Evaluating the Lung Function of Infants

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In this review we introduce the reader to the basic fundamental features and utilization of an array of laboratory tests, some old and some very new, that are available at present in Israel. Measurements of lung function have been recognized as essential for understanding respiratory physiology and for the clinical assessment of patients with lung disease. Lung function evaluation has been an important diagnostic tool for the past century in adults and, lately, in infants and children. Evaluating lung function in infants is important, not only for clinical reasons but also because of the considerable growth and development of the respiratory system that occurs with associated changes in lung mechanics.

Many pulmonary problems in children are either present at birth or become manifest in the first year or two of life and some cardiac conditions also affect lung function at this age. In adults and older children and even in the preschool age groups lung function is measured using well-standardized equipment and techniques. However, infants in the first 2 years of life cannot cooperate even minimally with tests of lung function and therefore research has concentrated on the development of equipment and techniques that are suitable for infants and require no active cooperation.

Techniques have been developed for the evaluation of lung function in infants that consider the needs for safety and the inability of the infant to cooperate actively in the performance of the tests

Some 60 years ago the late Professor Kenneth Cross and his colleagues began to make objective measurements of ventilation and the control of breathing in newborn infants [1,2] and a few years later the first reliable measurements of the mechanical function of the lungs in healthy and sick infants were made [3]. Since then great strides have been made both in the understanding of respiratory physiology and the development of equipment suitable for performing measurements in infants. The modern approach to lung function testing in infancy has been summarized in a detailed monograph by investigators from the American Thoracic and European Respiratory Societies [4].

Some 5 years ago we reviewed the accumulated experience [5] and suggested four situations in which lung function testing could be helpful in infants:

- the infant who presents with unexplained tachypnea, hypoxia, cough or respiratory distress in whom a definitive diagnosis was not apparent from physical examination and other less difficult investigations
- the infant with severe, continuous chronic obstructive lung disease who does not respond to an adequate clinical trial of combined corticosteroid and bronchodilator therapy
- the infant with known respiratory disease of uncertain severity where there is a need to justify management decisions for research and development.

In this review we shall concentrate on those tests that we and others have been using regularly for the evaluation of lung function in infants almost all of whom were under the age of 2 years. It is recognized that the function of the lungs is not restricted to moving air in and out but includes cardiovascular and metabolic functions, which are not part of this review. Likewise, airway inflammation is a most important feature of lung disease, especially asthma, and the measurement of exhaled nitric oxide collected using respiratory techniques is now available for infants.

WHAT DO WE NEED TO MEASURE AND WHY?

Gas exchange in the lungs of mammals is served by a pump whose function is to bring respired gas into intimate contact with the blood in the pulmonary alveolar capillaries as efficiently as possible. Like any bellows-type of pump the respiratory system has three characteristics that define it mechanically: its volume, the resistance to flow through its tubing, and the stiffness of the material of the bellows. Disease processes that affect lung function in infants can be largely divided into two groups:

- the restrictive lung diseases in which, for whatever reason, the respiratory system (either lungs or chest wall) is too stiff and almost always too small (interstitial lung diseases, engorgement of pulmonary blood vessels, scoliosis)

- The obstructive lung diseases in which the airways are too narrow and their resistance is increased and that is usually accompanied by some trapping of gas in the lungs and an increase in volume.

The purpose of testing various aspects of the mechanical function of the lungs can be summarized as follows:

- to determine whether lung function is normal or abnormal
- to determine whether any abnormality is of the restrictive or obstructive origin
- in obstructive disease, to determine whether the problem is chiefly inspiratory or expiratory and whether the obstruction is primarily in the larger or smaller airways
- to determine to what extent an obstructive abnormality is reversible
- to follow the changes in lung function, whether improving or deteriorating, during the course of a disease or in response to treatment
- for research into lung disease and its treatment.

PRACTICAL PROBLEMS COMPLICATING THE TESTING OF LUNG FUNCTION IN INFANTS

Infants from birth to about 2–3 years of age are unable to cooperate and breathe voluntarily through respiratory apparatus and are therefore required to breathe through a face mask sealed tightly over the mouth and nose for taking measurements. For relatively non-stressful tests during tidal breathing some infants will tolerate the procedure without sedation but for most investigations light sedation is required with an appropriate agent such as triclofos, which imposes limitations as to which infants should be investigated. The fact that infants cannot be expected to perform voluntary maneuvers such as taking a maximum inspiration or exhaling forcefully means that the techniques used have to be different from conventional tests of lung function in older subjects. The severity of the illness may render it very difficult or even unsafe to undertake measurements of lung function under even light sedation. Taking these practical problems into consideration, lung function tests for infants need to meet the following safety and ethical standards:

- the test is likely to contribute meaningfully to the management of the infant
- the test does not expose the infant to any significant risk of harm while recognizing that mild sedation is usually needed
- simple tests that can be performed quickly and yield meaningful results should be used unless there are good reasons to use more complex and lengthy tests.

The determination of maximum forced expiratory flow rates, at low lung volume yields important information on small airway function while lung volume, compliance and airway resistance help in the differential diagnosis

For a complete evaluation of the mechanical function of the lungs we would ideally like to know the lung volume and its subdivisions, the stiffness of the lung tissue or its reciprocal, compliance, and the airway resistance and its subdivisions. The accurate measurement of lung volume and airway resistance requires complicated equipment and techniques that are only available in a few very specialized laboratories in the world, including our own institutions. Nevertheless, it is possible to obtain an understanding of the physiology of the lungs by means of a variety of relatively simple and easy to perform tests.

MEASUREMENTS MADE DURING TIDAL BREATHING

THE SIZE AND SHAPE OF THE TIDAL FLOW-VOLUME RELATIONSHIP

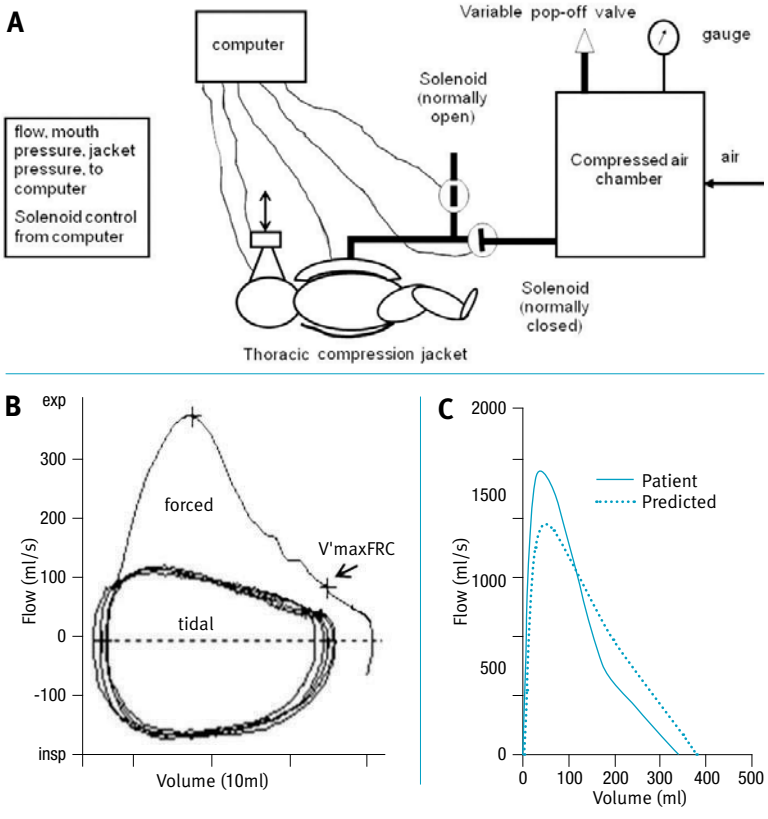
Measurements during tidal breathing only require the lightly sedated or sleeping infant to breathe through a soft-rimmed face mask held firmly in place or sealed to the face with silicone putty to prevent leaks. Appropriate equipment is attached to the face mask, and nowadays the sensors are connected to a computer that provides a record of the volume of each breath, respiratory rate and minute ventilation. If the ventilation is abnormally high (hyperventilation), it is possible to determine whether it is due primarily to a high respiratory rate or whether the tidal volume is also elevated. Additional information can be obtained from the shape of the relationship between the flow and volume of inspired and expired gas during tidal breathing, which is distorted in a characteristic fashion by obstruction of the smaller airways or large, central airways [6]. A number of attempts to quantify such changes have been made, but most investigators agree that the shape of the tidal flow-volume loop, while informative, is difficult to quantify [7,8].

LUNG VOLUME BY GAS MIXING DURING TIDAL BREATHING

Lung volume can be measured by gas dilution during tidal breathing provided there is no leak around the face mask and the infant is breathing regularly for the few minutes needed for the measurement. In the oldest method the infant breathes from a mixture containing a known concentration of inert gas such as helium, and the dilution of this gas by the gas in the lungs enables the lung volume to be calculated. A modern version of this method uses the inert gas sulfur hexafluoride, which the infant breathes through an open circuit [9]. During the wash-in phase the infant inspires a dry air mixture containing 4–6% SF6, 21% oxygen and balance nitrogen, and wash-in is maintained until inspiratory and expiratory SF6 concentra-

SF6 = hexafluoride

Figure 1. [A] Diagram of equipment used to measure forced expiratory flow and volume in an infant. **[B]** Partial forced expiratory flow-volume loops in a wheezy infant. The central loops are the tidal flow-volume (F-V) loops before the application of the thoracic compression ('squeeze') and the outer expiratory loop is the forced expiratory flow-volume loop. The expiratory portion of the tidal F-V loop is flattened and the VmaxFRC (shown by the arrow) is markedly reduced. **[C]** Raised lung volume maximal expiratory F-V loop from the same infant. The FVC of the infant is slightly reduced, peak flow is normal but the flows during the latter part of expiration are lower than predicted.



tions are stable. At this point the SF6 flow is stopped and washout is started using room air until the end-tidal SF6 concentration is less than 0.1%. The functional residual capacity is obtained by dividing the measured expired SF6 volume by the end-tidal SF6 concentration before washout. In addition, the Lung Clearance Index, an index of ventilation inhomogeneity, can be calculated as the cumulative expired volume needed to lower the end-tidal SF6 to a concentration of less than 0.1% divided by FRC, that is, the number of lung volume turnovers needed to clear the lungs from the tracer gas. This test thus provides information on both lung volume and the efficiency of gas mixing and has been noted to provide better information than spirometry where parenchymal involvement is present in diseases such as cystic fibrosis [10]. However, like all gas-dilution methods, the calculated lung volume underestimates true lung volume when there is a significant amount of trapped gas in the lungs or where parts of the lung are very poorly ventilated.

INDICES OF RESISTANCE

There are two methods for estimating the resistance of the total respiratory system (Rrs) during tidal breathing through a face mask. In one method expiration is briefly interrupted by closing a shutter – the respiratory interrupter or Rint technique – and the pressure on the patient side of the shutter is related to the flow at the moment of closure to calculate resistance (resistance = pressure/flow). This method has been used successfully in infants and correlates well with Rrs measured by another method [11]. On the other hand, the agreement with direct measurement of airway resistance by whole body plethysmography has not yet been confirmed [12], probably because both the Rint and Rrs methods measure resistance at only one point in the respiratory cycle and resistance is not constant in sick infants. The other method, the forced oscillation technique, employs small-amplitude pressure oscillations superimposed on the normal breathing. It has the advantage that it does not require the performance of respiratory maneuvers and is well suited for lung function measurement in young children who are willing and able to breath through a mouthpiece [13]. A mathematical model is applied to the oscillating pressure and flow signals from which various parameters related to the performance of the respiratory system can be derived, including an index of airway resistance. The resistance measured by this technique is related to other indices of lung function [14] and is accepted as sensitive and reliable in detecting airway obstruction in preschool children [15]. However, the relationship between the parameters measured by the FOT method and physiologically determined resistance is far from clear in infants.

TESTS REQUIRING FORCED EXPIRATION

PARTIAL FORCED EXPIRATORY FLOW-VOLUME CURVES

Forced expiration has long been used to measure lung function because it gives a good estimate of the severity of any limitation and, moreover, the forced expiratory flow at low lung volume is effectively effort independent and reflects the function of the smaller airways [16-18]. In adults and older children the patient is asked to inhale maximally and then expire completely as quickly as possible through a suitable recording device. Because infants cannot be asked to inspire maximally and then expire forcefully, a simple and practical test of forced expiration suitable for infants was developed some 25 years ago in Israel [19,20]. This technique uses a thoraco-abdominal compression ("squeeze") jacket to obtain data on expiratory flow during

FRC = functional residual capacity

FOT = forced oscillation technique

forced expiration [Figure 1A]. The equipment comprises a jacket wrapped around the chest and abdomen of the infant, inside of which is an inflatable (squeeze) bag attached to a pressure reservoir through a computer-controlled three-way tap. The infant breathes through the face mask and flow-measuring device, and when the computer senses that the infant has reached the end of a normal inspiration the tap is rapidly turned to briefly connect the squeeze bag to the pressure reservoir, which causes the infant to exhale forcibly. This produces a partial PEFV curve [Figure 1B]. The forced expiration is quantified by measuring the forced expiratory flow at end expiration (functional residual capacity) and is termed VmaxFRC. The expected normal value for infants in relation to size has been well established for this parameter [21], although some caution is needed because higher values for normal have been obtained in our laboratory [22]. In diseases associated with obstruction in the smaller airways the VmaxFRC is reduced [Figure 1B] and this test can also be used to monitor the effect of medications. This technique yields important information, requires a minimum of equipment and is undemanding for both the infant and the investigator.

RAISED LUNG VOLUME MAXIMAL EXPIRATORY FLOW-VOLUME CURVES

The PEFV maneuver yields information only within the tidal breathing range. In order to make forced expiration resemble that used in adults the thoraco-abdominal "squeeze' technique has been modified by arranging to first inflate the lungs to their maximum volume (total lung capacity) and then apply the squeeze [23,24]. This results in a complete forced expiration down to the point where no further gas can be expelled from the lungs (residual volume) and the total amount of gas thus expelled forcibly is the forced vital capacity. From this MEFV maneuver [Figure 1C] it is possible to make measurements of parameters exactly analogous to those obtained in adults where forced expiratory flows are reported at specific fractions of the FVC. The advantage of this technique as compared with the simpler partial forced expiratory maneuver is that extra information is obtained on the FVC and the forced expiratory flow rates can be accurately and reproducibly related to the FVC. Studies in normal infants have yielded prediction equations for all the important parameters derived from the raised lung volume forced expiration maneuver [25,26].

The raised volume technique is more complicated than the partial flow-volume technique because the lungs of the infant have to be inflated to TLC. This is usually performed by inflating the lungs to a standard pressure of 30 cm H_2O through the face mask and then simultaneously releasing the inflating pressure and applying the squeeze. Various automated computer-controlled systems have been developed to perform these maneuvers. However, the test can also be performed manually by inflating the lungs with a simple T-piece and pop-off valve arrangement to deliver the pressure and then triggering the squeeze at the moment the inflating pressure is released. It has been suggested that the parameters derived from the inflated maximum expiratory flow-volume tests are more reliable and reproducible than those from the partial expiratory flow-volume test [27,28] but others have found the VmaxFRC to be equally reliable [29]. In our experience we found an excellent correlation between the VmaxFRC and the forced expiratory flow after 75% and 85% of the FVC has been expelled. This suggests that the partial forced expiratory flow-volume test is particularly sensitive to changes in the smaller airways.

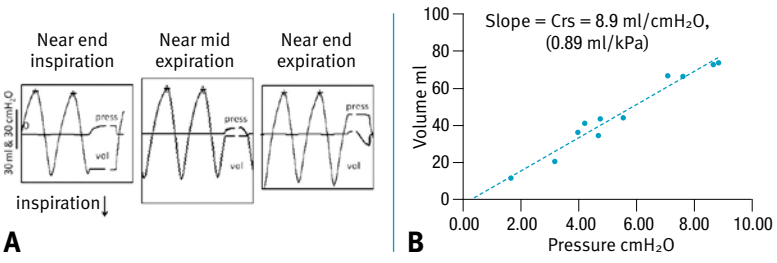
Objective assessments of pulmonary function in infancy contribute to clinical management and improve our understanding of the disease processes

TESTS USING PASSIVE EXPIRATION

TOTAL RESPIRATORY SYSTEM COMPLIANCE AND RESISTANCE

The Herring-Breuer reflex, which inhibits respiration on inflation of the lungs, is much stronger in infancy than in later life. It can be used to cause the infant to relax the muscles of expiration so that the pressure measured at the mouth during a brief occlusion of the airway reflects the elastic properties of the combined lungs and chest wall. The subsequent expiration on release of occlusion is passive and reflects the mechanical properties of the respiratory system comprising the lungs and chest wall [30]. For these tests the infant breathes through a face mask and recording apparatus, as used for tidal breathing, and the exit from the apparatus is briefly occluded at different lung volumes during expiration. The volume at the moment of occlusion above lung volume at the end of normal expira-

Figure 2. [A] Three occlusions at different lung volumes showing how the pressure recorded at the mouth is related to lung volume. The interruptions in the traces show where the computer sampled the result. **[B]** Plot of volume above resting lung volume plotted against pressure recorded at the mouth for 11 points from the same infant. The slope of the line gives the compliance of the respiratory system, Crs, which was 90% of the predicted normal.



PEFV = forced expiratory flow volume
MEFV = maximal expiratory flow volume
FVC = forced vital capacity
TLC = total lung capacity

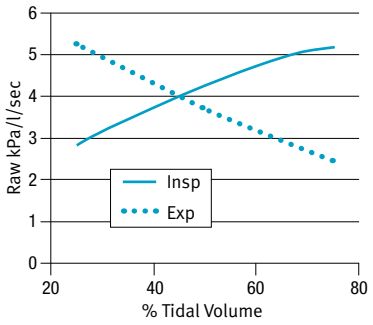


Figure 3. Airway resistance (Raw) plotted against lung volume during tidal breathing in an infant with both upper airways obstruction (rising inspiratory resistance) and small airways obstruction (rising expiratory resistance).

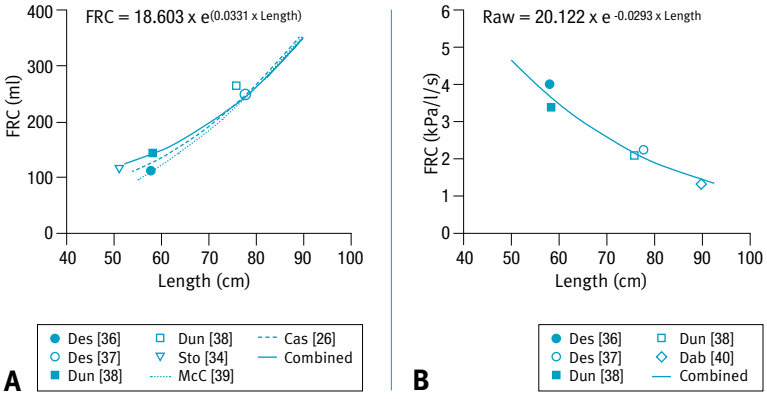


Figure 4. [A] Relation between FRCpleth and length. The origins of the data points and regression lines are indicated by the abbreviation of the name of the first author and the citation in the list of references. Combined = mean of the regression lines from references 26 and 39. **[B]** Relation between Raw and length. The origins of the data points are indicated by the abbreviation of the name of the first author and the citation in the list of references. Combined = regression based on the five data points.

tion and the pressure at the mouth is recorded. Examples of occlusions at different lung volumes are shown in Figure 2A. Plotting data obtained from a number of occlusions yield a graph in which the slope, termed Crs, indicates compliance of the respiratory system [Figure 2B]. When the occlusion is made in early expiration, the subsequent expiratory flow when plotted against the expired volume is linear after the initial portion of expiration and reflects the time constant of the respiratory system from which Rrs can be determined, since the time constant is the product of compliance and resistance. These tests are very simple to perform with a computer program to analyze the data and yield a good estimate of compliance, which is important in differentiating between lung diseases and between lung and cardiac disease. Unfortunately, the assumption that Rrs can be estimated as a single value is only true in the absence of significant small airways obstruction [31].

Crs = respiratory system compliance
Rrs = respiratory system resistance

WHOLE BODY PLETHYSMOGRAPHY

LUNG VOLUME (FRC) AND AIRWAY RESISTANCE

For over 50 years the gold standard for the measurement of lung volume and airway resistance in all subjects has been the whole body plethysmograph [32,33]. This comprises a closed chamber in which the infant lies and breathes through a respiratory circuit attached to a face mask held in place with silicone putty. By measuring the ratio of mouth pressure to chamber pressure during a brief occlusion of the airway by a remotely controlled tap it is possible to calculate FRC. By switching the taps to allow the infant to breathe warmed and humidified air from a very compliant bag within the plethysmograph, the ratio of chamber pressure to the flow rate during breathing yields Raw.

The whole body infant plethysmograph is a complicated piece of equipment and requires skill and experience for its correct operation but has been used successfully for studies in healthy and sick infants for many years [34]. Modern computer techniques have greatly simplified its use and, moreover, the plethysmograph can provide continuous measurements of resistance throughout the respiratory cycle [35]. A plot of resistance against tidal volume shows how Raw changes in infants in whom pulmonary disease causes resistance to rise during inspiration or expiration [Figure 3]. Despite the difficulties in studying healthy infants, large amounts of data have been accumulated over the years which allow us to define the relationship between FRCpleth, Raw and length in the first year or two of life. A summary of the currently available data taken from published studies on FRCpleth [26,34,36-39] and Raw [36-38,40] together with suggested prediction equations is shown in Figure 4. The rapid increase in lung volume and decrease in airway resistance occurring in infancy as seen in Figure 4 emphasizes the potential harmful effects of disease in this age group.

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Raw = airways resistance
FRCpleth = FRC by plethysmography

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