. Dynamic flow restrictors are simple manual or mechanical devices that vary their resistance depending on the forced expiratory pressure and their use is highly recommended in children.

Off-line method with constant flow and dynamic flow restriction. When there is no analyser available, exhaled gas samples can be obtained and analysed later. Such exhaled air samples are stable for up to 9 h after collection, and can be transported to the lab. The child blows through a mouthpiece into a NO-inert balloon. Nasal contamination is prevented by exhaling through a resistance that generates an oral pressure of at least 5 $\text{cm H}_2\text{O}$ to close the velum [92, 93]. The gas is collected in inert Mylar or Tedlar balloons. Wearing a noseclip and breath holding potentially affect FE_{NO} and are not recommended [95]. Flow standardisation improves the reproducibility of off-line methodology. With identical flows, the off-line results are similar to those of on-line methods in school children and adolescents [96]. A major improvement in off-line collection can be expected from the incorporation of a dynamic flow restrictor in the collection system, which is feasible in children as young as 4 yrs [97]. It is recommended to use flows of $50 \text{ mL}\cdot\text{s}^{-1}$ for both off-line and on-line collection [89].

Alternative methods for pre-school children and infants

On-line measurements: In children aged 0–2 yrs there is limited experience with on-line tidal NO measurements and practical recommendations and suggestions for measuring FE_{NO} in preschool children and infants are lacking. Measurements have been performed during quiet, regular tidal breathing. Expiratory air collected *via* a facemask covering nose and mouth (mixed air) is contaminated by ambient NO and NO from the nose. However, such measurements have been shown to correlate with values obtained through oral breathing. FE_{NO} may be measured on-line during spontaneous breathing in children aged 2–5 yrs while the expiratory flow is adjusted by changing the expiratory resistance. Sources of variability include the characteristics of the breathing pattern, expiratory flows, and the level of inflation. FE_{NO} measured during spontaneous breathing do not

equate SBOL measurements [98], and separate characterisation is required, including definition of normal values in healthy children. The development of hand-held miniaturised NO analysers will likely contribute to the use of this test.

Off-line measurements. Exhaled air can be collected during tidal breathing *via* a mouth piece or a facemask which are connected to a non-rebreathing valve that allows inspiration of NO free air to avoid contamination by ambient NO. Exhaled breath samples are collected into an NO-inert bag fitted with the expiratory port once a stable breathing pattern is present. Methodological issues need to be resolved with all these approaches before these techniques can be recommended for routine use in infants and preschool children

Breath condensate. Cooling of exhaled air causes condensation of water vapour. Breath condensate can be analysed for the presence of inflammatory mediators and other putative markers of inflammation, among which are hydrogen peroxide (H₂O₂), leukotrienes (LT), prostanoids, thiobarbituric acid reactive products, and metabolites of nitric oxide. The methodology for these measurements has not been standardised.

H₂O₂ is produced by inflammatory cells and pulmonary macrophages, and elevated levels have been found in breath condensate of cigarette smokers [99], and in subjects with respiratory disease [100–102]. In adult asthmatic patients, the H₂O₂ concentration in breath condensate correlates with sputum eosinophilia, but not with hyper-responsiveness [103]. Exhaled H₂O₂ seems to respond to antibiotic treatment in exacerbations of airway infection in cystic fibrosis [102]. Reference ranges for exhaled H₂O₂ have been published for school-aged children [104].

Condensate can be obtained by passing exhaled air through a cold tube, the material of which should be appropriate for the retrieval of the substances under examination (*e.g.* glass in the case of H₂O₂, teflon for cysteinyl LTs). Various types of glass tubes or vessels have been used [100, 101, 105]. Cooling can be accomplished by countercurrent circulating ice water in a double jacketed tube. Alternatively, condensate can be obtained by blowing air through a glass vessel that is placed in liquid nitrogen, capturing water vapor in the exhalate as ice on the walls of the vessel [105]. Frozen condensate can be stored until analysis depending on the substance of interest. Its H₂O₂ content remains stable for at least a month [104].

Airway responsiveness to bronchodilators and bronchoconstrictors

Assessment of the bronchodilator response is one of the most important clinical investigations performed in older children and adults. The response to bronchoconstricting agents is less frequently examined and such measurements do not play a central role in clinical management. They may be useful for confirming or excluding a diagnosis of asthma in older subjects but the role of such assessments during the first five years of life is less clear, due to the difficulty in both performing and interpreting these tests and, until recently, the lack of available tests for use in preschool children. The effectiveness of bronchodilators in wheezy infants remains controversial, reflecting the fact that, in many infants who wheeze, the reduction in baseline airway function is not due to reversible bronchoconstriction, but transient conditions associated with diminished airway patency [41, 106]. In asthmatic children, the degree of bronchodilator response appears to be age related, increasing from minimal or absent below 18 months of age, till well established by 8 yrs of age [4]. It should be noted that many healthy preschool children also demonstrate a significant response to bronchodilators. Responsiveness to

bronchoconstrictors in infants may result from anatomically small airways or increased smooth muscle tone, from relatively thicker airway walls, decreased chest wall recoil or increased airway wall compliance. Together with the difficulties in estimating the dose of agonist delivered to the lung, such factors make it virtually impossible to determine age-related changes in bronchial reactivity during the first few years of life [107]. Bronchial challenge tests are described in more detail in Chapter 8.

Methodological issues

Important issues to address in the assessment of airway responsiveness include the technique used to assess the change in airway function, the agent used, the dosage and delivery efficacy of aerosol, quantification of the airway response, and the potential clinical implications of the test result. Routine tests for assessment in older children are spirometry and plethysmography. In infants, most studies have used the partial or raised volume RTC technique. Spirometry has been used in preschool children, but because of its demanding nature this is usually limited to older children [108]. Commonly used tests for preschool children include the interrupter technique, forced oscillation or plethysmographic assessments of specific resistance, or more indirect methods [108–111]. Technical and physiological problems can influence interpretation of airway responsiveness in early life. Bronchoconstrictor-induced changes in FRC may result in paradoxical changes in $V'_{\max\text{FRC}}$ and in underestimation of airway responsiveness, whereas failure of rapid pressure equilibration during airway occlusions may invalidate results from the interrupter or occlusion techniques.

Choice of provocative stimuli and mode of administration.

Histamine and methacholine are the most commonly used direct-acting agents, whereas adenosine monophosphate and hypertonic saline have been used to provide a more indirect and more physiological stimulus. Cold or dry air challenges have been used in preschool children. Aerosol output and lung dose vary according to characteristics of the nebuliser and the drug, the inspiratory volume, nasal *versus* oral inhalation and the breathing and flow patterns. If the inspiratory flow is greater than nebuliser flow (as is common above 6 months of age), the individual will entrain air that does not contain aerosol, thereby lowering aerosol concentration [4]. However, because lung deposition increases with age, a relatively constant dose is probably administered over the paediatric age range. The dose of nebulised salbutamol/albuterol has commonly been 2.5 mg and, when using pressurised metered dose inhalers with a spacer, the dose varies between 400 and 800 mg.

Evaluation of response

There is no consensus on how to evaluate bronchodilator responsiveness in an infant or young child. Different approaches include: 1) comparison of the best pre and post values; 2) comparison of the pre and post mean values from several replicates; and 3) definition of a specific pre-post change for the individual based upon the variability of the measurement in the population. The assessment of the within-subject variability between occasions in the absence of any intervention is needed to correctly interpret such tests [112]. When using forced expiratory flows to assess airway responsiveness in infants, the provocative concentration of the agonist to produce a 30% reduction (PC₃₀) from baseline in $V'_{\max\text{FRC}}$ or MEF₂₅ (FEF₇₅) has been used. This decrease exceeds

the intra-subject within test variability of the measurement and is frequently associated with a change in the flow volume curve from convex to concave [42].

Interpretation of lung function results in infants and children

Within an individual infant or child, the clinical usefulness of any lung function test will always be enhanced if serial measures can be undertaken rather than a single assessment, and if the choice of test is based on the question to be answered, clinical reasoning and a knowledge of the suspected underlying pathophysiology, rather than simply on the equipment that happens to be available in any given centre. Given the marked influence of factors such as preterm delivery, intrauterine growth retardation, sex, ethnic group and maternal smoking during pregnancy, it is particularly important to take a careful history from the parents when performing such tests during early life.

Reference equations

Reference equations are essential to express pulmonary function in relation to that which would be expected for healthy children of similar age, sex, body size and ethnic group; to characterise and monitor disease severity; to expand knowledge regarding growth and development; and to study mechanisms of normal and abnormal function and the natural history of disease. The addition of age as an independent variable may be particularly important to optimise reference equations during the pubertal growth spurt [113–115], whereas separate reference equations, based on arm span and or ulna length, are required for children in whom height cannot be measured accurately (*e.g.* those with progressive scoliosis and/or neuromuscular disease) [116–119].

As a result of secular changes in both the age at which puberty commences [120] and final height attained [121], regular updating of reference equations is required. Additional trends in predicted values can also occur due to alterations in equipment and protocol [15]. The choice of reference equations directly influences the interpretation of paediatric lung function data and this can have a significant impact on patient care and research [113, 114, 122].

Most lung function data are normally distributed or can be transformed to a normal distribution, such that 90% of "normal" values are found within the range -1.64 and $+1.64$ SD (with 95% within -1.96 and $+1.96$ SD). When studying adults, values outside these ranges are considered "unusual" or "abnormal". In paediatrics, lung function variables of healthy subjects and those with respiratory symptoms and/or disease often overlap to such an extent that a "normal" lung function parameter does not exclude disease. Clearly abnormal lung function parameters will, however, often – but not by definition – be associated with symptoms and disease.

Z scores, or standardised deviation (SDS) scores, are defined as: $Z = (\text{observed value} - \text{predicted value}) / \text{RSD}$, where RSD is the residual standard deviation of the reference population. Z scores are by definition normally distributed with a mean of 0, and RSD of 1. Hence, the Z score indicates how many SDs an individual or group is below or above predicted for any given parameter. Z scores indicate how likely a result is to occur within a "normal population" and how far removed the result is from that predicted, having taken the natural variability of that parameter into account; they are useful for tracking changes in lung function with growth or treatment, and allow comparisons of various lung function results from different techniques. Several recent publications have reported Z-scores that can be used in infants and young children [26, 35, 61, 123]. It is particularly

important to avoid "back extrapolation" of spirometric reference data collected in older children and adults as these will generally underestimate predicted values in the under fives, resulting in loss of sensitivity with which to detect changes due to disease. This is of considerable practical importance, since most commercially available equipment will automatically default to pre-selected (or factory loaded) prediction equations based on adult data. When selecting reference data with which to interpret paediatric lung function results it is essential to check how appropriate those data are [124], including whether:

- the same equipment, technique, and methods of analysis were used;
- a comparable and sufficiently large population was studied, with even distribution of age/body size;
- raw data are available for inspection;
- appropriate statistical techniques were used. It is of practical importance to agree on the choice of reference equations on a national level and to aim for regular updated reference values for that specific population, since evaluation of medical treatment and study results heavily depend on that choice.

Conclusions

During the past decade there has been remarkable progress in the field of infant and preschool lung function testing, with measurements once thought impossible to obtain below the age of 5–6 yrs now being performed regularly in children as young as 3 yrs. Commercially available equipment and international recommendations are now available for most routine infant lung function tests. Forced expiratory manoeuvres can be performed over the full lung volume range throughout infancy and the preschool years, while noninvasive assessments of gas mixing efficiency that are applicable from birth to old age offer the possibility of detecting early changes in airway function in children with respiratory disease. Similarly, the development of reliable and child-friendly techniques to assess inflammatory markers in exhaled air has markedly improved the possibilities of monitoring airway inflammation in asthma in recent years, and these techniques may also have applications in other respiratory diseases. The potential prognostic value of such tests within individual subjects is as yet unknown, since it is only during the last few years that more routine assessments of lung function have been possible throughout the preschool years. Longitudinal studies are currently being undertaken in infants and preschool children with a range of respiratory diseases. Interpretation of such data will require similar longitudinal measurements to be performed among healthy children from birth to school age.

Lung function testing in infants and young children will, nevertheless, always present a challenge and it is therefore essential that the purpose of any test is clearly defined at the outset and that dedicated operators with the necessary expertise and patience are available to undertake and interpret such measurements. Despite its vital role in clinical and epidemiological research, given the need for sedation, the specialised equipment and the difficulty in repeating measurements at frequent enough intervals, it is unlikely that lung function testing will ever gain a routine place in the clinical assessment of infants with respiratory disease. By contrast, provided guidelines and standardised protocols can be developed that incorporate appropriate quality control criteria for young children, together with reliable reference data and information regarding the relative sensitivity and specificity of the various tests in differentiating children with and without respiratory disease, lung function tests in preschool children could soon assume a similar role to those used in their school age counterparts (in table 1 the feasibility of the various tests are summarised). To achieve this goal, continuing international collaboration will be

Table 1. – Illustrates the feasibility of various techniques according to (developmental) age. Age range listed is rough indication

Technique	Preterm infants children 0–2 yrs	Children 2–3 yrs	Children 3–6 yrs	Children 6–18 yrs
Tidal breathing	X	X	X	X
Respiratory mechanics (R_{rs} , compliance, time constants)	X	X	X	X
Partial and raised volume RTC technique (MEFV curves)	X			
Spirometry (MEFV curves)			X	X
PEF			(X)	X
R_{aw}	X			X
sR_{aw}	X	X	X	X
R_{int}	(X)	(X)	X	X
FRC (plethysmography)	X			X
FRC (helium)	X	(X)	X	X
Forced oscillation	X	(X)	X	X
TLC and RV	X (composite)			X
Multiple breath gas washout: gas mixing efficiency	X	(X)	X	X
Exhaled NO: single breath on-line			X (5–6 yrs)	X
Off-line method with constant flow and dynamic flow restriction			X (4–6 yrs)	X
Breath condensate				X
Diffusion technique			X	X
Comments	Spontaneous sleep or sedation needed	Passive/minimal cooperation, careful timing needed	Some active cooperation possible	Full cooperation possible

R_{rs} : respiratory resistance; RTC: rapid thoraco-abdominal compression; MEFV: maximal expiratory flow volume; PEF: peak expiratory flow; R_{aw} : airway resistance; sR_{aw} : specific airway resistance; R_{int} : interrupter resistance; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; Brackets: measurements may be feasible but validity not firmly established and/or likely success rate relatively low.

required together with input from manufacturers to ensure that the available equipment and software is optimised for this very important age group.

Summary

- Measurements of ventilatory function can be carried out in children of almost all ages, except between 2–3 yrs of age, which remains a very difficult age group to assess.
- The type of measurements that are feasible strongly depends on developmental age of the child, always requiring considerably more time and effort than measurements in adults
- Methodological guidelines exist for most measurements in infants and school-children, and are being developed for preschool children
- It is strongly recommended to work according to published guidelines, and to choose appropriate reference equations
- Reliable reference data need to be established for young children aged <7 yrs. Prediction of values for such children should never be based on those extrapolated from older subjects.

Keywords: Infants, preschool children, respiratory function tests.

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