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Assessing respiratory function in young children: Developmental considerations

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The purpose of this review is to provide practitioners and clinical investigators with an update on methods of assessing respiratory function in young children. The importance of this topic is presented in light of the natural history of asthma, as well as maturational changes that occur early in life in terms of airway development. Models of disease are cited to support the concept that injury of the mammalian airway early in postnatal life might have far-reaching consequences in terms of control of airway caliber and responsiveness. The methods currently available to measure respiratory function in our younger patients are outlined. The ability of children to perform the maneuvers necessary for this testing is considered as a function of age. Areas in which research and development are needed are highlighted. (*J Allergy Clin Immunol* 2005;115:657-66.)

Key words: Airway development, childhood asthma, forced oscillation techniques, interrupter techniques, pulmonary function tests, spirometry, whole body plethysmography

Abbreviations used

COV:	Coefficient of variation
Crs:	Compliance or capacitance of the respiratory system
Fres:	Resonant frequency
FVC:	Forced vital capacity
Irs:	Inertance of the respiratory system
MEFV:	Maximum expiratory flow volume
NANCe:	Nonadrenergic noncholinergic excitatory
NANCi:	Nonadrenergic noncholinergic inhibitory
PEFV:	Partial expiratory flow volume
Pint:	Mouth pressure during interruption of flow
Pmo:	Mouth pressure
Rint:	Resistance measured by the interrupter technique
Rrs:	Resistance of the respiratory system
sRaw:	Specific airway resistance
Xrs:	Reactance of the respiratory system
Zrs:	Impedance of the respiratory system

When evaluating children with pulmonary symptoms, the ability to assess respiratory function is important in terms of establishing a diagnosis, evaluating severity of

impairment, and providing effective care.¹ For example, Bye et al² found that failure to perform spirometry in older children with asthma resulted in underdiagnosis of airflow obstruction. More recently, Fuhlbrigge et al³ demonstrated a strong association between FEV₁ (expressed as a percentage of predicted value) and the risk of an asthma attack over the subsequent year. For clinical research into pulmonary problems, including asthma, physiologic tests are commonly used to define entry criteria and the natural history of disease, as well as the effects of intervention. Although various tests might be used, values obtained from spirometry are most commonly used in school-aged children. Yet the ability to perform spirometry with commonly accepted criteria varies with age.⁴ In addition, spirometric tests might be less helpful than other measures of respiratory function in certain clinical situations.⁵

The purpose of this review is to provide an update on methods of assessing respiratory function in younger children with asthma. We will concentrate primarily on children 2 to 5 years of age given the challenges this group presents in terms of regular care and clinical research. The importance of this topic is presented in light of current concepts of asthma pathogenesis, as well as changes in

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airway development and control of airway function that occur early in life. Models of disease are cited to support the concept that insults to airways early in postnatal development might have far-reaching consequences on airway function. The methods now available to measure respiratory function in our youngest subjects are outlined. Areas in which research and development are needed are highlighted.

PATHOGENESIS OF ASTHMA IN INFANTS AND CHILDREN

The onset of symptoms for many chronic respiratory diseases, including asthma and cystic fibrosis, is common during preschool years. In terms of asthma, this early onset has been noted in several studies, including work from Europe⁶ and the United States.⁷ Of relevance to this review, Yunginger et al⁷ documented significant increases in the incidence of disease over 2 decades, with this increase noted only in children from 1 to 14 years of age. With use of invasive studies, much has been learned about asthma pathogenesis during the last 2 decades. However, the subjects in the majority of investigations have been adults. Given the early age of onset, as well as this increased incidence, it is important to focus more closely on the disease in young children.^{8,9} Yet it is pertinent to recall some of the problems encountered in trying to perform clinical studies when the age of disease onset is early in life.

First, all infants and children with wheezing illnesses do not progress to have the clinical syndrome we recognize as asthma.¹⁰ More than half of all children who wheeze with viral infection during the first years of life have a transient condition that subsides during preschool and the early school years. Thus selection of subjects for study after an episode of wheezing early in life will lead to inclusion of individuals that have a process other than asthma accounting for this symptom.

Second, pulmonary function tests for documenting airway obstruction and reversibility in an objective manner are not always readily available or easily performed in preschool children.¹¹ Although detailed pulmonary physiology, including assessments of airway responsiveness, can be performed in sedated infants,^{12,13} this is impractical in most clinical and research settings. The expense and complexity of the instrumentation required for infant pulmonary function testing plus the time required for these studies limits their widespread use. This equipment, although appropriate for infants, is not used in studying the preschool age group that is the focus of this review.

Another limitation in studying younger subjects is that use of invasive procedures might not be as easily justified in asthma as it is in conditions such as cystic fibrosis. Thus identification and characterization of young children for studies addressing asthma pathogenesis is challenging and far from an exact science. This does not mean the endeavor is unworthy of effort. The increase in incidence in early life noted above suggests just the opposite: we need more information on airway function and factors that influence

this in positive or negative manners closer to the onset of symptoms.⁸

The conclusion of Sears et al¹⁴ that outcomes in adult asthma might be primarily determined in early childhood also give impetus to studies closer to the age of onset.^{10,15} Characterization of physiologic function plus cellular, biochemical, and genetic markers of risk might eventually allow identification of young children at greatest risk for development of asthma.^{16,17} This is the subset of subjects that must be characterized and followed as we design strategies to intervene and possibly prevent childhood asthma.

MATURATION OF IMMUNE RESPONSES AND AIRWAY CONTROL

Concerns about the increasing incidence of asthma in pediatric patients have helped focus attention on maturation of immune responses, as well as mechanisms of airway control early in life. Both appear to undergo dynamic postnatal changes. In terms of the former, the expression of a T_H2-skewed immunity against soluble protein antigens in the environment is thought to possibly be a primary cause of allergic inflammation in atopic individuals. Conversely, nonallergic individuals have a T_H1-skewed immunity against the same antigens. Thus much attention is being given to how regulatory T cells control development of allergic disease and asthma.¹⁸ This is not the focus of this review but is dealt with in recent overviews of this topic.^{18,19}

In addition to immune maturation, mechanisms that determine an airway's caliber and responsiveness likely undergo significant postnatal changes. In this respect a mix of cells and their products are thought to interact in complex ways with structural elements within an airway to determine function.²⁰ For this review, structures important in airway control might be considered to be neural or nonneural in nature. However, nonneural structures might influence airway caliber and responsiveness through effects on neural tissue. For example, airway epithelial cells influence function through their effect as a barrier to environmental pathogens and by producing mediators that directly influence neural function.²¹ Thus an airway's patency and responsiveness reflects a balance of multiple inputs. This being said, a significant part of that balance is likely provided by neural control mechanisms.^{22,23} Four neural pathways are involved in this process: adrenergic, cholinergic, nonadrenergic noncholinergic inhibitory (NANCI), and nonadrenergic noncholinergic excitatory (NANCIe) pathways. The adrenergic system functions in most species (including human subjects) through catecholamines released from the adrenal medulla or ganglia, whereas the other pathways act through direct innervation of airway smooth muscle. In general, the cholinergic and the NANCIe systems act to decrease airway patency, whereas the NANCi system mediates bronchodilation. The mediator of the cholinergic system is acetylcholine, and peptides, including substance P, are effectors of the NANCIe system. In terms of neurally mediated

bronchodilator effects, peptides such as vasoactive intestinal peptide, as well as nitric oxide, have been implicated as mediators of this process.²²

Just as the immune system undergoes postnatal changes, so does neural control appear to change with maturation. Autopsy material obtained at various postnatal ages from subjects who died nonpulmonary deaths demonstrated changes in airway innervation as a function of age.²⁴ In this study fewer peptide-containing nerves were found in adult bronchioli and respiratory units. In addition, the relative number of vasoactive intestinal peptide-containing nerves to bronchial and bronchiolar smooth muscle increased with age.

Additional information on developmental aspects of neural control is available from studies using models. For example, the NANCi response is functionally absent early in life in 2 species: rabbits²⁵ and ferrets.²⁶ In both species NANCi responses normally develop before the animal is fully grown. Other studies have described normal postnatal changes in the cholinergic system.^{27,28} The NANCe pathway also changes with age, with greater airway levels of substance P present early in life.²⁸

MODELS OF AIRWAY DYSFUNCTION IN DEVELOPING SPECIES

The difficulties of conducting clinical studies in infants and young children were noted. Although studies involving invasive procedures, such as bronchoscopy with lavage, have been performed in children,²⁹⁻³¹ the body of knowledge related to the immunopathogenesis of airway dysfunction early in life is limited. One method of circumventing some of the limitations has been to study models of immune and airway dysfunction that might be relevant to the human process.³² By using this tact, it has been noted that various insults (allergen sensitization, respiratory syncytial virus infection, and aspiration) early in postnatal development can alter the normal balance of neural control within an airway toward a hyperresponsive pattern for prolonged periods of time.^{25,26,33} Observations such as these have been made not only within the laboratory of authors of this review (GLL and J-KBK) but also by other investigators with an interest in the importance of the stage of development on the outcome of a pulmonary insult. For example, studies with parainfluenza type 1 virus (Sendai) showed neonatal infection of genetically susceptible rats led to chronic abnormalities in airway morphology, histology, and physiology.³⁴⁻³⁶ Conversely, infections in weanling and older rats resolved more quickly without permanent airway structural abnormalities.³⁷ Thus the outcome of an insult in terms of airway structure and function is likely determined by the type and magnitude of the insult and the stage of development of the host at the time the insult occurred. These observations imply there are critical periods during airway development when insults might have far-reaching consequences. The importance of these observations in terms of human processes can only be assessed when lung

function in young children can be used as part of longitudinal investigations.

ASSESSING RESPIRATORY FUNCTION IN YOUNG CHILDREN

Two general areas of assessing respiratory function in younger children will be reviewed. We will first discuss use of spirometry in preschool children and then review 3 methods of assessing resistance: whole-body plethysmography, interrupter techniques, and forced oscillation techniques. This order is being followed because of greater familiarity with spirometry on the part of most readers. The measures of resistance are less commonly used in day-to-day care of asthmatic patients and clinical research relevant to this disease. Although these latter methods have the disadvantage of somewhat greater intrasubject and intersubject variability compared with spirometry, they have one advantage: they require more limited subject cooperation. This might be especially important in younger children. The measures of resistance also have the theoretical advantage of assessing the respiratory system in the volume range of tidal breathing. Thus they might be more sensitive to increases in resistance because bronchodilation associated with deep inspiration (part of spirometry) is avoided.³⁸

Spirometry in young children

Spirometry is the most commonly used method of assessing lung function in older children and adults. For these age groups, spirometry is well characterized in terms of standards for performance^{39,40} and interpretation.⁴¹ Although maximum expiratory flow volume (MEFV) maneuvers have been obtained in sedated infants and toddlers,⁴² efforts to voluntarily obtain MEFV maneuvers in awake 2- to 5-year-old children had a low success rate, with few curves meeting American Thoracic Society criteria.⁴³ Use of partial expiratory flow volume (PEFV) maneuvers with assessment of maximal flow at functional residual capacity has had higher success rates.^{44,45} This method has been used to detect airway obstruction associated with persistent wheezing in early childhood,¹⁰ as well as obstruction produced by cold air challenge.⁴⁶ It might also be sensitive to subtle increases in airway tone.^{45,47} However, compared with MEFV maneuvers, PEFV testing is limited by increased variability caused in part by variation in functional residual capacity between maneuvers. Its utility is also limited by lack of the necessary software on most commercial spirometry systems. Thus assessment of PEFV curves has not been widely reported.

Although spirometry in young children can be performed, standards different from those for adults and children must be applied.^{4,48,49} A study conducted by Arets et al⁴ highlighted this point. They studied 446 children experienced in spirometry to evaluate their ability to meet criteria established by both the American Thoracic Society and European Respiratory Society.

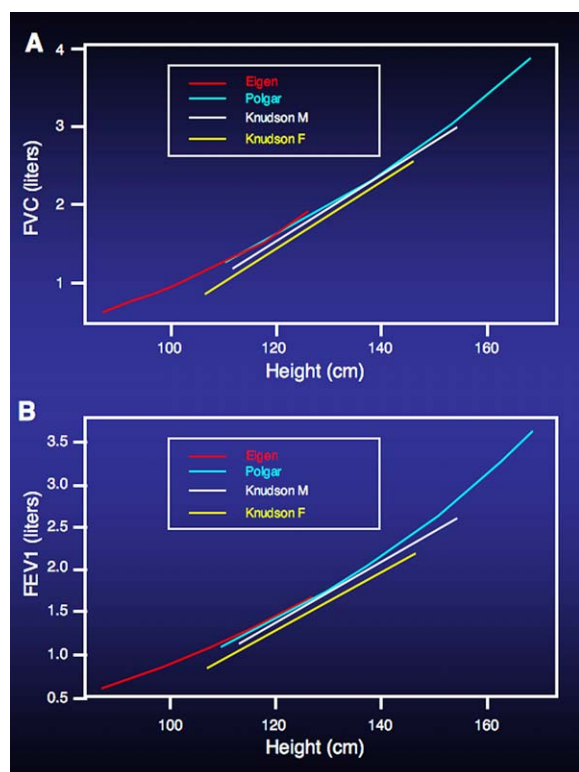


FIG 1. A comparison of regression equations from work by Eigen et al,⁴⁸ as well as Polgar and Promadhat⁵⁰ and Knudson et al.⁵¹ For the latter, predicted values for both male (M) and female (F) subjects are given. Both FVC and FEV₁ are plotted versus standing height. Reproduced from Eigen et al⁴⁸ with permission.

They concentrated on standards that 90% of tested children could achieve. On the basis of this, they found the end-of-test criterion of a forced expiratory time of greater than 6 seconds was least feasible. They suggested that a forced expiratory time of at least 1 second for children less than 8 years of age was more realistic provided the flow-volume curve demonstrated a gradual and asymptotic approach to the volume axis. They also suggested that the reproducibility of FEV₁ and forced vital capacity (FVC) should be less than 5%.

Kanengiser and Dozor⁴³ reported spirometric data from almost 100 patients 3 to 5 years of age. Ninety-five percent produced at least one maximal effort in which exhalation lasted at least 1 second. Success rates and reproducibility improved with age.

Eigen et al⁴⁸ studied 259 untrained healthy children in a preschool setting. Five criteria were used to define acceptability and included clearly determined peak flows, no cessation in flow while flow was greater than 25% of peak flow, and forced exhalation lasting at least 1 second. They found that 83% could accomplish successful spirometry during their first test session, with 95% of these having 3 technically acceptable curves. Reproducibility and coefficients of variation (COVs) for FEV₁ and FVC were comparable with results in older children. Prediction equations were developed against the natural

logarithm of height and were virtually coincident with predicted values for older children (Fig 1).^{50,51}

Other investigators have also addressed the utility of spirometry in younger children. Crenesse et al⁵² studied 355 preschool children with pulmonary complaints, and found at least 2 reliable maneuvers (FVC and FEV₁ reproducible within 0.1 L) could be obtained in 55% of this population. Values for FEV₁ and FEV_{0.75} were close to FVC in volume, with roughly 21% of children having valid forced expiratory times of less than 1 second. They concluded that FEV_{0.5} and FEV_{0.75} might be more useful tests of airway function than FEV₁ in children less than 6 years of age. Thus spirometry software used to test young children should ideally display real-time tidal breathing, as well as the MEFV trace, and report a range of timed volumes (FEV₁, FEV_{0.75}, and FEV_{0.5}).

Spirometry has been used in younger children when conducting provocative challenges. Bisgaard and Klug⁵³ used spirometry during methacholine challenge in 21 children 4 to 6 years of age who were suspected of having asthma. They screened 48 children to find 21 able to perform the many steps required in methacholine challenges. Thus a relevant percentage completed testing. A comparison of spirometric changes found in these children to responses in healthy children was not reported. Although the study demonstrated that spirometry can be used with methacholine challenge in this age group, more studies are needed in young children with recurrent wheezing and asthma to better understand its utility in research and clinical care.

Factors that support use of spirometry in young subjects include the availability of high-quality spirometers with appropriate software for testing young children plus our understanding of spirometry in terms of health and disease in older subjects. As noted by Eigen et al,⁴⁸ spirometry can be accomplished in young children with limited training. Yet obtaining adequate maneuvers in young children is dependent not only on the child but also on the skill of the individual supervising the measurement. The tester must exhibit enthusiasm and patience plus an ability to help children focus. Although computer-driven incentive programs might aid in testing,⁵⁴ they are not a substitute for well-qualified testers. Individuals interested in obtaining spirometric results in young subjects must be prepared to devote financial resources to equipment and well-trained technicians who are given adequate time to work with the children.

Whole-body plethysmography

The use of whole-body plethysmography to assess airway resistance is a commonly used technique that was described almost 5 decades ago.⁵⁵ It has been used primarily in older children and adults. More recently, the measurement of specific airway resistance (sRaw) by means of plethysmography has been accomplished in young children.⁵⁶ To measure sRaw, the child must sit inside a closed, constant-volume, whole-body plethysmograph for several minutes; wear a nose clip; and breathe quietly through a pneumotachograph with a good lip seal,

without occluding the mouthpiece. Although measurement of absolute airway resistance requires that subjects breathe against a closed system (pant) to allow measurement of thoracic gas volume, specific airway resistance ($sRaw = \text{Thoracic gas volume} \times \text{Absolute airway resistance}$) is assessed during quiet breathing, without the need for the difficult panting maneuver.^{56,57} During quiet breathing, flow is plotted against box volume to provide flow-volume loops. The effort driving air flow is reflected as the pressure swing in the box, with pressure expressed as changes in plethysmographic volume by means of calibration of box volume and pressure before subject measurements are collected. Calculation of $sRaw$ uses the inverse slope of the flow-volume plot.⁵⁶ A parent-caregiver can also sit in the plethysmograph to reassure the child and improve the likelihood of success without significantly changing the results. The adult must slowly exhale after a deep inspiration during the measurement of $sRaw$ to avoid measurement artifact. Klug and Bisgaard⁵⁶ used this technique to study 131 children with asthma who were 2 to 8 years of age. A total of 57 accomplished measurements both with and without an adult in the plethysmograph. $sRaw$ values were virtually identical in these children. The mean within-subject COV with an accompanying adult (8%) was comparable with other methods of measuring resistance.

This approach to assessing respiratory function has been applied in many ways. Nielsen and Bisgaard⁵⁸ looked at the response to inhaled bronchodilator in healthy and asthmatic 2- to 5-year-old children using $sRaw$, as well as interrupter and forced oscillation techniques. These latter 2 methods are outlined below. In this study all techniques of assessing respiratory function showed impairment before bronchodilator in children with asthma ($n = 55$) versus healthy control subjects ($n = 37$). Improvements in lung function were noted with bronchodilator by using all techniques, with improvements greatest in children with asthma. The discriminative capacity of $sRaw$ was greater than that of the other methods in separating the 2 groups.

Measures of $sRaw$ were used in a prospective birth cohort study in which one goal was identification of risk factors associated with low lung function in early childhood.⁵⁹ At 3 years of age, children with a history of wheeze had significantly higher $sRaw$ than nonwheezers. Yet even in nonwheezing children, $sRaw$ was higher in those whose parents were both atopic compared with the subgroup with either one or no atopic parent. Nonwheezing children with at least one positive allergen skin test response also had significantly higher values for $sRaw$ than those with negative skin test responses. Thus even in the absence of respiratory symptoms, young children with atopic parents and those with personal atopy had impaired lung function reflected by $sRaw$.

Whole-body plethysmography has been used to monitor decreases in lung function produced in the laboratory. For example, Badier et al⁶⁰ measured $sRaw$ while conducting carbachol challenge in 3- to 6-year-old children. They studied 44 children with clinical asthma, 44 children with

chronic cough, 38 asymptomatic children with wheezy bronchitis in the first 2 years of life, and 40 healthy control subjects. There was no difference in baseline $sRaw$ values between the groups with values in a normal range.⁶¹ However, the asthma, cough, and wheezy bronchitis groups had significantly greater reactivity than control subjects. The asthma group also had greater reactivity than the cough or wheezy bronchitis groups. These and other findings^{62,63} suggest children with asthma might be phenotypically and immunologically distinct from children with early transient wheeze or nonatopic cough and wheeze.

This method of assessing respiratory function has been used with other provocative challenges in young children. Bisgaard and Nielsen⁶⁴ used $sRaw$ to demonstrate that montelukast protected against bronchoconstriction induced by cold, dry air challenge in 13 asthmatic children 3 to 5 years of age. Nielsen and Bisgaard⁶⁵ also defined the effects of formoterol and albuterol in terms of protection against cold, dry air. They found significant bronchodilation and bronchoprotection with both medications compared with placebo. Thus in young subjects measurement of $sRaw$ helped demonstrate protection against cold, dry air conferred by a leukotriene receptor antagonist and bronchodilators.

Although this method has been successfully applied under various research conditions, some limitations exist. They include the expense required in purchasing the necessary equipment, as well as the patience needed on the part of the tester and child in performing the study. The placement of the child (and possibly a parent or caregiver) in the plethysmograph also makes testing more complex.

Interrupter techniques

Measuring resistance by using an interrupter technique (R_{int}) requires relaxed tidal breathing through a mouthpiece-shutter-pneumotachograph system. This makes it attractive for assessing respiratory function in young children with limited ability to cooperate. The physiologic basis of this technique is based on 2 concepts.⁶⁶ First, during uninterrupted tidal breathing, the difference between pressure at the mouth (P_{mo}) and alveolar pressure at any instant is the driving pressure for flow through airways. Second, during the brief interruption of tidal flow by a shutter, pressure at the mouth during interruption (P_{int}) rapidly equilibrates with alveolar pressure. The difference between P_{mo} before interruption and P_{int} can be related to flow just before interruption to give airway resistance as follows: $R_{int} = (P_{int} - P_{mo}) / \text{Flow}$.

The timing of closure is commonly programmed to occur at or close to peak inspiratory or expiratory tidal flow to achieve closure at midtidal volume. Digital systems are available that meet commonly accepted standards⁶⁶ and automatically calculate R_{int} .⁶⁷⁻⁶⁹ Measurement of R_{int} can be made in one or both phases of tidal breathing. Assessments during expiration usually demonstrate higher R_{int} than during inspiration,⁷⁰⁻⁷² but this might vary with age (see below).⁷³

The technical challenges in making this measurement include avoiding leaks at the mouthpiece and not allowing extreme flexion or extension of the neck. Other actions to be avoided during the procedure include vocal cord closure, irregular breathing patterns, subject movement during shutter closure, and incompletely relaxed breathing.⁶⁶ Applying these standards, short-term reproducibility assessed in healthy children 4 to 16 years of age demonstrated an intrasubject COV of 9%.⁷⁰ In 3-year-old children with a history of wheeze, a 13% intrasubject COV was seen.⁷⁴ Variability might be decreased by obtaining several measurements and then taking the median to avoid outliers; however, the mean might also suffice.⁷¹ Success rates for use of this technique of 56%, 81%, and 95% have been reported in children 2 to 3, 3 to 4, and 4 to 5 years of age, respectively.⁷⁵

Longer-term repeatability of Rint has also been addressed. Lombardi et al⁷⁶ studied healthy children with a mean of 2.5 months between measurements. The mean of the first expiratory Rint measurements in 26 children was 1.094 kPa·l⁻¹·s, whereas the second was 1.060 kPa·l⁻¹·s. Repeatability assessed by other investigators has shown more variation in values when measurements were separated by weeks.⁶⁸

Reference values have been published from several sources. Lombardi et al⁷⁶ reported values for 284 healthy children 3 to 6.4 years of age. Multivariate regression demonstrated Rint on expiration was inversely related to height, and Rint on inspiration was inversely related to a function of age, weight, and height. Sex differences were not apparent. Reference Rint values obtained from healthy Dutch white preschool children similarly showed an inverse relationship to height.⁷⁷ Higher expiratory than inspiratory resistances were noted. In a multicenter study of 91 healthy white French children 3.5 to 7.2 years of age, Beydon et al⁷³ noted that differences in inspiratory and expiratory Rint decreased with age, so that 3- to 4-year-old children had higher inspiratory than expiratory resistances, with older children having the converse. McKenzie et al⁷⁸ studied 236 healthy children of 3 ethnic backgrounds (Afro-Caribbean or African, Bangladeshi, and white British) and found neither ethnic nor sex-related differences, with predicted values similar to other published values. Collectively, these studies demonstrated that height is the major predictor of Rint, with little variation caused by age, sex, weight, or ethnicity after accounting for height.

Studies using Rint have demonstrated a response to bronchodilator in healthy children^{73,79} and children with a history of wheeze or asthma.^{75,79-81} In younger children McKenzie et al⁸² studied 3 groups 2 to 5 years of age in terms of baseline Rint and response to albuterol. They compared children with a history of recurrent wheeze, children with a history of recurrent cough without wheeze, and healthy control children. Median baseline Rint was higher in the wheeze group versus the cough and control groups (1.16, 0.94, and 0.88 kPa·l⁻¹·s, respectively). Both the cough and wheeze groups had a greater response to albuterol than control subjects. Beydon et al⁸⁰ compared

baseline Rint (during expiration) and bronchodilator responses in 74 preschool children with asthma with values from 84 healthy control subjects. The asthmatic patients had a higher mean Rint value compared with that seen in control subjects (0.92 ± 0.22 vs 0.77 ± 0.20). Response to albuterol demonstrated substantial overlap between groups.

The interrupter technique has also been used to monitor provocative challenges. However, in a study of 3-year-old children with a history of wheeze, Phagoo et al⁷⁴ noted that use of Rint appeared less sensitive in documenting bronchoconstriction with methacholine than in 5-year-old children.

Sly and Lombardi⁶⁷ reviewed theoretical and technical challenges of the interrupter method and outlined unsettled issues in its use. They concluded that the technique has considerable promise, but standard procedures must be developed and followed when performing this measurement. With airway obstruction, the long-time constants of the most obstructed units might preclude their assessment, leading to underestimation of resistance. As obstruction increases, the in-series compliance of the extrathoracic airways and mouth has a greater effect on dampening the early and rapid increase in pressure and can lead to reduced precision in measuring Rint.⁶⁶ Supporting the cheeks and floor of the mouth can help reduce this compliance and limit error.⁷⁰

Forced oscillation techniques

Evaluation of respiratory function by means of forced oscillation is based on the concept that the respiratory tract has the mechanical properties of resistance (Rrs), capacitance or compliance (Crs), and inductance (Irs).⁸³⁻⁸⁵ When an oscillating pressure is applied to the airway, the flow generated can be related to the forcing pressure to estimate these variables and their vector sum: impedance (Zrs). The out-of-phase component of Zrs is termed the reactance of the respiratory system (Xrs) and is the vector sum of Irs and Crs. At low-oscillation frequencies, Crs predominates, and the pressure wave caused by Xrs lags behind flow with a negative value. At high frequencies, Irs predominates, and the pressure wave leads flow and has a positive value. At the resonant frequency (Fres) of the system, Irs equals Crs, and the vector sum of Xrs is zero. At Fres, flow and pressure are in phase, and Zrs equals Rrs. These concepts are reviewed and illustrated by Morgan et al.⁶⁶

Like interrupter techniques, forced oscillation requires limited cooperation: the subject breathes quietly through a mouthpiece connected to the measurement system (Fig 2). The subject must not block the mouthpiece with the tongue while support is provided to the cheeks. The major limitations of forced oscillation techniques include overly simplistic models of the respiratory system that do not adequately account for inhomogeneities in ventilation and viscoelastic properties of the lung and chest wall. In addition, with increased Zrs, capacitance of the mouth and upper airways represents a shunt for pressure, allowing energy loss that can lead to reduction of Zrs.⁸⁴ This is minimized by supporting the subject's cheeks by a parent

or caregiver in the youngest subjects or by the child after familiarization with the technique (Fig 2).

Forced oscillation has been applied to young populations by using various forcing functions. Published reference values for younger subjects have been developed. In addition, estimates of variation, as well as success in obtaining meaningful results, have been addressed. For example, Lebecque et al⁸⁶ studied 377 healthy Belgian children 3 to 18 years of age and found subjects less than 6 years of age had no trouble performing the maneuver. Malmberg et al⁸⁷ noted that 2- to 7-year-old healthy Finnish children performed successful tests approximately 90% of the time, with a within-test COV of 6.2% for Rrs and 5.6% for Zrs at 5 Hz. No significant bronchodilator response was noted in this healthy cohort. Klug and Bisgaard⁸⁸ used a forced oscillation plus an interrupter technique and sRaw to study 151 healthy children 2 to 7 years of age. They were successful in obtaining data in 121 participants. The within-subject COV for sRaw, Rint, and Zrs at 5 Hz plus Rrs at 5 Hz was 11.1%, 8.1%, 10.8%, and 10.2%, respectively. Significant linear negative correlations were found between age, height, and weight with Zrs and Rrs at 5 Hz. Values for Xrs at 5 Hz were positively correlated to age and body size. None of the indices varied with sex. Ducharme et al⁸⁹ studied 206 healthy 3- to 17-year-old Canadian children of varied ethnicities. Height was the best predictor of Zrs parameters, with neither sex nor weight playing a significant role. Hellinckx et al⁹⁰ used the forced oscillation technique of impulse oscillometry to study lung function in preschool children 2.7- to 6.6 years old. The participants included 247 healthy children and 34 children with asthma identified by means of questionnaire. There were no differences in parameters between healthy and stable asthmatic children, suggesting physiologic dysfunction was limited or the method was unable to detect reductions in lung function in the asthmatic group.

A recent study⁹¹ of 24 older children with asthma described another forced oscillation parameter: the low-frequency reactance area. This is the integral of Xrs from 5 Hz to Fres, where Xrs is zero. The benefit of low-frequency reactance area might be an improved signal/noise ratio by virtue of combining multiple Xrs values and the value of Fres into a single parameter. In this study inspiratory Rrs at 5 Hz and the low-frequency reactance area showed significant within-subject day-to-day variability when spirometry did not. Thus some forced oscillation parameters might be more sensitive to day-to-day variation in airway tone than spirometric parameters. This needs confirmation in additional studies involving younger subjects.

Potential uses of forced oscillation include the emergency management of acutely ill asthmatic patients. This approach does not require the effort of peak flow measurements and does not expose subjects to the risk of bronchospasm, as sometimes seen with spirometry in this setting. Ducharme and Davis⁹² studied 150 children 3 to 17 years of age being treated for acute asthma. Of the 114 children able to complete testing, all were able to



FIG 2. A young child is shown while undergoing assessment of respiratory function using a forced oscillation technique. For this method of assessing respiratory function, as well as when using an interrupter technique, the child breathes tidally through a mouthpiece while measurements are made. Support for the cheeks is provided when performing either assessment. This support is usually provided by a parent or caregiver for the youngest subjects, whereas older children with experience with the measurements (*above*) might effectively provide this support themselves. These methods of assessing respiratory function have the potential advantage of allowing serial measurements over a fairly long period of time. The 5-year-old child pictured above began serial testing with this approach at 2 and 3 years of age as part of a longitudinal study.

reproduce Rrs at 8 Hz, whereas only 57% were able to perform spirometry. In those who completed spirometry, change in Rrs at 8 Hz after bronchodilator paralleled changes in FEV₁ and 4 clinical signs (respiratory rate, wheezing, air entry, and suprasternal retractions). In children unable to do spirometry, forced oscillation was comparable with these signs in assessing response. The authors concluded that Rrs measured by means of forced oscillation was reproducible in children with acute asthma who were too young or too sick to perform spirometry.

Forced oscillation has the potential to assess airway lability in young children at risk for asthma. An investigation involving 4- to 5-year old children enrolled in the Childhood Asthma Prevention Study demonstrated little difference in baseline oscillation parameters between children with and without clinically active asthma.⁵ When the subset of atopic children was analyzed, those with active asthma had significantly greater improvement after bronchodilator in Rrs at 5 and 10 Hz, as well as Xrs at 10 Hz, than those without symptoms. There were no significant differences in spirometric studies conducted at the same time. The authors suggested these bronchodilator responses identified lung dysfunction in children at greater risk for persistent asthma. In addition, they speculated that forced oscillation might be helpful in obtaining objective outcome measures in studies of early intervention. These issues require additional study.

Forced oscillation has been used to monitor decreases in lung function produced by bronchial challenge. For example, this technique has been used to quantify responses to methacholine⁹³⁻⁹⁶ and histamine⁹⁴ in young asthmatic patients when clinically stable. The results of these and other studies (reviewed by Oostveen et al³⁸ and

Goldman⁸⁵) suggest forced oscillation is feasible when using challenges to evaluate responses to therapy and to follow the course of the disease.

The European Respiratory Society³⁸ published a statement regarding forced oscillation techniques. They concluded that this approach is sensitive to environmentally induced impairments in lung function and is reliable in assessing airway responsiveness. One advantage of forced oscillation over interrupter techniques and plethysmography is that it partitions respiratory system mechanics into resistance and reactance. At any given frequency, the more negative Xrs, the more energy is being used to overcome the apparent elastance of the respiratory system. Abnormal Xrs might provide important information about reductions in small-airway conductance and increased lung elastance.

SUMMARY

Asthma is the most common chronic respiratory disease in children. The economic burden imposed by this disease is substantial.^{97,98} Of additional concern, disease incidence might be increasing in infants and children. Unfortunately, this group of patients is most difficult to approach when addressing mechanisms of disease. Given limited cooperation on the part of young subjects, assessment of lung function is difficult. Although detailed physiology can be assessed in sedated-anesthetized infants, and spirometry plus techniques to assess resistance can be used in preschool children, this work can be painstakingly slow and tedious. Yet this young group is of interest because this is the age when asthma most often presents. Critical factors that likely determine that disease expression are the genetic makeup of the individual, environmental influences (allergen sensitization, early childhood infections, and aspiration of foreign proteins), and the age of the subject when airway insults occur. Early in life, dynamic changes in immune function, as well as mechanisms that control airway caliber, likely occur. Models of disease suggest that insults early in life might lead to prolonged alterations in airway control. It thus becomes important to consider expression of altered airway function (including airways obstruction and enhanced airway responsiveness) in the context of normal developmental processes. The techniques outlined in this review will assist in this endeavor and allow quantitative assessment of respiratory function in clinical research, as well as the day-to-day care of our younger patients.

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