American Thoracic Society Documents

An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children

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Section 1. The Next Frontier

In older children, measuring lung function is integral for understanding respiratory physiology and for clinical assessment. Pulmonary function tests for infants and children younger than

2 years are used as both research and clinical tools. The usefulness of these tests has benefited from approximately 15 years of work by joint American Thoracic Society (ATS)/European Respiratory Society (ERS) working parties and task forces (1, 2). However, children aged 2 to 6 years old represent one of the major challenges in lung function assessment. Evaluating lung function in this age group is important, not only for clinical reasons but also due to the considerable growth and development of the respiratory system that occurs, with associated changes in lung mechanics (3). Children commonly present with recurrent cough and wheeze during this period. Many of these children will lose their symptoms as they grow, yet others will continue to have asthma that persists into adult life (4). The treatment implications of these two clinical patterns are different, yet we are currently hampered by a lack of objective assessments to help distinguish between these two patterns. In addition, children recovering from chronic neonatal lung disease and children with cystic fibrosis (CF) are prone to recurrent or persistent respiratory symptoms. Objective assessments of pulmonary function in these children would be expected to improve clinical management. The importance of continuous, longitudinal assessments of lung function from birth throughout childhood cannot be underestimated in understanding the evolution and natural history of disease processes.

Preschoolers present a number of special challenges. The children are generally too old to sedate for pulmonary function testing (PFT), as is done with infants, and measurement of lung function under anesthesia is neither ethically acceptable nor physiologically relevant to clinical management. Children in this age group are not able to voluntarily perform many of the physiological maneuvers required for the pulmonary function tests used in older children and adults. They have a short attention span and are easily distracted. Due to these issues, the children need to be engaged and encouraged by the operator to participate in the test.

A number of pulmonary function tests have been attempted in conscious children within the preschool age group. These include the following: standard spirometry (5–11), maximal flow referenced to functional residual capacity ($\dot{V}max_{FRC}$) (12–14), forced oscillation (FOT) (15–20), interrupter resistance (Rint) (19–27), specific airway resistance (sRaw) measured in a plethysmograph (19, 20, 28), functional residual capacity (FRC) using gas dilution techniques (13, 26, 29), and measurements of gas-mixing indices (30, 31). Unlike the situation that existed when pulmonary function tests for infants were first developed, commercial equipment is available for most of these tests, although not specifically designed for preschool-aged children. The implications of using equipment in this age group that is designed for older and larger individuals must be understood. Equipment dead space, resistance, and software programs designed for adults, not young children, must be evaluated to understand how these issues impact pulmonary function measurements in the preschool child.

As has been stressed by the ATS/ERS Working Party on Infant Pulmonary Function Testing, no matter which test is being used the operator must be given access to raw data from the equipment. As the field develops and the knowledge of respiratory physiology in this age group expands, having access to raw data will allow investigation of different and more appropriate algorithms and may result in improved disease discrimination.

The joint ATS/ERS task force has produced recommendations for the tests currently used in the preschool age group. Each section of this document was written by a subcommittee of the present task force, and includes the current knowledge and recommendations to guide technical and clinical practice. These recommendations were based on reliable scientific evidence, documented by references, and validated by the subcommittee experts. However, in many situations, insufficient data exist to make definitive recommendations. This document highlights the current state of knowledge and where further data are needed. Recommendations will need to be revised periodically until sufficient evidence has been collected to make definitive guidelines in certain situations. This document will address the following topics: (*1*) clinical implications of PFT in preschool children, (*2*) spirometry, (*3*) tidal breathing measurements, (*4*) the interrupter technique, (*5*) the FOT, (*6*) gas washout techniques, and (*7*) bronchial responsiveness tests.

Specifications for equipment used in an infant/preschooler pulmonary function laboratory have been previously reported (32), and a review of these systems and their hygiene aspects is beyond the scope of these recommendations. However, it is important to highlight that the total apparatus dead space should be minimized where possible, although this requirement does not preclude the use of bacterial filters, and should in general be lower than 1.5 to 2 ml/kg body weight (32).

The main aim of these recommendations is to provide a resource for the user of these preschool techniques, to facilitate good laboratory practice, interpretation of measurements, and comparison among centers. These recommendations are expected to help the development of future methodological research in either single- or multicenter clinical studies, which are needed to support strong recommendations. Manufacturers may refer to the technical aspects of this document for developing proper equipment and software.

The ideal pulmonary function test in preschool children is one that is applicable to any age so that longitudinal studies can be conducted monitoring individual children from infancy to adulthood, simple to perform, safe, reproducible, sensitive enough to detect changes with growth and distinguish clearly between health and disease, and acceptable to both the subject and parents. As with pulmonary function tests in infants, special attention must be paid to the measurement conditions under which the tests are performed, and the impact of these measurement conditions on the accuracy of test results must be considered. A pulmonary function laboratory that is "preschool-aged child friendly" is of the utmost importance. These young children must be made to feel comfortable in the laboratory environment if they are to perform the measurements accurately. The pulmonary function technician has a significant impact on the comfort level of the child. This type of environment may be achieved through a combination of friendly conversation, songs, or through distraction with a videotape or book. During tidal breathing, the level of distraction must be enough to take the child's attention away from his or her breathing, but not so exciting that the child breathes irregularly. Accurate measurements of height and weight using calibrated stadiometers and scales are essential; however, these procedures can be challenging in an active preschooler. Safety and hygiene requirements have been covered in adult guidelines, but it should be noted that additional safety precautions are necessary for preschool subjects. These include, but are not limited to, the need for constant adult supervision while the child is in the laboratory. For accurate interpretations of the lung function data, particularly where longitudinal assessments are to be made, it is essential to record data on environmental and hereditary factors likely to impact on lung growth, including the following: sex; ethnic group; family history of asthma and atopy; cigarette smoke exposure, both pre- and postnatal; allergen exposure, including pets; and relevant current and past medical history and medication use.

The developmental stage of the preschool-aged child will be an important determinant of the child's success at performing pulmonary function tests. This influence will be greatest in tests

requiring more active cooperation from the child. For example, young children frequently have difficulties in performing the forced expiratory maneuvers required for spirometry. They can either blow "hard" or "long," but frequently cannot blow both hard and long. Measurements that can be made during tidal breathing, such as forced oscillation, the interrupter technique, and gas washout techniques, may be more suitable for the child unable to accurately perform spirometry. If forced expiratory measurements are to be performed, these should be performed after the tidal measurements, because it is easier to "wind up" young children than to wind them down. In addition, deep inhalation may change bronchial tone in children with asthma.

The physiological developmental stage of the respiratory system must also be considered in determining which outcome variables are applicable to this age group. For example, recent studies have demonstrated that the forced expiratory volume at 1 second to forced vital capacity (FEV_1/FVC) ratio in healthy 5- to 6-year-old children is approximately 90 to 95% (5, 6, 30, 31, 33), and is even higher in younger children. In older children and adults, the physiological and clinical utility of FEV_1 is due to its location on the effort-independent (flow-limited) part of the maximal forced expiratory flow–volume (MEFV) curve, which descends to lung volumes as low as 85 to 90% of exhaled vital capacity and reflects intrinsic properties of the respiratory system. The ability to maintain flow limitation at low lung volumes depends largely on the strength of the chest wall muscles to maintain sufficient driving pressure. It is highly likely that children in the preschool age group will not have the chest wall muscle strength to maintain flow limitation to lung volumes as low as 90% of exhaled vital capacity. Although this concept is not new (34), forced expiratory volumes at 0.75 second ($FEV_{0.75}$) or at 0.5 second ($FEV_{0.5}$) have not been adopted in clinical practice. Systematic research will be needed to determine the appropriate outcome variables for spirometry in this age group.

The answer to the question "Which test should be used in the preschool age group?" depends on the clinical/research question being asked. As is the case in other age groups, no one test will answer all questions. The interrupter technique is easily implemented and is suitable for use in epidemiological studies, particularly those involving measurements in the field. Measurements capable of reflecting changes in the lung parenchyma, such as gas washout techniques and, potentially, forced oscillation, are likely to be more suitable for detecting early lung disease in a condition such as CF, which is known to start in the lung periphery. The clinical and research role of measuring bronchodilator responses and of provocation testing will need to be evaluated. Again, systematic studies using a number of tests will be needed before we know with certainty the place for each test in our clinical armamentarium.

In summary, measurement of lung function in preschool-aged children is now feasible. However, much work remains to be done in standardizing how these tests are performed, and in understanding the most appropriate role for the various tests in the study of growth and development of the respiratory system and in the clinical management of children in this age group.

Section 2. Clinical Implications

SUMMARY

It is now recognized that, given encouragement and suitable measurement conditions, most children between 2 and 6 years old can undertake PFT. Although there is little doubt about the value of these tests in clinical or epidemiological research, their influence on clinical management in an individual remains debat-

able. The clinical usefulness of any measurement depends on how well it can discriminate between health and disease and how reproducible it is from day to day so that disease progression and response to treatment can be assessed within each child individually.

Considerable further work is required to develop appropriate reference data for this age group, with which to reliably distinguish the effects of disease from that of growth and development, together with information on within-subject repeatability and the relative sensitivity and specificity of these tests for distinguishing health from disease. In the meantime, the following recommendations apply:

1. Reference data derived from older subjects should not be extrapolated for use in children younger than 6 years.

2. The validity of the selected reference data for use in those with respiratory disease should be checked by studying at least 30 to 50 healthy preschool children using identical techniques and comparing their results with those of the similar reference population (same age, body size, sex, and ethnic group).

3. Results should, by preference, be expressed as *z* scores (i.e., multiples of the standard deviation [SD] from the mean) and not as percentages of predicted values.

4. Variability measurements should not be extrapolated from healthy children to those with disease. Within-subject variability (within and between occasions) assessments need to be made in at least 30 (preferably more) subjects of similar age and diagnostic category. Reproducibility of measurements is established at intervals relevant to the intended uses of the tests.

5. The diagnostic profile of measurements made using each technique, with respect both to baseline measurements and ability to detect change during assessments of bronchial responsiveness, needs to be established to make informed decisions as to which test(s) to use for specific clinical (or research) applications.

6. Further multidisciplinary work is required to investigate the best combination of tests (e.g., structure, function, inflammation, atopy) and challenges (e.g., pharmaceutical vs. physical) to investigate specific clinical entities during early childhood.

INTRODUCTION

Evidence accumulating over the last 5 years indicates that PFT in children aged 2 to 6 years produces technically satisfactory measurements using tidal breathing, the interrupter technique, forced oscillation, spirometry, and multiple-breath washout (MBW) methods (26, 31, 35–43). However, the extent to which these measurements are clinically useful in the management of the individual child needs careful consideration. This section will consider the evidence base for the clinical value of lung function measurements in the individual preschool child. It should be noted that many of the issues raised may be equally true in the older child or adult (44), and the clinical value of infant pulmonary function tests also has to be determined (45).

It is often claimed that the assessment of a pulmonary function test will help diagnosis, assist prognosis, monitor disease progress, and measure the effect of therapeutic interventions (46). An objective test would supplement history and physical examination in subjects with respiratory problems, which are notoriously difficult to obtain in childhood wheezing disorders (47). The evidence base of clinical decision making (i.e., deciding what is the best test or group of tests for the individual) lags far

behind that for treatments (44). A recent review of the value of PFT in adults suggested that many tests used for diagnosis and for assessing a known condition were not supported by high-level evidence (48).

For the clinician, it is important to know how helpful PFT is in distinguishing health from disease and in monitoring disease progress in the individual. The epidemiologist and clinical researcher are more interested in comparing measurements in groups and describing the average effects of interventions. PFT could also be helpful in monitoring progress and the response to treatment in children suffering from wheezing disorders, CF, and chronic lung disease of infancy.

FEASIBILITY

Under perfect conditions, most pulmonary function tests discussed in this document can be undertaken successfully in the majority of preschool children older than 3 years. These tests were developed by researchers primarily interested in their application to groups of children to understand the progress of lung development and disease, and the effect of interventions. For their application to the management of individuals, feasibility depends on many more factors than just whether the patient can undertake the test. For example, of 72 preschool children with and without CF, only 58% were able to produce an acceptable forced expiration lasting 1 second, although 73% could manage an $FEV_{0.5}$ (11). In other words, the international quality-control requirements for spirometry, which are commonly derived from studies in adults, could not be met, although alternative criteria may be feasible.

The ATS has made recommendations for training and qualifications of personnel conducting pulmonary function tests. Unlike the measurement of peak flow in a respiratory clinic by the physician managing the patient's care, preschool tests require time and patience by technicians trained in the techniques that can help young children to perform at their best, who can maintain the equipment, and who can understand the procedure well enough to know when a result is or is not acceptable. In some cases, a laboratory operator may not meet normal training criteria for PFT but has particular skills in working with young children. In such cases, flexibility is recommended. Some of the tests are suitable for use in the ambulatory setting or in the community, but most require laboratory equipment.

WHAT IS NORMAL?

Choosing Reference Data

Reference equations are essential to express pulmonary function in relation to that which would be expected for healthy children of similar age, sex, body size, and ethnic group. The choice of reference equations directly influences the interpretation of pediatric pulmonary function data, and this can have a significant impact on patient care and research (49–52). Most lung function data are normally distributed or can be transformed to such, so that 90% of "normal" values are found within the range of mean ± 1.65 SD (with 95% within ± 1.96 SD). Lung function variables in healthy subjects and those with respiratory symptoms and/or disease often overlap to such an extent that a normal lung function measurement does not exclude disease. Clearly abnormal lung function measurements will often, but not necessarily, be associated with symptoms and disease. The tests for which preliminary reference data are available are listed in

Table 1. Ideally, data from healthy children should be evenly distributed across the age range from 2 to 6 years, but in many studies, there are few data in children younger than 4 years, and this could result in distortion of any derived prediction equations. Inspection of the datasets should identify those in which there are a disproportionate number of older children, although, regrettably, plots of raw data are not always presented in published reports. Display of the raw data plotted against height or age also allows the potential user to assess whether linear regression is appropriate when modeling the data and whether data are normally distributed about the regression line (e.g., whether approximately equal numbers lie above and below 2 SDs from the regression line). Evidence for differences among ethnic groups and between sexes should also be considered. Data from spirometry, and resistance measured by Rint and plethysmographic sRaw, have so far shown similar results for boys and girls, but some sex differences may exist with respect to the FOT technique (see SECTION 6).

The most important consideration when choosing reference data is that the method, equipment, and software used to collect the data should be the same as that used by the clinician for his or her patients. In the oscillation technique, regression equations for total respiratory resistance can differ considerably (16), which may reflect the different methods used. This is true also for the interrupter technique, in which the most important consideration is the calculation of pressure (53), which differs according to the algorithm used (see SECTION 5). Particular caution is required when undertaking techniques such as plethysmography and spirometry using commercially available equipment. The default prediction equations from such equipment will almost always be based on reference data derived from older subjects, possibly resulting in serious misinterpretation if applied to preschool children.

Using Reference Data

Selection. Once the clinician has selected the dataset that satisfies the above criteria, it has been suggested that the validity of using a specific set of reference equations be checked by testing between 30 (46) and 50 healthy local children (54), preferably 50, and checking whether their results fall within the predicted reference range. Although testing of local healthy control subjects is always advisable, and will alert the operator to major discrepancies (54), subtle biases may be missed unless a larger number of children are studied, who are evenly distributed over the age range of interest and are of similar sex, ethnic group, and socioeconomic background compared with the clinical population.

Height or age as the main predictor? If the data are to be related to height, then accurate anthropometric measurements using a carefully calibrated stadiometer must be made according to the manufacturer's recommendations. Data that are better related to age (54) are particularly suitable for field studies and for disabled children in whom height is difficult to measure. Predicted values based on age may, however, overestimate expected values if the child suffers from any significant degree of growth retardation associated with his or her respiratory disease. Due to the limitations of age, height is the preferred predictor of pulmonary function tests.

Expressing results. z Scores—or SD scores (SDS)—are defined as follows: z score = (observed value − predicted mean value)/RSD, where RSD is the residual SD of the reference population (31, 55, 56). z Scores can be interpreted in probability terms when data are normally distributed with a mean of 0, and an SD of 1. Hence, the z score indicates how many SDs an individual or group is below or above the predicted mean for any given parameter. z Scores indicate how likely a result is

TABLE 1. SUMMARY OF PUBLISHED REFERENCE DATA (50 OR MORE SUBJECTS)

Published Normative Data	No. of Subjects	Age (yr)	Notes
FRC: helium dilution			
Beydon and colleagues, 2002 (26)	79	3–7.9	9 <100 cm*
Spirometric measurements			
Eigen and colleagues, 2001 (5)	214	3–7	25 <100 cm
Nystad and colleagues, 2002 (9)	603	3–6	None <100 cm; 158 aged 3–4 yr
Zapletal and colleagues, 2003 (10)	173	3–6	4 <100 cm; 24 < 5 yr
Interrupter resistance (Rint)			
Merkus and colleagues, 2001 (22)	54	2–7	3 <100 cm
McKenzie and colleagues, 2002 (53)	216	2–10	27 <100 cm
Lombardi and colleagues, 2001 (21)	284	3–6.4	10 <100 cm
Beydon and colleagues, 2002 (25)	79	3–7.9	9 <100 cm
Klug and Bisgaard, 1998 (174)	120	2–7	16 <3 yr
Plethysmography: sRaw			
Klug and Bisgaard, 1998 (174)	119	2–7	28 <3 yr
Lowe and colleagues, 2002 (292)	303	3	
Forced oscillation technique			
Duiverman and colleagues, 1985 (15)	255	2.3–12.5	18 <100 cm
Ducharme and colleagues, 1998 (195)	206	3–17	16 at 100 cm
Mazurek and colleagues, 2000 (16)	61	2.8–7.4	8 <100 cm
Klug and Bisgaard, 1998 (174)	121	2–7	16 <3 yr

The Notes column identifies the number of children in the cohort who are at the short or young end of the height or age range.
* Raw data from authors.

to occur within results from a normal population and how far removed the result is from the predicted mean; they are useful for tracking changes in lung function with growth or treatment, and allow comparisons of various lung function results from different techniques. It is therefore recommended that results be expressed as z scores, which account for the interindividual variability of the normal distribution, rather than as percentages of predicted values. This provides far more information than a description of whether a result is simply inside or outside the reference range. Software for calculating results as z scores should be provided with commercial equipment.

VARIABILITY OF A TEST

In this document, the different aspects of variability are named as follows: repeatability is the within-occasion (short-term) variability and reproducibility is the between-occasion (long-term) variability. Therefore, variability refers to either short- or long-term changes. To evaluate the variability of a test, it is necessary to know both the within-occasion repeatability and between-occasion reproducibility of the measurements in healthy children and in those with respiratory complaints. If PFT is to be used to measure the effect of an intervention, such as response to a bronchodilator, then the variability of the test over the same time interval as the expected response to treatment should be known. Only then can the clinician decide whether any observed change can be ascribed confidently to the bronchodilator (or other intervention) rather than simply reflecting intrinsic variability of the measurement or disease state over the same period (57). Variability may differ between studies due to factors such as technical differences and differences in population, or issues such as the interval between repeated tests, methods of analyses, inclusion criteria for technically acceptable data, and so forth.

Within-Occasion Repeatability

For PFT, it is assumed that within-occasion, between-test repeatability measures the stability of the measuring instrument and the short-term consistency of the technical expertise of the subject undertaking the test (58). Although this is a reasonable generalization, it is not strictly accurate. In subjects in whom airway lability is part of the clinical condition and in whom maneuvers involving rapid changes in lung volume can themselves change

airway properties, biological factors can contribute to instability between measurements on the same occasion.

The definition of a single "measurement" varies among different techniques. Thus, with the interrupter technique, it is generally reported as the median of five or more satisfactory readings, whereas with spirometry, the best of three technically acceptable readings is usually reported. The intrameasurement repeatability is usually expressed as a coefficient of variation (CV), which is the SD expressed as a percentage of the mean (i.e., $100 \times SD/mean$). For example, the repeatability of Rint assessed by CV may differ among studies (*see* the tables in the online supplement) (25). The within-occasion intermeasurement repeatability is often reported as the coefficient of repeatability (CR)—that is, twice the SD of the mean difference between two series of baseline measurements, performed a few minutes apart, without any intervention, in a group of children. The CR defines the limits above and below an individual measurement within which 95% of second measurements will lie. Finally, some authors have expressed variability using the SD of the mean difference between two measurements and divide it by $\sqrt{2}$ to obtain the within-subject SD (SDw) (28, 59). The response to bronchodilators and/or bronchoconstrictors is then expressed as postbronchodilator or postbronchoconstrictor value $-$ baseline value/SDw.

Between-Occasion Reproducibility

To successfully monitor disease progress and/or response to treatment in an individual, the day-to-day (or month-to-month) reproducibility should be known. Between-occasion reproducibility (*see* the Appendix in the online supplement) is influenced by disease and biological variation in lung function in addition to the measuring instrument's stability, and the technical consistency of the subject. Very limited data are available for preschool children, but those available are summarized in Table E4 of the online supplement.

DIAGNOSING RESPIRATORY DISORDERS

The arguments about the potential usefulness of tests in clinical decision making have been discussed recently (44). Although clinical decision making is not an exact science, it may be guided by international recommendations. Because diagnosing mild asthma does not necessarily imply treatment with drugs, such
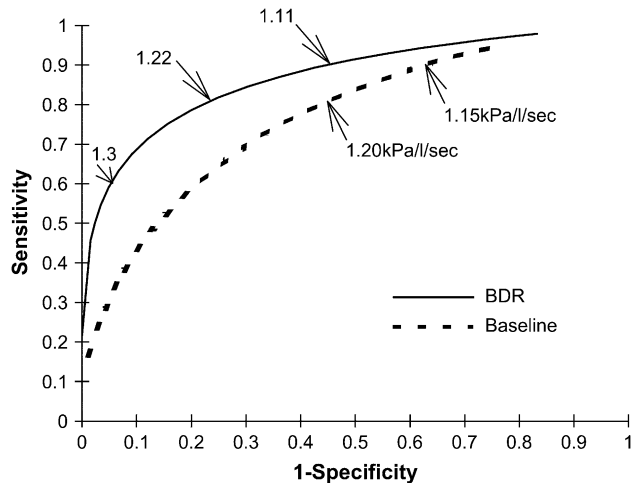
Figure 1. Measurements of baseline interrupter resistance (Rint; kPa · L^{-1} · s) and bronchodilator responsiveness (BDR; baseline Rint:post-bronchodilator Rint) plotted as receiver operating curves for previous wheeze.

as corticosteroids, then the typical threshold values that have been quoted recently for a positive test in preschool children (Table E5) are probably useful, provided the clinician knows the likelihood of a false-positive test (Figure 1). This is where clinical judgement and other tests, such as tests of atopic status, must complement PFT (60).

Before the clinician selects a pulmonary function test, he or she must know what the results are likely to be in children with the disorder(s) that is being considered. There is a large overlap between measurements in children with mild asthma or isolated cough and healthy children (40).

Asthma

When a child presents with acute wheeze and is observed to respond to a bronchodilator, there is little doubt that there is symptomatic reversible airway disease. For the purposes of this section, this will be called asthma. In this event, PFT is not needed for the diagnosis. Asthma is much more difficult to diagnose in the child who presents with vague symptoms, such as cough or shortness of breath, and in whom physical examination is normal (47). This is a situation in which it could be hoped that PFT would be helpful in the diagnosis. There is growing evidence that mild intermittent asthma is often wrongly diagnosed (61), with the main alternative diagnosis being persistent isolated cough (62).

Because of the great overlap of measurements between healthy subjects and those with previous wheeze, the diagnostic accuracy of baseline PFT is generally very poor in any age group. Bronchodilator responsiveness (BDR) has been recommended in the workup of adults and children with asthma for whom measurements of BDR give a much better diagnostic profile than that obtained from baseline lung function data. For example, in a study of 48 healthy and 82 previously wheezy children aged 2 to 5 years or younger, 76% of those with asthma had a BDR (expressed as a ratio of baseline Rint–postbronchodilator Rint) of 1.22 or greater (40). The sensitivity for this value was therefore 0.76. By contrast, although 70% of healthy children had values below 1.22 (indicating a specificity of 0.70), 30% did not—that is, their BDR was 1.22 or more (giving a value for 1-specificity [i.e., false positive] of 0.3). Plotting sensitivity and 1-specificity against each other for a range of baseline and BDR Rint values produces receiver operating curves (ROC) (62) (*see* Figure 1).

The diagnostic profiles for PFT for asthma and their threshold values are detailed in Table E5. It should be noted that the confidence intervals for these figures are quite wide. Rint, FOT (measured at 5 Hz), and plethysmographic sRaw appear to have similar profiles for the thresholds given (Table E5).

Data to calculate the specificity and sensitivity of BDR measurements for wheeze in preschool children measured using spirometry are not available. The data available from a small group of young children suggest that the diagnostic profile of spirometry for BDR may be poor because there is so much overlap between measurements in children with and without lung disease (39).

Although challenge testing to demonstrate bronchial hyperresponsiveness in preschool children is possible (*see* Section 8), the feasibility of pharmacological challenges in consecutive children younger than 5 years as a clinical tool outside a research laboratory has yet to be reported. The accuracy and repeatability of the bronchial hyperresponsiveness tests are dependent on the technique used (63, 64).

CF Lung Disease

Although significant group differences between young children with CF and healthy control subjects have been observed in several studies (26, 38, 65), the number of individuals with "abnormal" results is relatively low for most pulmonary function tests during early childhood. Inert gas MBW is a promising technique for measuring efficiency of gas mixing as a measure of small airway disease in the lung. Data from school-age children suggest that MBW is more sensitive than spirometry for detecting early CF lung disease (30, 66, 67). Similar results have been reported recently for preschool children (31). Among 30 2- to 5-year-old children with CF and an equal number of healthy matched control subjects, 73% of the children with CF had abnormal gas mixing (lung clearance index [LCI] outside 2 z scores for the normal range), whereas only 47% and 13% of this CF population had an abnormal sRaw or $FEV_{0.5}$ (31).

MONITORING DISEASE PROGRESS AND RESPONSE TO INTERVENTIONS

There is a paucity of information regarding between-occasion reproducibility for spirometric or FOT techniques in children younger than 5 years. For 7-year-old children, the CV for FEV_1 was found to be 8.3%, which corresponded to a between-occasion reproducibility of 23% (68). This means that we cannot be 95% confident that any difference less than 23% between two measurements made on different occasions represents a true change. In a clinical trial of the effect of inhaled corticosteroids, FEV_1 changed by a mean of 5% over 6 weeks (69). This change would not be detected in the individual with confidence using spirometry. However, in a more recent study that included a large population of healthy preschool children, the CV for FEV_1 was found to be 2.7% (5), and more studies are needed to document this issue.

Similarly, in a study using the interrupter technique, the between-occasion reproducibility in healthy children was 32% of predicted, but, for stable children who had been heard to wheeze within the previous 6 weeks, this rose to 52% of predicted (Table E4) (57). In a trial of the effect of corticosteroids on Rint in preschool children, the group of children who were skin-prick-test positive were shown to benefit significantly after 6 weeks of treatment (41). However, the mean group improvement in Rint of 16% would not have been detected with confidence for the individual.

Between-occasion reproducibility of bronchial responsiveness, using an increase of sRaw of 40% to define a positive response,

has been assessed using both cold air challenge (13 young children) (64) and methacholine challenge (8 children) (70). Although these preliminary results are encouraging, far more children need to be studied to confirm these findings.

Thus, for measuring progress in the individual, changes in measurements between occasions must be interpreted with caution.

CONCLUSIONS AND FUTURE DIRECTIONS

Although there is little doubt about the value of PFT in clinical or epidemiological research, its influence on clinical management in an individual remains debatable. Reference data derived from older subjects should not be extrapolated for use in younger children and standardized equipment and techniques to derive appropriate reference data for this particular age group should be developed. The clinical usefulness of any measurement depends on how well it can discriminate between health and disease and how reproducible it is from one occasion to another so that disease progression and response to treatment can be assessed. For these purposes, we need to know the within-subject variability both within and between test occasions. The within-occasion repeatability of some tests is good enough to make the diagnostic profile of BDR testing reasonably robust, but there is little information about the clinical value of these tests for bronchial challenge (BC) testing in very young children. Little is known about the between-occasion reproducibility for these tests, and more data are needed if we are to distinguish what constitutes a clinically significant change within an individual as a result of disease progression or response to treatment. There is increasing evidence of the significant contribution of these tests as a means of providing objective outcome measures in clinical or epidemiological research studies.

Section 3. Spirometry

SUMMARY

Technically acceptable spirometry is possible in the preschool-aged child. This section of the document provides an update on existing reviews and makes recommendations specific to the preschool age regarding measurement conditions, data collection, interpretation, and reference values. A number of issues still need clarification, but the following recommendations may facilitate comparison among centers:

1. The flow–volume curve ideally should be presented to the operator in real time with the ability to also view the volume–time trace. Alternatively, the operator should be able to view the previous flow–volume curve before the next expiration attempt.

2. The following indices from each spirometry attempt should be available to the operator before the next attempt: FVC, FEV in t seconds (FEV_t), back-extrapolated volume (VBE), and the point at which flow ceases, presented as a proportion of peak expiratory flow (PEF).

3. If it is the subject's first attempt at spirometry, a period of training is essential. The child should be familiarized with the equipment and technician.

4. Interactive computerized incentives may be used to encourage the maneuver, but these are not mandatory. If incentives are to be used, then a volume-driven incentive, or a flow- and volume-driven incentive must be used when maneuvers are to be recorded.

5. Posture and noseclip use should be recorded and reported.

6. The operator should observe the child closely to ensure there is no leak, and that the maneuver is performed optimally.

7. A minimum of three maneuvers should be recorded, but no maximum number is stipulated.

8. Both volume–time and flow–volume curves should be visually inspected. The attempt should be excluded if the flow–volume curve does not demonstrate a rapid rise to peak flow, and a smooth descending limb, without evidence of cough or glottic closure.

9. If the VBE is greater than 80 ml, or 12.5% of FVC, then the curve should be reinspected, but need not necessarily be excluded.

10. If cessation of flow occurs at greater than 10% of peak flow, then this maneuver should be classified as showing premature termination. It may be possible to report timed expiratory volumes from such a maneuver, but FVC and forced expiratory flows should not be reported.

11. The highest FEV_t and FVC should be reported, after examining data from all of the usable curves, even if they do not come from the same curve.

12. The starting point for FEV_t should be determined by back extrapolation.

13. The method of identifying best flows should be recorded and reported. If flows are to be reported from the "best" maneuver, then this should be identified as that with the highest sum of $FEV_{0.5}$ and FVC.

14. Ideally, the subject should produce at least two acceptable curves, where the second highest FVC and FEV_t are within 0.1 L or 10% of the highest value, whichever is greater. If a single satisfactory maneuver is recorded, then these results should not be excluded simply because of poor repeatability. The number of technically satisfactory maneuvers and the repeatability results should always be reported.

INTRODUCTION

Spirometry is the most frequently used method for measuring lung function. The reliability of this technique is dependent on standardized methodology with regard to equipment, data acquisition, and data interpretation. Detailed criteria for spirometry in adult subjects have been published by the ATS, and by the ERS (71, 72), and have recently been updated in a combined document by these societies (73).

Spirometry is commonly performed in adults and in school-age children (those aged 6–16 yr), but recent reports have confirmed that preschool children are also able to perform these maneuvers (5, 6, 8–11, 65, 74, 75). Recent reports have demonstrated that both preschool and school-age children have difficulty meeting some of the quality-control criteria (11, 74, 76) outlined in the ATS/ERS guidelines.

The aims of this section of the document are to summarize what is currently seen to be good laboratory practice, and to provide recommendations for users of this technique in preschool children. Although consensus has been reached on some aspects, there are few published data regarding quality control in this age group, and many of the recommendations in this section are based on the consensus of the working party members rather than on published evidence.

PHYSIOLOGICAL BACKGROUND

To perform spirometry, the older child or adult must inspire to total lung capacity (TLC), exhale forcefully to residual volume

(RV), and repeat the maneuver several times until reproducible flow–volume curves are evident. The repeatability of these curves is dependent on expiratory flow limitation (defined as the flows being independent of effort). A trained adult subject should be able to perform repeated maneuvers in which FEV_1 and FVC are within 5% of each other. Quality-control criteria for adult subjects specify how quickly the subject should increase flow at the beginning of the expiration and what the duration of the expiratory maneuver should be.

Acceptability criteria for preschoolers should differ from adult criteria for two reasons. First, young children have small absolute lung volumes and large airway size relative to lung volume compared with older children and adults. Forced expiration is therefore completed in a shorter time, certainly more quickly than the 6 seconds recommended for adults, but sometimes more quickly than 1 second. More than one report has described how the descending limb of the flow–volume curve is convex in young children, indicating rapid cessation of flow toward the end of the maneuver (10, 11, 74). It is not yet clear whether this pattern is entirely the result of physiological differences, or whether it is partly effort related, but either way the criteria to determine the end of test in adults are not appropriate for the preschool age group. Second, the start of test in adults is assessed by measuring the VBE, either as an absolute or as a percentage of FVC. A recent report has confirmed that VBE in children is typically lower than in adults, whereas VBE/FVC is higher (11). Both findings can be simply explained by the much smaller absolute lung volumes of very young subjects.

Results from spirometry, specifically FEV_1, serve as outcome measures for clinical trials in older children and adults. However, preschoolers often do not exhale for more than 1 second; therefore, FEV_1 may not be an accurate index of bronchial obstruction in this age group. Recent studies have explored the utility of $FEV_{0.5}$ or $FEV_{0.75}$ as outcome measures in this age group (11, 74).

The terminology and definitions for the indices from forced expiration are reported in Table 2. There are no published data regarding measurement of slow vital capacity or maximal voluntary ventilation in the preschool age group. These measurements are not covered by this document.

PROCEDURES

Equipment

Hardware. Spirometers for use in preschool subjects must be capable of measuring instantaneous flows with an accuracy of at least ±5%. Dead space should be minimized where possible, although this requirement does not preclude the use of bacterial filters. Otherwise, recommendations for equipment for use in adult subjects apply.

TABLE 2. DEFINITION OF INDICES OBTAINED FROM FORCED EXPIRATION

Description	Abbreviation
Forced vital capacity	FVC
Forced expiratory volume in t seconds	FEV_t
Forced expiratory flow when X% of FVC has been expired*	FEF_X
Mean forced expiratory flow during the middle half of the FVC†	FEF_{25-75}
Peak expiratory flow	PEF
Forced expiratory time	FET
Back-extrapolated volume	VBE

* In some countries, the term maximal expiratory flow (MEF_X), when X% of FVC remains to be expired, is favored. It should be noted that MEF_{75} is equivalent to FEF_{25}, and MEF_{25} is equivalent to FEF_{75}.

† In some countries, this is termed the maximal midexpiratory flow (MMEF).

Software. Success in achieving maximal forced expiration in preschool children may be increased by use of incentive spirometry computer programs. These programs display interactive cartoon games in which the task of the game is achieved if the subject produces a forced expiration (6, 11). Animations can be designed to encourage tidal breathing, deep inspiration, rapid expiration, and prolongation of expiration. Use of such incentives is not essential, and some centers have reported creditable success rates for preschool spirometry using only verbal training and encouragement (5, 9). If incentives are to be used, then it is important that these are designed and applied correctly. There are convincing data that incentives that encourage rapid expiration alone are only suitable for early training, or for encouraging peak flow maneuvers. If these flow-driven incentives are used in isolation, then underestimation of FVC and FEV_t is likely (77). If a full forced expiration is required, then an incentive that encourages prolonged expiration is required (6, 11). There are no data testing the use of incentives that encourage tidal breathing or maximal inspiration (78).

Manufacturers of spirometry equipment should consider animated incentives in software intended for preschool children. These incentives should be designed to encourage rapid and prolonged expiration. Incentives that encourage tidal breathing and maximal inspiration may also be helpful.

Graphics display. Visual inspection of the flow–volume and volume–time curves is essential for quality control. Preschool subjects are more likely to produce technically inadequate expirations than older subjects, and are also likely to become bored or tired if the test session is prolonged unnecessarily. It is therefore advantageous if the operator is able to visualize these curves onscreen, or at least before the next effort. Ideally, the display should also present FVC, FEV_t, VBE, time to PEF, and the point at which flow ceases, presented as a proportion of PEF. These measurements should be available to the operator before the next effort, so the operator can encourage the child to alter his or her technique if necessary.

Personnel

For pulmonary function tests in preschool subjects, it is essential that the operator have the ability to gain the trust of the child, and that he or she is able to obtain measurements without causing distress. (*See* SECTION 1 for more details regarding personnel.)

Measurement Conditions

Similar to other preschool lung function techniques, there are no data testing the effect of environment on success rates for preschool spirometry. However, the working party still recommends that the laboratory environment be as child-friendly as possible, with adequate time, games, and space for play, and videos that may be helpful.

Data Collection

A number of centers have reported methodology for obtaining spirometry in preschool subjects. The common feature of these reports is the emphasis on a short period of training before data collection (5, 6, 9, 11). During this period, the child is encouraged to play with the mouthpiece (and noseclip, if used). Age-appropriate descriptions and stories are used to explain to the child that a deep inspiration and prolonged rapid expiration are required. Some laboratories use balloons or party whistles to assist teaching. Explanations and teaching should be adjusted to the individual child. Depending on whether animations are to be used, the operator may give a more detailed description of what is required for the maneuver, or may explain the purpose of the interactive game. This training session may be truncated

or omitted if the child has successfully attempted spirometry previously, and is familiar with the technique.

The maneuver may be performed with the child in the standing position, or in an upright, seated position. There are no data testing whether body posture or the use of noseclips has any effect on spirometry results in preschool children. During the maneuver, the operator should ensure that the child's lips are sealed around the mouthpiece, and that the maneuver commences with minimal hesitation. Online observation of the flow–volume and volume–time traces is helpful for assessing adequate start of test, expiratory flow limitation, and whether the end of test has been achieved.

If an incentive program is to be used, the style of this incentive should be tailored to the child. The aim is to stimulate the child to produce a maximal expiration, and this is best achieved by allowing the child to almost achieve the target on early expirations, and to just achieve it when the operator judges that the child is making a maximal effort. If the target is set too low, then the child will cease expiration prematurely. If the target is set too high, then the child may be discouraged. It may be helpful to use a flow-driven incentive for initial training, but this should be substituted for a volume-driven incentive (that encourages prolonged expiration) when maneuvers are to be recorded (4, 10).

A minimum of three maneuvers should be recorded. For some children, it may be helpful to allow 10 or more attempts, and this should be considered if technique is improving with successive maneuvers. Again, this must be tailored to the individual, and the operator should be wary of exhausting the child or inducing bronchoconstriction in subjects with asthma.

INTERPRETATION OF RESULTS

Criteria for Accepting Data

The principles of spirometry quality control in preschool children are the same as for adults. First, it is necessary to visually inspect the flow–volume and volume–time traces, and exclude maneuvers that are visibly inadequate. Maneuvers should be excluded if the flow–volume curve does not demonstrate a rapid rise to peak flow, and a smooth descending limb, with no evidence of cough or glottic closure.

The start of test should be quantified by calculating the VBE. There is only one published study reporting this index in the preschool age group, and this suggests that the VBE criteria for adults are inappropriate for the preschool age group (11). These investigators reported that more than 80% of the studied preschool population achieved a VBE of less than or equal to 80 ml or less than 12.5% of the FVC. Alternative criteria are presented, but these should be viewed as a guide to assist visual inspection, rather than as exclusion criteria *per se*. The end of test should be quantified by reporting the point of cessation of flow. It is known that many preschool children cannot sustain forced expiration for 1 second, let alone the 6 seconds previously stipulated for adults (11), and the forced expired time should be reported but should not be used to exclude maneuvers. Several centers have reported that the descending portion of the flow–volume curve is convex in healthy preschool children (6, 10, 11, 74). This pattern should not be misinterpreted as early termination. One study has reported exponential curve fitting from the volume–time trace as a method for estimating end of test in school-age children (79). This method has not been tested in the preschool age group, and cannot be recommended at this time. If cessation of flow occurs at greater than 10% of peak flow, then this maneuver should be classified as showing premature termination. It may be possible to report timed expiratory volumes from such a maneuver, but FVC and forced expiratory flows cannot be reported.

Data Reporting

The highest FVC and FEV_t from any of the technically satisfactory maneuvers should be reported. These need not come from the same maneuver: for example, $FEV_{0.5}$, $FEV_{0.75}$, and FVC can be reported from three different maneuvers if these are the highest results. Some laboratories may wish to report the best two (or more) FVC and FEV_t values. Flows should be reported from the maneuver that has the highest sum of $FEV_{0.5}$ and FVC, because many preschool children are unable to produce an FEV_1. The spirometry indices that should be recorded and reported from each session are listed in Table 3.

Repeatability

The current repeatability criteria for adult spirometry are not appropriate for preschool children (11), and modifications are suggested. Ideally, the subject should produce at least two acceptable curves, where the second highest FVC and FEV_t are within 0.1 L or 10% of the highest value, whichever is greater. Using a noninvasive approach of applying negative pressure during the forced exhalation maneuver, it has been demonstrated that the preschool-aged child is capable of achieving flow limitation (75). It is also recognized that preschool children may produce one technically excellent maneuver during a session but be unable to produce a second that is within the usual repeatability boundaries. In such cases, laboratories should have the option of reporting results from this single maneuver, if the operator is convinced that it was technically satisfactory. For each child, an estimate of repeatability should be made where possible, but poor repeatability should not lead to automatic rejection of results. The number of technically satisfactory maneuvers and the repeatability results should always be reported.

Reference Data

There are four recent studies describing spirometry in healthy preschool children, in which authors have calculated reference equations for other laboratories to use (5, 9, 10, 74). These studies are presented in Table 4, for the reader's convenience. Publication of these reference equations in this document does not imply that they are endorsed by the ATS or ERS.

TABLE 3. INDICES TO BE RECORDED AND REPORTED FROM SPIROMETRY

Indices That Should Always Be Reported*	Indices That Must Be Recorded for Quality-Control Purposes, and May Be Reported If Desired
FVC	$FEF_{25–75}$[†]
$FEV_{0.5}$	FEF_{25}[†]
$FEV_{0.75}$[‡]	FEF_{50}[†]
FEV_1[‡]	FEF_{75}[†]
Repeatability for parameters above	PEF
Number of satisfactory attempts	FET
Posture	VBE
Use of noseclips	Point at which expiratory flow ceases, expressed as a proportion of PEF

Definition of abbreviations: $FEF_{25–75}$ = mean forced expiratory flow during the middle half of the FVC; FET = forced expiratory time; VBE = back-extrapolated volume.

* Date and time of test, and subject height and weight must also be reported.

[†] At least one flow index must be reported. However, it is recognized that different laboratories have their own preferences regarding which of these indices to report.

[‡] Some preschool children will not be able to sustain expiration for 1 second, and in these cases timed expiratory volumes must not be reported inappropriately. For example, if the FET is 0.6 second, then $FEV_{0.75}$ and FEV_1 cannot be reported from this maneuver. It should be noted that some spirometry software will currently report these indices erroneously, particularly if the child removes their mouth from the apparatus before his or her next inspiration. It may therefore be necessary for the operator to manually delete these results.

TABLE 4. PUBLISHED PREDICTION EQUATIONS FOR SPIROMETRY INDICES IN PRESCHOOL CHILDREN

	No. of Children	Age Range (yr), Height Range (cm)	Notes	Indices	Prediction Equation
Eigen and colleagues (5)	214	3–7, 85–130	Few subjects < 95 cm	FVC (L) FEV$_1$ (L) FEF$_{25-75}$ (L/s) PEF (L/s)	**Girls and Boys** $\ln(FVC) = -13.63 + 2.95 \times \ln(\text{height in cm})$ $\ln(FEV_1) = -12.26 + 2.63 \times \ln(\text{height in cm})$ $\ln(FEF_{25-75}) = -8.13 + 1.81 \times \ln(\text{height in cm})$ $\ln(PEF) = -10.99 + 2.54 \times \ln(\text{height in cm})$
Nystad and colleagues (9)	603	3–6, 90–130	Includes some subjects with asthmatic symptoms*	FVC (L) FEV$_{0.5}$ (L) FEV$_1$ (L) PEF (L/s)	**Girls** $FVC = -1.93 + 0.0279 \times (\text{height in cm})$ $FEV_{0.5} = -1.17 + 0.0192 \times (\text{height in cm})$ $FEV_1 = -1.66 + 0.0251 \times (\text{height in cm})$ $PEF = -3.72 + 0.0589 \times (\text{height in cm})$ **Boys** $FVC = -2.52 + 0.0337 \times (\text{height in cm})$ $FEV_{0.5} = -1.35 + 0.0210 \times (\text{height in cm})$ $FEV_1 = -2.11 + 0.0295 \times (\text{height in cm})$ $PEF = -4.04 + 0.0620 \times (\text{height in cm})$
Zapletal and colleagues (10)	173	3–6, 90–130	Few subjects < 105 cm	FVC (ml) FEV$_1$ (ml) FEF$_{25}$ (L/s) FEF$_{50}$ (L/s) FEF$_{75}$ (L/s) PEF (L/s)	**Girls and Boys** $\ln(FVC) = -12.88 + 2.767 \times \ln(\text{height in cm})$ $\ln(FEV_1) = -12.06 + 2.584 \times \ln(\text{height in cm})$ $\ln(FEF_{25}) = -9.681 + 2.244 \times \ln(\text{height in cm})$ $\ln(FEF_{50}) = -8.578 + 1.943 \times \ln(\text{height in cm})$ $\ln(FEF_{75}) = -7.559 + 1.608 \times \ln(\text{height in cm})$ $\ln(PEF) = -9.575 + 2.232 \times \ln(\text{height in cm})$
Vilozni and colleagues (74)	109	3–6, 85–126		FVC (L) FEV$_{0.5}$ (L) FEV$_1$ (L) FEF$_{50}$ (L/s) FEF$_{75}$ (L/s) FEF$_{25-75}$ (L/s) PEF (L/s)	**Girls and Boys** $FVC = 0.0834 \times \exp(0.0243) \times (\text{height in cm})$ $FEV_{0.5} = 0.0777 \times \exp(0.0223) \times (\text{height in cm})$ $FEV_1 = 0.0831 \times \exp(0.0231) \times (\text{height in cm})$ $FEF_{50} = 0.4030 \times \exp(0.0144) \times (\text{height in cm})$ $FEF_{75} = 0.1642 \times \exp(0.0189) \times (\text{height in cm})$ $FEF_{25-75} = 0.3080 \times \exp(0.0165) \times (\text{height in cm})$ $PEF = 0.2150 \times \exp(0.0234) \times (\text{height in cm})$

Definition of abbreviations: FEF = forced expiratory flow.

* The authors report that presence of asthmatic symptoms did not influence lung function.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent studies have shown that the preschool-aged child is capable of performing a reliable, reproducible forced expiratory maneuver. Adult criteria for acceptability are not appropriate for this age group, and modified preschool criteria are recommended. Preschool recommendations for spirometry are essential to facilitate multicenter collaboration and comparisons among laboratories. The working party recommends that these guidelines be reviewed and updated regularly. Future areas of research include the following:

1. Development of reference equations that can cross from preschool- into school-age children

2. Investigation of the utility of shorter timed expiratory volumes (e.g., FEV$_{0.5}$)

3. Development of software that automatically identifies maneuvers that may not meet these quality-control criteria, and which better assesses end of test in very young children

4. Assessing both short- and long-term variability of these spirometric maneuvers in the preschool-aged child

5. Defining bronchodilator response in the individual child

6. Assessing the clinical applicability of this technique in various disease states

Section 4. Tidal Breathing Measurements

SUMMARY

Tidal breathing measurements include (*1*) analysis of tidal expiratory flow and (*2*) analysis of thoracoabdominal motion. For both techniques, much of our knowledge is based on studies in infants.

Tidal expiratory flow analysis can be performed either on flow signals collected at the airway opening (with mask/mouthpiece and pneumotachometer) or volume signals collected at the chest wall (with ribcage and abdominal bands).

For tidal expiratory flow analysis,

1. The child should be in a sitting position and the respiratory pattern should be stable and natural before initiating data recording.

2. A minimum of 30 seconds of tidal breathing should be recorded to obtain 10 stable tidal breaths.

3. Raw signals should be inspected and a minimum series of 10 regular breaths analyzed.

4. The mean of the 10 tidal breaths should be reported along with the SD or CV.

Most published data relate to the pattern of early expiration (placing of the expiratory flow peak: time to peak tidal expiratory flow [t$_{PTEF}$]/total expiratory time [t$_E$] or volume at peak tidal expiratory flow [V$_{PTEF}$]/expired tidal volume [V$_E$]) but measures of the flow pattern of late expiration also show some promise.

Thoracoabdominal motion analysis is performed on volume signals collected at the chest wall (rib cage and abdomen) usually by respiratory inductance plethysmography (RIP).

For thoracoabdominal motion analysis,

1. Recordings should be made during quiet wakefulness, preferably in the sitting position if the clinician is interested in lung or airway pathology.

2. Raw signals must be visualized to select suitable breathing sequences for analysis.

A variety of markers of thoracoabdominal asynchrony (TAA)—a reflection of increased work of breathing—have been proposed: some require volume calibration of RIP but others do not. These indices show promise; however, due to the limited number of studies, further work is needed in this field.

For both types of analysis, further study is needed before the techniques can be applied to clinical practice. In particular, the inherent variability, sensitivity to change in airway caliber, and relationship to other measures of airway obstruction specifically in preschool children require further investigation. It is unlikely that either technique will prove to be a very sensitive measure of small airway obstruction, but either or both may find a place, for example, in assessment of acute illness or in epidemiological studies.

INTRODUCTION

Techniques included here are all those in which spontaneous tidal breathing is studied without any interference other than simply recording—that is, no interruption to flow, no forced flow, no change in inspired gases. Recording tidal breathing without interference is appealing because it requires minimal cooperation, and may reflect "real life" because frequent measurements are possible, even during acute respiratory conditions. These measurements can be made awake or during sleep, but sleep measurements, focusing on apnea, are not the focus of these recommendations. Two techniques are discussed.

Tidal expiratory flow analysis evaluates the configuration of tidal expiratory flow–time and flow–volume traces. Analysis of thoracoabdominal motion evaluates the relationship between rib cage and abdominal excursions during tidal breathing.

TIDAL EXPIRATORY FLOW ANALYSIS

Background

Analysis of flow patterns during forced expiratory maneuvers has long been accepted to be useful (80). Furthermore, it has been recognized (81–83) that flow patterns during tidal expiration may appear different in adults and children with respiratory problems, whether these are examined on a flow–time plot or a flow–volume plot. The challenge has been to move from such general gestalt observations, to measurements that relate in a meaningful and proportionate way to underlying properties of the respiratory system.

Tidal breathing is a complex phenomenon. Flow ($\dot{V}$) at the airway opening at any time point during expiration is determined by driving pressure (P) and resistance (R) ($\dot{V} = P/R$). P is determined by net elastic recoil of the respiratory system (lung and chest wall compliance) and net pressure due to respiratory muscle activity. Net pressure due to respiratory muscle activity depends on complex outputs from respiratory control centers. Expiratory muscle activity is minimal at rest in healthy individuals, but may appear with exercise, disease, or conscious effort. Inspiratory muscle activity normally continues into early expiration at all ages to "brake" expiratory flow.

Total respiratory system resistance is determined by chest wall, lung tissue, and airway resistance. Airway resistance derives from (1) small and large intrapulmonary airways; (2) the glottis, which changes aperture during the respiratory cycle under complex neural control; (3) the pharynx, a muscular tube under neural control; and (4) the mouth/nose.

Clearly, it is unlikely that any measurement derived from tidal expiratory flow patterns will relate in a simple way to one of these factors (e.g., small airway resistance). Measurements made on tidal expiratory flow have been shown to be empirically useful in certain circumstances. However, both researchers and clinicians need to be aware that, although making these measurements is simple, interpreting them is not.

Procedures

Equipment and data collection. A detailed analysis of the technical requirements for equipment and software to record and ana-

lyze tidal breathing parameters in infants was previously published by this ERS/ATS task force (84). These considerations are equally applicable to measurements made in preschool children, although the larger size and lower respiratory rate make the requirements regarding dead space and sampling rate less stringent, and sedation and posture issues are quite different (*see below*).

The measurements required are as follows: flow ($\dot{V}$) and volume (V), measured over time (*t*). Flow or volume is measured and integrated or differentiated with respect to time to calculate the other. The flow is measured at the airway opening using a pneumotachometer (or other flowmeter) via a mask (85) or via a mouthpiece (86). Relative volume changes are estimated at the chest wall using impedance bands (87). Although absolute volumes and flows may not be needed to calculate all the indices, it is important to ensure linearity across the range encountered. If measurements are made at the airway opening, we would therefore recommend that the flow-measuring device be calibrated using a known volume signal (calibration syringe) before each measurement session.

Data should be digitized at a minimum of 50 Hz (100 Hz minimum is recommended at high respiratory rates) (88). Equipment dead space should be minimized to avoid altering respiratory control and pattern (*see* SECTION 1).

The "best" method for collecting flow data (mask, mouthpiece, or chest wall measurements) has not been determined, and in terms of variability and ability to detect airway obstruction, the three methods have not been compared. It cannot be assumed that normative values collected using one method can be applied to data collected using another.

Although, in infants, measurements have usually been made during sleep, this is not feasible in preschool children. Because arousal and respiratory drive are likely to affect tidal flow patterns, measurements should be standardized to the quiet awake state (86, 89). Posture (supine, sitting, or standing) may also affect tidal measurements (90): it should preferably be standardized to sitting, but in any event should be stated clearly.

Measurement conditions are very important (91). A specific point for tidal breathing measurements is that the child's breathing pattern must be both natural and stable, despite the unfamiliarity both of surroundings and of breathing through a face mask or mouthpiece (for details, *see* SECTION 1).

It is essential to be able to visualize the signal in real time to ensure that the respiratory pattern is stable and regular before starting data recording. Ideally, both types of plot should be available: $\dot{V}$–V to ensure repeatability of shape, $\dot{V}$–*t* to ensure stable respiratory rate and volume (92). Once a stable pattern is observed (steady end-expiratory level, respiratory rate, and tidal volume [VT]), a minimum of 30 seconds of tidal breathing should be recorded to obtain a stable epoch of 10 tidal breaths. Breaths should not be included for analysis (92) if they are obviously different in shape or size from surrounding breaths (e.g., sighs), if there are doubtful points of zero flow (e.g., pause between inspiration and expiration), or if there is more than one peak of expiratory flow. Published reports have used from 4 to 50 breaths (85, 86, 93), but 10 breaths seem to be adequate to yield a reliable mean value (93). If, after several attempts, it is impossible to record a continuous segment of 10 stable tidal breaths, it is acceptable to combine segments from separate epochs to provide 10 breaths for analysis, but this may increase data variability.

Finally, although computerized algorithms (and breath selection [92]) are helpful, it is essential that the software be transparent. It should be clear to the operator how the values are derived, and it should be possible to go back to the raw data to inspect tidal curves, to select manually which epochs are to
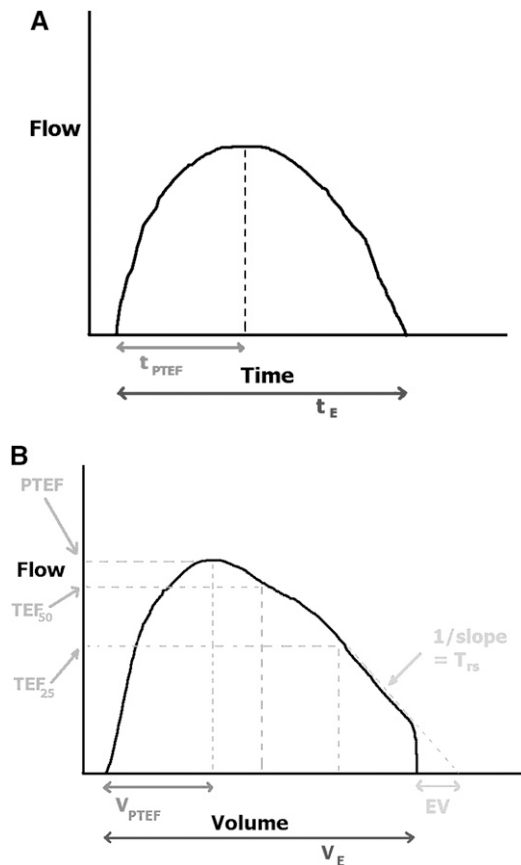
Figure 2. Tidal expiratory flow indices. (*A*) Flow–time plot illustrating measurement of time to peak tidal expiratory flow (t_{PTEF}) and total expiratory time (t_E); (*B*) flow–volume plot illustrating measurement of volume at peak tidal expiratory flow (V_{PTEF}), expired tidal volume (V_E), tidal time constant of the respiratory system (T_{rs}), extrapolated volume (EV), PTEF, flow at 50% of tidal volume (TEF_{50}), and TEF_{25}.

be analyzed, and if necessary, calculate the indices (and any new indices developed in the future) by hand (84).

Data Analysis

The following indices have been calculated from tidal expiratory flow recordings (Figure 2):

Measures related to timing of peak tidal expiratory flow (83): (*1*) Time to peak tidal expiratory flow (t_{PTEF}) (s), (*2*) total expiratory time (t_E) (s), (*3*) the ratio of these (t_{PTEF}/t_E), (*4*) volume at peak tidal expiratory flow (V_{PTEF}) (ml), (*5*) expired tidal volume (V_E) (ml), and (*6*) the ratio of these (V_{PTEF}/V_E).

Measures based on fitting a linear regression to flow–volume plot in late expiration (94): (*1*) Tidal time constant of the respiratory system (T_{rs}) (s), the reciprocal of the slope of the regression line, and (*2*) extrapolated volume (EV) (ml), how far beyond end expiration the regression line meets the volume axis.

Measures of shape of flow–volume loop after peak flow (convex/concave to volume axis) (95, 96): (*1*) Flow at 50% of tidal volume/peak tidal expiratory flow ($TEF_{50}/PTEF$) and (*2*) flow at 25% of tidal volume/peak tidal expiratory flow ($TEF_{25}/PTEF$).

Each of these indices is an imperfect attempt to describe an aspect of the shape of expiratory tidal flow, whether plotted with respect to time or volume. It is likely that much more information could be extracted from the loops, either to quantify small airway obstruction or to distinguish it from large or upper airway obstruction, but currently the appropriate mathematical analysis remains elusive.

Thus far, most research has considered the two (closely related) peak tidal expiratory flow measures, t_{PTEF}/t_E and V_{PTEF}/V_E. In general, it is observed that adults (83) and children (86) with obstructive respiratory diseases reach peak tidal flow earlier (and hence after a smaller expired volume) during expiration. There is increasing evidence that the timing of PTEF is due to an interaction between the mechanical properties of the lungs and airways, on the one hand, and central control of breathing, on the other. In tracheostomized cats, it is possible to predict the timing of PTEF using a model based on two factors: the time constant of the respiratory system and the time constant of decay of postinspiratory inspiratory muscle activity (97, 98). It has been speculated (83) that individuals with airway obstruction "sense" that they do not "need" as much braking of expiration, and relax their inspiratory muscles more promptly at the end of inspiration.

The measures based on fitting a linear regression to late expiration (94) are an attempt to mimic the single-breath measurement of passive mechanics of the respiratory system (99), requiring the assumption that there is no muscle activity in late expiration. The measures of the shape of the flow–volume loop after peak are an attempt to quantify the more rapid fall-off in flow in the presence of small airway obstruction.

Interpretation of Results

Repeatability. Indices should be calculated for 10 (ideally consecutive) individual breaths, then these should be expressed as a mean. The CV of the mean should be reported (*see* SECTION 2). If repeated baseline measurements are performed, then the CR is calculated (59). The repeatability of baseline measurements sets the context for determining when a genuine change (bronchodilator response or bronchial provocation) has occurred.

Most studies reporting variability of tidal breathing indices have reported CV, rather than CR, and have only studied t_{PTEF}/t_E and V_{PTEF}/V_E. Only one study has reported variability in a sample including (but not exclusively) preschool children (86). The results for t_{PTEF}/t_E are summarized in Table 5.

Repeatability differs with age and possibly with disease status. Stocks and colleagues (93) found a wider repeatability coefficient in infants younger than 6 weeks compared with older infants. However, all studies reporting intraindividual CV in normal subjects have found very similar results, between 20 and 26%. For t_{PTEF}/t_E, in contrast to forced expiratory parameters, Morris and Lane (analyzing 10 breaths) found that variability was lower in adults with severe airway obstruction than in healthy adults (83), but van der Ent and coworkers (86) did not find this in their children with (milder) airway obstruction.

Reference values. There are currently no satisfactory normative data for tidal flow measurements in preschool children. Two studies have reported data in normal preschool children, using different methods and yielding conflicting results. van der Ent and colleagues (86), in 120 sitting children aged 3 to 6 years, used a mouthpiece and pneumotachometer with a "relatively large" dead space and found mean (SD) t_{PTEF}/t_E of 0.447 (0.078). They found weak negative correlations with age ($r = -0.27$) and height ($r = -0.22$). In contrast, Mayer and colleagues (90) used chest bands in 50 healthy 3 to 5 year olds, and reported a sitting mean (SEM) t_{PTEF}/t_E of 0.303 (0.014), and no correlation with age, height, or sex.

Clinical applications. Published studies in children have almost exclusively used t_{PTEF}/t_E and V_{PTEF}/V_E, and most of these have looked only at infants. Due to the paucity of data in

TABLE 5. REPEATABILITY REPORTED FOR t_{PTEF}/t_E

Study	Age	No. of Breaths	Mean Intrasubject CV %	Repeatability Coefficient, Absolute (%)
Morris and Lane (83)	Adults	10	Normal, 23%; Severe obstruction, 13%	
van der Ent and colleagues (86)	3–11 yr	15	Normal, 23%; Asthma/CF, 26.5%	Normal, 0.053 (12.3%)
Stocks and colleagues (93)	0–62 wk	50		All, 0.133 (36%) < 6 wk, 0.165 (37%) ≥ 6 wk, 0.082 (30%)
Lødrup Carlsen and colleagues (293)	0–4 d	4	20–26%	
Fisher and colleagues (294)	Newborn	?	23–37%	
Stick and colleagues (87)*	1–5 d	10	13%	0.066 (13.6%)
Hunter and colleagues (109)*	14–22 yr	57	Normal, 22%; CF, 26%	

Definition of abbreviations: CF = cystic fibrosis; CV = coefficient of variation; t_E = total expiratory time; t_{PTEF} = time to peak tidal expiratory flow.

* Using respiratory inductance plethysmography.

preschool children, the data in infants and older children will also be reviewed briefly.

A number of studies (100–103) have shown that reduced t_{PTEF}/t_E in early infancy is associated with increased subsequent wheezing, but with low predictive value, and no data on tidal breathing parameters beyond infancy.

Adults (83, 94), children (86, 89), and infants (104–107) with wheezing disorders have lower mean t_{PTEF}/t_E and V_{PTEF}/V_E values than control subjects in most reported studies—although with considerable overlap between groups. One study in school-children with asthma (108), and one in adolescents with CF (109), found no difference in tidal parameters compared with control subjects. Attempts to correlate tidal measures with direct measures of lung function have yielded mixed results. In infants, V_{PTEF}/V_E have correlated poorly with measures of respiratory resistance such as Raw (104), specific airway conductance (sGaw) (105), and lung resistance (R_L) (110), but correlated reasonably well with $\dot{V}max_{FRC}$ (105, 114). In older children (86, 108), t_{PTEF}/t_E has correlated significantly with FEV_1 and forced expiratory flow at 50% of FVC (FEF_{50}), but with r values only around 0.5. In response to histamine or methacholine challenge in infants, one study reported a significant decrease (111) in t_{PTEF}/t_E, whereas another reported no change (112). Histamine challenge studies in children (≥ 4 yr) have shown a significant change in tidal parameters (86, 108). Nebulized epinephrine in infants with bronchiolitis (113) and β_2-agonist in wheezy infants (106) and young children with asthma (86, 89) have resulted in an increase in t_{PTEF}/t_E.

THORACOABDOMINAL MOTION ANALYSIS

Background

This method is an attempt to quantify the clinical sign of rib recession in young children with increased work of breathing from any cause, which may be due to increased resistance or reduced compliance. In health, the rib cage moves outward during inspiration completely in phase with the outward movement of the abdomen. With progressive increase in the work of breathing (and hence negative intrathoracic pressure generated), the rib cage (particularly, the compliant rib cage of the young child) lags behind abdominal movement, and in severe cases may even move inward initially (114). Thoracoabdominal motion analysis examines the degree to which chest and abdominal excursions are out of phase (asynchronous).

TAA should, then, be increased by increased respiratory resistance (upper or lower airways, lung tissue), decreased lung compliance (C_L) (parenchymal disease), and increased chest wall compliance (floppy rib cage, neuromuscular disease).

Procedures

Equipment and data collection. Chest and abdominal wall excursions are detected by external devices placed circumferentially around the chest and abdomen. Although strain gauges (wire, mercury in silastic, piezoelectric) have been used to detect excursions semiquantitatively, most work in this area has been done using RIP. This uses sinusoidal coils of wire sewn into elasticated cloth bands: a change in the cross-sectional area of the band around the chest or abdomen alters the self-inductance of the coil, producing a change in the frequency of a low-voltage alternating current passed through the coil. This frequency change is demodulated to give a voltage signal proportional to the cross-sectional area of chest or abdomen. It is possible to calibrate RIP so that the sum of the chest and abdominal signals gives a measure of V_T, or to use it uncalibrated so that the chest and abdominal signals reflect the timing and direction of volume change, but not absolute volume changes. RIP requires an oscillator module, an appropriately sized inductance band, a connector cable, and a computer for data recording. Currently available oscillator units produce a sine wave with an amplitude of 20 mV at 300 kHz. The inductance bands should be placed firmly around the patient to maximize signal transmission, with care not to distort the sinusoidal arrangement of the wires. With currently available software, data sampling is performed at 200 Hz with 12-bit resolution, well above the 50-Hz frequency believed to be sufficient (115). Real-time recording using available software allows for almost simultaneous evaluation of the data stream to ensure proper signal and data quality.

Relative calibration using the Qualitative Diagnostic Calibration (116) method can be performed electronically using analytic software. Volume calibration can also be performed with input from a pneumotachometer through an analog-to-digital convertor. The pneumotachometer should be linear over the flow range appropriate for patient size and breathing pattern. We would recommend that relative calibration be used for all measures of TAA, with ideally an absolute volume calibration for the measures listed in the list below under "Measures requiring volume calibration." A recent refinement of RIP uses a single spiral coil around chest and abdomen to measure absolute volume change (without the need for pneumotachometer calibration), which can be partitioned into chest and abdominal components.

If lung or lower airway pathology is the issue of interest, as with tidal flow analysis, recordings should be made during quiet

wakefulness, preferably in the sitting position (99). It is feasible to measure both thoracoabdominal motion and tidal flow parameters at the same time in awake preschool children (99).

Data Analysis

The following indices (117) all represent ways of expressing the degree of asynchrony—that is, the extent to which chest excursions lag behind abdominal excursions, or are out of phase with Vt changes. Each has its advantages and problems, which are briefly indicated.

Measures feasible without volume calibration: (*1*) Phase shift, as angle (ϕ, "phi") or %. This can be calculated from X–Y plots of rib cage against abdominal excursion (117, 118) ("Lissajous figures" or "Konno-Mead loops"; Figure 3A). This has the advantage of incorporating data from the whole of the respiratory cycle, but the disadvantage of assuming both rib cage and abdominal excursions are sine waves. Irregular or "figure 8" rib cage–abdominal loops cause problems. Phase shift can also be calculated from time-based plots (119, 120), usually as the lag between the start of abdominal expansion and the start of rib cage expansion (Figure 3B). This depends on accurately defining the troughs, but is robust to irregularities of excursion. If phase shift is expressed as an angle (ϕ), the lag is expressed in relation to the *total respiratory cycle* (taken as 360°), so that "paradox" (where rib cage and abdomen are completely out of phase) is equivalent to a phase shift of 180°. If phase shift is expressed as %, the lag is usually expressed in relation to *inspiratory time*, so paradox is equivalent to a

phase shift of 100%. However, it is sometimes expressed in relation to total respiratory cycle: the denominator should therefore be clearly stated. (*2*) Percent time paradoxical to Vt (120): The rib cage or abdomen may be assessed during inspiration, expiration, or in relation to the total breath. For example, the percentage of inspiration during which the rib cage is moving inward while Vt is increasing (i.e., when flow is inspiratory) is referred to as the Rib Cage Inspiratory Percent Time Paradoxical (RCIPT). (*3*) Phase Relation during Total Breath (PhRTB) (90): This index is similar to the above and measures the percentage of the total breath duration for which the rib cage and abdomen are moving in opposite directions.

Measures requiring volume calibration: (*1*) Asynchrony index: the area between the rib cage–abdominal loop and straight line connecting ends, divided by Vt to normalize for size of breath (ml²/ml) (121). During inspiration, the area lies between the line connecting ends and inspiratory portion of the loop. During expiration, the area lies between the line and expiratory portion. (*2*) Labored breathing index (LBI) (122) (*see* Figure 4). Maximal Compartmental Amplitude (MCA) is the sum of the maximal peak-to-trough amplitudes of rib cage and abdominal excursion, and represents the Vt that would result if these were perfectly in phase (MCA/Vt). Thus, if there is no asynchrony, LBI or MCA/Vt = 1; the greater the asynchrony, the more it exceeds 1. (*3*) Rib cage contribution to Vt (%rib cage/Vt) (123): maximum rib cage excursion as a percentage of Vt.

Computerized analysis of some of the above is available and satisfactory, but it is essential to check that the raw data are suitable. For example, phase angle analysis on rib cage–abdominal loops is meaningless for figure-8–shaped loops.

Interpretation of Results

Repeatability. There are no published data on repeatability of any of the above measures in infants or young children.
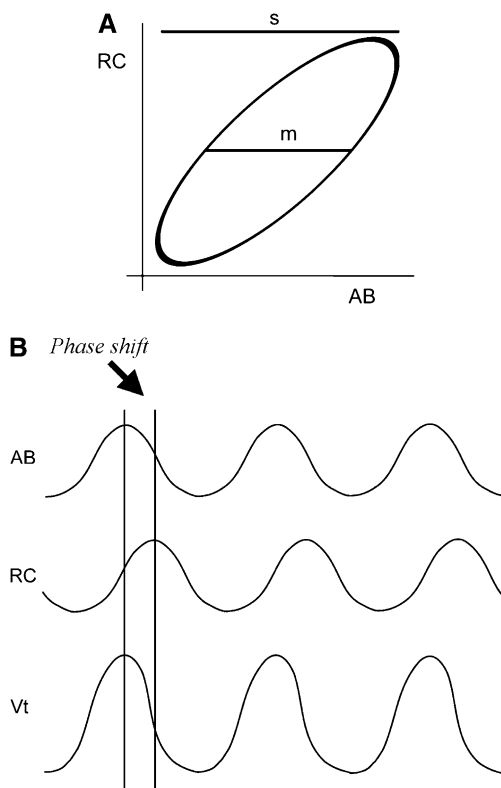

Figure 3. Thoracoabdominal motion indices: phase angle and shift. (*A*) Plot of rib cage (RC) versus abdominal (AB) excursion plot illustrating calculation of phase angle ϕ. s = maximal AB excursion; m = horizontal width of RC–AB loop at halfway between maximal and minimal RC excursion. For $\phi < 90°$, $\sin \phi = m/s$; for ϕ 90° to 180°, $\sin \mu = m/s$, and $\phi = 180°-\mu$. (*B*) Time plot of AB and RC excursions and sum (Vt) showing phase shift.
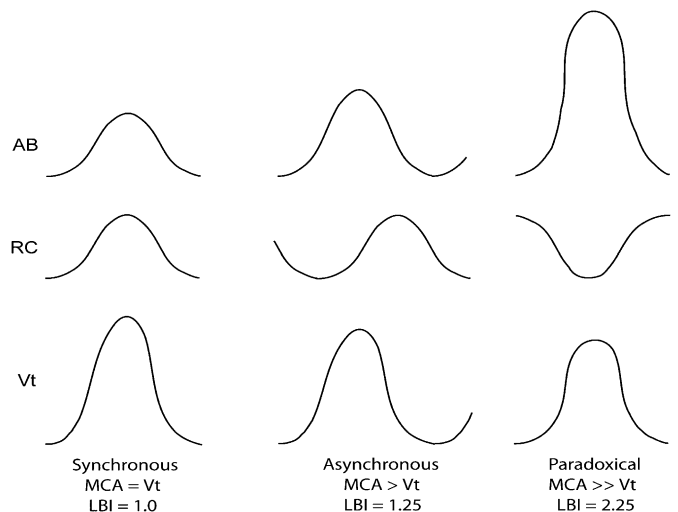

Figure 4. Thoracoabdominal motion indices: labored breathing index (LBI). Time plots of AB, RC, and Vt showing LBI in three situations. Maximal compartmental amplitude (MCA) = maximal (max) AB + max RC; LBI = MCA/Vt. Where there is complete synchrony (*left panel*), max AB and max RC coincide, so LBI = 1. With progressive asynchrony (*center* and *right panels*), Vt become progressively smaller in relation to MCA.

Reference Values. Only one study has reported normative data, in 50 healthy children aged 3 to 5 years (90). Mean (SEM) sitting values for phase angle were 15.7 (4.0), for PhRTB were 10.0 (1.8), and for LBI were 1.01 (0.01). There was no significant association with age or height.

Clinical Applications. Like tidal flow analysis, thoracoabdominal motion analysis can only ever be an indirect measure of lung function.

There have been few studies in children comparing TAA measures either with other measures of pulmonary function, or between children with airway disease and control subjects. Studies in adults with chronic obstructive pulmonary disease have shown MCA/VT values above 1.0 (124) (no comparison with controls), and an asynchrony index significantly greater than that in control subjects (125) (but no difference in ϕ or MCA/VT). In adolescents and young adults with CF (109), ϕ was higher than in controls, but did not correlate with FEV_1. In infants with airflow obstruction (114) due to bronchopulmonary dysplasia or bronchiolitis, changes in ϕ after β_2-agonist, although inconsistent, correlated with changes in RL and CL. In a further study in infants with bronchopulmonary dysplasia (126), ϕ was significantly higher than in control subjects (102° vs. 8°) and correlated with baseline values of RL and CL. In infants with recurrent wheeze undergoing methacholine challenge (122), there was a significant rise in ϕ, which in most cases occurred at the same concentration as that provoking a 40% drop in $Vmax_{FRC}$.

CONCLUSIONS AND FUTURE DIRECTIONS

Analysis of tidal expiratory flow patterns and analysis of thoracoabdominal motion are both promising techniques for assessing lung function in the preschool child, but there are significant limitations and major gaps in our knowledge. Both techniques have the ability to make measurements rapidly and repeatedly with minimum disturbance to the child, and they are applicable from infancy to adulthood. In research, these tests can be used in large-scale epidemiological studies, and may be one way of bridging the gap between infant and cooperative measurements. In clinical work, these methods have potential in acute respiratory diseases where other techniques cannot be applied. Both techniques have the drawback of being indirect measures of lung function, influenced by other factors (respiratory drive, chest wall characteristics). It is unlikely, on current evidence, that either is a particularly sensitive measure of small airway disease. Much of our present knowledge is extrapolated from infants and adults: considerable work remains to be done on the technical aspects and clinical relevance of tidal techniques in the preschool child.

Section 5. The Interrupter Technique

SUMMARY

The interrupter technique is currently in routine use in several laboratories for the evaluation of lung function in preschool children. Multiple reports have established the interrupter technique to be feasible and repeatable in preschool children, to have a good correlation with "gold standard" techniques, and to be able to detect changes in airway caliber. The clinical interpretation of the interrupter resistance (Rint) in preschool children has been recently made easier by the availability of reference values for this age group. However, the use of different methods makes it difficult to compare the results obtained in different laboratories and underlines the need for standardization for the interrupter technique.

In this section of the document, we provide the current recommendations for the use of the interrupter technique in preschool children, including measurement conditions and data collection, quality control of measurements, data analysis and report, and interpretation of results. However, many issues regarding the interrupter technique still need to be clarified. Future studies will have to determine the best algorithm to calculate mouth pressure during the occlusion and to establish the cutoff value for a decrease in Rint beyond which bronchodilator response should be considered clinically significant. The role of Rint as the primary outcome in challenge tests and its place in PFT in preschool children also remain to be determined.

With the current state of knowledge, the following recommendations are presented in an attempt to make the technique used to measure interrupter resistance more uniform and to facilitate data comparison between centers:

1. Measurements should be made with the child seated, breathing through a mouthpiece and bacterial filter, noseclip *in situ*, and cheeks supported.
2. Occlusions should be made with a valve closing in less than 10 milliseconds and lasting for 100 milliseconds.
3. Occlusions should be triggered by a flow set to coincide with PEF and made during expiration.
4. Ten occlusions should be recorded, with the aim of retaining a minimum of five acceptable maneuvers.
5. The median of all technically acceptable occlusions should be reported.
6. All technical details, including interruption trigger, method for calculating mouth pressure, phase of respiration, and means of determining technically acceptable occlusions, should be reported.

INTRODUCTION

The interrupter technique was first reported in 1927 (127) and was improved in the 1970s–1980s (128–135). With the availability of commercial devices, the assessment of Rint in preschool children has recently become increasingly popular. However, different implementations of the technique make it difficult to compare the results obtained in different laboratories and highlights the need for recommendations for the interrupter technique. A variant of the classical technique was also proposed, the so-called opening interrupter technique, in which mouth pressure (Pmo) is measured at the end of the occlusion and flow is measured right after valve opening (136). This section discusses the classical interrupter technique, because the opening technique has not been widely used and Rint values obtained with this variant are not comparable to those obtained with the classical technique.

BACKGROUND

The principle of the interrupter technique is that, during a sudden airflow interruption at the mouth, alveolar pressure and Pmo will rapidly equilibrate. Rint is defined as this pressure divided by the airflow measured immediately before interruption. The total time of interruption is not longer than 100 milliseconds as this time is too short to be recognized and too short to allow the initiation of voluntary breathing against the occlusion (137).

Schematically, when mouth airflow is suddenly interrupted (Figure 5), there will be a rapid initial change in Pmo (Pinit) followed by a slower change (Pdif) up to a plateau (Pel) (138). Pinit is virtually instantaneous and reflects the pressure difference due to the airway resistance at the time of interruption (132, 133). Pinit will reflect the pressure drop across all Newtonian resistance of the respiratory system, which includes conducting
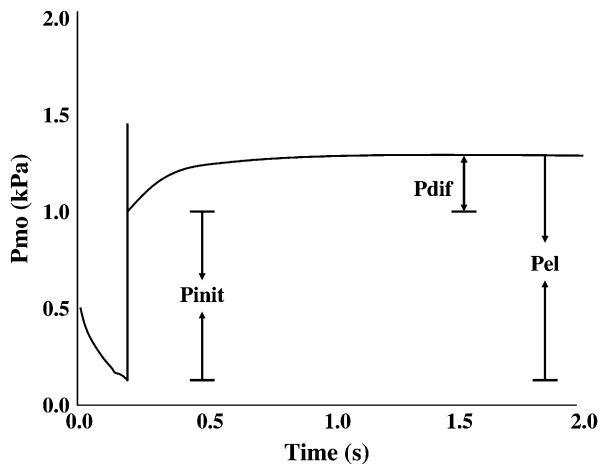
Figure 5. Schematic description of the pressure–time curve showing mouth pressure (Pmo) changes after a sudden airflow interruption at midexpiration. Pdif = secondary slower change in Pmo; Pel = final plateau representing the pressure due to the elastic recoil of the respiratory system; Pinit = rapid initial change in Pmo. Modified by permission from Reference 138.

airways, lung tissue, and the chest wall (130). During tidal breathing, Pinit, and thus Rint, will include a component of both lung tissue and chest wall resistance, not only airway resistance. Pdif is due to the viscoelastic properties of the respiratory tissues and reflects stress adaptation (relaxation or recovery) within the tissues of the lung and chest wall, plus any gas redistribution (pendelluft) between pulmonary units with different pressures at the time of interruption (132, 133, 138). The final plateau represents the pressure due to the elastic recoil of the respiratory system and may take several seconds to be reached (138).

In the real world, between the rapid and the slow change in Pmo after airflow interruption there is a series of rapid oscillations in pressure (Figure 6A) due to the inertia and compressibility of the air column in the airways. These oscillations are more or less damped depending on the time constant of the system (chest wall–lungs–upper airways–equipment) (132). The presence of the rapid oscillations in Pmo makes it difficult to determine Pinit. Several methods have thus been proposed to extrapolate Pinit, and it has also been suggested to use the pressure at the end of the interruption instead. An analysis of the postocclusion rapid oscillations has also been proposed (139, 140), which can give additional information about the inertive and elastic properties of the thoracopulmonary system. The greater the component of Pdif that is incorporated into Rint measurement, the higher Rint will be with respect to pure airway resistance, and the more it will approach resistance of the whole respiratory system. Even when Pmo is linearly back-extrapolated to the beginning of the interruption (as in Figure 6A), it still partially depends on the final parts of the pressure–time curve. A comparison of the different methods of calculation of Pmo is reported below, in DATA ANALYSIS.

The main assumption of the interrupter technique is that Pmo and alveolar pressure rapidly equilibrate after interruption. Ventilation dishomogeneities or severe bronchial obstruction, as well as compliance of the upper airways (mainly cheeks), may increase the time necessary for Pmo and alveolar pressure to equilibrate. This is a crucial point, because in this case, alveolar pressure will be underestimated. Theoretical studies have suggested that, when mild or moderate bronchial obstruction is present, airway resistance may be estimated with enough accuracy by the interrupter technique if compliant upper airways
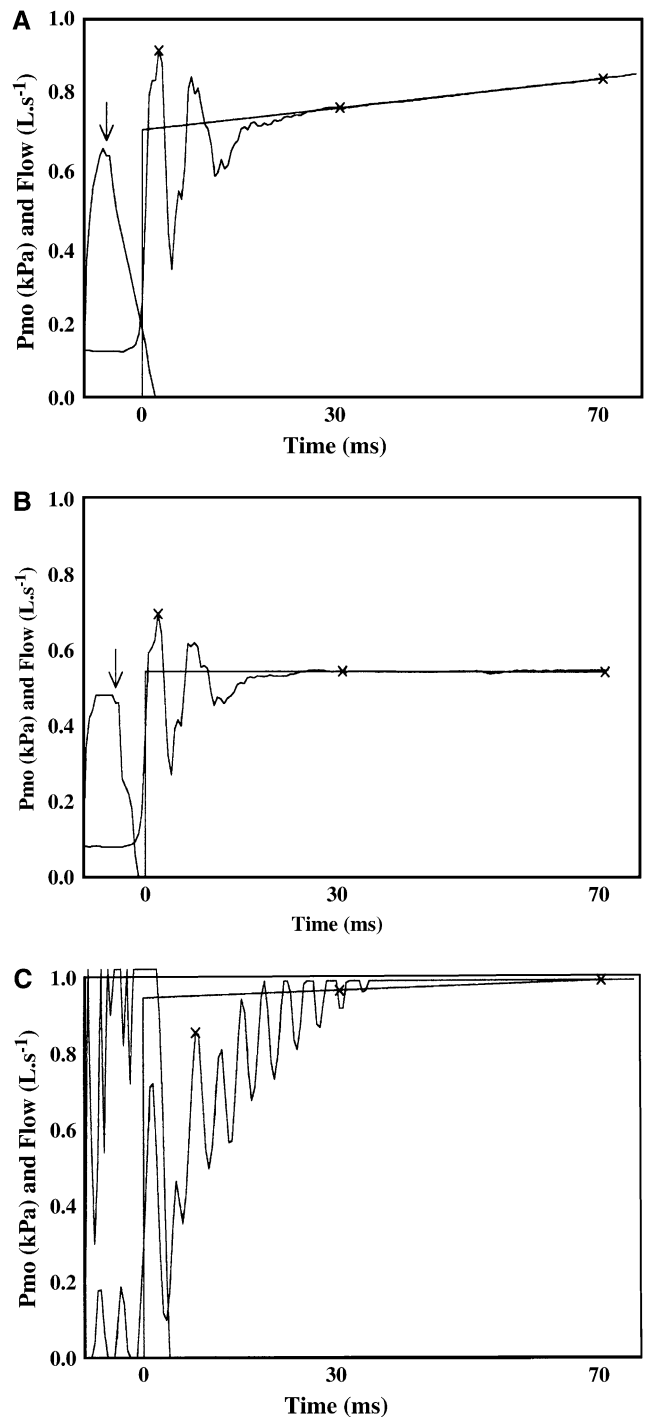

Figure 6. Actual pressure–time and flow–time traces showing mouth pressure (Pmo) and flow during a 100-millisecond interruption. The *arrow* shows the timing of the interruption on the flow trace (at peak tidal flow during expiration). The *straight line* represents the linear back-extrapolation of Pmo to the beginning of the interruption (T0 = when Pmo reaches 25% of the difference between the first peak and baseline value) using pressures measured 30 and 70 milliseconds later. The *X* located on the *left* represents the first peak; *X*s located in the *middle* and on the *right* represent mouth pressure measured 30 and 70 milliseconds, respectively, after the interruption. (*A*) Acceptable interruption; (*B*) unacceptable interruption, leak at the mouth; (*C*) unacceptable interruption, the child was vocalizing.

are supported during measurements (132, 140). Supporting the child's cheeks during Rint measurements is then an effective method to reduce the influence of upper airway compliance when bronchial obstruction is mild to moderate. When bronchial obstruction is severe, however (airway resistance increased 10-fold above normal), the time necessary for Pmo and alveolar pressure to equilibrate may be extremely long and Rint may then be lower than airway resistance (141).

PROCEDURES

Equipment

The interrupter technique is performed using a flowmeter, a pressure measurement device, and a flow interruption system (valve) (Figure 7). Specifications for equipment used in an infant/preschooler pulmonary function laboratory have been previously reported (32). Commercial equipment is readily available and is in common use. A review of these systems and their hygiene aspects is beyond the scope of these recommendations.

Total apparatus dead space should be minimized (*see* SECTION 1). Low-resistance bacterial filters should be used. If a filter other than the one recommended by the manufacturer is used, the potential effect of the filter on flow and pressure measurements must be investigated and reported and the filter resistance taken into account when reporting results.

The efficiency of the valve is critical for the accuracy of Rint measurements, because a small volume of gas continues to pass through the valve during closure. Valve closure time should be less than 10 milliseconds (32, 142) and the absence of valve leakage verified by the manufacturer (143). The distance between the valve and the pressure transducer is also important, as it can affect the postocclusion pressure transients, and this should be reported by the manufacturer (32).

Calibration or verification of the accuracy of the flowmeter should be performed each day. Pressure measurement devices of the latest technology are usually very stable, but pressure calibration should be checked on a regular basis using a calibrated pressure manometer (32).

Data Collection

Measurement conditions. Before starting the test, the child has to become acquainted with the environment and the operator(s) and overcome any initial fears or concerns. Some children are afraid of the noise of the closing valve and it may be useful to let them get familiar with it before starting the test.

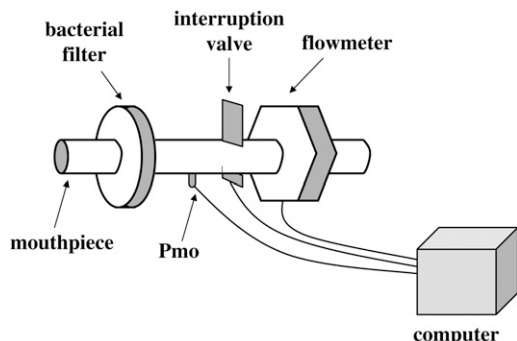The test should be performed with the child seated. The child is asked to wear a noseclip and breathe quietly through a disposable mouthpiece and bacterial filter (Figure 8). The mouthpiece has to be held between the teeth and the lips must be sealed around its circumference. The child's neck should be slightly extended, with the cheeks supported by the operator's hands to decrease upper airway compliance (Figure 8). The test is best performed by two operators, one keeping the mouthpiece in the right position and checking that the lips are sealed around it and the other one supporting the child's cheeks to detect any tongue movements. Although studies in healthy children have not shown a significant difference between measurements made with and without the cheeks supported (21), this practice is still recommended because cheek support is likely to be important in children with obstructive airway diseases and during challenge tests. When the child is breathing quietly, the valve automatically closes in response to a preset trigger (flow or volume) and stays closed for about 100 milliseconds. The child cannot predict the valve closure but can hear its noise. This procedure is repeated until the desired number of interruptions has been obtained.

Mouthpiece. A mouthpiece (2.0–2.7 cm in diameter) and a noseclip should be used for Rint measurements in preschool children. Standard oronasal face masks should be avoided because these masks add an additional compliant compartment and do not allow any assessment to be made of the relative contributions from nasal and oral pathways. This is a very important point, because nasal resistance is a major contributor to total airway resistance. In an attempt to overcome this problem, a modified face mask with an integral mouthpiece was proposed (144). One study has compared Rint measurements using this modified face mask with measurements using a mouthpiece and noseclip in 50 children aged 4 to 7 years (145). The two measurements were equally repeatable, but mean Rint values obtained using the face mask were significantly higher than those using the mouthpiece and noseclip. Furthermore, the wide CR suggests that the two methods cannot be used interchangeably (145).

Interruption trigger. Most studies in preschool children have used flow as the interruption trigger (usually 0.2–0.7 L · s^{-1} or

Figure 7. Schematic picture of the equipment used for the interrupter technique. Pmo = mouth pressure.

Figure 8. Measurement conditions: position of the child and the operator's hands during the test.

peak tidal flow) (21, 146–149), and most commercial devices only allow flow to be used as the interruption trigger. Because there is an inverse correlation between lung volume and respiratory resistance, the use of inspiratory or expiratory volume (e.g., half of V_T) (23, 150) as the interruption trigger is theoretically appealing. However, respiratory system resistance is also flow dependent, with a direct correlation between flow and resistance, and using flow as the interruption trigger may be a valid approximation. It has been demonstrated that occlusions occurring at reproducible lung volumes are achievable with a suitable triggering flow in infants (151). No studies are currently available on the actual impact of the different triggers on Rint measurements in preschool children in clinical practice. Future studies should report the triggering flow and occlusion volumes to allow comparisons between laboratories.

Expiration/inspiration. Many studies on Rint in preschool children have been performed during inspiration to avoid airway collapse (146). Although some studies reported that inspiratory Rint values were significantly lower than expiratory Rint values (23, 147), other studies suggested that this difference is small ($\sim 4\%$) (148), and some investigators found no significant difference between inspiratory and expiratory Rint values (21). Finally, it has been reported that the difference between inspiratory and expiratory Rint decreased with age, being positive before the age of 5 and negative after the age of 5 years (25). Expiratory Rint was found to be more sensitive than inspiratory Rint to changes in intrathoracic airway caliber (22). In the absence of systematic studies in this age group, we recommend on theoretical grounds (better signal-to-noise ratio with higher flows during expiration than inspiration and the fact that, during expiration, we are probably dealing more with a passive mechanical system) that expiratory Rint be used for routine clinical purposes. It is of the utmost importance that authors report, and reviewers insist that they report, in which phase of respiration occlusions are made and that measurements made during inspiration are not used interchangeably with those made during expiration.

Number of acceptable interruptions. The first studies on Rint in preschool children in clinical practice proposed to report the mean from six technically acceptable interruptions (146). Many commercial devices automatically calculate the median or mean of five Rint values. Recent studies have found that, although reliable Rint values can be obtained after one or two interruptions (152), measurement precision was significantly improved by the use of 10 interruptions (22). The question of whether one should report the mean of all technically acceptable measurements or only those which fall within preset limits of reproducibility, as in the ATS recommendations for spirometry in adults and older children, can only be settled by systematic studies, preferably including the ability to discriminate between health and disease as an outcome variable. Until this issue is settled, we recommend performing at least 10 interruptions with the objective of obtaining a minimum of 5 technically acceptable interruptions.

Quality Control of Measurements

Each single interruption should be considered acceptable when the trace of Pmo versus time has the shape shown in Figure 6A. A trace in which Pmo decreases or stays flat (Figure 6B) after the initial rapid change suggests air leakage around the mouthpiece or an altered ventilatory pattern (22, 24) and should be discarded. Pressure–time traces obtained during irregular breathing, with the neck hyperextended or flexed, during vocalization (Figure 6C) or with tongue movement, should also be discarded.

Some commercial devices allow the operator to see the pressure–time trace after each interruption and decide right away whether or not the interruption was acceptable before going on with a new interruption. Other devices allow the operator to see the pressure–time curves only after a certain number of interruptions. In the latter case, at least 10 interruptions should be performed before reviewing the traces. The ability to also visualize flow–time traces and Pmo–flow as an X–Y plot would be advantageous, and manufacturers are encouraged to include these features in future software developments.

In some studies (23, 150), measurement sets with an intrameasurement CV higher than 15 to 20% have been rejected. However, each technically acceptable interruption should be included in the analysis.

Data Analysis

Calculation of mouth pressure. After an airway occlusion, the change in airway-opening pressure representing the resistive pressure drop across the respiratory system is partially obscured by oscillations in the pressure signal. A variety of methods have been used to calculate the resistive pressure drop. These have included the following: curvilinear back-extrapolation, two-point linear back-extrapolation (usually from 70 and 30 ms to 15 or 0 ms after interruption), end-oscillatory pressure, and end-interruption pressure. Phagoo and colleagues (153) compared airway resistance obtained with body plethysmography (Raw) with Rint calculated using these different methods and found that the curvilinear back-extrapolation gave the most accurate results, with the other methods resulting in Rint values that were significantly higher than Raw. However, curvilinear back-extrapolation may be less sensitive in detecting airway caliber change during methacholine challenge tests (154). The method used to calculate Pmo has also been reported to influence the repeatability of Rint in both preschool children (155) and infants (151). Measurements of Rint changes after bronchodilator inhalation are, on average, unaffected by the use of different algorithms, although within individuals there could be significant differences (156). Until further systematic studies are conducted to determine the relative advantages of the various algorithms, we see no merit in changing previous recommendations (157) that the linear back-extrapolation of Pmo for Rint calculation be used. The method used should be reported for all studies.

Mean/median. Rint values obtained in clinical studies are generally not normally distributed; thus, reporting median and range is theoretically more correct (22). However, a recent article has shown that mean and median Rint values were not significantly different during routine clinical assessments (148). This situation may not apply during bronchial provocation or bronchodilator testing.

INTERPRETATION OF RESULTS

Variability

The interrupter technique has been shown to have a good variability in preschool children. Using 2 SDs from the mean difference between two sets of measurements as the definition of repeatability, Bridge and coworkers (24) found a within-occasion repeatability (about 30 s apart) in expiration of 0.21 kPa · L^{-1} · s in 2- to 3-year-old children, 0.17 kPa · L^{-1} · s in 3- to 4-year-old children, and 0.15 kPa · L^{-1} · s in 4- to 5-year-old children. Similar repeatability values have also been reported by other within-occasion studies ($\sim$ 1–30 min between the two sets of measurements) (21, 23, 57, 158). The studies so far published on between-occasion reproducibility (21, 22, 57, 158) also show similar results, with a between-occasion reproducibility (11 d to 2.5 mo between the two sets of measurements) similar to within-occasion repeatability, in healthy children (22, 57, 158) and children with a history of wheeze or cough (21). However, a higher between-occasion variability has been reported in children with chronic cough or a history of wheeze (57). Table 6 shows the

TABLE 6. INTERRUPTER TECHNIQUE: INTRA- AND INTERMEASUREMENT VARIABILITY

Authors	Diagnosis	n	Age Range (yr)	Intrameasurement Variability CV (%)	Time Interval	Intermeasurement Variability CR (kPa · L^{-1} · s)
Beydon and colleagues (25)	Healthy	91	2.9–7.9	12.1 (SD, 3.2%)		
Beydon and colleagues (27)	Asthma	74	3.2–7.8	11.7 (SD, 3.9%)		
Beydon and colleagues (26)	Cystic fibrosis	39	3.0–8.2	11.9 (SD, 3.6%)		
Delacourt and colleagues (159)	Stable asthma/cough	118	3–16	11.4 (SD, 6.4%)		
Merkus and colleagues (22)	Healthy, cough/wheeze	139	1–7	11.6 (SD, 5.6%)		
Bridge and colleagues (24)	Healthy, cough/wheeze	22	2–3		30 s	0.21
		40	3–4		30 s	0.17
		58	4–5		30 s	0.15
Beelen and colleagues (158)	Healthy (field conditions)	32	3.7–4.9		20–30 min	0.28
	History of wheeze (field conditions)	25	3.7–4.9		38 d	0.37
	Healthy (standardized conditions)	15	3.2–5.9		11 d	0.28
Chan and colleagues (57)	Healthy, cough, stable wheeze	85	2.0–9.9		15 min	0.17
	Healthy	72	2.2–9.8		3 wk	0.23
	Cough	57	2.0–9.4		3 wk	0.38
	Stable wheeze	95	2.0–9.5		3 wk	0.44
Lombardi and colleagues (21)	Stable wheeze/cough	69	2.6–6.5		1 min	0.24
	Stable wheeze/cough	26	3.1–5.8		2.5 mo	0.21

Definition of abbreviations: CR = coefficient of repeatability (2 SD of the mean difference between two sets of measurements); CV = coefficient of variation (SD/mean × 100).

within-occasion repeatability and between-occasion reproducibility of the interrupter technique, as well as its intrameasurement variability, in the various studies (21, 22, 24–27, 57, 158, 159). Interobserver variability using the classical interrupter technique is also acceptable in preschool children. Bridge and colleagues (24) found that interobserver variability was similar to the individual variability between two sets of measurements, albeit one operator was inexperienced.

Reference Values

The availability of reference values obtained from a sample of the healthy population is also important for the interpretation of a pulmonary function test. Several studies have recently been published on reference values for the classical interrupter technique in preschool children (21–25, 53, 56) (Table 7). A comparison of the reference values obtained by the different labs is complicated by the fact that the methods used were not always identical. No difference in reference values was found between males and females (21–23, 25, 53, 56). In most studies (21–23, 25, 56), standing height was the main predictor of Rint in children after adjusting for age and weight. Further large-scale longitudinal studies are required to produce internationally applicable reference values for use in preschool children.

It is important to note that the intersubject repeatability of Rint in the general population is quite wide (21, 22, 25, 53, 56) and higher than the intrasubject repeatability (21–24, 57, 157).

Response to Bronchodilators

Studies evaluating Rint changes in response to bronchodilator treatment have shown that the interrupter technique is able

TABLE 7. INTERRUPTER TECHNIQUE: REFERENCE VALUES IN CHILDREN

Authors	Interruption Trigger	No. of Subjects, Ethnicity	Age (yr)	Rint (kPa · L^{-1} · s)
Oswald-Mammosser and colleagues (23)	Mid-V$_T$	36 White	4–16	RintI mean (SD), 0.43 (0.14) RintE mean (SD), 0.52 (0.19)
Merkus and colleagues (22)	Peak tidal flow	54 White	2–7	RintI = 2.59 − 0.017 H (RSD = 0.12) RintE = 2.61 − 0.016 H (RSD = 0.13)
Lombardi and colleagues (21)	Peak tidal flow	284 White	3–6	RintI = 2.276287 − 0.013710 H (RSD = 0.1908) RintE = 2.126878 − 0.012538 H (RSD = 0.2038)
McKenzie and colleagues (53)	Peak tidal flow	236 White, Afro-Caribbean, Bangladeshi	2–10	$\log_{10}$RintE = 0.116 − 0.0396 A (RSD = 0.101) $\log_{10}$RintE = 0.528 − 0.00569 H (RSD = 0.104)
Merkus and colleagues (56)	Peak tidal flow	208 White	3–13	$\log_{10}$RintE = 0.645 − 0.00668 H (RSD = 0.093)
Beydon and colleagues (25)	20–80% of V$_T$	91 White	3–7	RintI = 2.289 − 0.0137 H (RSD = 0.17) RintE = 2.021 − 0.0112 H (RSD = 0.18)

Definition of abbreviations: A = age in years; H = height in centimeters; Rint = interrupter resistance; RintE = expiratory Rint; RintI = inspiratory Rint; RSD = residual standard deviation.

to measure the magnitude of changes in airway caliber after inhalation of a bronchodilator in preschool children (19, 27, 160, 161). The cutoff value for a decrease in Rint beyond which a bronchodilator response may be considered clinically significant remains to be established. One study in preschool children has proposed to use the short-term repeatability between two sets of measurements (0.21 kPa · L^{-1} · s) as a cutoff for a bronchodilator response (24). Another study found that a pre/post measurement ratio greater than 1.22 was able to distinguish the bronchodilator response of healthy preschool children from that of children with a history of wheezing (40). A recent study (25) has assessed the bronchodilator response of 91 healthy preschool children. Mean bronchodilator-induced changes (% of predicted values) were −15% (95% confidence interval [CI], −46 to +15%) for inspiratory Rint and −12% (95% CI, −46 to +22%) for expiratory Rint (25). In another study by the same group, a 35% decrease in resistance after bronchodilation expressed as the percentage of predicted values had a specificity of 92% and a sensitivity of 24% for separating children with and without asthma (27).

Until more studies are published on the bronchodilator response in healthy preschool children using the classical interrupter technique, a bronchodilation test should be considered clinically significant when the decrease in Rint after bronchodilator exceeds within-occasion repeatability between two sets of measurements established in 30 to 50 subjects for each individual laboratory.

Challenge Tests

Several studies have shown the usefulness of the interrupter technique in evaluating airway response to methacholine (63, 150, 160) in asthmatic preschool children, although its sensitivity has been reported to be lower than that of body plethysmography (63) and transcutaneous partial pressure of oxygen measurements (150, 160). Rint may underestimate the airway response to the BC, due to an increase in the time required for Pmo and alveolar pressure to equilibrate as well as to ventilation dishomogeneities in obstructed subjects. To ensure patient safety, transcutaneous partial pressure of oxygen (150) or oxygen saturation with a pulse oximeter should be monitored when performing a BC test using Rint. It should also be noted that no studies have so far evaluated the response to methacholine BC in healthy preschoolers using the classical interrupter technique.

The use of the interrupter technique in the exercise BC test is extremely difficult because of the need for taking measurements during tidal breathing at the end of the exercise. However, one study has performed Rint measurements 10 minutes after the exercise challenge in 50 schoolchildren (162). When compared with spirometry performed 10 minutes after the exercise challenge and PEF 5, 10, 15, and 20 minutes after the exercise challenge, the interrupter technique had a good sensitivity and specificity in detecting the airway response (162).

CONCLUSIONS AND FUTURE DIRECTIONS

We have provided the current recommendations for the use of the interrupter technique in preschool children. However, many issues regarding the interrupter technique still need to be clarified. Future studies will have to determine the best algorithm to calculate mouth pressure during the occlusion and to establish the cutoff value for a decrease in Rint beyond which bronchodilator response should be considered clinically significant. The role of Rint as the primary outcome in challenge tests and the usefulness of the interrupter technique in comparison with other techniques for PFT in preschool children remain to be determined.

Section 6. The Forced Oscillation Technique

SUMMARY

The FOT is a simple, noninvasive technique performed during tidal breathing that is relatively easy to apply in preschool children. An external pressure wave is applied, usually at the mouth, and the resulting pressure–flow relationship is analyzed in terms of respiratory impedance. The latter expresses the impediment to flow in the respiratory system that includes both frictional losses and elastic and inertial loads. The FOT has been successfully performed in settings ranging from the field study to the emergency room. A number of studies have demonstrated that the FOT was able to identify airway obstruction and responses to bronchodilators and bronchoconstrictors.

This section of the document provides an update on existing reviews and issues recommendations specific to the preschool age. A number of issues yet need clarification, particularly those relevant to identification of airway obstruction.

1. The FOT system should be able to measure a reference impedance of at least 1.5 kPa · L^{-1} · s within ⩽ 10% or ⩽ 0.1 kPa · L^{-1} · s, whichever is greater.
2. The optimal excitation frequencies should include the range 4–8 Hz.
3. The child should be seated, breathing through a mouthpiece, and wear a noseclip with the cheeks and mouth floor firmly supported.
4. An acquisition period should cover several breathing cycles, typically lasting 8–16 seconds.
5. Three to five measurements should be performed.
6. Results should be reported as the mean of the three to five measurements and a CV should be calculated from the SD to mean ratio.

INTRODUCTION

Lack of active cooperation and noninvasiveness are key features of the FOT, which is therefore increasingly used in young children. The measurement has been successfully performed in various settings: for example, the pulmonary function laboratory, patients' bedside, the emergency room, in school and in kindergarten. This section of the document will update existing reviews (163, 164) and issue recommendations relevant to routine applications in PFT.

BACKGROUND

Lung mechanics is most easily understood when pressure generated by the respiratory muscles (transpulmonary pressure) is related to VT and flow. Dividing the relevant pressure difference by flow and by the change in volume yields, respectively, lung resistance (kPa · L^{-1} · s) and elastance (kPa · L^{-1}), the reciprocal of compliance. These terms do not add up algebraically, but lung impedance, as the complex sum of lung resistance and reactance, expresses the overall impediment to flow within the lung. Lung resistance is the part of impedance associated with frictional losses in the airways and the lung parenchyma (i.e., with the component of the transpulmonary pressure in phase with flow). Lung reactance, a much less familiar term, is, in this

simple example, proportional to elastance or to the component of pressure in phase with volume, a close estimate of which is transpulmonary pressure during breathing at very slow frequency (i.e., near zero flow). Instead of the respiratory muscles, the FOT uses an external P or $\dot{V}$ fluctuation and measures the mechanical response of the respiratory system in terms of the resulting $\dot{V}$ or P (165–167). The P–$\dot{V}$ relationship is described by the respiratory impedance (Zrs). As in the above example, Zrs has an in-phase component, or real part or respiratory resistance (Rrs), and an out-of-phase component, or imaginary part or respiratory reactance (Xrs). Rrs represents the sum of viscous resistances of which airway resistance is the most significant. Xrs is determined by apparent elasticity (the relationship between P and volume), and inertive properties (the relationship between P and volume acceleration), which are opposite in sign. Rrs and Xrs are expressed as a function of oscillation frequency (f) and the use of different frequencies offers an extra dimension of data, which can be used via model-based estimations of mechanical components of the respiratory system (166, 168, 169). The reader unfamiliar with complex arithmetic may find the relevant and detailed information elsewhere (*see*, e.g., Reference 164), although a full understanding of these mathematical concepts is not necessary to the routine clinical use of the FOT.

PROCEDURES

Equipment

Setups. The FOT can be implemented in several configurations, depending on the sites of application of the driving signal and recording of the mechanical response. The most commonly used arrangement is the measurement of the input impedance and this will be detailed here. The oscillatory signal is applied at the airway opening where $\dot{V}$ and P are measured. Alternatively, the transfer respiratory impedance may be obtained by varying P at the chest and measuring $\dot{V}$ at the mouth. The technique has the advantage of eliminating most of the upper airway artifact (*see below*) and separating airways and tissues impedances. Its application in children has been limited mostly to research studies (170, 171).

In the standard input impedance technique, Zrs is defined as the relationship between transrespiratory pressure and the airway $\dot{V}$. In the typical measurement setup (Figure 9), the computer-generated oscillatory signal is delivered by a loudspeaker to the subject via a pneumotachometer and a low-resistance bacterial filter connected to the mouthpiece or a face mask. A bias tube is arranged between the loudspeaker and the pneumotachometer
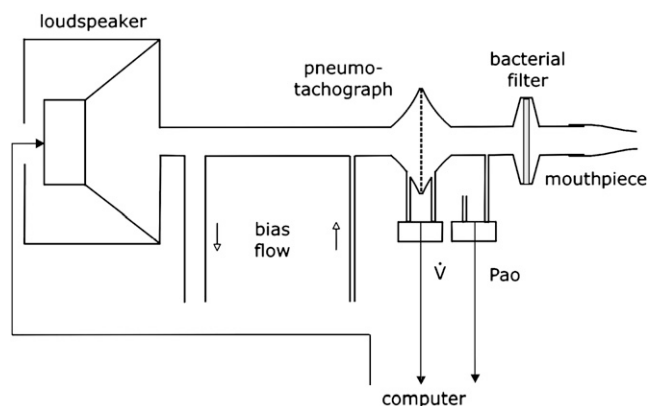

Figure 9. A typical arrangement of the forced oscillatory impedance measurement.

to offer a low-resistance pathway to atmosphere for the spontaneous breathing, and a bias flow can be maintained to minimize rebreathing. The dead space is represented by the equipment volume not flushed by the bias flow. Mouthpiece, bacterial filter, and flowmeter may altogether represent a total volume of 50 to 70 ml. In an alternative measurement of the input Zrs, the subject's head is enclosed in a chamber (the head generator technique), so that the oscillatory pressure is developed both at the pneumotachometer opening and around the upper airway walls, thus minimizing the upper airway wall shunting (172).

Transducer specifications. For detailed technical specifications, the reader is referred to previous publications (163, 164).

Oscillation signal. The amplitude of the input signal, usually 0.1 to 0.2 kPa peak to peak at the airway opening, should not interfere with breathing or cause discomfort. The frequency interval may range from 4–8 Hz, depending on breathing frequency, to 30–50 Hz. The higher frequency is limited by the frequency response of the measuring system and upper airway artifact. The single-frequency sinusoid has optimal signal-to-noise ratio; allows the description of Zrs variations with time, within- and between-breath and in relation to flow and volume; and does not allow an easy assessment of Zrs frequency response. The general periodic signal contains several harmonics of the fundamental frequency (pseudorandom noise or recurrent impulses). Zrs is estimated simultaneously at a number of frequencies; hence, insight is gained into the frequency-dependent mechanics of the respiratory system. The collected data represent an average impedance spectrum for inspiration and expiration. When a pseudorandom oscillation is used, the signal-to-noise ratio may be optimized at the lowest frequencies (172). It is mandatory that all signals undergo analog low-pass filtering to eliminate high-frequency noise.

Calibration. A calibrated syringe and a water or, best, low-density fluid manometer (0.1–0.2 kPa full scale) are required to determine the initial calibration. Daily calibration may then be checked using a known reference impedance that should always be measured at the same flow amplitude. To ensure the measurement accuracy is maintained at the relatively high Zrs values encountered in the preschool age, the magnitude of the reference impedance should range from 1.5 to 2.5 $kPa \cdot L^{-1} \cdot s$. The required accuracy in recovering the theoretical calibration impedance at all frequencies studied is $\leqslant 10\%$ or $\leqslant 0.1\ kPa \cdot L^{-1} \cdot s$, whichever is greater.

Data Collection

Pulmonary function technicians will rapidly learn to master the FOT (173) after performing at least 10 to 15 supervised tests. Technicians should learn to identify the most frequently encountered problems from the real-time visual display of breathing flow and/or volume and observation of the child (*see below*). The most frequent reasons for noncooperation are the refusal to use a mouthpiece or face mask, inability to breathe without a leak at the mouthpiece, or difficulty in breathing against imposed oscillations (17, 174).

Trials should first be performed to allow the child to learn to breathe calmly into the apparatus through an appropriately sized mouthpiece. Standard oronasal face masks should be avoided because these masks add an additional compliant compartment and do not allow assessment to be made of the relative contributions from nasal and oral pathways. The child should be seated comfortably with his or her head in a slightly extended or neutral position. A noseclip is worn if a mouthpiece is used. The child should be instructed to breathe calmly and avoid obstructing the mouthpiece with his or her tongue. It is imperative that the child's cheeks and floor of the mouth are firmly supported by the parents or a technician to minimize upper airway wall vibrations.

The acquisition should cover several breathing cycles but be short enough to limit possible episodes of hyperventilation and swallowing. An acceptable acquisition time is 8 to 16 seconds. The number of acquisitions should be sufficient to calculate and report a mean and CV (*see below*) of at least three to five technically acceptable measurements. Data should always be reported as Rrs measured at one or several frequencies. In this document, Rrs at a given frequency (f) will be noted Rrs_f. The measured data cannot be substituted by any curves or parameters from model fittings.

Quality Control

Visual control. The real-time display of tidal flow and/or volume is critical to identify data corruption. Mouthpiece obstruction, glottis closure, or swallowing are detected as reduction or interruption of flow oscillation (Figure 10A) or as plateaus on the V_T tracing (Figure 10B). Irregular breathing and/or rapid shallow breathing may easily be detected from these signals (Figure 10B). Sudden drifts on the volume tracing are suggestive of incomplete expiration or leak around the mouthpiece. The child's mouth should also be watched for incomplete seal at the mouthpiece and chewing activity. An advantage of having a technician support the cheeks and floor of the mouth is accurate feedback on the subject's activity during the measurement.

Measurement reliability. The coherence function (γ^2) has been proposed to characterize the quality of the estimates of Zrs with pseudorandom oscillations. The γ^2 is a number between 0 and 1, similar to a correlation coefficient that provides an index of causality between the input and the output of a linear system. It is therefore decreased in the presence of nonlinearities or extraneous noise (175). An empirical value of $\gamma^2 = 0.95$ has been suggested as an acceptance limit for the Zrs values. However, the appropriateness of this value as a reliability index of Rrs and Xrs depends on the signal-to-noise ratio in the measurement and on the computation method (e.g., size and number of blocks) (176). In addition, there has so far been no systematic study of which cutoff value may most accurately eliminate corrupted data

in preschool children. It is believed that no general recommendation can be given on the threshold value of the γ^2 in preschool children. The reproducibility of successively recorded Zrs data (e.g., in terms of CV) provides a solid and computation-independent assessment of the quality of the measurements at every frequency point, and is therefore recommended as a reliability index (*see below*). With a single frequency, the Zrs mean and SD for all oscillation cycles may be computed within a measurement and it is possible to automatically reject those Zrs data lying outside the 99% confidence interval (177). An alternative is to assess the divergence of each flow oscillation cycle with the reference sinusoid (178).

INTERPRETATION OF RESULTS

The routine interpretation of FOT measurements is based on the assumption that Rrs represents the sum of airway and tissue resistances, of which airway resistance is the most significant component above a few Hz, and Rrs is therefore considered a reasonable surrogate of airway resistance (179). The fact that Rrs decreases with increasing frequency and approaches a plateau indicates the presence of parallel pathways. In children, the upper airway wall motion is perhaps the most significant factor (180). In patients with airway obstruction or induced bronchoconstriction, peripheral inhomogeneity (181–183) and bronchial compliance (184) represent additional pathways. Elevation of Rrs toward lower frequencies also reflects the contribution of tissue resistance, which has marked negative frequency dependence (168). In healthy subjects, Rrs exhibits an increase with frequency above 10 to 15 Hz: this is attributed to multiple mechanisms, such as airway wall compliance, gas compressibility in the central airways, and inertial distortion of the velocity profile (185). Xrs is negative at low frequencies, reflecting the elastic properties of the respiratory tissues, whereas its higher frequency values are determined by the increasing inertial forces. The frequency dependence of Xrs is also affected by inhomogeneities and central airway shunt. Despite interpretation problems of
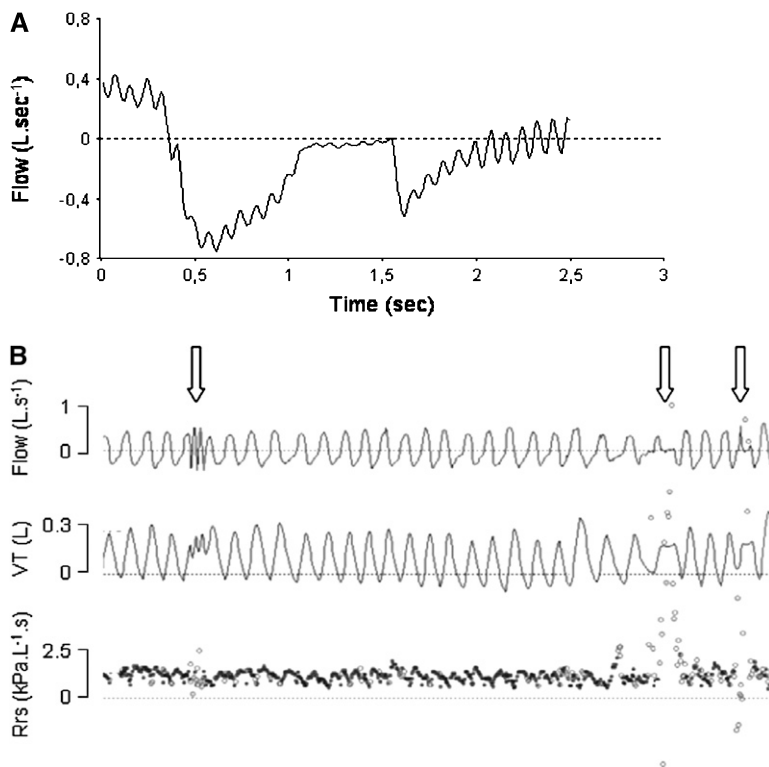

Figure 10. (*A*) Tracing showing oscillations superimposed on breathing flow. Note damping of flow oscillation during glottis closure at midpart of recording. Reprinted by permission from Reference 173. (*B*) Recording of tidal flow, volume (V_T), and respiratory resistance (Rrs) illustrating common causes for data corruption. *Arrows* point at rapid breathing (*left*) and glottis closure (*right*). Data were obtained with a head generator.

the frequency dependence of Zrs, the multiple-frequency measurements have the potential to allow the structural exploration of respiratory mechanics, whereas, as noted above, the single-frequency oscillations are more applicable in the tracking of Rrs within the respiratory cycle. Figure 11 illustrates the frequency dependence of Zrs measured pre- and post-bronchodilator in a 4-year-old child.

Variability

A test should include a minimum of three measurements. The repeatability within that test is expressed for Rrs or Zrs by CV (*see* SECTION 2). The average CV was reported to be 6.2% for Rrs_5 in preschool children (186), 8% for Rrs_8, and 9% for Rrs_{16} (187). The values are similar to those in older children (188–190) and healthy adults (191, 192). In healthy preschool children, the reported within-occasion between-test CR (*see* SECTION 2) of Rrs_5 ranges from 6.1 to 10.2% (174, 186, 193).

Reference Values

A few studies have measured healthy preschool children to obtain normal values of Zrs specifically for this age group (16, 166, 174, 186); however, there have been a number of studies designed to obtain reference equations of Rrs in healthy children ranging from the preschool age up to adolescence (188–190, 194, 195). An overview of the studies included is listed in Table 8. All studies have shown that Rrs falls with height, and in most of them, no gender difference was observed.

Despite the lack of standardization in measuring procedures and equipments (many studies used a number of custom-made devices), Figure 12 shows reasonably good agreement among most studies. Nevertheless, two curves are clear outliers. The uppermost corresponds to data obtained with the child breathing through a face mask and nasal breathing likely accounted for a generally higher Rrs (174). Rrs in the lowermost curve was calculated from the measured Zrs using an approximation for the phase between pressure and flow (188). Some studies have reported average Rrs values obtained from several Zrs measurements (186, 188, 189), but others report Rrs values obtained from one single measurement (174, 193).
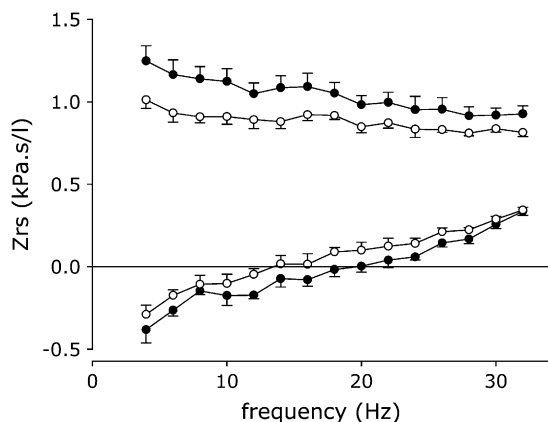

Figure 11. Real part or resistance (*top*) and imaginary part or reactance (*bottom*) of the total respiratory impedance (Zrs) as a function of frequency in a 4-year-old healthy child before (*closed circles*) and after (*open circles*) bronchodilatation. Mean and SD values (*bars*) from five successive measurements in each condition, using a conventional input impedance setup, are shown.

CLINICAL APPLICATIONS

The summary information reported here is based mainly on data pertaining only to preschool children, although some are derived from studies also involving school-aged children. Most studies were designed to validate the FOT with other techniques, to assess its ability to detect airway obstruction in children with disease as compared with healthy children, and to quantify airway obstruction and airway responsiveness to bronchodilators or bronchoconstrictors. The feasibility of the FOT in acutely ill, untrained preschool children measured in the emergency room ranged from 20% in 3 year olds to more than 80% in 5 year olds (17). In laboratory or field settings, higher values of 80 to 100% have been obtained in healthy preschool children or stable preschool patients (19, 174).

Asthma

The degree of respiratory impedance abnormality appears to depend on patient selection and diagnostic criteria. Children classified as asthmatic or healthy based on questionnaire or risk factors exhibited no significant difference in respiratory impedance (193, 196), whereas children with asthma diagnosed in a clinic showed significantly larger Rrs_5 than healthy control subjects (19). In the emergency room, acutely ill preschool children showed consistent increase in Rrs_8, low hemoglobin saturation, and decreased FEV_1 (187).

In placebo-controlled studies, FOT was useful to document therapeutic response to bronchodilators, such as theophylline, terbutaline, or ipratropium bromide (197–207). The criteria (and cutoff values) for diagnosis of meaningful reversibility post-bronchodilation are reported in Table 9. Significant Rrs_5 responses to β_2-adrenergics were demonstrated in both patients with asthma and healthy subjects (19, 193). The response was similar in kindergarten attendees classified by questionnaire as controls or asthmatics (193), but significantly larger in subjects with asthma diagnosed in a clinic than in healthy subjects (19). Larger Rrs_5 response to a bronchodilator was suggested at 4 years of age when asthma was present than when it was not, and in atopic compared with nonatopic subjects with asthma (196). Several studies suggested expressing the response to bronchodilation as number of SDw to improve sensitivity (19, 208). FOT assessment of response to bronchodilators was found to be in agreement with FEV_1 (187) and airway resistance by plethysmography (209), but appeared larger than with the interrupter technique (159). There is little information on changes in FOT induced by antiinflammatory therapy. However, encouraging data in preschoolers are provided by recent controlled studies (20, 210).

The FOT was probably one of the first techniques applied to preschool children to estimate the airway response to methacholine and histamine (211). Here also, the most useful parameters are obtained at the lowest frequencies. In wheezy preschool children, changes in FOT paralleled those observed with plethysmography, interrupter resistance, or spirometry (144). In contrast, response to methacholine measured by FOT compared with transcutaneous partial pressure of oxygen provided conflicting results, which may reflect different characteristics of the subjects as well as of the equipment (63, 144, 212, 213). FOT tracking of changes in airway caliber with time during methacholine-induced bronchoconstriction allowed the demonstration of significant alteration in the mechanical coupling between conducting airways and lung parenchyma in the form of increased volume dependence of Rrs (214) and significant reversibility of Rrs after deep inhalation (215). Rrs at 5 or 6 Hz was reported to differentiate healthy from asthmatic airway response to a free run challenge (216) but, when evaluating cold air challenge, appeared to be less sensitive than the sRaw (64).

TABLE 8. OVERVIEW OF THE REGRESSION EQUATIONS OF Rrs AS A FUNCTION OF HEIGHT IN HEALTHY (PRESCHOOL) CHILDREN

				No. of Subjects				f		RSD
Ref.	Input*	t (s)	Nm	Total	H < 130 cm	Age (yr)	H (cm)	(Hz)	Rrs (kPa · L^{-1} · s)	(kPa · L^{-1} · s)
174	Multi	30	1	121		2–7	88–140	5	Rrs = 1.29 − 0.0091 · (H − 112.3)	0.189
186	Multi	20	3	109		2.1–7.0	89–130	5	ln(Rrs) = 8.286 − 1.786 · ln(H)	0.155
188	Mono	2.5	3	377	108†	3–18	90–180	10	Rrs = 1.361 − 0.00621 · H	0.065
189	Multi	16	3	138	∼ 70†	2–16	81–174	6	Rrs = 9.0 · 10^{-5} · H^2 − 0.0333 · H + 3.44	0.20†
193	Multi	25–35	1	247		2.7–6.6	93–131	5	Rrs = 2.064 − 0.009528 · H	0.267
190	Mono	‡		218	∼ 57†	2–18	90–185	4	log(Rrs) = 4.403 − 2.18 · log(H)	§
194	Mono			130	60	3–14	95–160	4	Rrs = 2.416 − 0.0127 · H	
295	Multi	30	1	121	∼ 46†	4–16	93–175	4	Rrs = 1.83 · 10^4 · H$^{-2.12}$	
15	Multi	16	5	255	62∥	2–12.5	90–175	6	Rrs = 0.000166 · H^2 − 0.05288 · H + 4.668	0.171
195	Mono	15–20	3	199	144¶	3–17	95–205	8	ln(Rrs) = 10.990 − 2.370 · ln(H)	
16**	Multi	16	2–3	126		3–7	89–129	20	ln(Rrs) = 11.2048 − 2.3837 · ln(H)	0.125

Definition of abbreviations: f = frequency; H = height; Nm = number of measurements averaged; Rrs = repiratory resistance; RSD = residual mean standard deviation from regression; t = measurement time.

* Input = type of oscillatory signal used: multiple frequencies simultaneously (multi) or monosinusoidal (mono).

† Estimated number.

‡ ⩾ 30 acceptable cycles were used.

§ Coefficient of variation = 10.2%.

∥ Number of subjects < 6 yr.

¶ Number of subjects ⩽ 135 cm.

** Rrs measured by head generator.

Other Conditions

There are few data on the use of FOT in airway diseases other than asthma in preschool children, and the few available studies concern small numbers of patients. CF usually shows few abnormalities in Rrs in the usual range of frequency, consistent with findings in school-age children (217–219). However, a recent study of low-frequency oscillation mechanics in children aged 1 to 3 years under general anesthesia indicated a significant relationship beween biological markers of inflammation and tissue impedance parameters (220). Abnormal FOT findings were also described in preschool children with a history of chronic lung disease of prematurity (221) or bronchiolitis (222).

CONCLUSIONS AND FUTURE DIRECTIONS

The FOT holds the promise of significantly improving the diagnosis of airway obstruction, quantifying the magnitude of airway reversibility and hyperreactivity, helping in the adjustment of therapy, and monitoring disease progression. The commercial development of the FOT has allowed the rapid expansion of the technique to a broader range of clinical laboratories. This
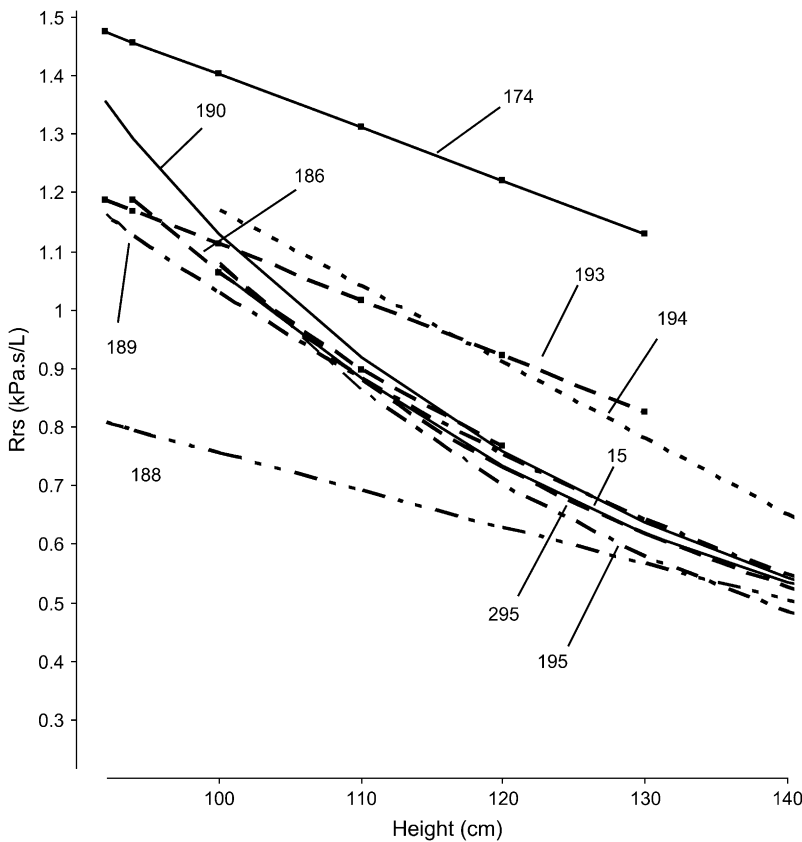
Figure 12. Respiratory resistance (Rrs) measured at different frequencies is plotted against height. The *lines* correspond to normative Rrs values established in studies including a significant number of healthy preschool children.

TABLE 9. CRITERIA TO IDENTIFY Rrs RESPONSE TO BRONCHODILATOR REPORTED IN THE LITERATURE

Criterion	Formula	Hz	Ref.	Cutoff
% Change from B	$(Rrs_B - Rrs_{BD}) \cdot 100/Rrs_B$	5	19, 39, 193	20–25%
				29%
				40%
		8	187	19%
		10	39, 186	15–20%, 30%
Change from B as % pred	$(Rrs_B - Rrs_{BD}) \cdot 100/Rrs_{pred}$	5	19	27%
No. of SDw	$(Rrs_{BD} - Rrs_B)/SDw$	5	19	1
No. of intrasubject coefficient of variation	Not specified	5	217	2
Rrs (SD)*	$Rrs(SD)_B - Rrs(SD)_{BD}$	"0"†	159, 208	$\leqslant -0.1$ kPa $\cdot$ L$^{-1} \cdot$ s

Definition of abbreviations: B = baseline; BD = post-bronchodilator; f = frequency; Rrs = respiratory resistance; SDw = intrasubject between-measurement SD.

* Difference between observed and predicted Rrs extrapolated at "zero frequency" divided by residual SD from regression of Rrs_0 against height and weight (2.27 hPa $\cdot$ L$^{-1} \cdot$ s).

† Rrs obtained by extrapolating Rrs at "zero frequency."

increase in use as a clinical tool needs to be carefully assessed to ensure that the FOT develops in such a way as to allow comparisons between different centers. The majority of reports in the literature have defined Rrs at a specific frequency as the primary outcome variable. Further studies are needed to establish firm criteria based on *z* scores. It is likely that a panel of other FOT indices including Xrs and resonant frequency may be useful in diagnosing airway obstruction. The model analysis of Zrs data also represents a tool for better description of airway obstruction and understanding of mechanisms involved, such as heterogeneous bronchoconstriction, central versus peripheral airway constriction, parallel inhomogeneities, airway wall compliance, or lung distension.

Before general criteria for reversibility can be firmly established, a clearer picture of the within-occasion, between-test repeatability must emerge. Furthermore, characterization of healthy subjects' airway response to placebo and β_2-agonists is necessary. There is a significant influence of the upper airway shunt in preschool children. The head generator technique offers an approach that minimizes the effect; however, the technique is limited to a small number of specialized laboratories. The use of respiratory system admittance, the reciprocal of Zrs, as an outcome variable may increase the value of the FOT in studying the response to bronchodilators and bronchoconstrictors (223). However, studies are required to test the sensitivity and specificity of this parameter in separating health and disease. Extending the excitation frequency spectrum beyond the conventional range could provide further insight into the airways at higher frequencies (224) and into the tissues at lower frequencies (167). The latter approach has been shown to be particularly useful in assessing the physiological properties of the lung parenchyma in a variety of situations. A drawback to the routine application of the technique in uncooperative subjects is that the breathing signals must be suppressed (i.e., the subject must remain apneic). Measurements in the intensive care unit have received little attention but deserve further investigations, especially in view of the fact that the low frequency range may be easily studied when the patient is anesthetized and paralyzed (225, 220).

Section 7. The Multiple-Breath Inert Gas Washout Technique

SUMMARY

The MBW method is used to assess ventilation distribution in the lungs and to measure the FRC. MBW can be performed in

children from any age group because it requires a minimum of cooperation. The lung clearance index (LCI), which is the cumulative expired volume required to clear an inert gas from the lungs, divided by the FRC, is a sensitive marker of airway disease. The MBW method appears to be particularly useful as a tool to evaluate lung function in preschool children because it requires only passive cooperation and tidal breathing. Currently, MBW is performed routinely in preschool children in only a limited number of laboratories, presumably because suitable equipment is not commercially available. Several different inert marker gases with low solubility in blood and tissues can be used for MBW. The most well known is nitrogen (N_2), which can be washed out from the lungs by letting the patient breathe pure oxygen (100% O_2). Other gases, such as argon (Ar), helium (He), or sulfur hexafluoride (SF_6), may also be used, but measuring these gases may require expensive equipment, such as a mass spectrometer. More recently, an MBW method has been introduced that is based on indirect assessment of inert tracer gas concentrations by continuous mainstream recording of the molar mass of the gas inspired and expired using ultrasound technique. There is a lack of comparative studies assessing the importance of using different marker gases, equipment, and procedures. Furthermore, in published MBW studies, different indices on ventilation maldistribution have frequently been reported. Consequently, there is a need for standardization of the MBW procedures.

Apart from recommendations about the use of the MBW method in preschool children, this document provides some suggestions regarding more advanced use of the recordings for detailed assessment of peripheral airway function by analysis of the progression of the concentration-normalized phase III slope from each subsequent breath in the washout. It is not expected that any particular MBW system, equipment, or setup will be used universally; therefore, general recommendations are given to facilitate uniformity between the centers using MBW.

1. To avoid systematic errors, several components and features of the performance of the equipment and recording system need special attention—for example, the linearity of the gas analyzer, proper alignment in time of tracer gas and respiratory flow signals, adequate dynamic response of the gas analyzer, sufficient data acquisition rate, adequate algorithms for breath detection, and integration of expired and reinspired tracer gas volumes.

2. Measurements should be done with the child upright and seated, breathing through a mouthpiece or a sealed face mask covering the nose and mouth. A regular breathing pattern is desirable.

3. The external dead space, including that of the mask if used, should ideally be less than 1.0 and not exceed 2.0 ml per kilogram of body weight.

4. If a nonresident inert marker gas is used, then a sufficiently long wash-in period is needed to allow the marker gas to equilibrate in the lung. Adding a period of 10 seconds (i.e., approximately three breaths) after having attained equivalent inspiratory and expiratory marker gas concentrations is regarded as adequate.

5. Washout should continue until the end-tidal marker gas concentration has fallen below 1/40th of the starting concentration over three subsequent breaths.

6. Efforts should be taken to detect any inert gas leaks during washout. This can be done by observing the patient and by monitoring V_T and marker gas concentration traces on a computer screen.

7. FRC and indices of ventilation inhomogeneity should be calculated separately for each washout. For routine purposes, the mean values from two washouts, in which FRC differs less than 10% (in relation to the lower), can be reported.

8. Several different indices of overall ventilation inhomogeneity can be reported. The LCI is the cumulative expired volume (CEV) minus the number of washout breaths multiplied by external dead space outside the lips, divided by the patient's FRC (up to the lips). The LCI is simple to calculate, understand, and compare between laboratories and should always be reported. It is questionable whether any other index is more sensitive, robust, and clinically useful.

9. Concentration-normalized phase III slope analysis may provide some additional information about airway disease, but data are lacking in this age group, and such analysis requires a more regular breathing pattern than many children in this age range produce (*see* the online supplement).

BACKGROUND

Effective mixing of the resident gas in the lungs with the fresh inspired gas via the peripheral airways is essential for gas exchange. Several serious chronic lung diseases in children, such as CF lung disease and obliterative bronchiolitis, affect particularly the peripheral airways (arbitrarily defined as airway generation 8 or higher). The resistance of the peripheral airways contributes little to overall airway resistance (226, 227), and spirometry findings or airway resistance measurements are often normal in the early stages of peripheral airway disease (31, 66).

Because oxygen (O_2) and carbon dioxide (CO_2) participate in the gas exchange, they cannot be used to assess the effectiveness of ventilation distribution and gas mixing. Instead, inert marker gases must be used, which readily mix with the resident gas in the airspaces of the lungs and have a relatively low solubility in blood or other tissues (228, 229). Examples of gases that have been used for this purpose are N_2, Ar, He, and SF_6. Studies on ventilation distribution started after the introduction of the respiratory mass spectrometer in the late 1940s and the N_2 analyzer a few years later (230). Fast online data acquisition using breath-by-breath tests came with the personal computer in the 1980s (231–234). There are two principal ways to perform ventilation distribution tests with inert marker gases: (*1*) closed-circuit systems (e.g., the closed-circuit He method for FRC determination) (235, 236) and (*2*) open-circuit systems for multiple- or single-breath inert gas washout (231–234, 237, 238).

The closed-circuit He method is used routinely in many laboratories for FRC determination in adults and older children, and has also been adapted for infants (235, 236). The helium dilution technique is not suitable for assessing ventilation inhomogeneity because the time needed for achieving equilibration of helium concentration depends not only on the patient's airway disease but also to a large extent on the size and construction of the equipment to which the patient is connected.

Open-circuit systems for single-breath inert gas washout are commonly used to determine ventilation inhomogeneity from the slope of the phase III (alveolar phase) generated during a vital capacity (VC) maneuver (e.g., by the VC single-breath N_2 test) (239, 240). Preschool children are rarely capable of producing satisfactory VC single-breath recordings.

Open-circuit systems for multiple-breath inert gas washout include the bias flow N_2 washout method for FRC determination in infants (238) and true breath-by-breath washout tests (30), which are the focus of this section of this document.

PROCEDURES

Equipment

Breath-by-breath washout systems generally consist of a gas analyzer and a flowmeter, which record the inert gas concentration and the inspiratory and expiratory flows close to the mouth, plus a device for delivering gas mixtures (Figures 13 and 14). With the exception of a recently marketed ultrasound-based apparatus (not described here) for inert gas washout, which measures molar mass and flow in a single transducer (241), most systems have a sidestream gas analyzer (30, 31, 66, 231–234). In a conventional system, the analyzer can be a respiratory mass spectrometer (30, 31, 66), an N_2 analyzer (emission spectrophotometer) (231–234), or an infrared gas analyzer (242, 243) (Table 10).

Figure 15 shows a 3-year-old girl performing an MBW test. The patient is breathing through a face mask sealed with therapeutic putty. The mask is connected to a Fleisch No. 0 pneumotachometer (Metabo, S.A., Lausanne, Switzerland) via a short plastic connector through which the tip of the capillary leading sample gas to a respiratory mass spectrometer is connected. When an N_2 MBW test is performed, 100% O_2 is commonly administered during washout. By applying a sufficient bias flow
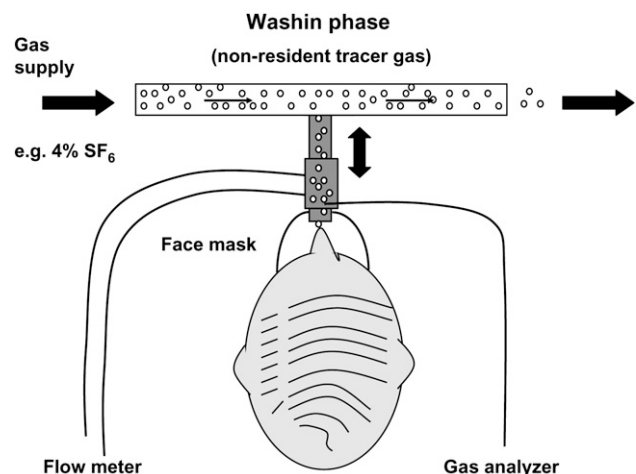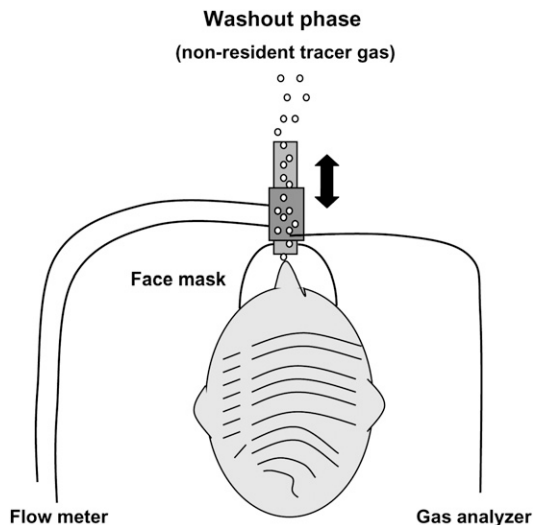
Figure 13. Schematic illustration of setup of a system for multiple-breath washout for determination of FRC and ventilation distribution in young children. The illustration shows the situation when a nonresident inert marker gas (in this case 4% SF_6 in an air mixture) is being washed in. The setup can be identical when N_2 washed by breathing 100% O_2 is undertaken. Reprinted by permission from Reference 296.

Figure 14. Schematic illustration of setup of a system for multiple-breath washout for determination of FRC and ventilation distribution in young children. The illustration shows the situation when letting the patient breathe room air to wash out a nonresident inert marker gas. Reprinted by permission from Reference *296.*
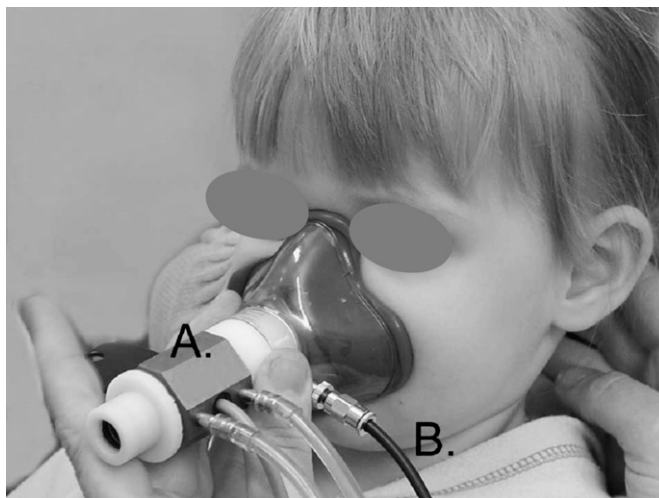

Figure 15. A 3-year-old girl with cystic fibrosis, but without chest symptoms, performing a multiple-breath washout, while sitting on her mother's lap and watching a video show. The transparent face mask sealed with therapeutic putty is connected to a Fleisch No. 0 pneumotachometer (A) via a short plastic adapter to which the sampling capillary (B) from a mass spectrometer is attached.

of pure O_2 via large-bore tubing and a T-piece connected to the flowmeter, as illustrated in Figures 13 and 16, a leak-free washout can be achieved. More sophisticated arrangements, such as a demand valve, can be used but that leads to increased external dead space and resistance to breathing, and possible application of positive end-expiratory pressure. When performing MBW tests by use of a nonresident marker gas, such as SF_6, the lungs must first have an even concentration of this tracer gas. This can be achieved by first washing in the tracer by use of a bias flow of the gas mixture, as illustrated in Figures 13 and 16, and then washing it out after equilibration (Figures 14 and 15).

A previous standardization paper has given recommendations on accuracy of V_T and respiratory flow measurements (84). Reasonable requirements include volume accuracy within 3% or 3 ml when checked with a 100-ml precision calibration syringe, and instantaneous flow accuracy within 5% at a flow of 100 ml · s^{-1}. All volumes should be reported as BTPS (body temperature, pressure, saturated with water) (66). For more details on equipment, *see* the online supplement.

Calibration

Preparations of the equipment include the following: calibration or calibration check of the flowmeter with a precision calibration syringe adapted to the size and flow range of the flow transducer used, a two-point calibration of the gas analyzer, a linearity check

of the gas analyzer in accordance with the recommendations of the manufacturer (applicable for N_2 analyzers but not necessary with mass spectrometers), and assessment of the delay time of the gas signal in relation to flow (244, 245).

Data Collection

Measurement conditions. Preschool children are best investigated while watching a video and sitting upright in the lap of a parent or caregiver or any other person whom they trust.

Mask or mouthpiece. A transparent face mask suitable for sealing with therapeutic putty is preferable in this age group.
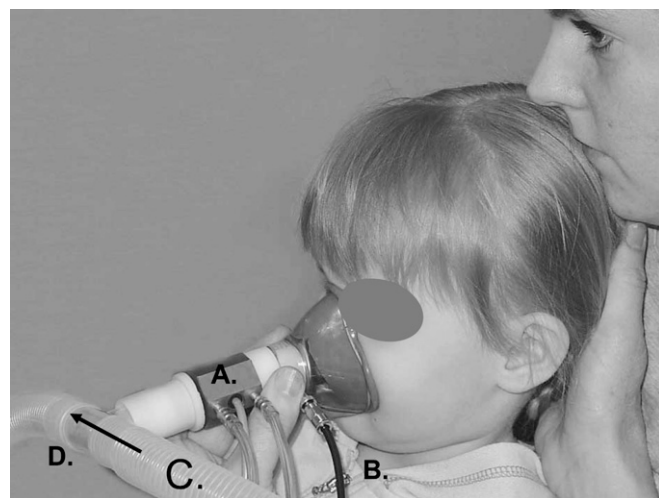

Figure 16. The same patient as in Figure 15. The photograph is taken during the wash-in phase when a tracer gas mixture containing 4% SF_6, 21% O_2, and 75% N_2 is inspired via a bias flow. (A) denotes the Fleisch No. 0 pneumotachometer, (B) denotes the sampling capillary from a mass spectrometer, and (C) is the large bore anesthesia tubing providing the bias flow. The tubing is approximately 80 cm long on both sides of the T-piece (D) that connects it to the pneumotachometer.

TABLE 10. EXAMPLES OF GAS ANALYZERS USED IN SYSTEMS FOR BREATH-TO-BREATH ASSESSMENT OF VENTILATION DISTRIBUTION IN CHILDREN AND EXAMPLES OF INERT GASES THAT HAVE BEEN USED WITH THESE ANALYZERS

Gas Analyzer	Inert Marker Gas
Mass spectrometer	Ar, He, N_2, SF_6 (sulphur hexafluoride)
Infrared (IR) detector	SF_6
Nitrogen analyzer	N_2
Ultrasound technique	SF_6, He

The face mask should be as small as possible without allowing leaks. Therapeutic putty should be placed at the rim of the mask in such amounts that a good seal is achieved and so that unnecessary dead space is avoided. A total external dead space, including the flowmeter, of less than 1.0 milliliters per one kilogram of body weight is desirable and most often achievable, and total apparatus dead space should not exceed 2.0 milliliters per one kilogram of body weight (32). The use of a mouthpiece and noseclip eliminates the dead-space problem to a large extent, but few children breathe normally through a mouthpiece.

Inert gas wash-in or washout. When a nonresident gas is used for MBW, this tracer gas must be washed in and equilibrated in the lungs before the washout can start (*see* Figures 13 and 16). The bias flow must exceed the child's peak inspiratory flow. An insufficient flow is readily detected as a drop in marker gas concentration during an inspiration. Wash-in of the tracer gas mixture should continue until the expirations have the same tracer concentration as the inspirations, plus another 30 seconds to secure equilibration among the ventilated lung regions. The washout phase starts by disconnecting the bias flow during expiration. Washout should continue until the end-tidal tracer gas concentration has fallen below 1/40th of the starting concentration over several breaths. In general, three MBW tests are sufficient for obtaining at least two tests, which are reproducible in terms of FRC—that is, a difference of less than 10%, when comparing the higher to the lower FRC value.

Quality control. Software and routines should be arranged so that it is always possible to reanalyze MBW recordings. Data files, including the flow and gas concentration signals as recorded sample by sample as well as the calibration factors and details of delay time, should be available. Documentation on the equipment used, including face mask or mouthpiece and its size, should be available. External dead space, together with precise details of how this has been estimated, should also be documented. An acceptable MBW recording includes a prewashout phase in which equilibration of the marker gas concentration in the lungs can be demonstrated by stable inspiratory and expiratory tracer gas concentrations over three subsequent breaths. The disconnection of the wash-in tracer gas should result in a sudden drop in marker gas concentration to zero (Figure 17). A sudden offset or a drift in VT suggests a face mask leak. A sudden drop in tracer gas concentration indicates a leak when a nonresident tracer is washed out by breathing air. During N_2 MBW, a sudden spike in N_2 concentration indicates a leak. By convention, the washout should continue until the end-tidal marker has fallen below 1/40th of the starting concentration over several breaths.

Data Analysis

Software requirements. The software should correctly detect the start and end of expirations and inspirations, and end-tidal tracer gas concentrations. The software should accurately calculate the amount of inert tracer gas inspired and expired by integration of gas concentration over flow, taking into account the delay of the gas signal, the effect of the dynamic viscosity of each gas sample on the flow signal when a pneumotachometer is used, and BTPS conditions.

Basic variables. Figure 17 shows gas concentration and VT traces from an MBW test performed by the 3-year-old patient. The test was done using a Fleisch No. 0 pneumotachometer and a mass spectrometer, and the tracer gas mixture contained approximately 4% SF_6 (66). Dead space within the face mask (precapillary dead space) is estimated at 10 ml and the geometrically calculated dead space after the mass spectrometer capillary (postcapillary dead space) is 5 ml. Table 11 shows the variables calculated from the washout. These contain all information necessary for calculation of the ventilation distribution indices.

FRC calculation. The FRC can be calculated from the cumulative expired volume of tracer gas divided by the difference in end-tidal concentration at the start and end of the washout (246, 247). The last column of Table 11 gives the FRC calculated for each subsequent breath in the MBW. It is calculated by dividing the cumulative volume of gas expired minus the inspired gas over the whole MBW (Cum Vol Gas Net) by the difference between the end-tidal SF_6 starting concentration and each subsequent end-tidal value, respectively. The FRC value from the last breath in the MBW is used when reporting the patient's true FRC, which is the calculated FRC minus the total external dead space (i.e., $443 - 15$ ml = 428 ml, in this case). In theory, the FRC value from N_2 MBW should be greater than FRC obtained when using a nonresident marked gas such as SF_6, because N_2 dissolved in blood and other tissues is washed into the lungs and further washed out via the airways during the test (246, 248). The repeatability of the FRC is better than 10%.
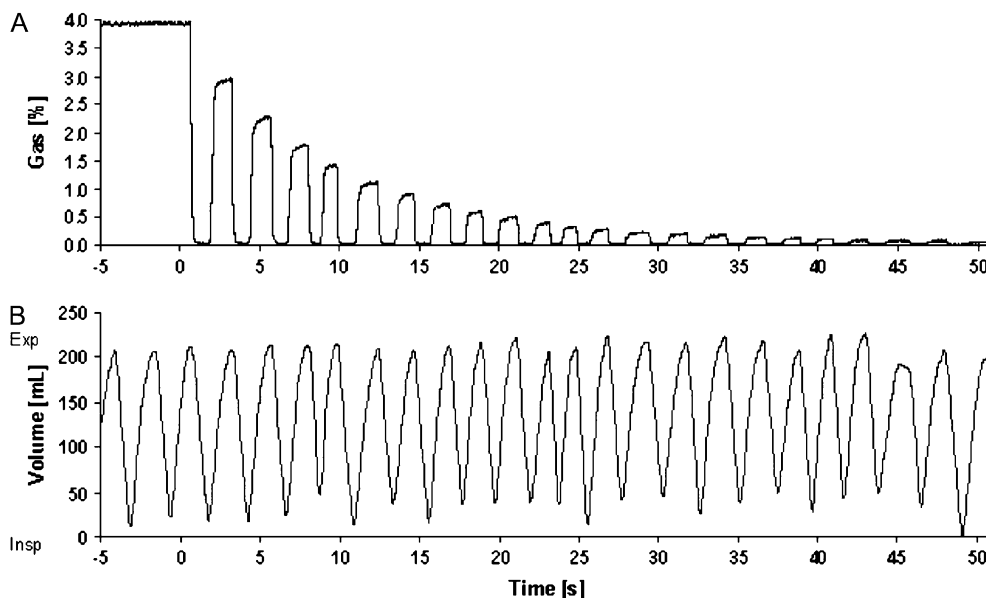

Figure 17. Original traces from a multiple-breath washout recording performed by the patient in Figures 15 and 16. (*A*) The tracer gas concentration plotted versus washout time; (*B*) the volume trace. A tracer gas mixture containing 4% SF_6, 21% O_2, was used for wash-in. Please note the stable tracer gas concentration before washout is started. This patient has a more regular breathing pattern than the majority of 3-year-old children.

Conventional ventilation inhomogeneity indices. Several indices of ventilation distribution inhomogeneity have been reported in the literature (249). They all reflect differences in specific ventilation between large and/or relatively small lung regions, resulting in delayed washout of the marker gas from the poorly ventilated regions. Sequential filling and emptying of the different regions is not usually a prerequisite for these indices. The LCI has been reported in several recent pediatric studies and has been shown to be a more sensitive marker of CF lung disease than spirometry in both school-age (31, 66) and preschool children (30). The LCI is the CEV minus the number of washout breaths multiplied by the external dead space outside the lips, divided by the patient's FRC (up to the lips). The LCI reports the number of lung volume turnovers (i.e., FRCs) that the child must breathe to clear the lungs from the marker gas (to 1/40th of the starting concentration). Because the external dead space is ventilated throughout the washout, it is reasonable to include it in the calculation, and hence, the CEV should be divided by the true FRC plus the external dead space. The repeatability of the LCI is within one unit. Table 12 shows additional variables, generated directly from Table 11. The variables in Table 12 can be used for calculating other indices (e.g., the slope index [250] and moment ratios [249]) (*see* the online supplement).

Normalized phase III slope analysis. New, alternative approaches to analyzing MBW data can provide additional information about the mechanisms causing ventilation inhomogeneity. A relatively new technique, normalized phase III slope analysis (Sn_{III}), takes into account both the convective and the diffusive mixing of the marker gas. For further information, *see* the online supplement.

INTERPRETATION OF RESULTS

Data Reporting

It is recommended that the mean values from a minimum of two washouts be reported for each variable and that the number of washouts, on which the report is based, be given. It is suggested that the report is based on two MBWs resulting in FRC values that differ by less than 10% (higher value compared with the lower).

Reference Values

A limited number of MBW studies involving healthy control subjects between the ages of 2 and 6 years have been published. Interestingly, reference values for the LCI appear to be similar across the age range from infancy to adolescence and show a narrow distribution. This adds to the clinical usefulness of the method and is particularly helpful when doing longitudinal follow-up of patients. LCI values obtained in healthy preschool children have been published by Aurora and colleagues using an SF_6 MBW method (31). The reference values proposed for this age group are very similar to those obtained in healthy school-age children in the same laboratory (30), and in healthy Swedish children aged 3 to 18 years (66). These values are summarized in Table 13. Normative data for other indices, such as the slope index, moment ratios, or various Sn_{III} variables in the preschool age group, remain to be published.

Clinical Interpretation

Uneven ventilation distribution as manifested in an abnormal LCI or other variable can be the result of generalized peripheral airway obstruction or more focal airway disease associated with reduced specific ventilation regionally. In CF, abnormal ventilation

TABLE 11. VARIABLES FROM THE MULTIPLE-BREATH WASHOUT THAT SHOULD ALWAYS BE AVAILABLE

Breath No.	Time (s)	$C_{ET_{SF_6}}$ (%)	Cnorm	V_E (ml)	Vol Gas Insp (ml)	Vol Gas Exp (ml)	Vol Gas Net Exp (ml)	Cum Vol Gas Net (ml)	FRC (ml)
0		3.94	100.0						
1	0.0	2.94	74.7	175	0.238	3.959	3.722	3.722	373
2	2.7	2.25	57.0	181	0.198	3.160	2.963	6.684	395
3	5.1	1.77	44.9	173	0.203	2.336	2.133	8.817	406
4	7.4	1.41	35.9	154	0.124	1.628	1.504	10.320	409
5	9.2	1.12	28.4	181	0.114	1.549	1.434	11.755	417
6	11.8	0.91	23.1	157	0.098	1.075	0.977	12.732	420
7	14.1	0.74	18.7	180	0.082	0.999	0.917	13.648	426
8	16.3	0.58	14.8	165	0.067	0.726	0.659	14.307	426
9	18.3	0.49	12.5	168	0.060	0.615	0.554	14.862	431
10	20.5	0.39	10.0	152	0.060	0.459	0.399	15.261	430
11	22.6	0.31	7.9	159	0.053	0.386	0.333	15.594	430
12	24.3	0.29	7.2	191	0.052	0.399	0.346	15.941	436
13	26.2	0.23	5.9	162	0.040	0.280	0.240	16.180	437
14	28.8	0.20	5.1	158	0.032	0.232	0.199	16.380	438
15	31.2	0.18	4.5	181	0.036	0.231	0.194	16.574	441
16	33.6	0.14	3.6	165	0.026	0.173	0.147	16.721	440
17	36.0	0.13	3.2	145	0.023	0.131	0.108	16.829	441
18	38.3	0.11	2.8	180	0.021	0.145	0.124	16.953	443
19	40.2	0.09	2.4	168	0.024	0.110	0.086	17.040	443

CEV (ml)   3,195

Definition of abbreviations: CEV = cumulative expired volume, BTPS; $C_{ET_{SF_6}}$ = end-tidal concentration of SF_6; Cnorm = normalized end-tidal concentration of SF_6; Cum Vol Gas Net = total volume of gas expired minus the volume of gas inspired over the whole multiple-breath washout, BTPS; V_E = expiratory tidal volumes; Vol Gas Exp = volume of marker gas expired through the pneumotachometer in each breath cycle; Vol Gas Insp = volume of marked gas residing in the pneumotachometer; Vol Gas Net Exp = the net volume of tracer gas expired in each cycle.

The numbers in this table originate from the washout in Figure 17. These variables are used for calculation of the lung clearance index (LCI) and other indices of ventilation inhomogeneity, and for quality control. *See* text for explanation of calculations.

TABLE 12. THE MULTIPLE-BREATH WASHOUT VARIABLES DERIVED FROM TABLE 11

Breath No.	V_E (ml)	CEV (%)	TO	$C_{ET_{SF_6}}$	Cnorm	Log (Cnorm)	Cnorm × TO	Cnorm × TO²
0		0	0.00	3.94	100.0	2.0	0.0	0.0
1	175	175	0.39	2.94	74.7	1.9	29.4	11.6
2	181	355	0.80	2.25	57.0	1.8	45.8	36.7
3	173	528	1.19	1.77	44.9	1.7	53.6	63.9
4	154	682	1.54	1.41	35.9	1.6	55.2	85.0
5	181	863	1.95	1.12	28.4	1.5	55.2	107.6
6	157	1020	2.30	0.91	23.1	1.4	53.2	122.4
7	180	1200	2.70	0.74	18.7	1.3	50.6	137.1
8	165	1365	3.08	0.58	14.8	1.2	45.5	140.3
9	168	1533	3.46	0.49	12.5	1.1	43.3	150.1
10	152	1686	3.81	0.39	10.0	1.0	38.0	144.7
11	159	1845	4.17	0.31	7.9	0.9	32.8	136.4
12	191	2036	4.60	0.29	7.2	0.9	33.3	152.9
13	162	2198	4.96	0.23	5.9	0.8	29.4	145.8
14	158	2356	5.32	0.20	5.1	0.7	27.2	144.6
15	181	2537	5.73	0.18	4.5	0.7	26.0	148.8
16	165	2702	6.10	0.14	3.6	0.6	21.7	132.2
17	145	2848	6.43	0.13	3.2	0.5	20.6	132.6
18	180	3027	6.80	0.11	2.8	0.5	19.3	131.8
19	168	3195	7.21	0.09	2.4	0.4	17.2	124.1

Definition of abbreviations: $C_{ET_{SF_6}}$ = end-tidal SF_6 concentration; CEV = cumulative expired volume (BTPS); Cnorm = normalized end-tidal SF_6 concentration; TO = lung volume turnover number (CEV/FRC); V_E = expiratory tidal volume.
The numbers in this table originate from the washout in Figure 17.

distribution is seen in a large proportion of patients with normal spirometry findings (30, 31, 66), suggesting that the MBW may be a more sensitive test to airway disease in general, or particularly because the peripheral airways are involved. In preschool children with CF, the MBW is a more sensitive method than airway resistance measurements in detecting lung function abnormalities (31). Little is known about the usefulness of the MBW in preschool children with asthma. The usefulness of Sn_{III} analysis in young children needs to be established.

CONCLUSIONS AND FUTURE DIRECTIONS

The MBW test can be performed successfully in the vast majority of children between the ages of 3 to 6 years because it involves only normal tidal breathing. In patients with CF, this test may be more sensitive to airway involvement than spirometry or airway resistance measurements. Knowledge about the usefulness of the MBW for monitoring the progression of disease or the response to treatment remains limited. The MBW test may be particularly suitable when screening for post-transplant bronchiolitis obliterans. Few systems for MBW adapted for the preschool age group are commercially available today. Because only a few centers have had experience with the MBW method, many of the proposals regarding equipment requirements, procedures, analysis, and interpretation mentioned in this document must be seen as tentative. They may, however, serve as a starting point for future discussions, which should involve both users and manufacturers.

Section 8. Bronchial Responsiveness Tests

SUMMARY

Bronchial challenge (BC) tests are easily performed in adults and children older than 7 years. During the last 15 years, new pulmonary function tests adapted to preschool children have demonstrated their ability to assess induced bronchoconstriction during BC. However, the multiple ways to perform BC tests, the variable relevance of the different pulmonary function tests used, as well as the lack of data in normal preschool children indicate the need for recommendations.

At this stage, the paucity of studies using physical tests for BC or parameters derived from forced expiratory maneuvers as an outcome measure preclude recommendations on these aspects. The following recommendations are based on our current knowledge about protocols for pharmacological tests, the changes in pulmonary function tests during BC, and the reproducibility of the BC tests performed in preschool children:

1. BC tests should be performed in preschool children who are free from recent respiratory infection (> 3 wk), with normal auscultation and with a normal pulmonary function test, including an oxygen saturation (Sp_{O_2}) above 95% before the test.

2. Trained staff, bronchodilator, resuscitation equipment, and oxygen must be readily available in the room.

TABLE 13. REFERENCE VALUES FOR THE LUNG CLEARANCE INDEX OBTAINED IN CHILDREN USING AN SF_6 MULTIPLE-BREATH WASHOUT METHOD

Authors	Population		Predicted LCI, Mean (SD)
	n	Age (yr)*	
Aurora and colleagues (31)	30	4.3 (0.8)	6.89 (0.44)
Aurora and colleagues (30)	33	11.3 (3.1)	6.45 (0.49)
Gustafsson and colleagues (66)	28	11.4 (range, 3–18)	6.33 (0.43)

* Values for age are mean (SD).

3. For pharmacological tests, saline (control) inhalation is not compulsory, but assessment of within-subject, between-test repeatability of pulmonary function tests is essential if results are to be used for clinical management within an individual child.

4. For delivery of the agent, the tidal breathing method should be performed with a standardized nebulizer output, during a maximal inhalation duration of 2 minutes of doubling or quadrupling concentration steps. The dosimeter method should be performed during deep inhalation with a maximal nebulization time of 0.6 seconds and repetition of the inhalations should occur every 5 minutes.

5. When using transcutaneous partial pressure of oxygen (Ptc_{O_2}) to determine bronchoconstriction, the BC protocol should be designed to provoke a decrease in Ptc_{O_2} of up to 20%, and attempting to avoid marked changes in breathing pattern is essential for this specific protocol.

6. Sp_{O_2} is not recommended as the sole indicator of bronchoconstriction but may be used for safety reasons in association with resistance measurements or with the auscultation method.

7. An increase of less than 35 to 40% in resistance is considered a negative test if the baseline value was close to the mean predicted value, but accurate thresholds for a positive test have yet to be established.

8. The auscultation method is a simple method to combine with other pulmonary function tests, such as Ptc_{O_2} or Sp_{O_2}.

9. BC is ended with bronchodilator administration, with a return to the baseline pulmonary function test being confirmed at the end of the test.

Adopting these recommendations should facilitate the comparison of results among different studies, particularly those involving normal subjects. Determination of the normal range of bronchial responsiveness in preschool children is the next fundamental step, because comparisons with older children are not relevant.

INTRODUCTION

Current guidelines for BC tests from the ERS and the ATS task forces are suitable for adults and schoolchildren but not for preschool children (251, 252). BC tests may contribute to the diagnosis of asthma in patients with nonspecific respiratory symptoms and normal baseline pulmonary function tests including response to bronchodilators. They may also be an epidemiological tool, because bronchial hyperresponsiveness has been shown to be a risk factor for developing subsequent symptoms of asthma in some (253–255) but not all studies (256, 257). Finally, BC tests can be used as a tool to establish the effect of pharmacological interventions in the field of clinical research (258, 259).

Little is known about bronchial responsiveness in preschool children. Preschool children are known to have a short concentration span and relatively poor cooperation with pulmonary function tests. This combination complicates the inhalation protocol and the assessment of bronchoconstriction in this age group. Moreover, physical tests that are commonly used in children and adults are much more difficult to perform in preschool children, such that most BC tests in preschool children have been performed using pharmacological agents. Methods to assess bronchoconstriction in preschool children have been used since the 1990s, with an increasing number of studies in this age group, but our knowledge is still incomplete. In the following, we will not consider issues that have already been extensively detailed

in the previous guidelines for adults and children (251, 252) but will focus on the particularities of BC tests in preschool children. We will review the protocols and pulmonary function tests used in preschool children, to propose recommendations when our knowledge seems sufficient.

BRONCHODILATOR RESPONSIVENESS

Before studying bronchial responsiveness during BC, the reader should be reminded that bronchial responsiveness can also be evaluated after bronchodilator administration. Despite different underlying phenomena, in practical terms these two tests exhibit differences and similarities (see the online supplement). For both BC test and BDR, interpretation of response is based on the within-subject between-test repeatability of the measured parameters in the lab for the specific studied population. For a change to be clinically or physiologically significant within a child, it has to exceed the CR, calculated from repeated measurements in the absence of any intervention over a similar time period (see SECTION 2). Once the repeatability of the PFT method is assessed, the determination of BDR in healthy subjects is of utmost importance to define what is normal and to discriminate healthy children from those with asthma. Depending on the PFT method used, there can be an overlap between the BDR in normal children and those with asthma. Specificity and sensitivity vary on opposition, and the proportion of children with asthma over- or underdiagnosed on the basis of their BDR relies on the chosen threshold (Figure 18). More information on repeatability of pulmonary function tests is available from other sections of the present document. Finally, the selection of the best method to express BDR (e.g., absolute value, % predicted, % baseline) (260–262) is not defined for the preschooler. The best method to express BDR depends on the relationship between pre- and post-bronchodilator values. In adults, this relationship has been found to be related to the chosen parameter analyzed on the flow–volume curves or from plethysmographic measurements (260). No extrapolation from studies on BDR assessed by spirometry or by the plethysmographic technique in adults can be made in preschool children tested using other pulmonary function tests. This section of the document will focus on BC testing, which cannot substitute for BDR, and other sections in this document present BDR data for various preschool techniques.

PHARMACOLOGICAL CHALLENGE TESTING

Protocols

Subjects. Children eligible for BC tests have to be free of respiratory infections for at least 3 weeks (252). Medications known to influence bronchial responsiveness should be withheld before the test, as described for adults and children. Briefly, oral and inhaled short-, medium-, and long-acting bronchodilators are withheld before the challenge for 8, 24, and 48 hours, respectively; leukotriene modifiers are withheld for 24 hours before BC, cromolyn sodium for 8 hours, nedocromil for 48 hours, and, except for methacholine challenge, antihistamines are withheld for their duration of action (252). Baseline pulmonary function should be within the normal range for the measured parameter(s) (including transcutaneous oxygen saturation > 95%), and on auscultation, the child's chest should be free of wheezing.

Acceptability. The acceptability of the test relies on the simplicity of the protocol. The challenge procedure and the duration of the test have to be adapted to the limited concentration span of a young child. Physical tests could seem more acceptable than pharmacological challenge to parents of such young children because they do not include drug inhalation. Finally, only noninvasive methods must be used to assess bronchoconstriction.
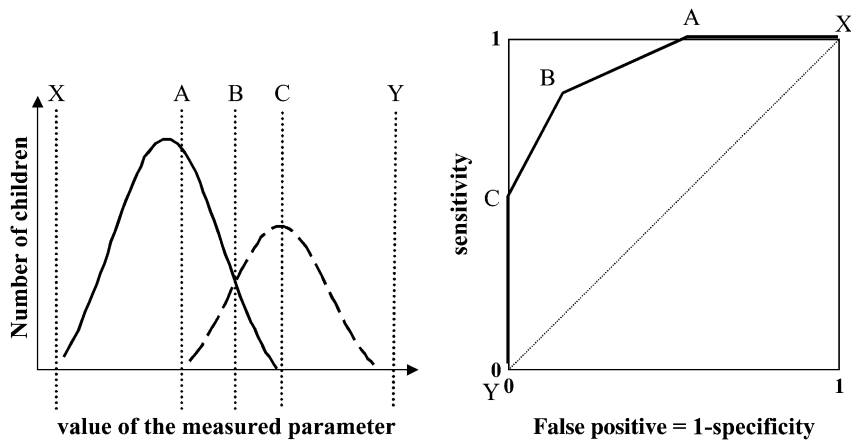
Figure 18. Example of receiver operating characteristic analysis in a measured parameter with an overlap between healthy (*solid line*) and sick (*dotted line*), normally distributed populations. A, B, and C refer to the three thresholds. Threshold A has a 100% sensitivity and detects all the sick subjects but a poor specificity, which results in overdiagnosis of sickness. Threshold C has the opposite characteristics with a 100% specificity, but underdiagnoses, in that case, half of the sick subjects. Threshold B is the best compromise between specificity and sensitivity. X and Y are the extreme values of the measured parameter in both healthy and sick subjects, with a 100% sensitivity, 0% specificity for X, and opposite characteristics for Y.

Feasibility. In most cases, with experienced technicians, BC tests can be performed in young children, especially when the child has previously and successfully inhaled treatment or performed PFT (*see* the online supplement).

Safety. A bronchodilator, as well as staff trained to use it, must be available in the room where the test takes place. Oxygen must be readily available, as well as resuscitation equipment, a stethoscope, a sphygmomanometer, and a pulse oximeter. The room in which pharmacological tests are performed needs to be efficiently ventilated, and staff with active asthma should not perform the test or be present in the room where it takes place. To minimize staff exposure to the pharmacological agent, nebulizers should include an exhalation filter and, if possible, a two-way valve (251, 252).

Subject preparation. After checking the medication washout period and the absence of any other contraindication, the young child is encouraged to play in the lab before beginning the test. When the child feels comfortable, explanations are given to her or him about the test and a demonstration of breathing through a mouthpiece or a face mask while wearing a noseclip is performed. The different devices and computers that will be used during the test are shown to the child. Finally, the child is asked if she or he wants to urinate, to avoid subsequent interruption of the test.

Drugs. Although methacholine (acetyl-β-methylcholine chloride) is the most commonly used drug, some investigators prefer to assess bronchial responsiveness with histamine (263, 264) or carbachol (265), and more recently with adenosine 5′-monophosphate (AMP) (266). Methacholine, histamine, and carbachol are bronchoconstrictors acting directly on the smooth muscle where AMP is believed to act via stimulating the release of constrictor mediators from mast cells. Challenge test procedures in preschool children are the subject of much current research, and newer agents are likely to be introduced in the future. In adults, significant induced bronchoconstriction is obtained at equivalent concentrations of methacholine and histamine (252). In preschool children, one study compared bronchial responsiveness to inhaled methacholine and histamine, and found a close correlation between the provocative doses (267).

Inhalation protocol. Two methods are recommended to deliver the pharmacological agent in adults: the tidal breathing method and the dosimeter method (252). The standardization of the delivered dose relies on three parameters: the duration of the inhalation, the output of the nebulizer, and the breathing pattern of the patient (inspiratory–to–total time ratio for the tidal breathing method and total duration of inspiration for the dosimeter method) (252). The cumulative effect of the doses depends on the pharmacological agent and on the timing of the inhalations (268).

Saline inhalation has been used at the beginning of the test in eight studies in preschool children (144, 150, 263, 264, 267, 269–271). However, postsaline pulmonary function tests have rarely been performed and were considered as the baseline value in only two of these studies. This suggests that this preliminary step has been used more to improve the child's ability to perform the inhalation and eventually the pulmonary function tests, than to allow the evaluation of the within-subject repeatability in response to a placebo. Although most authors have avoided saline inhalation to shorten the test in such young children, this may preclude interpretation of results within an individual (*see* Section 2).

The tidal breathing method has been detailed in nine studies that included only preschool children (*see* Table E1) (155, 160, 263, 264, 270–274). The duration of the inhalation was either 2 minutes (263, 264, 270, 271, 274) or 1 minute (155, 160, 272, 273). The excessive duration of the inhalation can annoy young children, particularly those without severe respiratory disease who are not familiar with inhaled treatment. In that case, quadrupling (instead of doubling) concentration steps can be proposed, whereas halving the inhalation duration is possible if the preceding level of bronchoconstriction is far from the endpoint (155, 160, 252, 272, 273). Finally, increasing the starting dose is possible, according to the respiratory symptoms of the child (270).

The dosimeter method has been detailed in six studies in preschool children (*see* Table E1) (63, 144, 150, 265, 267, 269). In those studies, the duration of inhalation, the volume delivered per inhalation, the number of inhalations by step, and the increase of concentration were quite variable. The duration of the inhalation should not exceed the 0.6 second recommendation in adults but may be decreased in the youngest children (150). Although the minimal inspiratory time required to inhale a dosimeter-delivered dose of solution is believed to be 3 seconds in adults, this has yet to be established for preschool children (275).

The cumulative effect of the inhaled agent is influenced by the timing of the dosing protocol. In studies of preschool children, the interval between inhalations ranged from 1 to 10 minutes. No study has established the duration of bronchoconstriction in children so far. In adults, however, Cartier and coworkers showed that bronchoconstriction lasted longer for methacholine than for histamine, with a large intersubject variability (268), which to some extent depends on the degree of bronchoconstriction induced.

Breathing Pattern

See the online supplement for more details.

Lung Deposition

See the online supplement for more details.

Bronchodilator Administration

At the end of the challenge, a bronchodilator (β_2-agonist) should be administered even if the child does not demonstrate significant bronchoconstriction (63, 144, 150, 155, 160, 263, 265, 267, 269–272). Depending on the age of the child and the presence or absence of respiratory symptoms post-BC, the bronchodilator can be nebulized with oxygen (150, 155, 160, 263, 270, 271) or delivered from a metered-dose inhaler via a spacer device (63, 144, 150, 265, 269, 272). In all cases, return to the baseline pulmonary function test is confirmed before the child leaves the laboratory.

Calculation and Expression of the Response

Most authors express the bronchial response according to the recommendations provided for adults and children (251, 252). The bronchial response is either expressed as a change in percentage of baseline of the selected functional parameter or as the occurrence of the study endpoint (e.g., wheezing, $Sp_{O_2} < 91\%$). The provocative concentration (PC) or provocative dose (PD) is the inhaled concentration (dose) necessary to obtain a given pulmonary function test change from baseline measurement. Calculation of PC or PD is obtained by linear interpolation between the last two points (second-to-last and final concentration) of the dose–response curve calculated from the log-linear dose–response curve. The dose that provokes a 20% baseline decrease of Ptc_{O_2} is referred as $PD_{20}Ptc_{O_2}$, and the concentration that induces a 40% baseline increase in Rrs is $PC_{40}Rrs$. The other way to express bronchial responsiveness is the calculation of the dose–response slope (DRS)—that is, the % change of the pulmonary function test divided by the amount of inhaled drug (265, 276). The DRS can always be calculated, even when the endpoint is not reached. Therefore, it allows comparisons in children with different levels of bronchial responsiveness and seems more efficient to differentiate children with asthma from other children (265, 276).

Recommendations (Protocol)

Given the difficulties of cooperation and the unresolved issues that are encountered in this age group, many different inhalation protocols have been used in preschool children. To allow comparisons between studies, the inhalation protocol, particularly the inhalation technique, should be better standardized. The initial saline inhalation is not compulsory if the within-subject repeatability of the pulmonary function tests used is known from studies in other preschool children of the same health status, within the same lab over the same interval, and while using identical methods and equipment. Otherwise, repeated measurements performed 5 minutes apart are necessary at baseline and ideally after saline inhalation to assess repeatability of the pulmonary function test. The tidal breathing method can be performed with a nebulizer (0.13 ml/min ± 10% output of solution), during a maximal inhalation duration of 2 minutes to perform doubling or quadrupling concentration steps. The dosimeter method requires deep inhalation with a maximal nebulization time of 0.6 seconds, which may be adapted in the youngest children. The interval between inhalations should be approximately 5 minutes, particularly in histamine challenge and in long protocols (> 4 inhalation steps). Unresolved issues previously mentioned (exact inhaled dose, relationship between respon-siveness and age/size; *see* the online supplement) are less crucial if results can be compared with tests performed in large groups of healthy age-related children, although such data are rarely available except in specialized research departments. Finally, the test ends with a bronchodilator administration to reverse bronchoconstriction and return to the baseline pulmonary function test must be confirmed.

Pulmonary Function Tests during BC

The poor and unpredictable cooperation of preschool children makes it difficult to obtain reproducible flow–volume curves throughout all stages of the BC test. In two studies conducted in daycare centers, more than 80% of preschool children were able to perform at least two technically correct flow–volume curves, but this proportion was significantly correlated with age (5, 9). In a recent study, from a large number of methacholine challenges in young healthy children (n = 440) and children with asthma (n = 80) (5–7 yr old), the sensitivity and specificity of $PC_{10}FEV_1$, $PC_{15}FEV_1$, and $PC_{20}FEV_1$ were not different in favor of a low accuracy of FEV_1 to assess bronchial responsiveness in young children (33). It is possible that increased use of animated computer programs, together with the establishment of appropriate quality-control criteria, a relevant outcome parameter, and data on repeatability for preschool children (11), will facilitate the use of forced expiratory maneuvers as an outcome measure during BC tests in this age group. However, this is currently not available; therefore, we will concentrate on alternative noninvasive methods that have been used recently to assess bronchial responsiveness in preschool children.

Ptc_{O_2}. Hypoxemia is a consequence of the BC tests due to induced bronchoconstriction and/or changes in pulmonary vascular resistance, resulting in increased perfusion–ventilation mismatch in children with asthma (277) and in adults (212). Ptc_{O_2} is a noninvasive method to assess hypoxemia during BC and has been recommended as an endpoint in laboratories with experience in its use (252). One may assume that hypoxemia truly reflects bronchial responsiveness provided the challenge method itself does not significantly change the breathing pattern of the child (263). Ptc_{O_2} measurement alone can lead to false-positive tests if the breathing pattern is irregular during the BC, and monitoring Ptc_{CO_2} is a reliable way to highlight this methodological defect (278). A 20% decrease in Ptc_{O_2} during BC has been related to bronchoconstriction assessed by spirometry (279) or by Rrs measured using the FOT (212, 280) in older children with asthma. Ptc_{O_2} has been tested in 12 studies in preschool children (*see* Table E1) (63, 144, 150, 155, 160, 263, 264, 269–273). In these studies, the Ptc_{O_2} electrode was heated at 44 to 45°C and placed on the chest wall or on the forearm of the children with no or minimal local erythema at the end of the test. Authors have mentioned a 20- to 30-minute lag time for stabilization of the Ptc_{O_2} (63, 144, 155, 160, 273). Baseline values of Ptc_{O_2} ranged from 8.5 to 11.8 kPa with a low intrasubject CV (1.6–3%) calculated from eight measures taken 1 minute apart or from duplicate measurements at the same interval as the BC test (63, 144, 155, 160, 273). Ptc_{O_2} was either the only endpoint of the test, using a threshold of a 20% decrease from baseline (155, 160, 263, 269, 270, 272, 273), or was one of several outcome measures (63, 144, 150, 264, 271). In two studies during which Ptc_{O_2} decrease was not the endpoint, the mean fall was –33 and –22% (63, 144). Although good baseline repeatability of Ptc_{O_2} measurements resulted in a statistically significant change for a 10% baseline decrease (273), comparison with other endpoints indicated that a 20% baseline decrease was a more clinically or physiologically relevant threshold with which to assess a positive BC test (212, 279, 280). In all but one study (271), no technical problems were reported with this method,

and there were no serious clinical side effects when Ptc_{O_2} decrease was the sole endpoint. After bronchodilator administration, Ptc_{O_2} returned toward baseline (144, 278), with no significant difference between baseline and post-bronchodilator values (63, 150).

Sp_{O_2}. Sp_{O_2} has been recorded in four studies of preschool children (265, 270, 271, 274) as well as in older children and adults (212, 281). Even though a decrease in Sp_{O_2} occurred during bronchoconstriction, the magnitude of decrease compared with the baseline variability of this measurement makes it an unsafe endpoint (212, 265), with no correlation between Sp_{O_2} decrease and the increase of Rrs (FOT) (212) or sRaw or bronchial responsiveness (265). In two studies, a 5% baseline decrease of Sp_{O_2} or an Sp_{O_2} under 91% was found to be the only marker of bronchoconstriction in 20 and 10% of the reactive children, respectively, when audible wheeze was the other endpoint (271, 274).

Recommendations (Ptc_{O_2}, Sp_{O_2})

Ptc_{O_2} is a robust marker of hypoxemia, provided there is evidence that the challenge protocol does not modify the breathing pattern of the child. A 20% decrease can be used as the endpoint of the test and a return to baseline value must be confirmed at the end of the test. Sp_{O_2} seems to be a much less sensitive marker of bronchoconstriction and should not be used as the sole indicator of bronchial responsiveness. However, it should be used as an additional safety measure when assessing bronchial responsiveness with auscultation or with resistance measurements.

Resistance Measurements

The descriptions and recommendations for resistance measurements are outlined in other sections of this document. In the following, we will refer to sRaw, total Rrs measured by the Rint, the opening method (Rint-o), the FOT, and reactance (Xrs) measured by the latter method. Resistance has been used as an outcome measure in eight BC studies in preschool children (*see* Table E1) (63, 144, 150, 155, 160, 265, 267, 273). In all these studies, resistance measurements of the studied groups increased in a significant way during the BC with respect to the baseline variability, but poor individual quality resistance measurements have been reported for Rrs (FOT and Rint) or sRaw (63, 150, 155, 273). In practice, a 100% increase in sRaw has been used as the endpoint in preschool children with miscellaneous health status (asthma, chronic cough, asymptomatic) (144, 265); this is a slightly larger change than that recommended in adults (252). However, in one of these studies, a 3 SDw (*see* SECTION 2) increase in sRaw corresponded to a 38% increase of the mean sRaw baseline value and was more sensitive in detecting bronchial responsiveness than FEV_1 measurements (144). In preschool children, a 35% increase in Rrs (FOT) was correlated with a 15% fall in Ptc_{O_2} during methacholine challenge (273). This is similar to the correlation between a 40 to 50% increase in Rrs (FOT) and a 20% decrease in FEV_1 (267) or in Ptc_{O_2} in children with asthma and normal adults (212, 280). Although the precise mechanism(s) remains uncertain, changes in Xrs may provide interesting information regarding bronchial responsiveness (164, 282). The Rint increased significantly with Ptc_{O_2} decrease during BC in preschool children (150, 155, 160). Data from two studies showed that, for a mean fall of 22 and 27% of Ptc_{O_2}, the mean $\pm$ SD increase in Rint was $40 \pm 21\%$ (range, 11–75%) and $35 \pm 24\%$ (range, –3 to 120%) of baseline, respectively (150, 160). However, no threshold value of Rint increase has been proposed for positive BC and evaluation of the DRS could be a more interesting method to differentiate normal from abnormal bronchial responsiveness (276). Resistance measured by all methods increased significantly during BC, but lack of

sensitivity and discrepancies between resistance and other functional parameter changes have been described. Studies that compared changes in pulmonary function tests during BC in preschoolers found that sRaw and Xrs were the most sensitive methods to detect bronchoconstriction, followed by Ptc_{O_2}, FEV_1, and Rrs (FOT, Rint, and Rint-o) (63, 144, 155). However, it is not appropriate to compare methods that require maximal inspiration with those that do not, due to the potential influence of deep inspirations on bronchial obstruction in subjects with asthma (283). On the other hand, the occurrence of a laryngeal constriction during the challenge (284) that would increase resistance independently from a bronchial reaction could also be a source of discordant tests. This artifact should be partially avoided by measuring resistance during inspiration (150, 214). Finally, the progression of the bronchoconstriction may result in phenomena that reduce the validity of the various resistance techniques, by violating the basic underlying assumptions. In the presence of induced bronchoconstriction, alveolar pressure changes may not equilibrate rapidly throughout the airways, lung volume and viscoelasticity of the respiratory system may change, and inertial forces may become nonnegligible; all these phenomena would unpredictably modify the resistance measurements.

Considerations on what can be a significant change in resistance measurements during BC are also discussed in other sections of the present document (*see* SECTIONS 2, 5, and 6).

The significance of increase in resistance has been related to the baseline value (percentage of baseline) or to baseline variability of the resistance (sensitive index = challenge-baseline value/within-subject SD). Percentage of baseline is a relevant way to express change in resistance when baseline values are close to the mean but may be less valid if baseline values are at the extremes of the normal range. Results expressed as multiples of the baseline variability (i.e., as within-subject SD units for between-test variability [285]) are more suitable to compare different methods of assessing bronchoconstriction than to determine a threshold value (144, 150, 155).

Recommendations (Resistance)

Resistance measurements change significantly during BC. sRaw and Xrs seem to be more sensitive than Rrs (FOT, Rint, and Rint-o) in detecting bronchoconstriction. From BC changes in FEV_1 and Ptc_{O_2}, it is obvious that the threshold for a positive test is greater than a 35 to 40% increase in resistance. However, the threshold remains to be precisely established for each method based on the test repeatability, as does the way to express it. An increase of Rrs of less than 35 to 40% of baseline can be considered as a negative test if the baseline value is close to mean predicted value.

Auscultation Method

Auscultation of the trachea or of the chest may reveal wheezing during BC and has been reported in six studies in preschool children (*see* Table E1) (150, 265, 269, 271, 273, 274). Wheezing was detected in 8 to 78% of sick, responsive children and in 8% of responsive, but asymptomatic, children; it was not observed in nonresponsive children. This large range of the occurrence of wheezing during BC in preschool children may be attributable to the heterogeneity of the study populations in terms of age, health status, dosing protocol, and chosen endpoint. Indeed, in older children with obstructive lung disease (13/15 with asthma), the provocative concentration of methacholine required to cause wheezing was found to be about 150% $PC_{20}FEV_1$ (286). No serious clinical side effects have been reported with the wheezing method in preschool children with asthma. However, it has never been used as the only endpoint of the challenge and its usefulness

and safety as the only indicator of bronchial responsiveness in sick and in healthy children remain to be determined.

Variability

The variability of some pulmonary function tests used during BC in preschool children is discussed in other sections of the present document. A significant change in a pulmonary function test should be larger than the within-occasion CR (*see* Section 2) in the study population. However, the clinically relevant BC change can be much larger than the CR, especially if baseline PFT repeatability is very good (e.g., FEV_1, Ptc_{O_2}; *see above*). Conversely, for resistance measurements that may have a large within-occasion CR, the relevant threshold may be close to the CR. Finally, the method to assess changes in resistance during BC is not established (absolute value, % baseline, % predicted, multiples of baseline SD of the study population or in individuals). Studies of large groups of healthy children and children with asthma are necessary to allow evaluation of the sensitivity and specificity of different thresholds for each pulmonary function test, using different methods to express the post-BC change.

Short- and long-term reproducibility of BC in preschool children has been reported in three studies in groups of 21 to 40 children (*see* details in the online supplement) (265, 267, 270). The reproducibility of BC in preschool children has been found acceptable and further studies on reproducibility in BC tests are needed to confirm these encouraging data.

What Is Normal?

Few studies on bronchial responsiveness to pharmacological agents have included healthy preschool children (33, 265, 270, 273). Two studies with similar sample sizes of preschool children with respiratory disorders (265, 270) demonstrated no overlap in bronchial responsiveness (assessed by $PC_{20}Ptc_{O_2}$ and $PD_{100}sRaw$) between healthy children and current wheezers, whereas children with chronic cough had an intermediate level of bronchial responsiveness. However, we need studies in larger populations to calculate the sensitivity and specificity of the different pulmonary function test outcome measurements during BC.

COLD AIR CHALLENGE

Cold air challenge (CACh) appears to be feasible in the majority of preschool children and could contribute to the assessment of bronchial responsiveness in the future. However, due to the limited number of studies, it is not yet possible to provide recommendations with respect to data collection, analysis, and interpretation in this age group. The CACh protocol and the PFT results are discussed in the online supplement.

CLINICAL APPLICATIONS

It is apparent that normative data from BC using standardized protocols in healthy preschool children are currently missing. Until these data are available, it will be difficult to assess the degree of bronchial responsiveness in a given child, and even more difficult to interpret longitudinal assessments in a meaningful way.

Assessment of bronchial responsiveness is interesting in clinical practice, as it seems that different respiratory symptoms correspond to different degrees of bronchial responsiveness. Groups of asymptomatic children have been found to have significantly lower bronchial responsiveness than symptomatic children (265, 270, 287). Furthermore, preschool children with chronic asthma had significantly increased bronchial responsiveness when compared with chronic coughers (265, 270, 287), and ex-wheezers demonstrated intermediate results (270).

BC may be a useful way of confirming or, perhaps even more so, excluding a diagnosis of asthma in preschool children with nonspecific respiratory symptoms. In this way, BC could contribute to the implementation of a specific treatment or the cessation of a noneffective and unnecessary one.

In recent studies, increased bronchial responsiveness at a young age has been found to correlate with lower pulmonary function in childhood and early adulthood (253, 288–290). Until now, guidelines for asthma treatment have not included the level of bronchial responsiveness when selecting the type and dose of the prescribed drugs (291). Two studies in adults and children have shown that such protocols may lead to increased doses of inhaled corticosteroids (258, 259). However, before recommending such treatment protocols for young children, any short-term benefits have to be balanced against potential long-term adverse effects.

CONCLUSIONS AND FUTURE DIRECTIONS

It is possible to safely perform BC tests in preschool children. Reproducibility of BC tests needs further evaluation, but the first published studies are in favor of an acceptable reproducibility of the test. In combination with other clinical features, such as recent wheezing or personal or familial atopy, BC may assist the diagnosis or exclusion of asthma in preschool children.

Further studies on physical tests and studies using forced expiratory maneuvers are needed before recommendations can be made.

It will not be possible to interpret the degree of hyperresponsiveness in an individual child or use these tests for clinical management until studies in many more healthy preschool children have been undertaken. These data together with studies in children with respiratory problems are needed to establish relevant thresholds for each type of pulmonary function test used in preschool children to determine its relative sensitivity and specificity.

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