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SERIES: LUNG FUNCTION IN PAEDIATRICS (III)

Lung Function Testing in Infants

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The neonatal period and the first year of life are times in which a significant amount of disease is caused by lung disorders related to a number of age-related factors. These include the lack of lung development due to preterm birth, the effects of intensive care treatment on the immature lung and early life infections with highly pathogenic agents including respiratory syncytial virus. Prenatal factors such as impaired foetal growth and maternal smoking in pregnancy can also have significant effects on lung function both in the immediate neonatal period but also throughout the first year of life and beyond.[1] It has become increasingly recognised that lung pathology in infancy and early childhood is an important predisposing factor in the aetiology of long-term lung diseases in later childhood and possibly into adult life.[2]

The measurement of lung function in the neonatal period and during infancy has required the development of equipment specially adapted to the physical size of the patient and the unique physiology of breathing throughout this early phase of life. During the latter part of the 20th century specific tests to measure respiratory mechanics and to enable forced expiratory manoeuvres using the forced expiratory technique were developed.[3] In more recent times forced inspiration to maximal lung capacity has also been developed.[4,5] Some lung function tests can be performed reliably and reproducibly in unsedated preterm neonates.[6] An important factor in measuring lung function after this period and especially during the first year of life is the need to sedate the patient in order to obtain cooperation during the specific respiratory manoeuvres mentioned above. Currently, chloral hydrate is the most frequently used agent. It has been shown to be safe and effective and also not to affect the results obtained as compared to unsedated infants.[7]

Standardisation of techniques and the establishment of normal values has been another major area of work in this field. The establishment several years ago of a joint European Respiratory Society/American Thoracic Society (ERS/ATS) task force on infant lung function has been responsible for many publications in this field and also the setting of standards for manufacturers of lung function equipment for this age group.[8–10]

Anatomical aspects are also important in this age group. During infancy, nasal breathing is predominant and can account for as much as 50% of total airway resistance,[11] this may be especially important if measuring lung function 3–4 weeks after an upper respiratory tract infection. Another important anatomical aspect in infancy is that the chest wall is much more compliant than in later life. This means that during normal passive expiration the inward pull of the intrinsic elastic properties of the lung parenchyma will result in a lower level of overall lung capacity as compared to that of older children and adults. The result of this is that in some infants small airway closure occurs very close to the end of normal tidal breathing.

Techniques of assessment

Tidal breathing

The assessment of tidal breathing is one of the most basic measurements of lung function in this age group.[12] Tidal flow-volume loops can be used to demonstrate obstruction

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both at large and small airway levels.[11] Tidal volume is classically measured in this age group using either an air-filled cushioned face mask or one sealed with therapeutic putty attached to a pneumotachograph or ultrasonic flowmeter. Because of the small volumes involved, it is important to take into account the dead space of the apparatus being used. The tidal flow-volume loop, similar in shape to maximal expiratory loops in older children, can also be useful in demonstrating airway obstruction even at these small volumes. Large airway obstruction such as a fixed narrowing of the larynx or trachea can also be detected.

A number of other parameters of tidal breathing can be calculated from tidal breathing loops, examples of which include inspiratory time (t_I), expiratory time (t_E), total breath time (t_{TOT}), time to peak expiratory flow (t_{PTEF}), time to peak inspiratory flow (t_{PTIF}), and tidal breathing ratio (t_{PTEF}:t_E) These parameters are among a number which have been shown to be useful in epidemiological studies looking at, for example, the effects of maternal smoking in pregnancy on early lung function and early determinants of asthma.[11]

Functional Residual Capacity (FRC)

The measurement of FRC is an important reflection of chronic airway obstruction at all ages.[13,14] In infants this can be assessed either by plethysmography or by gas dilution/multiple breath washout (MBW). Plethysmography measures total thoracic gas volume including gas trapped behind closed airways. FRC measured by gas dilution or MBW measures all gas in contact with open functional airways.[15] Specific methodology for these techniques in infants has been set out.[16] Present measurements in experienced laboratories produce a coefficient of variation of less than 4% on repeated measurements in each individual. In recent times MBW has become the more favoured technique.[17] This technique measures breath by breath analysis of changes in the concentration of an inert gas during a washout process following a full lung ''wash in'' of the relevant gas. This is not only useful for the assessment of FRC but also gives an analysis of the homogeneity of gas distribution throughout both lungs -the lung clearance index (LCI). This index is the cumulative expired volume required to clear the inert gas from the lungs, divided by the FRC. Currently the most useful inert gas used for such measurements is sulphur hexafluoride (SF6).[18] Another significant advantage of this technique is that it can be applied through all age groups from early infancy, during childhood and adolescence into adult life. Abnormalities of LCI indicate maldistribution of gas throughout subdivisions of the lung. In infancy this can be the result of various problems including, for example, chronic lung disease of prematurity, early viral insult such as adenoviral obliterative bronchiolitis or a long-term underlying lung disease such as cystic fibrosis.[18]

A recent multicentre study of FRC and LCI during the first few months of life in 209 unsedated ex-premature infants utilised the techniques described above.[19] The study evaluated determinants of the effects in infancy of early lung disease and its treatment. A reduction in FRC was found which was independently associated with prematurity, intrauterine growth retardation and neonatal lung disease. An elevated LCI was associated with the duration of supplemental oxygen therapy.

Lung mechanics

Plethysmography

Whole body plethysmography was one of the original methods adapted from lung function testing in older children for use in infants. It is particularly useful for the measurement of lung volumes and airway resistance. It has been used for many years in studies of airway growth and development in health and disease during the first year of life. Commercially available equipment is now available but specific issues regarding technical aspects such as the provision of respired gas at body temperature pressure saturated (BTPS), and control for possible thermal artefact during measurements remain to be fully resolved.[11]

Occlusion technique

The measurement of lung mechanics is also useful in the study of infant lung disease. In this age group temporary occlusion of the airway induces a brief period of apnoea due to the fact that the Hering-Breuer reflex persists throughout the first year of life. If there is no significant airway obstruction rapid equilibration of airway pressure can allow alveolar pressure to be measured. This leads to an assessment of elastic lung recoil even during tidal breathing. Lung compliance and airway resistance can thus also be assessed.[20] Commercially developed equipment for such measurements is now available for this technique.[11]

The use of the occlusion technique has been reported in a number of studies. Recent examples include a study of lung function in preterm infants at term.[21] This demonstrated that although airway resistance and specific conductance was within the normal range at term both parameters decreased significantly after the administration of salbutamol. Another study utilised the occlusion technique in the initiation of the long-term follow-up of infants with cystic fibrosis. The occlusion technique was utilised to determine initial lung function in early life which was then compared to spirometry at the age of 6 years.[22] Measurements of infant lung function, especially those of airway resistance, were strongly correlated with lung function at the age of 6 years. These studies are examples of how this technique can be very useful in establishing baseline measurements in infancy which can then be used for the evaluation of ongoing early lung disease and its treatment.

Interrupter technique

Another method that can be used for the measurement of airway resistance is the interrupter technique. This involves the sudden interruption of airflow at the mouth and the measurement of the pressure changes transmitted from the airway which follow immediately thereafter. Frey et al.[23] studied 23 asymptomatic infants with a history of wheezing and compared them to 19 healthy controls. Using the high speed interrupter technique (HIT) they were able to

demonstrate significantly lower airway wall compliance in the clinically affected group. They postulated that this could either be due to developmental differences in airway wall mechanics or post-inflammatory airway remodelling. Henschen et al.[24] used a similar technique to study the airway wall mechanics in 18 unsedated preterm infants with post-conceptional ages (PCAs) of 32–37 weeks versus 18 full-term infants with PCAs of 42–47 weeks. This technique demonstrated that airflow propagation was lower in the preterm group. They suggested that this indicated that the physical ability of the airway to conduct large flows is fundamentally different in preterm than term infants.

Forced oscillation technique

This technique is used to measure the impedance of the respiratory system. Small amplitude high and low frequency oscillations are applied to the airway and the resultant oscillatory flow is measured.[11] The method is non-invasive so can be applied during normal tidal breathing.[25] It can also be used to monitor respiratory mechanics during artificial ventilation and sleep. It has proved to be particularly useful in epidemiological studies of wheezing disorders in children. A full review of this technique has been published by Frey.[26]

Partial Forced Expiratory Manoeuvres

Spirometry is one of the most useful measures of respiratory function throughout life. This requires a maximal respiratory effort from total lung capacity (TLC) down to residual volume (RV). Infants are incapable of such manoeuvres but under sedation these can be induced by externally applied pressure to the thorax and abdomen.

Partial forced expiratory manoeuvres, breathing from the end of tidal inspiration down to residual volume can be induced in sedated infants, through a suitably sealed facemask and flowmeter, by enclosing the chest in an inflatable jacket to which a sudden high pressure is applied. Such techniques can now be used to produce both partial and also full expiratory manoeuvres in infancy. This enables the measurement of maximal flow at FRC[5] which is an important tool in assessing the level of airway closure in this age group. This method is known as the ''squeeze'' or ''tidal'' rapid thoracic compression (RTC) technique. Pressures of 20–30 cm H2O are applied at the end of tidal inspiration. Jacket pressure is then increased in steps of 10–20 cm H2O until further increases do not elicit a further rise in flow at FRC.

An example of the application of this technique is the study of Hoskote et al.[27] who measured such flows in infants treated with inhaled nitric oxide (iNO) in the neonatal period for persistent pulmonary hypertension of the newborn. Twenty-three infants studied at one year of postnatal age had reduced VmaxFRC, as did 46 infants treated either with ECMO or conventional therapy.

This technique is therefore useful for the study of the short term outcome of lung disease in early life but also for baseline measurements in epidemiological studies of lung disease in childhood and later life as well.

Raised lung volumes

During infant lung function testing a passive full inspiration to total lung capacity (TLC) can be induced by rapidly applying raised airway pressure through a sealed facemask. Pressures of 30 cm H2O released from a 50 L tank of compressed air fully inflate the lungs and this is then followed by rapid compression of the chest through an externally applied inflatable jacket. This is called the ''raised volume rapid thoracic compression (RVRTC) technique''. Some infants further inspire before reaching TLC but giving three to five of these augmented breaths before the measurement of forced inspiration is actually made, usually inhibits this reflex breathing activity.[11] An ATS/ERS consensus statement on this technique has been set out by Lum et al.[28] Further details on the analysis of forced expiratory volumes and the limitations of this technique have been reviewed by Stocks.[11] This methodology, which allows full lung volumes to be measured, is now one of the most frequently used tests in the measurement of infant lung function.

Studies which have used this technique to study the evolution of lung disease in early life include those of Lum et al.[29] who assessed 30 infants with cystic fibrosis (CF) compared to 21 controls during the first year of life. CF infants were found to have significantly reduced flow-volume parameters even at this age. This finding supports the view that inflammatory or structural changes in the CF lung start very early in life. Kozlowska et al.[30] utilised this technique to establish baseline lung function in 48 CF infants and 33 healthy controls. This was followed by incentive spirometry in the preschool years. They demonstrated significant decreases in expiratory airflow in CF patients which were independently associated with wheeze on auscultation, recent cough and Pseudomonas aeruginosa infection – even if apparently effectively treated. This is the first study to describe physiological measurements from infancy throughout preschool years in CF children. Borrego et al.[31] studied 44 wheezy infants and 29 controls aged less than 30 months. Compared to controls, significantly reduced expiratory flows were found in those with recurrent wheeze and particularly those at risk of subsequent asthma. Mallol et al.[32] studied 28 infants less than 2 years of age with recurrent wheeze during intercurrent acute viral respiratory tract infections. Using the RVRTC technique they demonstrated acutely reduced expiratory flow parameters not associated with a family history of asthma or environmental exposure to tobacco smoke. However, when asymptomatic, infants born to mothers who had smoked in pregnancy had significantly reduced baseline flow rates.

These studies, among many others, demonstrate the usefulness of this technique in the study of the evolution of early lung disease in infants and its epidemiology in the longer term.

Conclusions

Infant lung function testing, using the techniques described, has thus developed remarkably in recent years. Virtually all of the lung function tests which can be performed in older children and adults can now be carried out both in the

neonatal period and throughout infancy. Those involved in the field have been rigorous in their standard setting and this has been achieved through international cooperation, particularly via various ERS/ATS task force publications on the subject.

The application of the techniques described and new ones still under development is increasingly being used to assist our understanding of the pathophysiology of lung disease in early life; the evaluation and development of new treatment modalities applied to disease management in this age group; and to the initiation of life-long studies which will track early lung changes throughout childhood and into adult life.

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