Applied physiology: lung function testing in children

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Summary Recent developments in the techniques available to measure lung function in children have greatly improved our understanding of lung development in both health and disease. In everyday clinical practice, lung function tests can provide objective information about the severity and progression of disease and the response to treatment. Although spirometry remains the most useful and widely used test, newer techniques such as specific airways resistance (sRaw) and Rint (resistance measured by the interrupter technique) now allow children who are too young to co-operate with spirometry, to be tested. This is of great importance as it is increasingly recognized that many chronic respiratory illnesses in older children and adults have their origins in early life.

In this paper we describe the basic physiology of some standard tests and some of the newer tests which are increasing our understanding of lung disease.

Introduction

Pulmonary function testing is an increasingly important part of the assessment of lung disease in children. These tests are a sensitive and objective way of detecting and measuring the severity of lung dysfunction, of monitoring the progress of disease, and of assessing treatment. Lung function tests allow distinction between obstructive and restrictive disorders and indicate whether obstruction is reversible or fixed. They can help predict prognosis in progressive disorders such as cystic fibrosis, myopathies or scoliosis.

Lung function tests are not a substitute for a thorough history and examination, or for other investigations, but they are a valuable addition.

They are rarely diagnostic, although asthma is an exception. Changes in lung function often precede clinical features. Serial measurements are more informative than a single test in detecting worsening disease or response to treatment. The results must be compared with normal values for children of similar age, height, race and sex. There are comprehensive guidelines to ensure standardized performance and interpretation. If we are to be able to interpret lung function tests, we need to understand the physiological basis of the tests we request.

Age and lung function

In healthy individuals over a wide range of ages many indices of respiratory function remain remarkably constant if corrected for body size,
reflecting the close relationship between respiration and the body’s metabolic needs. Compared with adults, young children have more compliant chest walls and an increased reliance on diaphragmatic breathing. Their smaller airways and lower end-expiratory lung volumes result in a tendency to airway closure, peripheral airway obstruction and higher airways resistance. To counteract this and maintain airway patency, infants reduce their expiratory time by breathing quickly and increase their end-expiratory pressure by laryngeal braking.

From birth to 3 years of age, lung growth is by a 10-fold increase in alveolar numbers. After this, lung volume increases by alveolar enlargement. Tracking of airway growth occurs and infants born with small airways are likely to have lower expiratory flows throughout childhood. The growth of the airways does not parallel that of the air spaces (dysynapsis). Until puberty, girls have larger airways than boys: after puberty this ratio is reversed. Lung growth parallels skeletal growth in girls but continues for 2–3 years after skeletal maturity in boys. The effect of puberty on lung growth is poorly understood.

Because of the level of co-operation required, many tests used in adults cannot be performed in children below the age of 7 or 8 years. Until recently, measuring lung function in infants was restricted to research laboratories. Tests are performed with the child asleep in the supine position breathing through an airtight face mask, and often require sedation. As breathing patterns and end-expiratory lung volumes vary greatly in rapid eye movement (REM) sleep, the need for sleep or sedation limits the reliability of the results obtained. Also, as nasal resistance comprises 50% of total airways resistance, small changes in lower airways resistance may be unrecognized when measurements are taken using an oro-nasal mask.

With newer tests, more sensitive equipment and agreed standards, there has been a rapid expansion of infant tests, which have greatly aided our understanding of lung development in both health and disease in early life. Newer techniques, which require only passive co-operation rather than active co-ordination from the child, now allow lung function tests to be performed in the previously uncharted period between late infancy and the age of 6–7 years.

Types of lung function tests

Most tests are in one of three major categories:

- measurements of lung volumes;
- measurements of air flow and airway resistance; and
- measurements of gas exchange, gas mixing and diffusion.

As the most common lung diseases in children affect airway function, spirometry and other tests of airway calibre and function are the most widely used tests. Lung volume measurements are less commonly performed but give valuable extra information. Apart from blood and transcutaneous gas analysis, tests of gas exchange are rarely performed in paediatric clinical practice and are not discussed further here.

Measurements of lung volumes

The volume–time plot in Fig. 1 shows the major subdivisions of lung volume. The subject starts with normal tidal breathing and then takes as big a breath in as they can, to maximally fill the lungs. They are then asked to blow out for as long as they can and then resume tidal breathing. The tidal volume (VT) is the volume of air expired after each normal breath. The total lung capacity (TLC) is the volume of gas in the lungs at the end of maximal inspiration. The vital capacity (VC) is the maximal volume that can be exhaled after a maximal inspiration. It is impossible to completely empty the lungs on expiration because of peripheral airway closure. The volume in the lungs after maximal expiration is the residual volume (RV). The functional residual capacity (FRC) is the amount of air in the lungs at the end of a normal tidal breath. All these volumes are expressed in litres.

Although the VC can be measured with a spirometer, the other lung volumes (TLC, FRC and RV) cannot. They require either a gas dilution technique or plethysmography.
Gas dilution techniques

The child breathes in and out of a closed circuit consisting of a spirometer, a circulating pump, a carbon dioxide scavenger and a device for measuring the concentration of the marker gas, which is usually helium. Oxygen is added to the system during the test to compensate for the oxygen consumed. The volume of the circuit at the start of the test is known (Vsys) and the initial concentration of the marker gas is measured (Ci). As the child breathes into the circuit the gas concentration falls as it is diluted by the air from the child's lungs. When the gas concentrations have stabilized (final concentration, Cf) after 2–4 min, the FRC can be calculated:

\[Ci \times Vsys = Cf(Vsys + FRC),\]

\[FRC = Vsys(Ci - Cf)/Cf.\]

Once equilibration has occurred, if the child breathes in and out fully, the TLC and RV can be derived.

Although this technique is quite simple to perform, it is time-consuming and only valid if there is no leak around the mouthpiece. Gas dilution measures only the parts of the lung in free communication with the airway. If there are poorly ventilated areas of the lung, the marker gas does not equilibrate fully and volumes are underestimated.

Whole body plethysmography

This technique depends on Boyle's law, which states that for a given mass of gas, the product of the volume and the pressure is a constant. By measuring pressure and volume changes during breathing against a closed shutter, lung volumes can be calculated.

The subject sits within a sealed rigid transparent box and breathes through a mouthpiece, which contains a shutter and a pneumotachograph (flow measuring device). After a period of stabilization, the shutter is transiently closed by the technician at the end of a normal tidal expiration (at FRC) and the child is asked to pant for several breaths. As there is no gas flow in or out of the respiratory system, the changes in alveolar pressure produced by panting against the closed shutter are reflected by pressure changes measured at the mouth by a transducer. These changes at the mouth are generated by the respiratory muscles, which rarify and compress the gases within the chest during the respiratory cycle, and which also lead to pressure changes in the plethysmograph. These body-box pressure swings can be converted to changes in lung volume by using a large calibration syringe containing a known volume of air. Once allowance has been made for pressure temperature and saturation and for the dead space of the system, FRC can be obtained rapidly by computer analysis. TLC and RV can also be calculated if a slow vital capacity manoeuvre (maximal inspiration followed by maximal expiration) is performed. Unlike helium dilution, plethysmography measures all the gas in the lung and therefore the volume of gas within the lungs at the end of a tidal expiration is known as the thoracic gas volume (TGV).

Interpretation of lung volume measurements

In restrictive defects, lung expansion is reduced and lung volumes are small. A low TLC is the primary criterion for diagnosis. Restricted function occurs in children with rare lung conditions such as fibrosing alveolitis or hypoplasia, but the pattern is more common in children with disorders affecting the chest wall, such as scoliosis, pectus excavatum or myopathy. VC is also low and there is a characteristic pattern with spirometry (see below). Measuring lung volumes is less helpful in assessing airways obstruction than spirometry, or the other tests of airways resistance described below. However, narrowing of the peripheral airways (bronchi and bronchioles) is often associated with hyperinflation or gas-trapping, the degree of which can be assessed by measuring lung volumes. RV reflects airway closure on expiration and is elevated with airways narrowing. The ratio of RV to TLC (the RV/TLC ratio) is a sensitive and early indicator of hyperinflation in airway disease. There is often an associated increase in the FRC and a reduced VC, whilst TLC is relatively unchanged.

Measurements of air flow and airway resistance

Spirometry

Spirometry is the most commonly performed test of lung function in children. It rapidly provides information about lung volume and airway size. Many children over the age of 5 or 6 years can perform a reproducible forced expiratory manoeuvre. With animated incentive displays on the spirometer, it has been possible to lower the age at which children can perform spirometry.
The child is asked to take a maximal breath in and then to breathe out into a mouthpiece as hard, as fast and for as long as they can so that they empty all of the exchangeable gas volume from their lungs as quickly as possible. The volume of gas expired and the rate at which it is expired are measured using either a spirometer, or a pneumotachograph with integration of the flow signal to obtain volume. There should be three attempts, which agree within 5% to ensure reproducible results.

Presenting spirometry data

Results are presented as a graph and in a numerical table, with the best measures of forced vital capacity, FEV₁ (forced expiratory volume in 1 second) and other expiratory flows being compared to appropriate predicted values. Previously, it was conventional to plot volume (litres) against time (seconds) (Fig. 2a), but plotting flow (litres/second) against volume is more informative (Fig. 2b). The characteristic shapes of such flow–volume curves allow immediate distinction between mild, moderate or severe Airways obstruction and restrictive lung disease.

Patterns of flow–volume and volume–time curves

Normal

The volume–time plot of a healthy child is shown in Fig. 2. The maximal volume expired after a full inspiration is the forced vital capacity (FVC). Normal children exhale over 75–80% of their FVC in the first second. The final part of the volume–time curve is horizontal as no more gas can be exhaled. The forced expiratory flow (FEF₂₅₋₇₅%) is the gradient of the line joining the points on the volume–time curve at 25% and 75% of the FVC. It represents the mean maximal flow in the middle 50% of the vital capacity. The more rapid the expiration, the higher the FEF₂₅₋₇₅%.

With a flow-volume curve, the FVC is plotted on the x-axis and maximal expiratory flow on the y-axis. In healthy subjects, there is a rapid rise to the highest flow (peak expiratory flow, PEF) immediately after the start of expiration, followed by a linear decline in flow as the lung empties. Spirometers automatically measure the maximal expiratory flow when there is 75%, 50% and 25% of the FVC remaining in the lung (F₇₅ (or V₇₅), F₅₀ and F₂₅, respectively).

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**Figure 2** Normal volume–time (a) and flow–volume (b) curves.
It is the physiological properties of the lung parenchyma, the airways and the chest wall that determine the shape of the flow-volume curve. There is a complex interplay between the many dynamic factors, which determine maximal flow during a forced expiration and a detailed description is beyond the scope of this article (see further reading). The first 25–35% of expiration, which includes the PEF and F75, is dependent upon the expiratory effort of the subject, with a poor effort producing misleadingly low values. By contrast, the remaining two-thirds of the flow-volume curve, including F50 and F25, is largely effort-independent. In other words, increasing the force of contraction of the expiratory muscles does not increase expiratory flow, and the maximal flow measured at any point is entirely related to the resistance of the airways. This is because on forced expiration there is dynamic compression of the airways, leading to a reduced calibre and an increase in resistance of the intrathoracic airways.

Obstructive lung disease (airflow limitation)

Spirometry is the most sensitive way to assess narrowing of the intrathoracic airways such as in asthma and bronchiectasis.

Volume–time data and curves

Narrowing of the bronchi or bronchioles limits maximal expiratory flow: the more severe the narrowing the more marked the flow limitation. The FEV1 is reduced, but the FEF25–75% is reduced even more (Fig. 3a). Because of the gas-trapping caused by airways narrowing, the FVC is reduced, but to a lesser degree than FEV1, and so the FEV1/FVC ratio is lower. This ratio is a useful indicator of severity: for example, an FEV1/FVC of 45% indicates severe obstruction, whereas a ratio of 72% indicates mild obstruction.

Flow-volume data

Airways obstruction changes the contour of the FVC (Fig. 3b). The FVC is reduced to a degree that indicates the severity of the dysfunction. Flows measured in early expiration (PEF, F75) are reduced, but later flows (F50, F25), which reflect the function of the smaller, more peripheral airways, are more affected. As a result, the normally linear curve has a scalloped appearance, with increasing concavity towards the x-axis with more severe obstruction.

Reversibility of airways obstruction (bronchodilator responsiveness)

If obstruction is shown, it is important to assess if it is reversible. After baseline spirometry a short-acting bronchodilator such as salbutamol is given. Spirometry is repeated 15–20 min later. A positive response is defined as an increase in FEV1 of more than 0.16 l or 15% from baseline.

Obstructive Airway Disease

Figure 3 In obstructive airways disease, there is a slower rise to FVC on the volume–time trace (a). There is increasing scalloping of the flow–volume curve with increasing degrees of airways narrowing (b). F25 is reduced more than F50, which is reduced more than PEF.
Restrictive lung disease

In restrictive disorders the FVC and expiratory flows are all reduced in proportion. The more severe the restriction, the lower the values. The volume–time and flow–volume curves are a normal shape but proportionately small (Fig. 4). The FEV₁/FVC ratio is normal or above normal because of the increased elastic recoil of the lungs.

Mixed obstructive and restrictive lung disease

Some children display both obstructive and restrictive lung disease. For example, in children with CF and severe lung disease, bronchiectasis causes airway narrowing, and fibrosis or collapse results in a restrictive element.

Airways resistance (Raw)

Traditional measurements of airways resistance (Raw) are obtained using plethysmography. Changes in alveolar pressure (\(P_{alv}\)) during breathing are recorded as pressure changes within the plethysmograph. Raw can be calculated from the ratio between the change in \(P_{alv}\) and the air flow at the mouth. Raw measurements can then be corrected to give a specific airways resistance (sRaw) for the child’s lung volume by measuring TGV. These two-step measurements require the child to pant at a set rate against a closed shutter, and are rarely successful below the age of 8 years.

Specific airways resistance (sRaw)

An alternative method is to determine sRaw is from the slopes of specific resistance loops obtained during tidal breathing (Fig. 5). This single-step method does not require the measurement of alveolar pressure or TGV or the need to pant.

Restrictive Lung Disease

![Diagram of restrictive lung disease](image)

Figure 4 In restrictive lung disease, both the volume–time (a) and the flow–volume (b) curves are proportionally smaller than normal.
against a closed shutter. Reproducible measurements of sRaw can be obtained from children as young as 2 years of age, with success rates of 80% in children aged 2–8 years. Beyond infancy, measurements are independent of the child’s gender, size and age and only minimally influenced by breathing frequency. As with all measurements of airways resistance, they are critically dependent on the compliance of the upper airway. The position of the child’s head, the support of their cheeks and the type of mouthpiece or mask can all influence the results.

Compared with other lung function tests in young children, sRaw is highly sensitive at detecting the response to bronchial challenge or bronchodilator, where it has good within- and between-test reproducibility and can be used to discriminate between asthmatic and control subjects.

The interrupter technique (Rint)

The interrupter technique (Rint) allows airways resistance to be measured easily and repeatably in children as young as 3 years of age. Again, it is based on the assumption that, during transient occlusion of the airway at the mouth, alveolar pressure equilibrates rapidly with mouth pressure. Airways resistance is calculated from the ratio of mouth pressure (measured immediately after occlusion) to airflow at the mouth (measured just prior to occlusion). During a Rint measurement, a pressure time ($P_{m(t)}$) curve is produced following airway occlusion (Fig. 6). The relative contributions from the airways, lungs and chest wall to the measurement depend on how this curve is analyzed. Measurements may be taken in inspiration or expiration, but most authors prefer to use expiratory $R_{int L}$ measurements as these exhibit the least baseline variability and the greatest sensitivity for detecting induced airways obstruction.

Rint measurements may be obtained using plethysmography or portable equipment such as the MicroRint machine (Micro Medical Ltd). Plethysmographic methods require the subject to breathe against a closed valve inside a body box, which may be difficult for young children. Although the MicroRint machine also requires valve closure, children are not separated from their parents and success rates are good. Rint measurements correlate well with spirometry or transcutaneous oxygen levels in healthy children and children with asthma. The correlation between Rint and sRaw is also good, although Rint is less sensitive to changes in airway calibre and is affected more by the resistance of the lungs and the chest wall. Like other measurements of airway resistance, as equilibration of mouth and alveolar pressure occurs more slowly in obstructed airways, Rint may underestimate airways resistance. It is therefore more useful in measuring bronchodilator than bronchoconstrictor responses.

Bronchial challenge testing

Airway hyper-responsiveness (AHR) is the exaggerated bronchoconstrictor response of the airways to one or more stimuli. It is a key feature of asthma and can be assessed using different pharmacological and non-pharmacological agents. These have either a direct (methacholine, histamine) or indirect (cold air, hypertonic saline, exercise, antigen) effect on the bronchial wall. Each method gives slightly different information about the airways, and a positive response to one challenge does not necessarily predict a similar response to another.

The most widely used method of assessing AHR is by direct challenge with histamine or methacholine using a standardized protocol. These agents directly cause bronchoconstriction that is rapidly reversed by a bronchodilator. Methacholine produces fewer adverse effects than histamine and is therefore preferred by many.
Cold air, exercise, hypertonic saline or antigen may also be used. These cause broncho-constriction by an indirect route, involving cellular and neurogenic mechanisms. Although less well established than direct challenges, indirect challenges probably show a closer relationship to a true asthmatic response. This may be particularly important in young children where direct challenge methods can be insensitive or unreliable.

Children differ from adults in size and breathing frequency. These differences influence children’s responses to bronchial challenge and preclude direct comparisons between children of different ages and sizes. The deposition of nebulized drugs varies with age, depositing relatively more drug in their larger airways with smaller children. This may influence both drug absorption and the direct effects of methacholine or histamine on smooth muscle. It may also be important in the way a child responds to cold air. During a standardized challenge, children and adults inhale comparable amounts of methacholine, but children receive much larger doses of drug per kg of body weight than adults, and are therefore more likely to exhibit AHR at a given drug dose. Adult definitions of AHR may over-diagnose AHR in children. This may explain the higher prevalence of AHR in children than adults in many epidemiological studies.

Other lung function tests

Lung resistance and compliance may also be measured with oesophageal manometry. This technique gives a direct measurement of the pleural pressure but is highly invasive and poorly tolerated by most children. Its use is primarily as a research tool. Transcutaneous oxygen monitoring is well tolerated and reproducible. It provides an indirect measure of airway responsiveness and can be used as a stable comparator when exploring new lung function tests in young children. Measurements of exhaled nitric oxide (NO) are used in research as an indication of airway inflammation. NO is found in vascular and airway endothelium and can be induced in inflammatory cells by cytokines and endotoxin. Levels are measured using a photochemical reaction between NO and ozone (chemiluminescence). As NO concentrations in the nose are high, accurate bronchial/bronchiolar NO measurements depend on careful standardization and prevention of nasal contamination.

Further reading