

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Workshop Report: Optimal Lung Function Tests for Monitoring Cystic Fibrosis, Bronchopulmonary Dysplasia, and Recurrent Wheezing in Children Less Than 6 Years of Age

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Abstract

Although pulmonary function testing plays a key role in the diagnosis and management of chronic pulmonary conditions in children under 6 years of age, objective physiologic assessment is limited in the clinical care of infants and children less than 6 years old, due to the challenges of measuring lung function in this age range. Ongoing research in lung function testing in infants, toddlers, and preschoolers has resulted in techniques that show promise as safe, feasible, and potentially clinically useful tests. Official American Thoracic Society workshops were convened in 2009 and 2010 to review six lung function tests based on a comprehensive review of the literature (infant raised-volume rapid thoracic compression and plethysmography, preschool spirometry, specific airway resistance, forced oscillation, the interrupter technique, and

multiple-breath washout). In these proceedings, the current state of the art for each of these tests is reviewed as it applies to the clinical management of infants and children under 6 years of age with cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheeze, using a standardized format that allows easy comparison between the measures. Although insufficient evidence exists to recommend incorporation of these tests into the routine diagnostic evaluation and clinical monitoring of infants and young children with cystic fibrosis, bronchopulmonary dysplasia, or recurrent wheeze, they may be valuable tools with which to address specific concerns, such as ongoing symptoms or monitoring response to treatment, and as outcome measures in clinical research studies.

Keywords: infant; preschool; spirometry; resistance

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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Executive Summary

Pulmonary function testing plays a key role in the diagnosis and management of chronic pulmonary conditions, such as asthma and cystic fibrosis (CF), in children over 6 years of age. However, objective physiologic assessments play a limited role in the care of infants and children under 6 years of

age, due to the challenges of measuring lung function in these young patients. A number of lung function techniques have been developed and evaluated among children under 6 years of age in the research setting, and show promise as safe, feasible, and potentially useful clinical tests.

These proceedings reflect the results of official American Thoracic Society (ATS) workshops convened by the ATS/European Respiratory Society Joint Task Force on

Infant and Preschool Lung Function at the 2009 and 2010 ATS International Conferences to systematically review six lung function tests in children under 6 years of age: infant pulmonary function testing (raised-volume rapid thoracic compression and plethysmography); preschool spirometry; specific airway resistance; the interrupter technique; the forced oscillation technique; and multiple-breath washout.

Conclusions

- The six lung function tests have been demonstrated to be safe and feasible, with the caveat that sedated infant lung function testing requires extensive training.
- Reference data are predominantly from non-Hispanic white children, and are dependent on the specific device and technique employed. Thus, caution must be used in employing them in non-white children or when using devices/techniques different from those with which the reference ranges were derived.
- Better reference equations are urgently needed. Many existing equations are derived from small samples and/or are not necessarily incorporated into commercial devices, making them difficult to employ in a clinical laboratory.
- The paucity of data on between-test reproducibility limits the understanding of what constitutes a clinically meaningful change in lung function for an individual child.
- The ability of specific tests to detect abnormalities varies according to the underlying disease pathophysiology. Thus, the choice of test must be tailored to individual disease processes. Infant lung function tests (particularly the raised-volume rapid thoracic compression technique) have been shown to detect early cystic fibrosis (CF) lung disease; their role in the monitoring of bronchopulmonary dysplasia (BPD) and recurrent wheezing is less clear. Among preschool children, of the available measures, multiple-breath inert gas washout (MBW) appears to provide the greatest discrimination between children with CF and healthy control subjects, due to the regionally heterogeneous nature of early airway obstruction in CF. The resistance techniques appear helpful in

diagnosing bronchial hyperresponsiveness in a variety of conditions.

- The major clinical role of any of these lung function tests would be to monitor disease severity over time, evaluate response to treatments, and serve as objective outcome measures in clinical research studies. The results should always be interpreted in the context of other clinical signs and symptoms.
- No evidence yet exists for any of the measures as to whether incorporating them in to clinical care improves patient outcomes; such studies are urgently needed. Despite the lack of empirical evidence, clinical experience suggests that lung function monitoring might be helpful in some clinical settings:
 - In children with CF under 6 years of age, routine lung function monitoring may improve our ability to detect and treat early lung disease and exacerbations, particularly as more sensitive tests, such as MBW, become more widely available. This belief is based upon the observation that lung function assessments are central to the clinical care of older children with CF.
 - In infants and young children with CF, BPD, or recurrent wheeze, lung function monitoring may be valuable to address specific concerns, such as ongoing symptoms or monitoring response to treatment, and as objective outcome measures in clinical research studies.

A summary of the current strengths and weaknesses of these lung function tests is provided in the summary table (Table 1).

Introduction

Pulmonary function testing plays a key role in the diagnosis and management of chronic pulmonary conditions, such as asthma and cystic fibrosis (CF), in children over 6 years of age. Yet objective physiologic assessments play a limited role in the care of infants and children under 6 years of age, due to the challenges of measuring lung function in these young patients. A number of lung function tests have been developed and evaluated among children under 6 years of age in the research setting, and show promise as safe, feasible, and potentially useful clinical tests. In sedated infants, spirometry can be performed with

the raised-volume rapid thoracoabdominal compression (RVRTC) technique, and lung volumes can be measured by plethysmography or multiple-breath inert gas washout (MBW). In preschool children (3–6 yr of age), spirometry can be performed using modified acceptability criteria. Airway or respiratory resistance can be measured in three ways: by plethysmographically (specific airway resistance [sRaw]), by the interrupter technique, or by forced oscillometry. Finally, ventilation inhomogeneity (VI) and lung volumes can be evaluated across all ages by MBW.

Are any of these tests ready for translation into routine clinical care? These proceedings review the current state of the art for each of these tests as they apply to the clinical management of infants and children under 6 years of age with CF, bronchopulmonary dysplasia (BPD), and recurrent wheezing, using a standardized format that allows easy comparison between the measures.

Methods

This workshop report was prepared according to the standards of the American Thoracic Society. The methods are described in detail in the online supplement and in Table 2.

Infant Pulmonary Function Testing—RVRTC and Plethysmography

Introduction

Lung function has been assessed in infants for over 40 years in specialized research labs. The relatively recent availability of commercial devices and published international guidelines facilitates the potential clinical use of these tests for the assessment of common childhood respiratory conditions. These devices use the RVRTC technique to produce full expiratory flow–volume curves similar to those produced by spirometry in older, cooperative patients. Lung volumes are measured by whole-body plethysmography (or, using a separate device, by MBW).

This section describes the evidence related to infant pulmonary function testing and identifies gaps in knowledge. The available commercial equipment and

Table 1. Summary table (as of January, 2012)

	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*	Yes	Yes	Yes	Yes	Yes	Yes
Feasible	Yes*	Yes	Yes	Yes	Yes	Yes	Yes
Adequate population-based reference data	No [†]	No [†]	Yes [‡]	No	Yes [‡]	Yes [‡]	Yes [‡]
Within-test intrasubject variability measured	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discriminates disease population from healthy control subjects							
CF	Yes	Yes	Yes [§]	Yes	No	Conflicting	Yes
BPD	Yes	Yes	Unknown	Unknown	Unknown	Unknown	Probably not
Recurrent wheeze	Yes	No	Yes	Unknown	Yes	Unknown	Probably
Evidence for clinical utility	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Definition of abbreviations: BPD = bronchopulmonary dysplasia; CF = cystic fibrosis; FOT = forced oscillation technique; MBW = multiple-breath inert gas washout; Pleth = plethysmography; Rint = interrupter resistance; RVRTC = raised-volume rapid thoracoabdominal compression; Spiro = spirometry.

*In experienced labs after extensive training.

[†]Reference data not validated for any commercial devices.

[‡]Predominantly from non-Hispanic white children; dependent on precise equipment/technique used.

[§]Substantial overlap between CF and healthy control subjects; MBW more discriminatory in preschool ages.

^{||}Bronchodilator response, rather than baseline values, appears to discriminate best between healthy control and disease populations.

standardized procedures used for infant pulmonary function testing are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Infants with CF, BPD, and Recurrent Wheeze

CF. In observational studies involving 34–100 infants, investigators have demonstrated that RVRTC measurements can detect diminished lung function in infants with CF, although the degree of abnormality reported varies by cohort and measurement device/technique (1–4). In infants diagnosed by newborn screening, RVRTC measurements may be normal during the first few months of life, but are generally diminished later in infancy (1, 4). Diminished RVRTC measurements in early infancy appear to track into later infancy (2), through the preschool years (3) and into school age, where forced expiratory flow at 50% of vital capacity (FEF₅₀) measures in 41 infants correlated with lung function measured by spirometry (5, 6). The measurements appear to reflect airway structural changes (7) and, when measured

at the time of clinically indicated bronchoalveolar lavage in 16 infants, were inversely associated with the degree of neutrophilic inflammation and pathogen density (8). Greater decline in lung function has been reported in those with pulmonary infection due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* (9). RVRTC has been used to evaluate acute tolerability of hypertonic saline (10, 11).

A recent study reported an elevated FRC_{pleth} in nearly 70% of infants with CF (z score > 1.64) and an elevated residual volume in 55% (1), suggesting early gas trapping; however, these data need confirmation in other cohorts (12). FRC_{pleth} measured at the time of clinically indicated bronchoscopy was associated with pathogen density in lower airways (8). FRC_{pleth} has also been used to follow progress over time in longitudinal studies (6, 13), response to bronchodilators (BDs) (14), and the benefit of prophylactic antibiotics (15).

BPD. Published evaluation of the RVRTC technique in infants with BPD and in preterm infants is very limited (16, 17). In an observational study of 28 infants with BPD, FEV_{0.5} and FEFs were diminished

compared with control subjects (16), and these changes persisted with time (17). Diminished FEFs have also been reported in the first year of life among preterm infants without prior respiratory problems when compared with healthy full-term control subjects (18, 19). More data are needed to strengthen these findings.

FRC_{pleth} has been reported to be elevated in studies including between 16 and 43 infants with BPD (16, 17, 20–23), and a few studies have assessed FRC_{pleth} before and after intervention (21, 24). There are minimal longitudinal data; one study demonstrated that FRC_{pleth}/weight normalized by 6 months of age in patients with BPD (22), although results need to be interpreted with caution in the presence of disproportionate growth (25). Two groups have reported that FRC measured plethysmographically is higher than FRC assessed by nitrogen washout in these infants (21, 23), suggesting the presence of noncommunicating trapped gas. In a study of 15 infants with BPD, Kao and colleagues (21) demonstrated that FRC_{pleth} did not improve after BD administration (24) or oral diuretic therapy. In a study of

Table 2. Methods table

	Yes	No
Panel assembly		
Included experts from relevant clinical and non-clinical disciplines	X	
Included individual who represents views of patients and society at large		X
Included methodologist with appropriate document expertise		X (N/A)
Literature review		
Performed in collaboration with librarian For Review Only	X	
Searched multiple electronic databases	X	
Reviewed reference list of retrieved articles	X	
Evidence synthesis		
Applied pre-specified inclusion and exclusion criteria	X	
Evaluated included studies for sources of bias	X	
Explicitly summarized benefits and harms		X (N/A)
Used PRISMA 1 to report systematic review		X (N/A)
Used GRADE to describe quality of evidence		X (N/A)
Generation of recommendations		
Used GRADE to rate the strength of recommendations		X (N/A)

Definition of abbreviations: GRADE = Grading of Recommendations Assessment, Development and Evaluation; N/A = not applicable; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

18 infants, Filbrun and colleagues (17) showed that an elevated residual volume to total lung capacity (RV:TLC) ratio persisted over serial measurements. Finally, FRC_{pleth} was demonstrated to be similar at 1 year among 23 infants treated with conventional ventilation compared with those treated with high-frequency oscillation or a combination of conventional ventilation and high-frequency oscillation (26).

Recurrent wheeze. Diminished FEFs and FEV_{0.5} have been reported in studies that included between 16 and 40 infants with recurrent wheeze (27–31), with the most pronounced reductions among those at high risk for subsequent asthma (30). Interestingly, minimal BD responsiveness (BDR) has been reported in infants with recurrent wheeze when assessed using RVRTC (29, 31, 32). Also, Llapur and colleagues (31) reported no correlation of RVRTC with chest high-resolution computed tomography findings in 17 infants with recurrent wheeze. FEV_{0.5} has been shown to improve after 4 weeks of montelukast treatment in 26 infants with recurrent wheeze (33), and forced flows significantly improved after 3 months of inhaled steroid therapy (34) when compared with those receiving placebo therapy in 44 infants with recurrent wheezing.

Relatively few studies have evaluated FRC_{pleth} in infants with recurrent wheeze (29, 35, 36). FRC_{pleth} has been reported to

improve (i.e., decrease) after BD and inhaled corticosteroid treatment when compared with placebo in a study of 42 infants with wheeze (35).

Gaps in Knowledge and Future Directions

These studies highlight the potential clinical relevance of infant pulmonary function tests. There is now a need to evaluate rigorously whether routine monitoring of lung function in these infants improves outcomes. Many factors, including need for sedation, lack of appropriate reference data and time, and resource intensity, have limited the clinical role for the RVRTC and infant plethysmography. There needs to be a concerted effort to develop improved reference data. Only with appropriate reference data and knowledge of within- and between-test reproducibility will it be possible to develop studies to assess whether these tests can improve the management of patients with CF, BPD, and wheezing. The use of infant pulmonary function as an outcome measure in any clinical intervention trial will likely require large numbers of infants (1). Through collaboration with manufacturers of commercial devices, easier methods for sharing data to facilitate quality control, interinstitutional networking, and sharing of expert resources should be identified.

Preschool Spirometry

Introduction

Spirometry is widely used to assess lung function in older children and adults, and there are several reasons why it is an appealing technique to apply to the preschool population. Equipment is readily available, and published guidelines for the measurement and interpretation of spirometry in preschool children have been recently published (37). Longitudinal measures from young childhood to adulthood can be obtained. Clinicians are already familiar with FEF and volume measures. Nevertheless, a careful and rigorous approach must be taken to assure data quality, and there remain gaps in our knowledge that currently limit the application of this technique to clinical care.

This section describes the evidence related to preschool spirometry, and identifies gaps in knowledge. The available commercial equipment and standardized procedures used for preschool spirometry are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Children with CF, BPD, and Recurrent Wheeze

CF. There have been several studies of preschool spirometry in children with CF (3, 38–43). Overall, the results of these studies demonstrate that the majority of preschoolers with CF can perform acceptable spirometry, and that abnormalities in lung function, although on average mild, are already present at this age. Deficits noted in infancy persist into the preschool years (3, 6). The proportion with abnormal spirometric measures (defined as a z score ≤ -1.96) vary depending on the outcome measure and population studied, ranging from 9 to 36% (38–40, 42, 44, 45). Longitudinal evaluations demonstrate that lung function declines with age, but the rate of decline is highly variable (3, 6). These results suggest that, although less sensitive than the lung clearance index (LCI) from MBW, spirometry can be successfully performed in the majority of preschool children with CF, and early lung disease can sometimes be detected, although the abnormalities are on average mild and are highly variable (42).

BPD. Spirometry could potentially provide a useful longitudinal measurement for young children with BPD, in whom both lung growth and airway obstruction may be significantly abnormal in early life. Unfortunately, there is a paucity of data on preschool spirometry in children with BPD, and no data to show that spirometry is clinically useful in this population. Another obstacle to the clinical application of spirometry to preterm children is lower success rates associated with below-average cognitive function (46, 47).

Recurrent wheeze. In children with recurrent wheezing, spirometry can be performed to establish baseline lung function and document BDR. There are still limited data regarding the prevalence of BDR in normal preschool children and what constitutes a significant increase in FEV after BD inhalation. With these caveats in mind, studies have found that a post-BD increase between 12 and 15% in FEV_{0.5}, FEV_{0.75}, or FEV₁ is more commonly observed in preschool children with a clinical diagnosis of asthma (48, 49). The degree of BDR may also be affected by baseline disease severity (48) and the dose of BD used. As with older children and adults, the variability in flow-related values (e.g., FEF₂₅₋₇₅) is much greater than that of timed volumes (48), so that the use of FEF₂₅₋₇₅ as an outcome to assess BDR cannot be recommended. Protocols for bronchoprovocation and exercise in preschoolers have been reported (50, 51), but data are insufficient to allow their use in clinical practice.

Gaps in Knowledge and Future Directions

Spirometry can be successfully applied to the preschool population in the clinical setting to identify disease states and track lung function over time. As for all lung function testing, appropriate equipment and testing conditions, skilled and experienced personnel, and rigorous adherence to published guidelines are critical for ensuring high-quality, reproducible data. As with any diagnostic test, spirometry results should be just one additional data element used by clinicians in their assessment and clinical decision making.

Specific Airways Resistance

Introduction

sRaw is assessed while the child breathes tidally through a mouthpiece or modified

facemask in a body plethysmograph (52), without need for any special breathing maneuvers against an airway occlusion. It is therefore well suited for preschool children (53, 54). sRaw is calculated from the relationship between simultaneous measurements of flow at the airway opening and change of plethysmographic pressure. As sRaw is the product of airway resistance (Raw) and FRC, both of which may increase in the presence of airway obstruction and hyperinflation, it is a potentially useful method for identifying obstructive lung disease in young children.

This section describes the evidence related to specific airways resistance and identifies gaps in knowledge. The available commercial equipment and standardized procedures used to measure specific airways resistance are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Children with CF, BPD, and Recurrent Wheeze

CF. sRaw has been found to be significantly elevated in preschool children with CF when compared with healthy control subjects (39, 55), and appears to be more discriminative than spirometry to early lung disease, although less so than the LCI from MBW (55). It has been used in longitudinal studies of disease progression in both preschool (39) and school-age (56) children.

BPD. Although FRC_{pleth} and Raw have been used extensively as outcome measures in both infant and school-age survivors of BPD, to our knowledge, sRaw has not yet been applied to such children during the preschool years, which is probably related to reduced concentration levels and delayed maturity in many of these children.

Recurrent wheeze. Studies in children suggest that sRaw is as efficient as FRC_{pleth} and Raw in distinguishing between children with asthma and healthy children (53). sRaw has been found to be significantly higher in groups of children with asthma than in healthy control subjects (57), and was significantly related to history of recurrent wheeze in a longitudinal birth cohort study (58, 59). As summarized in recent review articles (53, 54), both bronchial hyperresponsiveness and BDR

can be successfully determined using sRaw, with fair discrimination between healthy young children and those with asthma or wheeze. The sensitivity to pharmacologically induced changes of airway patency is comparable for sRaw, transcutaneous oxygen, and impulse oscillometry measurements in young children, whereas sRaw appears to be more sensitive than either spirometry or interrupter Raw (53, 60). It is also important to remember that even healthy young children can have an inherent bronchomotor tone that is BDR responsive, with sRaw decreasing by, on average, 16% after administration of a BD (61). It has been recommended to use a 25% decrease in sRaw relative to the predicted value as the cut-off to screen for asthma in young children (61), but this needs to be confirmed in future studies. The effects of various antiasthma therapies have been documented using sRaw, including the bronchoprotective effect of BD and leukotriene receptor antagonist administration, and the beneficial effect of inhaled corticosteroids on bronchial hyperresponsiveness to cold air challenge (54, 62).

Gaps in Knowledge and Future Directions

Given the potential usefulness of sRaw in preschool and older children, there is an urgent need to establish standardized guidelines. There is growing evidence that the relative flows and lung volume at which the child breathes impact calculated sRaw values, so that software incentives that encourage the child to breathe in a regular and gentle rhythm, and the ability to record and display relevant factors, such as flows, respiratory rate, tidal volume, and end-expiratory level, are needed. There is an urgent need to update reference equations (63), and to ensure that results can be expressed as z scores, which provide more meaningful information than percent predicted values (64). Our knowledge of the evolution of lung function and response to treatment in preschool children with chronic lung diseases, such as CF and BPD, remains very limited. Plethysmographic sRaw could provide an objective and feasible outcome measure in studies designed to fill such gaps in our knowledge.

The Interrupter Technique

Introduction

The interrupter resistance (Rint) technique is a quick, noninvasive measure of respiratory resistance during tidal breathing that may be more easily performed in the preschooler than spirometry.

In this technique, the airway opening is briefly occluded (<100 ms). Resistance (Rint) is calculated from the ratio of pressure change to flow assessed at the airway opening before or after the occlusion (depending on the technique). Two important assumptions are that the valve closes quickly and that the pressure change at the airway opening equilibrates with pressure changes within the alveoli. The recent American Thoracic Society/European Respiratory Society guidelines recommend that occlusions for Rint occur during expiration (37).

This section describes the evidence related to the interrupter technique and identifies gaps in knowledge. The available commercial equipment and standardized procedures used for the interrupter technique are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Children with CF, BPD, and Recurrent Wheeze

CF. There are several studies of Rint in children with CF (39, 65–70), but only three involving children under 6 years of age (39, 67, 70). Although one study found a reasonable correlation between Rint and other lung function indices (sRaw, FEV₁, FEF_{25–75}) (66), most studies have shown that Rint measurements do not distinguish health from disease, either at baseline (39, 66, 68–70) or after BD (39, 67, 69). In addition, two longitudinal studies in 21 (70) and 30 (39) preschool children with CF and have shown no changes in Rint, despite radiographic worsening (70) and changes in sRaw (39). Taken together, these studies suggest that Rint will have limited clinical utility in the preschool population with CF.

BPD. The application of Rint in neonates and infants is limited by their low peak expiratory flows (71–73) and concerns over measurement validity in this age range with current equipment (74). However, a number of investigators have evaluated Rint in preschool children born

prematurely with and without BPD. Two studies have addressed the feasibility and clinical usefulness of Rint in preschool children with BPD, concluding that these vary according to the population and age (75, 76). By preschool age, Rint values were higher in ex-preterm infants with and without BPD compared with healthy term control subjects (76, 77). However, there was an overlap between Rint values in ex-preterm infants with and without BPD, and only in those with the most severe BPD were the Rint values significantly higher compared with those without BPD (72, 76).

Recurrent wheeze. Due to the large intersubject variability in Rint values in health, baseline Rint does not discriminate well between healthy children and those with recurrent wheeze; 5–40% of young children with recurrent wheezing exhibit abnormal baseline values while clinically stable (61, 78–80). Both intrameasurement (81) and short-term intermeasurement (82, 83) variability in children with recurrent wheeze are similar to those of healthy children. BDR has been found to be a better tool for distinguishing children with recurrent wheeze from healthy children (84). To date, three studies designed to assess the accuracy of BDR using Rint in distinguishing between children with current wheeze and healthy preschoolers reported specificity between 70 and 92%, and sensitivity between 24 and 76% (61, 80, 84). During assessment of BDR, a change in Rint values greater than the coefficient of repeatability may reflect bronchial reactivity, but interpretation of hyperresponsiveness should not be based on Rint alone (37).

There are no longitudinal Rint data in children with recurrent wheeze, and reports regarding long-term repeatability of Rint in children with wheeze and healthy children have been conflicting (85, 86). After pharmacological intervention, three small studies found a significant change in Rint (87–89), whereas two studies found no change (90, 91). The latter may, however, have been underpowered, as only a small percentage of children performed Rint measurements.

Gaps in Knowledge and Future Directions

Rint is able to detect changes in airway caliber. However, before Rint can be incorporated into routine clinical practice, certain technical issues need to be addressed.

The effects of factors such as compliant face masks need further investigation. The recommended method to assess pressure change during occlusion has to be compared with other methods described in the literature (92). In addition, the use of Rint as an endpoint in clinical studies, and its sensitivity to detect peripheral airways obstruction and structural damage, are unknown. The long-term change of Rint with treatment, or its predictive value in terms of prognosis, are unknown and need to be investigated.

Forced Oscillation Technique

Introduction

The forced oscillation technique (FOT) is another simple tidal breathing technique for the measurement of respiratory mechanics and Raw requiring less cooperation than spirometry. To perform FOT, the child breathes tidally through a mouthpiece as pressure oscillations are transmitted to the airway opening. Single-frequency sine waves or multiple frequencies may transmit these pressure oscillations, typically through a loudspeaker. The response to this signal is the respiratory impedance (Zrs), the frequency-dependent relationship between transrespiratory pressure and flow. The Zrs may be expressed as respiratory system resistance (Rrs) and reactance (Xrs), with the latter primarily determined by lung elastance at lower frequencies. Xrs represents inertial forces and respiratory system compliance. Rrs and Xrs are reported at different frequencies, from 4 to 48 Hz. The simplicity of the measure has led to its widespread use in preschoolers.

This section describes the evidence related to the FOT and identifies gaps in knowledge. The available commercial equipment and standardized procedures used for the FOT are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Children with CF, BPD, and Recurrent Wheeze

CF. There is limited information regarding the clinical utility of FOT in young children with CF. Young children with CF have been reported to have abnormal Rrs and Xrs in some (93, 94), but not all (39, 43), studies. Gangell and colleagues (95) reported that,

in addition to increased Rrs and decreased Xrs, those children with symptoms in the preceding month had worse Rrs and Xrs than asymptomatic children. To date, there are only two longitudinal studies of FOT in young children with CF, both of which found no association between FOT parameters and the presence of airway infections or cough symptom score (39, 43, 96). Studies of BDR in young children with CF have reported responses similar to those of healthy children (39, 97).

BPD. There are limited studies reporting FOT in young children born preterm with or without a diagnosis of BPD. Vrijlandt and colleagues (77) performed FOT in 77 preterm preschool children and 73 term control subjects. Both Rrs and Xrs were worse in the preterm group (combined BPD and non-BPD) when compared with healthy children born at term. The BPD group ($n = 41$) also exhibited increased frequency dependence of Rrs, higher resonance frequency, and a lower mean Xrs compared with the non-BPD group ($n = 36$). Udomittipong and colleagues (98) measured Zrs in children with BPD attending outpatient clinics, and showed abnormal Rrs and Xrs. In a multivariate analysis of the impact of neonatal factors on subsequent FOT outcomes, increased duration of neonatal O₂ supplementation was significantly related to worsening Rrs and Xrs (98).

Recurrent wheeze. Some studies using FOT in young children with asthma or recurrent wheeze have reported significantly higher Rrs and lower Xrs than in healthy subjects (61, 99–101), whereas others reported similar lung function in both groups (97, 102–105). A significantly larger BDR assessed by Rrs has been reported in young children with asthma compared with control subjects in most studies (61, 99–101, 103, 104), with some not showing differences (97, 102, 105). Changes in Rrs after BD have been reported to be correlated with change in clinical signs in preschool children with an acute asthma exacerbation (106). Most reports confirm the usefulness of FOT in detecting bronchial hyperresponsiveness in young children (107–112). Only two studies have examined the discriminative power of FOT to separate asthmatic young children from healthy control subjects using BDR (61, 99), and further studies are required. There are relatively few longitudinal studies tracking changes with treatments; however, FOT

outcomes were shown to be sensitive to short or prolonged treatment with anti-inflammatory therapy in preschool children with asthma (90, 110, 113).

Gaps in Knowledge and Future Directions

Little is known about which FOT outcome may offer the most clinically relevant information. Future studies should ensure that Rrs, Xrs, resonant frequency, the frequency dependence of Rrs, and the area under the Xrs are reported to allow an improved understanding of this issue. Further studies on the comparability of FOT setups and the intercenter comparisons are needed. The potential role of Xrs in diagnosing obstruction and bronchial responsiveness is not well understood. Longitudinal studies of Zrs in healthy children to document changes with growth and development are also required.

In young children with asthma, further work defining cut-off values for a positive BDR and clinically significant thresholds for the determination of respiratory dysfunction are required. In young children with CF, there is an urgent need for longitudinal studies in which FOT, respiratory symptoms, and the presence and extent of respiratory pathogens and structural lung disease are documented to address the ability of FOT to contribute to clinical management of young children with CF.

MBW Technique

Introduction

The MBW test assesses the efficiency of gas distribution and mixing within the lungs. MBW provides a measure of lung volume (FRC) and of VI due to the heterogeneous distribution of disease processes. To perform the MBW technique, the infant or preschooler tidally breathes an inert gas (tracer gas) through a modified facemask or mouthpiece. This gas (helium, argon, or sulfur hexafluoride) is first “washed in,” then “washed out.” Alternatively, 100% oxygen can be inhaled to wash out the resident nitrogen from the lungs. A range of VI parameters can be calculated, including measures of overall VI, such as the LCI, as well as indices derived from phase III slope (Sn_{III}) analysis. Sn_{III} analysis indices provide additional mechanistic insight, separating VI arising within the conducting airways (convection-dependent

inhomogeneity) from a more distal component arising within the region of the entry to the acinus (diffusion convection-dependent inhomogeneity). Derivation of these indices has been previously described in detail (114). Although recent publications have started to explore the utility of Sn_{III} analysis in this age range, these parameters remain a long way from achieving defined clinical utility, and, as such, this section concentrates on the potential utility of LCI as an outcome measure.

This section describes the evidence related to the MBW technique and identifies gaps in knowledge. The available commercial equipment and standardized procedures used for the MBW technique are presented in the online supplement, along with a description of the safety, feasibility, reproducibility, and reference equations.

Review of Studies Conducted in Children with CF, BPD, and Recurrent Wheezing

CF. Increased LCI values are a consistent finding in CF cohorts, detectable from infancy (115). Abnormal LCI values in the preschool age range are stronger predictors than preschool FEV₁ of subsequent abnormal school age FEV₁ (42), suggesting potential utility as a clinical outcome in early CF. In infants, a combination of MBW and RVRTC appears most useful (115).

BPD. The changing pathophysiology of BPD has altered the pattern of VI abnormality found in subjects with BPD. The increased VI and decreased FRC documented in small cohorts of infants with “old” BPD (116–118) have not been demonstrated in more recent, larger “new” BPD cohort studies (25, 119). This reflects not only the transition of BPD to a more diffuse fibrotic process (120), but also improved study design and methodology, adjusting for confounding factors, such as prematurity. Other studies have demonstrated only small effects of gestational age and intubation duration on FRC, but not LCI, in later infancy (121). These recent results suggest limited utility of MBW in the management and follow-up of “new” BPD (122).

Recurrent wheeze. Increased LCI and convection-dependent inhomogeneity values in multiple-trigger wheeze compared

with episodic (viral) wheeze and healthy control subjects have been reported (57), consistent with the pattern of VI abnormality described in older children and adults with established asthma (123, 124).

Gaps in Knowledge and Future Directions

The clinical utility of MBW is promising in CF, asthma, and preschool wheeze, but a number of challenges remain before the technique can be established in routine clinical care. Longitudinal trends need to be more clearly defined to establish clinically meaningful thresholds (42). Feasibility in routine clinical care of infants and preschoolers with CF, using mass spectrometry-based equipment, has been demonstrated in specialized centers; however, successful transition into *widespread* clinical practice will require well validated, more affordable commercial equipment, which is only now becoming available. Important steps to achieve this goal are being made. Nitrogen-based MBW remains a feasible option outside of the infant age range, but modern data incorporating the recent technological advancements in MBW, and addressing the discrepancies of past studies (125), are urgently needed. An upcoming consensus statement on inert gas washout, endorsed by the European Respiratory Society and American Thoracic Society, will be an

essential resource for researchers and manufacturers.

Conclusions

In these proceedings, we have provided reviews of lung function tests potentially applicable to the clinical evaluation and management of children under 6 years of age with CF, bronchopulmonary dysplasia, and recurrent wheezing. Key conclusions are presented in the EXECUTIVE SUMMARY, and a summary of the current strengths and weaknesses of these lung function tests is provided in the summary table (Table 1).

This Workshop Report was prepared by the Assembly on Pediatrics Working Group on Infant and Preschool Lung Function Testing.

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