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Clinical Applications of Pediatric Pulmonary Function Testing: Lung Function in Recurrent Wheezing and Asthma

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Pulmonary function testing remains the gold standard for the diagnosis and management of wheezing disorders in older children and adults. Although wheezing disorders are among the most common clinical problems in pediatrics, most young children and toddlers cannot perform most of the currently clinically available pulmonary function tests. In this article, we review the different types of pulmonary function tests available and discuss the applicability and utility in the different age groups with specific reference to suitability in the diagnosis and management of wheezing disorders.

Introduction

Asthma is a chronic reversible obstructive airway disease. In school-age children objective measurement of lung function is essential to the diagnosis and evaluation of asthma, as medical history and physical examination are not reliable means of assessment.[1] Although clinicians are generally able to identify airflow obstruction clinically,[2] they are unable to assess the degree or reversibility of the airflow obstruction.[3] In a recent study, up to a third of children with moderate-to-severe asthma were reclassified to a more severe asthma category when spirometry was assessed in addition to symptom frequency.[4] In contrast, another study found that most children with mild-to-moderate asthma by symptom classification were found to have normal lung function by FEV_1 [forced expiratory volume in one second (spirometry)].[5] These seemingly contradictory findings emphasize the importance of including pulmonary function testing (PFT) in a comprehensive assessment of asthma.

Recurrent wheezing affects 20%–30% of infants and toddlers, yet resolves in at least half of these children by school age. Eighty percent of school-age children with persistent asthma were symptomatic by age 6 years, with more than half symptomatic by age 3 years.[6] However, differentiating transient wheezing from persistent asthma in the early years is problematic since the 2 syndromes have only been described epidemiologically. Therefore, practical methodologies to objectively assess lung function in infants and toddlers for the purposes of accurately diagnosing asthma are highly desirable.

In this review, we will attempt to concisely review the literature of currently available pulmonary function techniques in children to assist in the diagnosis and management of asthma and recurrent wheezing.

Spirometry

Childhood

Spirometry is the gold standard for the diagnosis and management of asthma. It is the most commonly used method to assess lung function. Recent NIH guidelines[7] recommend the use of spirometry, specifically FEV_1 and FEV_1/FVC [forced vital capacity (spirometry)] ratio for the diagnosis and management of children older than 5 years. This is in part due to the fact that pulmonary function has been found to be more sensitive than clinical examination[2,3] or symptoms for the detection of obstructive pathology.[4] The greatest value in diagnosing asthma with the use of spirometry is the documentation of reversibility with short acting bronchial agonist. The degree of reversibility has been correlated with the degree of airway inflammation[8] and postbronchodilator measures can be used to follow lung growth and remodeling.[9] Further, those children with the greatest reversibility with a short acting bronchial agonist are most at risk for remodeling and loss of lung function over time.[10]

Other factors making spirometry a useful test in the assessment of asthma and bronchodilator response (BDR) include portability of the measurement device, ease of use for the operator, and repeatability of the maneuver. Spirometry

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is the least variable of the pulmonary function maneuvers currently commercially offered in most clinical laboratories. The coefficient of variation for FEV_1 ranges from 2.7% to 5%, whereas the variability of other measures such as specific airway resistance (sRaw), respiratory resistance during interruption (interrupter resistance) (Rint), and respiratory impedance (forced oscillation technique) (Xrs) are at least double to triple.[11,12] This low coefficient of variation would suggest that FEV_1 would be the most sensitive test to detect BDR; however, most studies have not assessed the between-occasion repeatability in disease states.[13] Only 1 study in adults studied this phenomenon and suggested that the variability of FEV_1 was significantly higher in disease states, thus suggesting that other measures may be more sensitive to BDR assessment.[13] This conclusion requires further study.

Other limitations of FEV_1 relate to the physiology underlying its measurement. Asthma is primarily a disease of the small airways[14] and studies in well-controlled asthmatics have shown continued obstruction and airway inflammation in the small airways despite normal measures of the large airways. The FEV_1 may remain preserved despite significant small airway obstruction, and hence the need for more sensitive measures of small airway obstruction. This is an active area of research and may in the near future lead to the development of novel strategies to monitor disease progression.

At the current time, FEV_1 remains the most studied lung function measure in asthma and remains the most recommended physiological assessment for the diagnosis and management of wheezing disorders in childhood.

Preschool children

Children as young as 3 years of age are capable of performing spirometry under ideal laboratory conditions when trained by technicians skilled in performing spirometry in this age group. In 2007 the American Thoracic Society (ATS) and European Respiratory Society (ERS) published a statement that included technical recommendations for the performance of spirometry in preschool children to facilitate comparison of data between centers.[11] Several studies describing spirometric data in healthy preschool-age children have been published over the past decade,[15–18] and recently Stanojevic et al. published robust reference equations for children ages 3 through 7 years based on an analysis of preschool lung function data from 3,777 children collated from 15 centers in 11 countries.[19]

An important limitation to clinical use of preschool spirometry is the lack of repeatability data, thus limiting interpretations of change in lung function following a clinical intervention, such as response to bronchodilators or corticosteroids. Another practical limitation is the feasibility of obtaining measurements in a busy clinical practice. Recently, Gaffin et al. conducted a real-world assessment of preschool spirometry feasibility in 248 children in a busy pediatric pulmonary function laboratory.[20] In their hands, 82% of preschool children performing spirometry for the first time were able to complete at least 1 technically acceptable maneuver, but only 54% were capable of performing spirometry that was acceptable and repeatable based on ATS/ERS preschool spirometry recommendations. Although, the group of children with asthma reported in the cohort by Gaffin et al., did not have forced expiratory volumes or flows that were significantly different from healthy children; 30% of the individual asthmatic children had evidence of airflow obstruction by FEV_1 or $FEF_{25–75}$ [forced expiratory flow at 25% to 75% of expiration (spirometry)], suggesting that preschool spirometry may provide clinically useful information for a substantial subset of individual patients in this age group.

Infants

Although infants and toddlers are not capable of independently performing spirometric maneuvers, the raised-volume rapid thoracoabdominal compression (RVRTC) technique can be used to measure forced expiratory flows and volumes in children ≤ 3 years of age under sedation with chloral hydrate. During the RVRTC maneuver an infant's lungs are inflated to near total lung capacity (TLC) followed by a forced expiration.[21–23] The RVRTC technique allows generation of flow–volume curves that are similar to adult-type flow–volume curves. RVRTC-forced expiratory flows and volumes have been used to assess infants with bronchiolitis and recurrent wheezing,[24,25] and bronchodilator responsiveness in healthy infants.[26] Reference values from healthy infants are published,[27] and 2 devices to perform infant PFT (iPFT) using the RVRTC method are commercially available.

However, there are several important barriers to using the RVRTC technique to obtain lung function measurements for clinical use. Little data exist regarding the within- and between-occasion repeatability of RVRTC measurements. Performing RVRTC measurements is complex and time consuming, requires sedation of the patient, and must be performed using expensive equipment operated by highly trained personnel. For these reasons, the ability to obtain high-quality RVRTC measurements is limited to a small number of laboratories around the world. Published normative data were derived from a relatively small sample size ($n = 155$), limiting its generalizability to populations around the world with different ethnicities as well as social and environmental backgrounds.[27] Further, longitudinal studies assessing the predictive value of RVRTC lung function values for persistent asthma among infants with recurrent wheezing is lacking. Although published data describing forced expiratory volumes and flows following administration of albuterol in healthy children exist,[26] a consensus does not yet reached on the definition of a clinical BDR during RVRTC maneuvers. Although infant lung function testing using the RVRTC technique is a powerful research tool, the technical issues summarized above may limit its use as a routine clinical tool in assessing infants and toddlers with wheezing disorders.

Lung Volume Measurements

Plethysmography

Lung volume measurements in preschool and school-age children are easily performed using multiple methodologies, including whole-body plethysmography or gas washout techniques. Plethysmographic measurements can be performed using either panting methods (only suitable for older children) or single inspiratory effort technique.[28] However, there are conflicting reports on the utility of lung volume parameters in children with controlled asthma.[29,30] This may be due in part to the selection of proper reference data and high variability in measurement of some of the parameters. The literature suggests that in older individuals, static lung volume measurement may be abnormal in asthmatic patients and more sensitive than FEV_1 to small airway dysfunction.[31,32] This methodology has been hampered by the need for bulky expensive equipment, lack of portability, and difficulty in performing the maneuver.

Whole-body plethysmography can be performed in infants and toddlers using commercially available equipment to obtain measurements of functional residual capacity (plethysmography) (FRC_{pleth}), residual volume (RV), TLC, and the ratio of RV/TLC.[33] However, there is very little published data assessing the utility of plethysmographic lung function measures in infants and toddlers with recurrent wheezing to predict asthma. Saito et al. reported that among children less than 3 years old with recurrent wheezing unresponsive to asthma medications, plethysmography revealed mean FRC and RV/TLC measurements greater than 2 z-scores above published normative data.[34] Unfortunately, the only available published normative plethysmography data[35] are based on a very small sample size, limiting generalizability of plethysmography measurements in the assessment of infants and toddlers with recurrent wheezing.

Multiple breath inert gas washout

The multiple breath inert gas washout technique is used to assess lung ventilation inhomogeneity as well as measurement of FRC. The advantage of multiple breath washout is that it is an effort independent technique and thus can be applied from infancy to adulthood using tidal breathing techniques.[11,36] The lung clearance index (LCI), the cumulative expired volume required to clear the inert gas to 1/40th of the initial gas concentration from the lungs divided by the FRC, seems to be a useful and sensitive measure of peripheral airway obstruction, especially in cystic fibrosis.[37–41] Other parameters can also be calculated such as the normalized slopes and moment ratios. The usefulness of these other parameters is limited by the small number of studies and the increasing complexity in understanding what they represent physiologically. The ideal parameter for reporting is elusive at present due to the paucity of data in the different age ranges and disease entities. Several studies have been published suggesting that LCI, moment ratios, as well as other parameters are significantly different in patients suffering from asthma and preschool wheeze.[42–46] One study has suggested that its utility may be superior to other pulmonary function parameters that are possible to perform in preschool children.[47] However, further work needs to be done to understand the relevance of abnormalities in LCI and whether it correlates to clinically meaningful outcomes longitudinally. The multiple breath washout methodology is currently available using different commercial devices; however, validation studies comparing different methodologies are lacking and standardization in reporting has not been established.

Airway Resistance Measurements

Specific airway resistance

Plethysmographic measurements of sRaw can be obtained during tidal breathing without the need for specialized breathing maneuvers or respiration against an airway occlusion.[48] sRaw is calculated as the product of FRC and Raw.[49] This technique has been successfully performed in children as young as age 2 years.[50] While limited data from a few specialized research centers suggest that sRaw is increased in preschool-age children with recurrent wheezing or asthma compared to healthy children,[51–56] it has been purported in older subjects to be more sensitive to bronchodilator changes than traditional lung function tests such as spirometry.[13,57] Further, sRaw has been demonstrated to improve following treatment with inhaled corticosteroids,[54] leukotriene receptor antagonists,[51] and β_2-agonists.[55,58]

Despite the appeal of sRaw as a lung function measurement that can be obtained in preschool-age children, there are a number of important limitations to the applicability of this measure in clinical decision making in preschool-age children. A consensus does not exist with regard to standardization of measurement equipment and conditions, and data analysis. Recently, as part of The Asthma UK Initiative, Kirkby et al. proposed reference equations constructed from sRaw data obtained from healthy children ages 3–10 years at 5 European centers.[59] However, Kirkby et al. caution that their reference equations should only be applied to populations studied using the same methodology as employed in the centers included in their analysis. The development of international consensus recommendations (eg, ATS/ERS) for equipment and methodology to perform sRaw measurements in preschool-age children would facilitate its utility as a lung function measurement technique for clinical use in the diagnosis or monitoring of asthma or wheezing disorders in this age group.

The interrupter technique

Respiratory tract resistance can be estimated during tidal breathing using the interrupter technique. Based on the assumption that during a brief airway occlusion mouth pressure rapidly equilibrates with alveolar pressure, respiratory Rint is defined as occlusion mouth pressure divided by the airflow measured immediately before an occlusion.[60] Measurement of Rint using commercially available equipment is possible in most children as young as 3 years old with acceptable within- and between-occasion repeatability.[11] Using data collected from more than 1,000 children, Merkus et al. recently published robust reference equations to allow better interpretation of Rint measurements obtained from young children.[61] Several clinical studies have demonstrated higher Rint values among preschool-age children with asthma or recurrent wheezing as compared to healthy controls; however, a large degree of overlap in distribution of Rint between healthy and asthmatic or wheezy infants has been noted.[55,62,63]

Although Rint has been used to estimate the magnitude of change in airflow resistance in response to a bronchodilator, an accepted cut-off to define bronchodilator responsiveness in preschool-age children does not currently exist.[11] Due to the poor discriminative power of Rint between asthma and health at the individual level, and lack of a defined clinical BDR, the utility of Rint in clinical diagnosis of asthma in preschool-age children is limited. However, with the advent of newly established reference equations,[61] Rint may prove to be useful to assess response to therapeutic interventions longitudinally.

Forced oscillometry

The forced oscillation technique (FOT) is a noninvasive lung function test that can be performed during tidal breathing with minimal cooperation from the patient.[64] Given the simplicity of the maneuver, the FOT technique is an attractive methodology for use in preschool-age children. Unfortunately, the complexity of the mathematic and physics assumptions upon which FOT is based have proven challenging for clinicians and researchers alike to fully understand. Several reviews are available for a more complete description of the underlying principal of FOT.[11,64–66] Briefly, an oscillatory signal, most commonly pseudorandom at frequencies between 4 and 10 Hz, is applied to the airway opening using a mouthpiece. Flow and pressure are measured at the mouth. Resultant pressure and flow fluctuations at the mouth in response to the applied oscillatory signal are measured. The pressure and flow relationship is described as Xrs, where Xrs is determined by the elastic and inertial properties of the respiratory system. Respiratory resistance (Rrs) represents the total Rrs, of which airway resistance is the most significant.

A recent ATS/ERS statement on PFT in preschool children attempted to standardize FOT measurements by recommending that the optimal measurement frequencies be between 4 and 8 Hz.[11] For preschool-age children mean coefficient of variation (CV%) and between-test coefficient of repeatability (CR%) for Rrs between 4 and 8 Hz are reported between 6% and 10%.[67–70] A number of published studies have proposed reference equations for FOT Rrs based on measurements in healthy children.[68–76] Unfortunately, these reference equations do not use a standard frequency and there is significant variability between studies in equipment and measurement protocols.

Some studies of preschool-age children have reported both greater Xrs and Rrs at one or more frequencies among children with asthma or wheezing, some studies have reported higher Rrs, yet no difference in Xrs in asthmatic or wheezy subjects, whereas other investigators report no differences in either Xrs or Rrs between asthmatic/wheezy subjects and healthy controls.[55,68,77,78] There is very little longitudinal FOT data in preschool-age children to assess the diagnostic utility of FOT in predicting asthma in young children with recurrent wheezing. Although several studies have proposed criteria to identify bronchodilator responsiveness in preschool-age children, proposed frequency and cutoff values vary significantly between studies.[55,67,70,77,79–81]

Measurements of Airway Inflammation

Exhaled nitric oxide

The fractional concentration of exhaled nitric oxide (FE_{NO}) is a proposed biomarker of airway inflammation in asthma.[82] FE_{NO} has repeatedly been shown to be elevated in adults and children with allergic asthma[83] and rhinitis[84] but has been minimally studied in infants and toddlers. In adults and school-age children with atopic asthma FE_{NO} is correlated with sputum and bronchoalveolar eosinophils, peak flow variability, and bronchial reactivity.[85–92] FE_{NO} decreases following treatment with systemic or inhaled corticosteroids in adults and school-age children with asthma,[93] and has been shown to have a superior diagnostic accuracy for asthma than conventional diagnostic approaches, including spirometry.[85,94–96] Several groups have demonstrated in cross-sectional studies that FE_{NO} is higher in wheezy infants and toddlers than in healthy controls[97–101]; however, FE_{NO} was measured during tidal breathing in all but one of these studies. In a longitudinal study of preschool children (mean enrollment age >3 years) elevated tidal breathing FE_{NO} was associated with a 3-fold higher risk of respiratory illness over 1 year of follow-up.[102] Major limitations of tidal breathing FE_{NO} measurement in infants/toddlers include nasal nitric oxide contamination because nasal nitric oxide production far exceeds lower airway production and widely variable expiratory flow because FE_{NO} measurement is highly flow dependent.[103,104] Recently, Debley et al. demonstrated in a longitudinal study of wheezy infants/toddlers that higher enrollment flow-regulated single-breath exhaled nitric oxide levels were associated with a subsequent decline in lung function, increased risk of subsequent treatment with systemic corticosteroids for wheezing exacerbations, and bronchodilator responsiveness.[105] Further, enrollment single-breath exhaled nitric oxide was superior to lung function and bronchodilator responsiveness as a predictor of wheezing exacerbations during follow-up. Despite its promise as a potential diagnostic test for asthma in infants and preschool-age children, due to the lack of a standardized approach to measurement in this age group and paucity of longitudinal data, FE_{NO} is not yet a suitable clinical tool for use in infants and preschool-age children.

Exhaled breath condensate

Analysis of constituents of exhaled breath may in the future prove useful to noninvasively evaluate the biology of lung or airway diseases. However, even in school-age children and adults the measurement of biomarkers in exhaled breath condensates (EBC) is an immature field with many unresolved methodological challenges.[106] Although a variety of volatile and nonvolatile compounds have been detected in EBC by many investigators, there is a dearth of data regarding the physiological factors that affect EBC composition.[84,107] A recent ATS/ERS Task Force report identified the need for studies that assess accuracy and reproducibility of EBC collection and analysis before the widespread introduction of EBC into clinical trials or practice.[107] Although there are reports of successful breath condensate collection and subsequent measurement of inflammatory mediators within EBC collected from infants and preschool-age children,[108–111] technical barriers to successful collection of adequate volumes of EBC to allow for assays of potential biomarkers are even more significant in this age range.

Summary

For school-age children measurement of lung function using spirometry is an indispensible component of the diagnostic approach to asthma and longitudinal monitoring of asthma control. Spirometry provides objective clinical data that are complimentary to an accurate medical history and physical examination for many children with asthma or recurrent wheezing.

A number of additional lung function testing modalities, including RVRTC iPFTs, preschool spirometry, the LCI, specific airway resistance, and forced oscillometry, have shown significant promise in research studies as potential tools for the assessment of infants, toddlers, and preschool-age children with recurrent wheezing. In our opinion, given the availability of commercial devices and published reference equations, preschool spirometry may be clinically useful in identifying airflow obstruction in individual children when performed by providers with appropriate expertise and experience. While limited in its ability to distinguish health from disease at the level of the individual, validation studies and reference equations are also sufficient to consider clinical measurement of airflow resistance with Rint to track response to therapeutic interventions longitudinally. At the present time, a lack adequate validation studies, reference data, or commercial devices, and technical complexity limit the clinical utility of RVRTC iPFTs, the LCI, specific airway resistance, and forced oscillometry in the routine assessment of preschool-age children with recurrent wheezing. Finally, there has been great interest in the measurement of FE_{NO} to assess lower airway inflammation in patients with asthma. Based on several recent randomized controlled trials, there is insufficient data to support its routine use to titrate inhaled corticosteroids in children with asthma. However, given that FE_{NO} is easy to measure in school-age children, it can be measured with clinically approved devices, and sufficient data exist establishing its diagnostic utility in steroid naïve patients, FE_{NO} can be recommended as an adjunctive diagnostic tool in children in whom the diagnosis of asthma is unclear despite standard clinical measures.

Author Disclosure Statement

No competing financial interests exist.

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