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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References

- Davis SD, Rosenfeld M, Kerby GS, Brumback L, Kloster MH, Acton JD, Colin AA, Conrad CK, Hart MA, Hiatt PW, *et al*. Multicenter evaluation of infant lung function tests as cystic fibrosis clinical trial endpoints. *Am J Respir Crit Care Med* 2010;182:1387–1397.
- Ranganathan SC, Stocks J, Dezateux C, Bush A, Wade A, Carr S, Castle R, Dinwiddie R, Hoo AF, Lum S, *et al*. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med* 2004;169:928–933.
- Kozłowska WJ, Bush A, Wade A, Aurora P, Carr SB, Castle RA, Hoo AF, Lum S, Price J, Ranganathan S, *et al*. Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med* 2008;178:42–49.
- Linnane BM, Hall GL, Nolan G, Brennan S, Stick SM, Sly PD, Robertson CF, Robinson PJ, Franklin PJ, Turner SW, *et al*. Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med* 2008;178:1238–1244.
- Harrison AN, Regelman WE, Zirbes JM, Milla CE. Longitudinal assessment of lung function from infancy to childhood in patients with cystic fibrosis. *Pediatr Pulmonol* 2009;44:330–339.
- Beardmore CS, Bar-Yishay E, Maayan C, Yahav Y, Katznelson D, Godfrey S. Lung function in infants with cystic fibrosis. *Thorax* 1988;43:545–551.
- Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, Howenstine MS, Saba O, Coxson HO, Tepper RS. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. *Am J Respir Crit Care Med* 2005;172:1133–1138.
- Peterson-Carmichael SL, Harris WT, Goel R, Noah TL, Johnson R, Leigh MW, Davis SD. Association of lower airway inflammation with physiologic findings in young children with cystic fibrosis. *Pediatr Pulmonol* 2009;44:503–511.
- Pillarisetti N, Williamson E, Linnane B, Skoric B, Robertson CF, Robinson P, Massie J, Hall GL, Sly P, Stick S, *et al*. Infection, inflammation, and lung function decline in infants with cystic fibrosis. *Am J Respir Crit Care Med* 2011;184:75–81.
- Subbarao P, Balkovec S, Solomon M, Ratjen F. Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis. *Pediatr Pulmonol* 2007;42:471–476.
- Dellon EP, Donaldson SH, Johnson R, Davis SD. Safety and tolerability of inhaled hypertonic saline in young children with cystic fibrosis. *Pediatr Pulmonol* 2008;43:1100–1106.
- Stocks J, Modi N, Tepper R. Need for healthy control subjects when assessing lung function in infants with respiratory disease. *Am J Respir Crit Care Med* 2010;182:1340–1342.
- Godfrey S, Mearns M, Howlett G. Serial lung function studies in cystic fibrosis in the first 5 years of life. *Arch Dis Child* 1978;53:83–85.

- 14 Kraemer R. Early detection of lung function abnormalities in infants with cystic fibrosis. *J R Soc Med* 1989;82:21–25.
- 15 Beardsmore CS, Thompson JR, Williams A, McArdle EK, Gregory GA, Weaver LT, Simpson H. Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment. *Arch Dis Child* 1994;71:133–137.
- 16 Robin B, Kim YJ, Huth J, Klocksieben J, Torres M, Tepper RS, Castile RG, Solway J, Hershenson MB, Goldstein-Filbrun A. Pulmonary function in bronchopulmonary dysplasia. *Pediatr Pulmonol* 2004; 37:236–242.
- 17 Filbrun AG, Popova AP, Linn MJ, McIntosh NA, Hershenson MB. Longitudinal measures of lung function in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 2011;46:369–375.
- 18 Friedrich L, Stein RT, Pitrez PM, Corso AL, Jones MH. Reduced lung function in healthy preterm infants in the first months of life. *Am J Respir Crit Care Med* 2006;173:442–447.
- 19 Friedrich L, Pitrez PM, Stein RT, Goldani M, Tepper R, Jones MH. Growth rate of lung function in healthy preterm infants. *Am J Respir Crit Care Med* 2007;176:1269–1273.
- 20 Nickerson BG, Durand DJ, Kao LC. Short-term variability of pulmonary function tests in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1989;6:36–41.
- 21 Kao LC, Durand DJ, McCrea RC, Birch M, Powers RJ, Nickerson BG. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr* 1994; 124:772–781.
- 22 Vural M, Kremp O, Cambier F, Krim G, Kilani L, Leke L, Freville M, Libert JP, Risbourg B. Evolution of the result of respiratory function studies in children with bronchopulmonary dysplasia. *Arch Pediatr* 1996;3:1229–1238.
- 23 Wauer RR, Maurer T, Nowotny T, Schmalisch G. Assessment of functional residual capacity using nitrogen washout and plethysmographic techniques in infants with and without bronchopulmonary dysplasia. *Intensive Care Med* 1998;24: 469–475.
- 24 Kao LC, Durand DJ, Nickerson BG. Effects of inhaled metaproterenol and atropine on the pulmonary mechanics of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1989;6:74–80.
- 25 Hulskamp G, Lum S, Stocks J, Wade A, Hoo AF, Costeloe K, Hawdon J, Deeptha K, Pillow JJ. Association of prematurity, lung disease and body size with lung volume and ventilation inhomogeneity in unsedated neonates: a multicentre study. *Thorax* 2009;64:240–245.
- 26 Hofhuis W, Huysman MW, van der Wiel EC, Holland WP, Hop WC, Brinkhorst G, de Jongste JC, Merkus PJ. Worsening of V_{max}FRC in infants with chronic lung disease in the first year of life: a more favorable outcome after high-frequency oscillation ventilation. *Am J Respir Crit Care Med* 2002;166:1539–1543.
- 27 Hall GL, Hantos Z, Sly PD. Altered respiratory tissue mechanics in asymptomatic wheezy infants. *Am J Respir Crit Care Med* 2001; 164:1387–1391.
- 28 Wildhaber JH, Dore ND, Devadason SG, Hall GL, Hamacher J, Arheden L, LeSouef PN. Comparison of subjective and objective measures in recurrently wheezy infants. *Respiration* 2002;69:397–405.
- 29 Saito J, Harris WT, Gelfond J, Noah TL, Leigh MW, Johnson R, Davis SD. Physiologic, bronchoscopic, and bronchoalveolar lavage fluid findings in young children with recurrent wheeze and cough. *Pediatr Pulmonol* 2006;41:709–719.
- 30 Borrego LM, Stocks J, Leiria-Pinto P, Peralta I, Romeira AM, Neuparth N, Rosado-Pinto JE, Hoo AF. Lung function and clinical risk factors for asthma in infants and young children with recurrent wheeze. *Thorax* 2009;64:203–209.
- 31 Llapur CJ, Martinez TM, Coates C, Tiller C, Wiebke JL, Li X, Applegate K, Coxson HO, Tepper RS. Lung structure and function of infants with recurrent wheeze when asymptomatic. *Eur Respir J* 2009;33: 107–112.
- 32 Hayden MJ, Wildhaber JH, LeSouef PN. Bronchodilator responsiveness testing using raised volume forced expiration in recurrently wheezing infants. *Pediatr Pulmonol* 1998;26:35–41.
- 33 Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL, Wildhaber JH. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. *Eur Respir J* 2005;25:289–294.
- 34 Mallol J, Aguirre V, Barrieto L, Wandalsen G, Tepper R. Effect of inhaled fluticasone on lung function in infants with recurrent wheezing: a randomised controlled trial. *Allergol Immunopathol (Madr)* 2009;37:57–62.
- 35 Kraemer R, Graf Bigler U, Casaulta Aebischer C, Weder M, Birrer P. Clinical and physiological improvement after inhalation of low-dose beclomethasone dipropionate and salbutamol in wheezy infants. *Respiration* 1997;64:342–349.
- 36 van der Wiel EC, Hofhuis W, Holland WP, Tiddens HA, de Jongste JC, Merkus PJ. Predictive value of infant lung function testing for airway malacia. *Pediatr Pulmonol* 2005;40:431–436.
- 37 Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007;175:1304–1345.
- 38 Marostica PJ, Weist AD, Eigen H, Angelicchio C, Christoph K, Savage J, Grant D, Tepper RS. Spirometry in 3- to 6-year-old children with cystic fibrosis. *Am J Respir Crit Care Med* 2002;166:67–71.
- 39 Nielsen KG, Pressler T, Klug B, Koch C, Bisgaard H. Serial lung function and responsiveness in cystic fibrosis during early childhood. *Am J Respir Crit Care Med* 2004;169:1209–1216.
- 40 Vilozni D, Bentur L, Efrati O, Minuskin T, Barak A, Szeinberg A, Blau H, Picard E, Kerem E, Yahav Y, et al. Spirometry in early childhood in cystic fibrosis patients. *Chest* 2007;131:356–361.
- 41 Mayer OH, Jawad AF, McDonough J, Allen J. Lung function in 3–5-year-old children with cystic fibrosis. *Pediatr Pulmonol* 2008; 43:1214–1223.
- 42 Aurora P, Stanojevic S, Wade A, Oliver C, Kozłowska W, Lum S, Bush A, Price J, Carr SB, Shankar A, et al. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2011;183:752–758.
- 43 Kerby G, Rosenfeld M, Ren CL, Mayer OH, Brumback L, Castile R, Hart M, Hiatt P, Kloster M, Johnson R, et al. Lung function distinguishes preschool children with CF from healthy controls in a multi-center setting. *Pediatr Pulmonol* 2011.
- 44 Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W, et al. Spirometry centile charts for young Caucasian children: The Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med* 2009;180:547–552.
- 45 Sonnappa S, Bastardo CM, Stafler P, Bush A, Aurora P, Stocks J. Ethnic differences in fraction of exhaled nitric oxide and lung function in healthy young children. *Chest* 2011;140:1325–1331.
- 46 Sinkin RA, Kramer BM, Merzbach JL, Myers GJ, Brooks JG, Palumbo DR, Cox C, Kendig JW, Mercier CE, Phelps DL. School-age follow-up of prophylactic versus rescue surfactant trial: Pulmonary, neurodevelopmental, and educational outcomes. *Pediatrics* 1998; 101:E11.
- 47 Burns YR, Danks M, O'Callaghan MJ, Gray PH, Cooper D, Poulsen L, Watter P. Motor coordination difficulties and physical fitness of extremely-low-birthweight children. *Dev Med Child Neurol* 2009;51: 136–142.
- 48 Vilozni D, Barak A, Efrati O, Augarten A, Springer C, Yahav Y, Bentur L. The role of computer games in measuring spirometry in healthy and “asthmatic” preschool children. *Chest* 2005;128: 1146–1155.
- 49 Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. *Thorax* 2005;60: 13–16.
- 50 Vilozni D, Bentur L, Efrati O, Barak A, Szeinberg A, Shoseyov D, Yahav Y, Augarten A. Exercise challenge test in 3- to 6-year-old asthmatic children. *Chest* 2007;132:497–503.
- 51 Vilozni D, Livnat G, Dabbah H, Elias N, Hakim F, Bentur L. The potential use of spirometry during methacholine challenge test in young children with respiratory symptoms. *Pediatr Pulmonol* 2009; 44:720–727.
- 52 Goldman M, Smith HJ, Ulmer WT; European Respiratory Society. Whole-body plethysmography. Lung function testing. Sheffield: ERS Journals Ltd; 2005. pp. 15–43.

- 53 Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest* 2005;128:355–362.
- 54 Nielsen KG. Plethysmographic specific airway resistance. *Paediatr Respir Rev* 2006;7:S17–S19.
- 55 Aurora P, Bush A, Gustafsson P, Oliver C, Wallis C, Price J, Stroobant J, Carr S, Stocks J. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2005;171:249–256.
- 56 Kraemer R, Blum A, Schibler A, Ammann RA, Gallati S. Ventilation inhomogeneities in relation to standard lung function in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2005;171:371–378.
- 57 Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, Aurora P. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010;126:519–526.e1–7.
- 58 Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet* 2002;359:1904–1908.
- 59 Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005;171:231–237.
- 60 Klug B, Bisgaard H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2–7 years. *Pediatr Pulmonol* 1998;25:322–331.
- 61 Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med* 2001;164:554–559.
- 62 Nielsen KG, Bisgaard H. Hyperventilation with cold versus dry air in 2- to 5-year-old children with asthma. *Am J Respir Crit Care Med* 2005;171:238–241.
- 63 Kirkby J, Stanojevic S, Welsh L, Lum S, Badier M, Beardsmore C, Custovic A, Nielsen K, Paton J, Tomalak W, et al. Reference equations for specific airway resistance in children: the Asthma UK Initiative. *Eur Respir J* 2010;36:622–629.
- 64 Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J* 2010;36:12–19.
- 65 Carter ER, Stecenko AA, Pollock BH, Jaeger MJ. Evaluation of the interrupter technique for the use of assessing airway obstruction in children. *Pediatr Pulmonol* 1994;17:211–217.
- 66 Oswald-Mammosser M, Charloux A, Donato L, Albrecht C, Speich JP, Lampert E, Lonsdorfer J. Interrupter technique versus plethysmography for measurement of respiratory resistance in children with asthma or cystic fibrosis. *Pediatr Pulmonol* 2000;29:213–220.
- 67 Beydon N, Amsallem F, Bellet M, Boule M, Chaussain M, Denjean A, Matran R, Pin I, Alberti C, Gaultier C. Pulmonary function tests in preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2002;166:1099–1104.
- 68 Lum S. Lung function in preschool children: applications in clinical and epidemiological research. *Paediatr Respir Rev* 2006;7:S30–S32.
- 69 Davies PL, Doull IJ, Child F. The interrupter technique to assess airway responsiveness in children with cystic fibrosis. *Pediatr Pulmonol* 2007;42:23–28.
- 70 Terheggen-Lagro SW, Arets HG, van der Laag J, van der Ent CK. Radiological and functional changes over 3 years in young children with cystic fibrosis. *Eur Respir J* 2007;30:279–285.
- 71 Chavasse RJ, Bastian-Lee Y, Seddon P. Comparison of resistance measured by the interrupter technique and by passive mechanics in sedated infants. *Eur Respir J* 2001;18:330–334.
- 72 Hall GL, Wildhaber JH, Cernelc M, Frey U. Evaluation of the interrupter technique in healthy, unsedated infants. *Eur Respir J* 2001;18:982–988.
- 73 Garbrielle C, Nieuwhof E, van der Wiel E, de Jongste JC, Merkus PJ. Feasibility and usefulness of Rint measurements in sedated infants with chronic lung disease. *Eur Respir J* 2007;30:E1431.
- 74 Adams AM, Olden C, Wertheim D, Ives A, Bridge PD, Lenton J, Seddon P. Measurement and repeatability of interrupter resistance in unsedated newborn infants. *Pediatr Pulmonol* 2009;44:1168–1173.
- 75 Thomas MR, Marston L, Rafferty GF, Calvert S, Marlow N, Peacock JL, Greenough A. Respiratory function of very prematurely born infants at follow up: influence of sex. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F197–F201.
- 76 Kairamkonda VR, Richardson J, Subhedar N, Bridge PD, Shaw NJ. Lung function measurement in prematurely born preschool children with and without chronic lung disease. *J Perinatol* 2008;28:199–204.
- 77 Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. *J Pediatr* 2007;150:256–261.
- 78 Merkus PJ, Mijnsbergen JY, Hop WC, de Jongste JC. Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001;163:1350–1355.
- 79 Beydon N, M'Buila C, Bados A, Peiffer C, Bernard A, Zaccaria I, Denjean A. Interrupter resistance short-term repeatability and bronchodilator response in preschool children. *Respir Med* 2007;101:2482–2487.
- 80 Beydon N, Pin I, Matran R, Chaussain M, Boule M, Alain B, Bellet M, Amsallem F, Alberti C, Denjean A, et al. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med* 2003;168:640–644.
- 81 Beydon N, Amsallem F, Bellet M, Boule M, Chaussain M, Denjean A, Matran R, Wuyam B, Alberti C, Gaultier C. Pre/postbronchodilator interrupter resistance values in healthy young children. *Am J Respir Crit Care Med* 2002;165:1388–1394.
- 82 Bridge PD, Ranganathan S, McKenzie SA. Measurement of airway resistance using the interrupter technique in preschool children in the ambulatory setting. *Eur Respir J* 1999;13:792–796.
- 83 Thamrin C, Frey U. Effect of bacterial filter on measurement of interrupter resistance in preschool and school-aged children. *Pediatr Pulmonol* 2008;43:781–787.
- 84 McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;15:833–838.
- 85 Lombardi E, Sly PD, Concutelli G, Novembre E, Veneruso G, Frongia G, Bernardini R, Vierucci A. Reference values of interrupter respiratory resistance in healthy preschool white children. *Thorax* 2001;56:691–695.
- 86 Chan EY, Bridge PD, Dundas I, Pao CS, Healy MJ, McKenzie SA. Repeatability of airway resistance measurements made using the interrupter technique. *Thorax* 2003;58:344–347.
- 87 Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500–1506.
- 88 Pao CS, McKenzie SA. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med* 2002;166:945–949.
- 89 Straub DA, Minocchieri S, Moeller A, Hamacher J, Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. *Chest* 2005;127:509–514.
- 90 Kooi EM, Schokker S, Marike Boezen H, de Vries TW, Vaessen-Verberne AA, van der Molen T, Duiverman EJ. Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. *Pulm Pharmacol Ther* 2008;21:798–804.
- 91 Schokker S, Kooi EM, de Vries TW, Brand PL, Mulder PG, Duiverman EJ, van der Molen T. Inhaled corticosteroids for recurrent respiratory symptoms in preschool children in general practice: randomized controlled trial. *Pulm Pharmacol Ther* 2008;21:88–97.
- 92 Seddon P, Wertheim D, Bridge P, Bastian-Lee Y. How should we estimate driving pressure to measure interrupter resistance in children? *Pediatr Pulmonol* 2007;42:757–763.
- 93 Cogswell JJ, Hull D, Milner AD, Norman AP, Taylor B. Lung function in childhood. III. Measurement of airflow resistance in healthy children. *Br J Dis Chest* 1975;69:177–187.
- 94 Solymar L, Aronsson PH, Sixt R. The forced oscillation technique in children with respiratory disease. *Pediatr Pulmonol* 1985;1:256–261.
- 95 Gangell CL, Horak F Jr, Patterson HJ, Sly PD, Stick SM, Hall GL. Respiratory impedance in children with cystic fibrosis using forced oscillations in clinic. *Eur Respir J* 2007;30:892–897.

- 96 Ren CL, Rosenfeld M, Mayer OH, Davis SD, Kloster M, Castile RG, Hiatt PW, Hart M, Johnson R, Jones P, *et al.* Analysis of the associations between lung function and clinical features in preschool children with cystic fibrosis. *Pediatr Pulmonol* 2012;47:574–581.
- 97 Thamrin C, Gangell CL, Udomittipong K, Kusel MM, Patterson H, Fukushima T, Schultz A, Hall GL, Stick SM, Sly PD. Assessment of bronchodilator responsiveness in preschool children using forced oscillations. *Thorax* 2007;62:814–819.
- 98 Udomittipong K, Sly PD, Patterson HJ, Gangell CL, Stick SM, Hall GL. Forced oscillations in the clinical setting in young children with neonatal lung disease. *Eur Respir J* 2008;31:1292–1299.
- 99 Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax* 2003;58:494–499.
- 100 Oostveen E, Dom S, Desager K, Hagendorens M, De Backer W, Weyler J. Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes. *Eur Respir J* 2010;35:865–872.
- 101 Vu LT, Demoulin B, Nguyen MT, Nguyen YT, Marchal F. Respiratory impedance and response to salbutamol in asthmatic Vietnamese children. *Pediatr Pulmonol* 2010;45:380–386.
- 102 Hellinckx J, De Boeck K, Bande-Knops J, van der Poel M, Demedts M. Bronchodilator response in 3–6.5 years old healthy and stable asthmatic children. *Eur Respir J* 1998;12:438–443.
- 103 Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. *J Allergy Clin Immunol* 2003;112:317–322.
- 104 Song TW, Kim KW, Kim ES, Park JW, Sohn MH, Kim KE. Utility of impulse oscillometry in young children with asthma. *Pediatr Allergy Immunol* 2008;19:763–768.
- 105 Harrison J, Gibson AM, Johnson K, Singh G, Skoric B, Ranganathan S. Lung function in preschool children with a history of wheezing measured by forced oscillation and plethysmographic specific airway resistance. *Pediatr Pulmonol* 2010;45:1049–1056.
- 106 Chalut DS, Ducharme FM, Davis GM. The preschool respiratory assessment measure (PRAM): a responsive index of acute asthma severity. *J Pediatr* 2000;137:762–768.
- 107 Lenney W, Milner AD. Recurrent wheezing in the preschool child. *Arch Dis Child* 1978;53:468–473.
- 108 Duiverman EJ, Neijens HJ, van Strik R, van der Snee-van Smaalen M, Kerrebijn KF. Bronchial responsiveness in asthmatic children aged 3 to 8 years measured by forced pseudo-random noise oscillometry. *Bull Eur Physiopathol Respir* 1986;22:27–33.
- 109 Wilson NM, Bridge P, Phagoo SB, Silverman M. The measurement of methacholine responsiveness in 5 year old children: three methods compared. *Eur Respir J* 1995;8:364–370.
- 110 Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2–5 years of age. *Am J Respir Crit Care Med* 2000;161:1805–1809.
- 111 Malmberg LP, Makela MJ, Mattila PS, Hammaren-Malmi S, Pelkonen AS. Exercise-induced changes in respiratory impedance in young wheezy children and nonatopic controls. *Pediatr Pulmonol* 2008;43:538–544.
- 112 Hall GL, Gangell C, Fukushima T, Horak F, Patterson H, Stick SM, Sly PD, Franklin PJ. Application of a shortened inhaled adenosine-5'-monophosphate challenge in young children using the forced oscillation technique. *Chest* 2009;136:184–189.
- 113 Moeller A, Lehmann A, Knauer N, Albisetti M, Rochat M, Johannes W. Effects of montelukast on subjective and objective outcome measures in preschool asthmatic children. *Pediatr Pulmonol* 2008;43:179–186.
- 114 Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. *Respiration* 2009;78:339–355.
- 115 Lum S, Gustafsson P, Ljungberg H, Hulskamp G, Bush A, Carr SB, Castle R, Hoo AF, Price J, Ranganathan S, *et al.* Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. *Thorax* 2007;62:341–347.
- 116 Gerhardt T, Hehre D, Feller R, Reifenberg L, Bancalari E. Serial determination of pulmonary function in infants with chronic lung disease. *J Pediatr* 1987;110:448–456.
- 117 Shao H, Sandberg K, Hjalmarson O. Impaired gas mixing and low lung volume in preterm infants with mild chronic lung disease. *Pediatr Res* 1998;43:536–541.
- 118 Hjalmarson O, Sandberg KL. Lung function at term reflects severity of bronchopulmonary dysplasia. *J Pediatr* 2005;146:86–90.
- 119 Latzin P, Roth S, Thamrin C, Hutten GJ, Pramana I, Kuehni CE, Casaulta C, Nelle M, Riedel T, Frey U. Lung volume, breathing pattern and ventilation inhomogeneity in preterm and term infants. *PLoS ONE* 2009;4:e4635.
- 120 Husain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. *Hum Pathol* 1998;29:710–717.
- 121 Schulzke SM, Hall GL, Nathan EA, Simmer K, Nolan G, Pillow JJ. Lung volume and ventilation inhomogeneity in preterm infants at 15–18 months corrected age. *J Pediatr* 2010;156:542–549.e542.
- 122 Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. *Eur Respir J* 2011;37:1199–1207.
- 123 Verbanck S, Schuermans D, Paiva M, Vincken W. Nonreversible conductive airway ventilation heterogeneity in mild asthma. *J Appl Physiol* 2003;94:1380–1386.
- 124 Macleod KA, Horsley AR, Bell NJ, Greening AP, Innes JA, Cunningham S. Ventilation heterogeneity in children with well controlled asthma with normal spirometry indicates residual airways disease. *Thorax* 2009;64:33–37.
- 125 Robinson PD, Latzin P, Gustafsson P. Multiple-breath washout: paediatric lung function. European Respiratory Monograph. Sheffield, UK: ERS Journals Ltd.; 2010.