Current Approaches in Infant Pulmonary Function Testing

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Abstract Pulmonary function testing in infants has grown from basic measurements of lung mechanics, volumes and breathing patterns to sophisticated measurements of forced expiratory flows, fractional lung volumes, and sensitive tests of small airway function. New tests continue to be developed that extend our understanding of lung function in health and disease. The indications for infant pulmonary function testing continue to be refined. This review highlights studies that involve some of the techniques, their role in detecting abnormalities in different conditions, and the information that they can provide about several diseases in recent years. Impediments to testing, including need for sedation, labor-intensive nature of the tests and lack of large normative data sets, remain obstacles for more widespread use of the techniques.

Keywords Raised volume rapid thoracic compression technique · Multiple breath washout · Infant plethysmography · Diffusing capacity · Lung Clearance Index

Introduction

For the last 50 years, infant pulmonary function testing (IPFT) has added to our understanding of normal lung growth, development, effects of lung injury and repair, and the natural history of some diseases. IPFTs have also provided objective evidence of the effects of therapies on lung

function. Initial studies involved basic measurements of tidal lung mechanics and functional residual capacity (FRC) [1, 2]. Measures of forced expiratory flows were subsequently developed [3, 4] and refined to resemble adult-type measurements [5, 6]. Commercially available systems were created, expanding the availability and utility of IPFTs. The repertoire of tests of infant lung function has continued to expand, so that over the last few years a technique for measuring diffusing capacity has been described [7], and sensitive tests of ventilation inhomogeneity that reflect early small airway disease have been studied in greater detail in infants and toddlers [8]. This review will discuss some of the recent applications of IPFTs, and will describe how new findings are informing our understanding of childhood lung diseases and their therapies.

Attitudes and Impediments Towards Infant Pulmonary Function Testing

The application of IPFTs to research studies has been well recognized for decades, but their role in the clinical care of infants is less well defined. Godfrey et al. [9] reviewed 5 years of publications to assess how IPFTs were being used a decade ago. Of the 62 publications with original data, only four (6 %) addressed clinical management. The remainder addressed underlying pathophysiology, IPFT techniques, short-term effects of interventions, and normal physiology. Infants with prematurity, chronic/recurrent wheezing, and normal subjects each comprised about 25 % of studies, while the remainder were divided between cystic fibrosis (CF) and either pediatric critical care or acute respiratory distress syndrome.

Since Godfrey's [9] publication, equipment for the measurement of forced expiratory flow from a volume at or

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near total lung capacity and fractional lung volumes by body plethysmography have become commercially available. These techniques make direct comparison with results of conventional spirometry and lung volume determinations in older children easier to conceptualize, but have not necessarily altered the way in which IPFTs have been used.

More recently, Peterson-Carmichael et al. [10] surveyed pulmonologists to determine how IPFTs are used clinically. Respondents most commonly used IPFTs to assess patients with CF, bronchopulmonary dysplasia (BPD), recurrent wheezing, and interstitial lung disease. Bronchodilator response was also commonly assessed. Reasons for testing included routine screening, evaluation at time of initial diagnosis, assessment after intervention, and acute change in clinical status. IPFT results changed therapy >50 % of the time for approximately one quarter of respondents, whereas half altered therapy 25–50 % of the time. Some impediments to IPFT use included need for patient sedation, time-intensive nature of the testing, and investigator uncertainty regarding how results might impact patient care and outcomes. Not all centers employed the same sets of normative data, thus contributing to the uncertainty of IPFT data analysis.

Chudleigh et al. [11] assessed the attitudes of parents of healthy newborns or infants with CF towards involvement of their children in clinical research studies where sedation or general anesthesia was involved. Their cohort consisted of 92 CF infants undergoing IPFTs at 3 and 12 months of age, as well as a chest CT scan and bronchoscopy at 12 months of age, and 77 healthy infants who underwent the same IPFTs at 3 and 12 months of age. At the time of first sedation, the most common reasons to participate cited by the CF parents were beliefs that the research would help their child (98 %), and would also help other children with CF (97 %). Parents of healthy children felt that their children's participation helped other children with CF (98 %) but only 25 % felt that the study would be beneficial for their child. Both groups felt overwhelmingly (≥ 80 %) that there was no risk of harm to their child. At 12 months, only 56 % of CF parents felt the research would help their child while 49 % felt it would help other children with CF. Nevertheless, 68 % of parents were happy and/or not worried that their child had participated in the research study. Furthermore, 95 % of parents would recommend being involved in research to other parents. The results suggest that at least among parents of infants with CF, participation in studies requiring sedation of the child are not viewed negatively.

Two workshops were recently convened to address the clinical indications for IPFTs for each of six IPFTs in diseases characterized by airway obstruction: CF, BPD, and recurrent wheezing [12•]. The tests discussed are listed in Table 1. The expert panel recognized that not every test

has been extensively studied in each of the selected populations. Additionally, the tests are not equally discriminative across diseases and so their utility might depend on the population being studied. For instance, reduced forced expiratory flows by the raised volume rapid thoracic compression (RVRTC) technique correlate with markers of inflammation and pathogen density detected in bronchoalveolar lavage fluid in infants with CF [13]; in contrast, measures of resistance by the forced oscillation technique do not correlate with symptoms of cough or presence of airway infection in CF infants [14, 15]. While each of the tests reviewed has a role in detecting lung disease in infants and preschool children with CF, BPD or recurrent wheezing, it has yet to be determined if the use of such testing in routine clinical practice improves outcomes in any of those disease states. Studies assessing this desperately need to be conducted to determine the role of IPFT in clinical practice for the conditions mentioned.

Recent Uses of IPFTs

To determine if IPFTs could yield similar information to that of standard spirometry in older CF patients, investigators retrospectively reviewed the results of IPFTs in 11 CF infants who underwent testing within 2 weeks before or 1 week after initiation of therapy for a pulmonary exacerbation, and had a second set of studies performed 2 weeks after or 1 week before completion of antibiotic therapy [16•]. At the time of initial testing, nine of the infants had evidence of obstructive lung disease and 10 had air trapping. Following therapy, three had persistent obstructive disease and nine had ongoing evidence of air trapping. Nevertheless, measures of forced expiratory flow improved significantly following antibiotic administration, and measures of hyperinflation decreased significantly as well. The authors speculated that IPFTs reflect clinical response in CF children experiencing a pulmonary exacerbation, and could be useful in monitoring therapeutic response. They cautioned, however, that the routine use of IPFTs as part of CF care requires additional study.

Infant spirometry and plethysmographic lung volume determinations have also been used to help define the characteristics of children with a rare interstitial lung disease, neuroendocrine cell hyperplasia of infancy (NEHI) [17•]. Kerby et al. retrospectively reviewed the lung functions of 15 infants and toddlers with biopsy-proven NEHI and another 22 subjects with all of the clinical characteristics and typical chest CT findings of NEHI but no biopsy or family history to support the diagnosis (called “NEHI syndrome”). Air trapping and significant airflow limitation with reduced forced expiratory flows were present in the children with NEHI or NEHI syndrome, but

Table 1 Clinical considerations for tests of lung function in infants and preschool children

	Infant RVRTC	Infant Pleth	Preschool Spiro	Preschool sRaw	Preschool Rint	Preschool FOT	MBW
Commercial equipment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Standard operating procedure	Yes	Yes	Yes	No	Yes	Yes	Yes
Safe	Yes ^a	Yes	Yes	Yes	Yes	Yes	Yes
Feasible	Yes ^a	Yes	Yes	Yes	Yes	Yes	Yes
Adequate population-based reference data	No ^b	No ^b	Yes ^c	No	Yes ^c	Yes ^c	Yes ^c
Within-test intrasubject variability measured	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discriminates disease population from healthy control subjects							
Cystic fibrosis	Yes	Yes	Yes ^d	Yes	No	Conflicting	Yes
Bronchopulmonary dysplasia	Yes	Yes	Unknown	Unknown	Unknown	Unknown	Probably not
Recurrent wheeze	Yes	No	Yes ^c	Unknown	Yes ^c	Unknown	Probably
Evidence for clinical utility	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

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RVRTC raised volume rapid thoracic compression, *FOT* forced oscillation technique, *MBW* multiple-breath inert gas washout, *Pleth* plethysmography, *Rint* interrupter resistance, *Spiro* spirometry

^a In experienced labs after extensive training

^b Reference data not validated for any commercial devices

^c Predominantly from non-Hispanic white children; dependent on precise equipment/technique used

^d Substantial overlap between CF and healthy control subjects; MBW more discriminatory in preschool ages

^e Bronchodilator response, rather than baseline values, appears to discriminate best between healthy control and disease populations

measurements between the two groups were not different from each other. The two measurements that best distinguished the two groups from a disease control population of children without lung disease were the residual volume to total lung capacity (RV/TLC) ratio and the forced expiratory flow between 25 and 75 % of the vital capacity (FEF_{25–75}). The authors proposed that results of IPFTs that show airflow obstruction and air trapping could be used as one other piece of information in determining whether or not to perform a lung biopsy on a child with typical clinical findings suspected of having NEHL.

In a similar use of lung functions to describe a population, Danzer and coworkers obtained forced expiratory flows by the RVRTC technique and plethysmographic lung volumes, as well as tidal mechanics by the single breath occlusion technique in 14 children 1–58 months of age with pulmonary hypoplasia resulting from a giant omphalocele [18]. There was evidence of a restrictive process: the forced vital capacity (FVC) and forced expiratory volume in the first 0.5 s (FEV_{0.5}) were significantly reduced, but the FEV_{0.5}/FVC ratio was normal, and total lung capacity (TLC) was also reduced. The residual volume (RV), RV/TLC and FRC were all normal, which was interpreted as evidence of possible lung overdistension. Supporting this, respiratory system compliance was decreased in the seven children in whom it could be

measured. Furthermore, 50 % of the subjects were older than 1 year, underlining the point that the pulmonary function abnormalities seen in these children do not necessarily resolve in infancy.

Techniques for measuring lung functions in infants continue to be developed and refined. The remainder of this review will focus on specific tests of lung function that have received increased attention over the last few years either because of their ability to extend observations conventionally made in older children and adults down to the infant group, or because they augment findings from conventional measurements and lend new insight into underlying disease processes or normal lung growth.

Forced Expiratory Flows by the Raised Volume Rapid Thoracic Compression Technique

Initial measurements of forced expiratory flow used the rapid thoracic compression (RTC) technique to measure flows over the tidal range of breathing [3, 4]. A modification of the RTC technique, where the infant's lungs were passively inflated to a volume near TLC before conducting the squeeze, resulted in an ability to measure timed flows (e.g., FEV_{0.5}) as well as flows over an extended volume range [5, 6]. This made such measurements less reliant on

changes in underlying volume, and highly reproducible. The combination of the RVRTC technique with measurement of FRC by plethysmography ($\text{FRC}_{\text{pleth}}$) allows for determinations of fractional lung volumes (TLC, FRC, and RV). Spirometry by the RVRTC technique can be tracked longitudinally from infancy through adulthood.

To determine if these measurements would be feasible to use as endpoints for multicenter trials, Davis et al. [19•] conducted a multicenter observational longitudinal study in 100 infants with CF across 10 centers. Studies were conducted at baseline and after 6 and 12 months. Making the measurements was both safe and feasible: in 342 studies, 44 adverse events were recorded, with vomiting occurring most commonly (29 events among 21 infants). One infant experienced wheezing, tachycardia and hypoxemia leading to an overnight hospitalization. There were no other serious adverse events. $\text{FRC}_{\text{pleth}}$ measurements could be made in 89 % of attempts, RVRTC measurements were acceptable in 72 % of attempts, and fractional lung volumes (requiring both successful FRC and RVRTC measurements) could be measured in 69 %. The number of studies meeting acceptability criteria were significantly greater among more experienced centers compared with those less experienced in conducting IPFTs. The measurements made were reproducible and they distinguished infants with CF from healthy controls. There was, however, considerable overlap between CF and published healthy control values, causing the authors to caution that IPFTs may not yet be suitable primary endpoints for multicenter studies, especially if inexperienced centers are involved in the data collection.

Reflecting this, IPFTs were assessed as a secondary exploratory endpoint in a multicenter randomized, double-blind, placebo-controlled trial of hypertonic saline inhalation in 321 infants and children with CF, 4–60 months of age [20•]. Inhaled hypertonic saline (7 %) was administered twice daily to 158 subjects while 163 received isotonic (0.9 %) saline. The primary outcome was the rate of pulmonary exacerbations, but a subset of infants between 4 and 16 months of age at enrollment underwent pulmonary function testing within 1 month of enrollment and again after 48 weeks. Only centers certified to conduct research-quality IPFTs conducted the IPFTs. Studies were over-read at a central site and rated for technical acceptability, and quality control feedback was given to each of the sites. Of the 73 infants who underwent testing, acceptable measurements of $\text{FRC}_{\text{pleth}}$ were obtained at both visits in 62 (85 %) subjects, forced expiratory flows in 45 (62 %), and RV in 36 (49 %). There was a significant effect of hypertonic saline inhalation on lung function. After adjusting for baseline lung function, sex, age, height and weight, the mean change in $\text{FEV}_{0.5}$ was 38 mL (95 % CI 1–76 mL) greater in the treatment group at the end of the 48-week

study period. The authors noted that early CF lung disease is relatively silent, and so sensitive measures like pulmonary function testing are required to detect it. This study also demonstrated the feasibility of performing IPFTs in the context of a multicenter trial, using experienced centers and careful quality control.

In another multicenter trial, Debley et al. [21•] used the RVRTC technique to assess the prevalence of bronchodilator responsiveness among children 4–36 months of age with a history of physician-diagnosed recurrent wheezing. Of 102 enrolled subjects, the investigators were able to obtain technically acceptable studies both before and after albuterol administration in 76. Using previously published data [22], 18 (24 %) subjects demonstrated significant bronchodilator responsiveness. The greatest post-bronchodilator change among responders was seen in the forced expiratory flow at 75 % of the vital capacity (FEF_{75}), compared with the FVC, $\text{FEV}_{0.5}$, or FEF_{25-75} . Family history of asthma or allergy, or personal history of eczema were not associated with bronchodilator responsiveness among this population of children. The lack of correlation of bronchodilator responsiveness with traditional risk factors for asthma or use of inhaled steroids among the study population suggests that bronchodilator responsiveness is not predictive of either the development of future asthma or responsiveness to inhaled corticosteroids in the infant/toddler population.

In contrast to the findings of Debley et al., Bisgaard et al. [23•] demonstrated in a single center study that bronchial hyper-responsiveness as demonstrated by methacholine challenge at 1 month of age correlated with the development of asthma at age 7 years. The authors obtained spirometry by the RVRTC technique in 403 (98 %) infants and response to methacholine in 362 (88 %) of 411 infants enrolled in the Copenhagen Prospective Studies on Asthma in Childhood birth cohort. They followed subjects with diary cards to determine who developed asthma, and had the subjects perform standard spirometry at 7 years of age. They also demonstrated that in the children with asthma the forced expiratory flow at 50 % of the vital capacity (FEF_{50}), a value they interpreted as being affected primarily by peripheral airway resistance, was diminished at 1 month of age, and fell further from normal levels over the ensuing 7 years. Thus, they reasoned that children at risk of developing asthma not only started with lower lung function, but also experienced a relative loss of function in early life. They speculated that strategies to alter prenatal factors leading to an asthma disposition could help prevent the development of asthma, and that there is a window of opportunity postnatally to intervene to alter airway remodeling. Not all studies of lung function in birth cohorts have arrived at the same conclusions, but the ability to measure lung function in

infants before any illness might alter results, and to make analogous measurements in older children so that changes can be tracked provides a powerful tool to explore the origins of disease.

Diffusing Capacity

To understand how the gas exchange surface of the lung grows, as well as how diseases affect the lung parenchyma, tests like the carbon monoxide diffusing capacity of the lung (DL_{CO}) can be used [24, 25]. Previous tidal breathing methods in infants [26, 27] were prone to methodological flaws. Castillo et al. adapted the RVRTC technique to induce a 4 s breath hold near TLC to measure DL_{CO} in sedated infants and toddlers in a way that is analogous to making the measurement in older children and adults [28]. Subsequently, the technique was used to explore the pattern of normal lung growth in healthy infants and toddlers [7]. The authors studied 50 healthy subjects between 3 and 23 months of age. Both DL_{CO} and alveolar volume (V_A) increased with increasing age and body length. The ratio of DL_{CO}/V_A remained constant with age and body length, suggesting that over the first 2 years of life the lung grows by increasing alveolar number rather than by expansion of existing alveoli.

The same group subsequently examined DL_{CO} of infants with BPD [29••]. They reasoned that published reports of diffuse alveolar simplification from autopsies or lung biopsies of BPD patients [30, 31] might reflect extremes of disease. Thirty-nine infants with BPD who were 4–18 months at the time of study had measurements of DL_{CO} and V_A compared with measurements obtained in 61 healthy control babies. For both groups, V_A increased with increasing body length at the same rate. The DL_{CO} , however, which also increased with length in both groups, was significantly lower in the BPD group compared with controls. The DL_{CO}/V_A was also significantly lower in the BPD group. Gestational age at birth was a significant covariate for V_A in both groups, so that the younger the gestational age the smaller the alveolar volume. Furthermore, gestational age also was a significant covariate for DL_{CO} among infants with BPD, such that those with lower gestational ages also had lower length-adjusted DL_{CO} . This association suggests that how well the lung parenchyma is developed at birth may be an important determinant of subsequent lung growth. The first demonstration that surviving infants with BPD have reduced diffusing capacity compared with controls supports the histologic findings of simplified parenchymal architecture among infants with BPD, with less surface area available for gas exchange.

The same technique for measuring DL_{CO} was also recently used to explore the parenchymal abnormalities of

an infant with pulmonary interstitial glycogenosis (PIG), a rare childhood interstitial lung disease [32]. A 3-month-old boy with biopsy-proven PIG underwent IPFTs, including measures of DL_{CO} and V_A . Spirometry by the RVRTC technique showed a significant restrictive process, and his DL_{CO}/V_A was also markedly reduced when compared with age-matched population values. At 20 months of age, along with clinical improvement, he also demonstrated normalization of the DL_{CO}/V_A although his FVC remained reduced. Studies like this help to characterize a disease whose natural history to date has been poorly described.

At present, equipment to measure DL_{CO} in infants with the raised volume technique is not commercially available. The studies, which use $C^{18}O$ in the test gas and a mass spectrometer to measure helium and carbon monoxide concentrations, are expensive to conduct. This has confined their use to a single center to date: until these obstacles are overcome, use of this measurement is likely to remain limited to research centers as an investigational tool.

Multiple Breath Washout Technique

The multiple breath washout (MBW) method measures breath-to-breath changes in the concentration of an inert gas and provides information about both lung volumes (FRC) and the degree of ventilation inhomogeneity present. Although the test as originally described in the 1950s used measurements of exhaled nitrogen washed out with 100 % O_2 , more recent descriptions of the test employ a wash-in and wash-out of various inert gases including helium, argon, and sulfur-hexafluoride (SF_6). Use of these alternate gases is especially germane in infants, since using 100 % O_2 may alter tidal breathing in this age group or promote the development of atelectasis. The MBW yields not only the FRC, but also several measurements reflecting ventilation homogeneity. These include the Lung Clearance Index (LCI), representing the number of “lung turnovers” required to complete the maneuver, the mixing ratio, which is the ratio of actual-to-estimated ideal number of breaths needed to achieve the final 1/40th concentration of tracer gas, and the distribution of ventilation inhomogeneity (VI), a calculation using moment analysis to determine the area under the curve of the washout over the first eight lung turnovers [33]. This type of analysis incorporates all of the data of the curve rather than just one or two points. The first and second moments (M_1 and M_2) are weighted towards the end of the curve, and when normalized to the area under the curve (the zeroth moment, M_0) higher ratios (M_1/M_0 and M_2/M_0) reflect greater ventilation inhomogeneity. These measures are sensitive indicators of peripheral airway obstruction. They are capable of detecting early airway disease and are more sensitive and easier to perform

than conventional lung function testing in infants and young children [12•].

Advantages of the MBW technique include its suitability for bedside measurements and its usefulness in all ages. In very young infants, however, a large equipment and/or physiologic dead space relative to the lung volume being measured can result in an elevation of the LCI value [34]. There is evidence that the LCI is dependent on body size, decreasing in a nonlinear pattern as height increases, especially in the first 5 years of life [35]. Normative data in children <6 years of age, therefore, are urgently needed. Another limitation of the MBW technique is that until recently, no commercial equipment was available to make the measurements, making standardization across sites untenable. Additionally, SF₆ is not commercially available in the United States, although it is commonly used elsewhere to conduct MBW measurements. Use of different inert gases alters the values of the LCI [36]. There are other limitations of the MBW technique when used in subjects with severe airway obstruction. These include its inability to measure gas trapped behind closed airways and, therefore, not in communication with the airway opening, and the need for a prolonged washout in those with severe obstructive disease.

The MBW has received increasing attention for its potential to identify early abnormalities in the lungs of infants with CF, well before clinical symptoms or structural changes appear. Ventilation inhomogeneity, hyperinflation and gas trapping were present in 71 CF infants studied at 11.4 ± 2.3 weeks of age, all of whom were identified by newborn screening at ~1 month of age and in whom standardized treatment protocols had been instituted [37•]. There were also signs of airway obstruction, with reduced FEV_{0.5}, FVC, and FEF_{25–75} z-scores. There was, however, no significant relationship between the LCI and FEV_{0.5}, which were the two primary outcome measures. The LCI was >1.96 z-scores in 21 %, while the FEV_{0.5} was <–1.96 z-scores in 25 % of CF infants; both tests were abnormal in only 12 %. When used in combination, however, 35 % of CF infants demonstrated some abnormality in lung function that reflected airway disease. Furthermore, 41 % of CF infants had at least one abnormal result when LCI, FEV_{0.5} and FRC_{pleth} were analyzed. The findings of this study raise a concern that even with standardized treatment in specialty centers including use of prophylactic antibiotics, a substantial number of CF infants already had evidence of abnormal lung function at 3 months of age. Thus, clinical wellness should not be reassuring in CF infants.

The relationship between airway inflammation and ventilation inhomogeneity in young patients with CF was recently demonstrated [38•]. Belessis et al. performed MBW tests followed by bronchoscopy and bronchoalveolar lavage (BAL) in 47 children with CF between 0.36 and

3.10 (mean 1.55) years of age. Values of LCI were higher in the CF patients than in healthy controls, and 15 (32 %) of the CF children had LCI values above the upper limit of normal. The LCI correlated with markers of inflammation (neutrophil count, IL-8 levels) in BAL fluid. Those CF children who harbored *Pseudomonas* in their lungs also had significantly higher LCI values and percentage of neutrophils in BAL fluid compared with those without evidence of *Pseudomonas*. These data suggest that isolation of *Pseudomonas* from the lungs of children with CF is associated with greater inflammation and ventilation inhomogeneity. Furthermore, an LCI of <7.41 had a negative predictive value of 93 % for the detection of *P. aeruginosa* in the airways of CF children, making it a potentially attractive test to rule out *Pseudomonas* infection in most young children with CF.

Kieninger et al. [39] were the first group to present longitudinal MBW data between infancy and school age in patients with CF. They compared measures of LCI in 11 infants with CF studied at the time of diagnosis (median age 21.9 weeks, range 14–45 weeks) and again at 9.7 (6.9–10.3) years. The LCI was elevated in seven at the time of diagnosis although all were asymptomatic, and higher values were noted in those infants who were older at the time of diagnosis. In contrast, those who were diagnosed early had a normal LCI. The LCI remained consistently abnormal in the four patients with the most severe disease, whereas the change in LCI over time was more variable among the other seven. Despite some methodological concerns, the data suggest that the LCI might track with disease in CF infants, and that the technique could be used to identify those infants most in need of therapeutic intervention, even before clinical symptoms arise.

The MBW was recently used for the first time to demonstrate the effect of a therapeutic intervention in CF infants and preschool children [40•]. One center involved in the Infant Study of Inhaled Saline (ISIS) study [20•] that compared the effects of 7 % saline inhalations to inhalations of normal saline in CF infants and children, conducted a pilot sub-study in 25 subjects comparing MBW results at enrollment and again after 48 weeks of treatment. Twelve subjects were randomized to receive hypertonic saline, and 13 received isotonic saline. The LCI did not differ between groups at baseline, but it decreased significantly from baseline to the 48-week endpoint in the hypertonic saline group. In contrast, the LCI did not change from baseline among those in the isotonic saline group at 48 weeks. This was the first study to use the MBW technique to determine the endpoint in an interventional trial involving infants and preschool children with CF. The investigators demonstrated both the feasibility of the maneuver and an ability to recognize a treatment effect with a fairly small number of subjects.

The MBW technique has been used in other diseases to provide some insight into characteristics of ventilation homogeneity. Landolfo et al. [41] measured FRC and LCI in 13 infants with isolated congenital diaphragmatic hernia before surgery (T_0), 24 h after surgery (T_1) and within 24 h of extubation (T_2). Median FRC values adjusted for body weight significantly increased immediately after hernia repair, although median LCI values did not change. Median duration of ventilation was 7 days (range 5–60 days). By T_2 , FRC values remained similar to those at T_1 , but the LCI had fallen significantly. It is possible that these changes reflected rapid overdistension of the ipsilateral lung from T_0 to T_1 , followed by some degree of remodeling that was accompanied by improvement in ventilation homogeneity from T_1 to T_2 . Such measurements have the potential to elucidate processes involved in lung growth and recovery from injury.

Not all diseases, however, can be discriminated by measurements made by MBW. Latzin et al. [42] measured FRC and LCI by the MBW technique, as well as other tidal breathing parameters in 127 infants with BPD, 58 preterm infants without BPD, and 239 healthy term infants. FRC values were higher in healthy term and preterm infants compared with the BPD infants. The LCI, however, was not different among any of the groups. The authors speculated that the normal LCI could reflect overall milder disease among infants with “new” BPD compared with classical BPD. Another possible explanation, however, is that while “new” BPD reflects arrested development and simplification of the pulmonary acinus, the disease is more homogeneous and therefore measures of ventilation inhomogeneity do not discriminate well.

Similar findings were described in a multicenter trial involving 219 infants from three neonatal centers [43]. Measurements of FRC and indices of ventilation inhomogeneity by MBW were made in 64 full term controls, 59 preterms with no lung disease, 54 who recovered from respiratory distress syndrome, and 42 with BPD. Values of FRC were affected by degree of prematurity and intra-uterine growth restriction, as well as duration of supplemental oxygen use. Once those factors were taken into account, there was no additional effect of diagnostic category. Similarly, the LCI did not differ among groups: the only factor that influenced LCI was disease severity, such that it increased by 0.003/day of supplemental oxygen use. The authors posited that measures of ventilation inhomogeneity might be less helpful in determining effects of prematurity or lung disease in infants compared to their value in assessing infants with CF.

A recent study described a modification of the MBW technique, using augmented breaths (similar to the RVRTC maneuver) in sedated infants and toddlers to permit the identification of the alveolar plateau (phase III) and

calculation of the slope of phase III (S_{III}) [44]. The authors studied 28 full term subjects from 3 to 28 months of age and 22 subjects with BPD at 12.2 ± 3.3 months of age. Among the healthy full-term subjects, there was a significant decrease in LCI as age increased ($P = 0.02$). Additionally, S_{III} , normalized for the mean helium concentration of each breath and the minute ventilation (referred to as S_{ND}) also decreased with increasing age ($P < 0.001$). The authors interpreted these findings as a reflection of increasing homogeneity of ventilation with age. When adjusted for age or body length, there was no significant difference in LCI, S_{ND} , or FRC between the term subjects and those with BPD. These findings confirm the observation that infants and young children with BPD do not have greater ventilation inhomogeneity compared with normals.

Conclusion

New tests of lung function are being developed and refined that broaden our understanding of physiology of the growing lung in health and disease. Over the last 5 years, IPFTs have been used in multicenter trials to help define characteristics of disease and responses to therapies. The indications for IPFTs continue to be elucidated. Major impediments to the widespread use of IPFTs include a lack of published normal values, the need for sedation of most subjects, and the time required to perform the tests. Until these issues can be addressed, use of IPFTs will continue to be largely relegated to research centers, and their clinical use will remain limited.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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