Neonatal and Pediatric Respiratory Diagnostics

Stephanie D Davis MD

Evaluating respiratory function in children, especially infants and preschoolers, is difficult because of lack of patient cooperation with and understanding of lung function testing. Because of recent advances in diagnostic tools, investigators are now able to assess normal lung physiology, the presence or absence of airway disease, and therapeutic interventions in this young age group. Recent advances in infant lung function testing, preschool spirometry, forced oscillation methods, and the interrupter respiratory resistance technique are discussed. Exhaled nitric oxide and carbon monoxide measurements in children are also reviewed. The technical aspects, advantages, disadvantages, and clinical applications of these tools are summarized. These remarkable advances have yet to be applied in multicenter trials with young children. Adhering to standards will be critical for future multicenter trials to assess the clinical utility of these potential outcome measures. *Key words: pediatric, respiratory, pulmonary, infant, pulmonary function testing, spirometry, oscillation, respiratory resistance, nitric oxide, carbon monoxide.* [Respir Care 2003;48(4):367–384.

Introduction

During the past several years, there have been marked advances in the diagnostic assessment of respiratory function of infants and children. These advances have improved our understanding of respiratory physiology and lung growth in infants and children. In addition, these diagnostic methods have increased our understanding of cystic fibrosis (CF), asthma, infants with recurrent wheezing, primary ciliary dyskinesia, and other lung diseases in children. These diagnostic tools may serve as outcome measures when assessing therapeutic interventions. Evaluating infants and young children has proven difficult because of their inability to cooperate with testing. However, recent advances have made lung function testing of infants and preschool children technically possible and reproducible. This review summarizes current techniques in infant lung function testing, spirometry in preschool children, the

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interrupter respiratory resistance technique (Rint) and forced oscillation measurements. In addition, the utility of exhaled nitric oxide (NO) and exhaled carbon monoxide measurements are reviewed.

Infant Lung Function Testing

Since lung disease is a major etiology of morbidity during infancy,[1] improving our knowledge of lung development and growth in infants is critical. This knowledge provides investigators with a better understanding of the pathophysiology of infant lung disease and how to treat the underlying disorder. In older children and adults with respiratory illnesses, pulmonary function testing is routinely used as an objective measure of airway disease, as well as a tool for aiding in therapeutic decisions. In order to obtain reliable data, the subject must be cooperative and understand the testing process. This type of cooperation is not possible with infants. To assess infant lung function, the subject is supine and must be asleep or sedated. Over the past 30 years investigators have explored several different techniques to assess lung function in infants. Because of the complexity of the testing, the measurements have mainly been assessed from the tidal breath; however, measurements from a raised lung volume are now possible. This review will summarize some of the published studies that have analyzed tidal breathing, resistance and compliance, lung volumes, partial expiratory flow-volume curves, and forced expiratory maneuvers obtained from a raised lung volume.

Measurements of Compliance and Resistance

Compliance and resistance may be measured through passive techniques or dynamically. Dynamic measurements include: (1) the analysis of airway resistance, using plethysmography, (2) the evaluation of lung resistance and compliance, using esophageal manometry, and (3) forced oscillation techniques.[1,2] Measuring airway resistance using the infant body plethysmograph simulates adult measurements, except that the subject is unable to pant during the maneuver. In adult measurements, panting helps to eliminate temperature and humidity fluctuations that occur between inspiration and expiration. Eliminating these fluctuations is essential because the calculation of airway resistance is dependent on accurate measurement of box pressure changes. (Box pressure changes may be affected by minor changes in volume measurements corresponding to temperature and humidity fluctuations.) Because the infant is unable to pant, the circuit contains a heated, humidified gas (at body temperature and pressure saturated) that the subject rebreathes. Airway resistance is calculated from the flow measured at the pneumotachograph and from the difference in pressure between the alveoli and the opening of the subject's airway:

$$R_{aw} = \Delta P/\dot{V}$$

in which R_{aw} is airway resistance, ΔP is the difference in pressure, and $\dot{V}$ is flow. This type of airway resistance measurement is technically difficult and only performed in highly specialized infant lung function laboratories.[1–3] The European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force on Standards for Infant Respiratory Function Testing has published guidelines for plethysmographic measurement of airway resistance.[4]

The evaluation of lung resistance and compliance via esophageal manometry involves the placement of an esophageal balloon. The esophageal balloon measurements simulate pleural pressure measurements. Based on the Mead-Whittenberger technique,[5–7] dynamic resistance is equal to change in transpulmonary pressure divided by change in flow. Transpulmonary pressure is defined as the difference between the pressure measured at the airway opening and the pressure measured in the esophagus, with an esophageal balloon. Dynamic compliance is defined as the change in volume divided by the change in transpulmonary pressure. These changes are measured between end-inspiration and end-expiration, when flow is zero. In addition, regression techniques[1,8] have been developed that analyze dynamic compliance via measurements of transpulmonary pressure, flow, and volume. These types of measurements are difficult because an esophageal balloon must be used and many infants do not tolerate this procedure. Because of this difficulty, this type of measurement is only performed in a few specialized laboratories.[1,2,8] Forced oscillation techniques are described in another section of this manuscript.

Passive respiratory mechanics can be measured via a multiple-occlusion technique or single-breath technique.[1,2,9,10] Weighted spirometry, the multiple-interrupter technique, and expiratory volume clamping are also used to measure passive respiratory mechanics.[10] Only the single-breath technique and multiple-occlusion technique will be reviewed in this article. These types of measurements are easy to perform, quick, and well tolerated by infants. In order to perform these measurements, the Hering-Breuer inflation reflex must be induced through an airway occlusion technique. These techniques rely on the assumption that this inflation reflex leads to relaxation of the respiratory muscles and thus equilibration between the airway opening pressure and the alveoli pressure.

During the multiple-occlusion technique the infant's airway is occluded at various lung volumes. The brief airway occlusions occur during the first two thirds of expiration. Pressure measured at the airway opening (assumed to re-

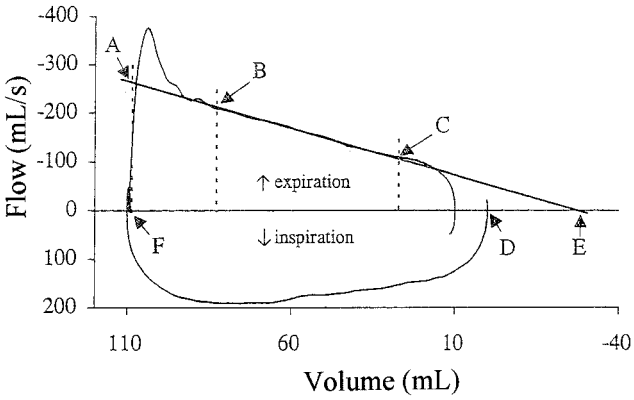

Fig. 1. Passive flow-volume curve obtained during the single-breath occlusion technique and from which compliance, resistance, and the expiratory time constant are analyzed. A: Extrapolation of the time constant slope to the "pseudoflow." The time constant is analyzed from the slope between points B and C. Point D is the end-expiratory level prior to occlusion. E is the extrapolation of the time constant slope to the point where flow is equivalent to zero on the volume axis. F is the release of the occlusion. (From Reference 9, with permission.)

flect elastic recoil pressure of the lung and chest wall) is plotted against the simultaneous volume measurement. Compliance is calculated from a regression analysis of several different measurements of volume versus airway opening pressure.[1,2,9,10]

During the single-breath technique, the Hering-Breuer inflation reflex is induced during a brief airway occlusion at end-inspiration. After this brief occlusion, the infant is allowed to passively exhale, and one assumes total relaxation of the respiratory system during this exhalation. This technique allows measurement of respiratory system compliance, resistance, and calculation of an expiratory time (T_E) constant. Compliance is calculated as the expired volume divided by the pressure change measured at the airway opening. The T_E constant is calculated from the slope of the passive expiratory flow-volume curve. Respiratory system resistance is equal to the T_E constant divided by the compliance.

An alternative method of measuring respiratory system resistance involves extrapolating the line of the T_E constant to evaluate "pseudoflow." "Pseudoflow" is an extrapolated flow that occurs at the time of occlusion. Resistance is calculated as the pressure change at the airway opening divided by the change in the extrapolated flow (Fig. 1**).**[1,2,9,10]

Several investigators have evaluated the utility of passive respiratory mechanic measurements in infants.[11–15] LeSouef et al[11] demonstrated that the single-breath technique could provide accurate assessment of lung mechanics in newborns and intubated infants. Hanrahan et al[12] evaluated the single-breath technique in 127 healthy infants and demonstrated that respiratory system resistance was higher at birth in boys than in girls. However, the respiratory system resistance decreased more rapidly in boys than in girls during their first 18 months. That report demonstrated the utility of these measurements in understanding lung growth and development. Mohon et al[15] demonstrated that infants with CF homozygous for the ΔF508 deletion had higher respiratory system resistance than control infants and CF infants with other genotypic variants. More studies need to be performed to analyze the utility of passive respiratory mechanics in evaluating lung development and disease.

Since the single-breath technique assumes that the respiratory system is a single compartment, this measurement may be accurate in healthy children; however, inaccuracies can occur in infants with lung disease. Another problem with this type of measurement is that the upper airway and nasal resistance significantly contributes to the respiratory system resistance. Infants with active glottic closure or high nasal resistance may have very elevated resistance measurements. Because of the large contribution of upper airway resistance to the measurement, lower airway resistance may not be accurately evaluated.[1] The ERS/ATS Task Force on Standards for Infant Respiratory Function Testing has published guidelines for these techniques.[10] More research is needed, especially in the form of multicenter trials.

Tidal Breathing Measurements

Tidal breathing measurements have led to an improved understanding of the control of breathing in infants and the respiratory adaptations this population exhibits under various conditions (ie, immediate newborn period, chronic lung disease [CLD] of prematurity). The variables commonly measured are respiratory rate, tidal volume (V_T), and the ratio of time-to-peak-tidal-expiratory-flow and total T_E (T_{PTEF}/T_E). The relationship of inspiratory time to the respiratory cycle has also been examined. These types of measurements are simple to perform, noninvasive, and rapid. To measure these variables, a pneumotachograph and face mask are used. Minimal dead space is critical during the measurements. The main difficulty with respiratory rate and V_T measurements is the variability associated with these results. Sleep state, weight, and gestational age may affect these measurements.[1,16] Normal values for V_T have been published,[17–20] and V_T is approximately 7–9 mL/kg during the first year of life.

T_{PTEF}/T_E has been studied as a potential tool for detecting airway obstruction. The mean value of this ratio was 0.27 ± 0.08 in 103 healthy infants (average age was 3.7 mo).[21] This ratio is lower in infants with obstructed airways.[22–24] In the study by Clarke et al,[22] T_{PTEF}/T_E was significantly lower in subjects with CLD of prematurity than in healthy infants (Fig. 2). Martinez et al[23] found that

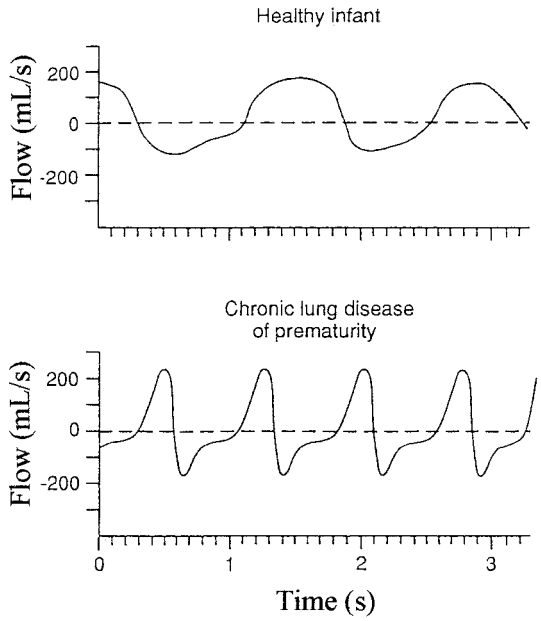

Fig. 2. Tidal breathing in a healthy infant versus an infant with chronic lung disease of prematurity. Flow during exhalation is below the dotted line. The infant with chronic lung disease has a higher tidal breathing frequency, shorter time-to-peak-expiratory-flow, longer expiratory time, and lower ratio of time-to-peak-expiratory-flow to expiratory time. (From Reference 22, with permission.)

male patients who later developed wheezing-associated respiratory illnesses had lower T_{PTEF}/T_E than male patients who did not develop wheezing. Dezateux et al[24] evaluated 29 healthy infants and 29 asymptomatic infants who had histories of hospital admission for respiratory syncytial virus (RSV) bronchiolitis. They found that T_{PTEF}/T_E was significantly lower in infants who had recovered from RSV bronchiolitis than in controls. As noted above, several studies have demonstrated that a low T_{PTEF}/T_E may indicate airway obstruction. However, the determinants of the respiratory system that lead to these measurements are not clearly understood. The ERS/ATS Task Force on Standards for Infant Respiratory Function Testing has published guidelines for tidal breathing measurements.[25] More research needs to be conducted to promote standardization and appropriate reference values.

Lung Volume Measurements

Functional residual capacity (FRC) can be measured in infants via gas dilution methods or plethysmography. FRC is defined as the lung volume at end-expiration of the tidal breath. The gas dilution methods include the helium dilution technique and the nitrogen washout technique. The gas dilution techniques measure the lung volume (at end-expiration of the tidal breath) that communicates with the larger (central) airways. The advantage of plethysmography is that FRC is measured in the communicating airways and also in areas that do not communicate with central airways. Plethysmography is more difficult to perform and requires more expensive equipment than the gas dilution techniques.[1–3,26]

The open-circuit nitrogen washout method analyzes lung volume by initiating the measurement at FRC and calculating the amount of nitrogen expired divided by the nitrogen concentration in the alveoli or lungs prior to the maneuver. The volume of nitrogen expired can be measured via a breath–by-breath technique, by collecting and then analyzing the expired gas, or via a bias-flow technique. The bias-flow technique is the method most commonly used with infants. To perform the bias-flow technique the subject is sedated and tidal breathing is observed prior to the maneuver, to ensure a stable FRC. At end-expiration of the tidal breath, the subject is switched to a circuit on which he or she is breathing 100% oxygen (0% nitrogen) and the expired gas is continuously analyzed as it exits the mixing chamber. During the technique, the bias flow of the inspired gas is constant. The maneuver is completed once the nitrogen concentration in the mixing chamber reaches a peak then drops to a baseline level. This washout period may last longer in infants with severe airway obstruction. FRC is equal to the volume of nitrogen expired divided by the initial volume of nitrogen in the lungs. One difficulty with this technique is the length of the washout period. In addition, errors when switching to FRC may lead to inaccurate data. It is critical that the operator be well trained to avoid these inaccuracies.[1,26,27]

The helium dilution technique is based on the technique used in the adult population. This technique is based on the theory of gas equilibration between 2 separate volumes. During this measurement, there is a known volume of helium gas (V1). Through normal minute ventilation, the gas in V1 is mixed with an unknown volume (V2). Once equilibration has occurred, V2 is calculated with the following equation:

$$V1 \times C1 = (V1 + V2) \times C2$$

in which C1 is the initial helium concentration and C2 is the helium concentration at the end of gas mixing. To perform this maneuver in infants, tidal breathing is observed until FRC is stable. Once FRC is stable, the infant is connected to a circuit with the known volume of helium gas (V1) at the end-expiratory part of the tidal breath. A rapid helium analyzer is required. The infant breathes in and out of this circuit until equilibration has occurred. With healthy infants the technique may take 1–2 min. Equilibration may take longer, up to 5 min, in infants suffering airway obstruction. Even though the technique is

simple, operator expertise is essential for accurate measurements.[1,26]

Plethysmography is a third technique to measure infant lung volumes. Using a whole-body infant plethysmograph, FRC measurements are obtained according to the principle of DuBois et al.[28] Plethysmography has been used with infants for the past 30 years. The advantage of plethysmography versus the gas dilution techniques is that all the thoracic gas is measured, including gas that is not communicating with the central airways. Plethysmography has obvious advantages for measuring FRC in infants with obstructed airways that might not be communicating with the central airways. To perform the maneuver, the sedated infant is placed supine in the plethysmograph and the face mask, attached to a pneumotachograph, is placed over the infant's nose and mouth. The plethysmograph box is then closed and the respiratory frequency is observed, to allow thermal equilibrium. To evaluate for leaks, tidal breathing is recorded to obtain a stable FRC and then the infant's airway is occluded. During the brief occlusion, the absence of decay in the mouth pressure confirms that there is no leak. After the brief occlusion, the absence of a leak is also verified by observing that the FRC baseline is unchanged. To measure FRC, the infant is occluded at end-inspiration or end-expiration (if at end-inspiration, the volume above the end-expiratory level is subtracted from the lung volume measured at end-inspiration). At the same time, an opening in the plethysmograph, referenced to atmosphere, is shut. The infant's airway is occluded for at least 2–4 respiratory cycles, to obtain a relationship between pressure changes at the infant's mouth and volume changes in the box. From that relationship, FRC is calculated.[1,3,4]

Recently, Castile et al[29] analyzed fractional lung volumes using measurements obtained from forced expiratory flow-volume maneuvers at a raised lung volume and FRC obtained from plethysmography. The technique of obtaining forced expiratory flow-volume maneuvers from a raised lung volume is described in detail in another section of this manuscript. From this maneuver, the expiratory reserve volume (ERV) and the forced vital capacity (FVC) are analyzed. ERV is defined as the lung volume between the stable end-expiratory level (FRC) and residual volume (RV) (the lung volume at which the forced maneuver ended). RV is calculated by subtracting the ERV (obtained from the forced expiratory maneuvers) from FRC (measured via plethysmography). Total lung capacity (TLC) is calculated by adding the values of RV and FVC.

Plethysmography with infants has typically been performed only in research laboratories because of the technical difficulty and expense. One controversy in obtaining plethysmographic values has been whether to occlude at end-inspiration or end-expiration. It has been reported that infants tolerate end-inspiration occlusions better than end-expiration occlusions. There is also less glottic closure at end-inspiration[1] and a better signal-to-noise ratio. Investigators have also hypothesized that there may be errors in FRC plethysmographic measurements with infants because of airway closure at low lung volumes,[30–32] which may lead to inaccurate measurements; the measurement at the mouth does not reflect pressure changes occurring in the small airways, due to air trapping. To avoid this problem, researchers have suggested that occluding the airway at end-inspiration reduces airway closure and inaccurate data.[30,33] Another controversial subject is possible inaccurate plethysmographic FRC measurement in a wheezy infant after a bronchiolitis episode.[34] A third subject of controversy is the effect that sleep state may have on FRC measurements. There is variability in the end-expiratory level of tidal breathing or functional residual capacity during different stages of sleep, which could affect FRC measurements. Further research is needed to resolve these controversial issues.[1]

Several investigators have measured FRC via the gas dilution techniques or via plethysmography with healthy infants and with infants suffering lung disease. Published studies have compared gas dilution techniques to plethysmography in healthy infants and adults.[33,35,36] In healthy adults, FRC values measured via gas dilution are similar to those measured via plethysmography.[35] However, in healthy infants, plethysmographically-measured FRC has been reported to be significantly higher than the values obtained via the gas dilution techniques.[33,36] Interestingly, in the study by McCoy et al,[33] this difference was more pronounced if the airway was occluded at end-expiration than at end-inspiration during plethysmography. This difference between gas dilution and plethysmography measurement may be due to a small amount of airway closure in sedated, supine, healthy infants.

Tepper and Asdell[37] compared the helium dilution technique to the nitrogen washout technique with healthy infants and infants suffering lung disease. There was no significant difference between the closed-circuit helium dilution technique and the open-circuit nitrogen washout technique. Henry et al[38] found increased plethysmographic FRC values in 43% of infants who had suffered from acute bronchiolitis 3 months prior to the lung function test. In that same group of infants, 17% had increased plethysmographic FRC values 1 year after the illness.

Using whole-body plethysmography, investigators have also measured FRC in CF infants.[39–43] Beardsmore et al[39]demonstrated that plethysmographic FRC values significantly correlated with respiratory symptoms. Godfrey et al[41] investigated plethysmographic FRC values in 8 CF infants and showed that the 2 infants with the most severe respiratory symptoms had the most elevated lung volumes.

Investigators have also analyzed FRC via gas dilution techniques in CF infants.[44,45] Tepper et al[45] demonstrated

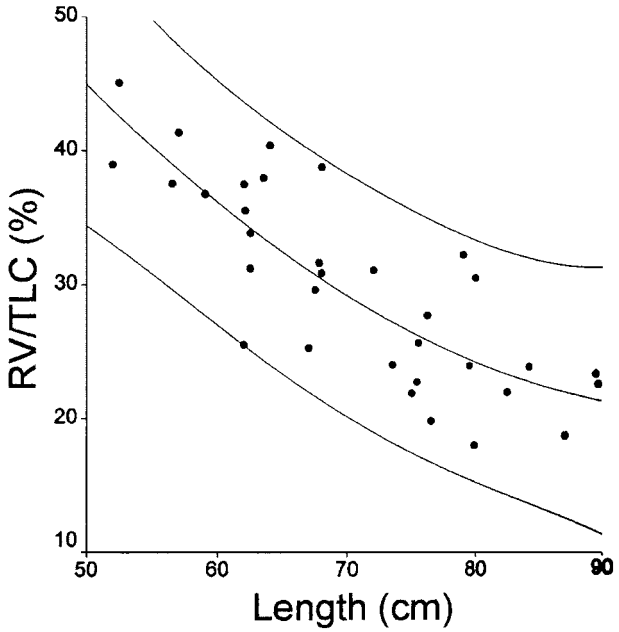

Fig. 3. Infant length versus the ratio of residual volume (RV) to total lung capacity (TLC). The RV/TLC is inversely related to length. Castile et al hypothesized that the decrease of RV/TLC over time is caused by the vital capacity increasing faster than the RV as the infant grows. (From Reference 29, with permission.)

that CF infants treated with hydrocortisone for lower respiratory illnesses requiring hospitalization had significantly lower FRC values (measured with the nitrogen washout technique 1–2 months after hospitalization) than CF infants not treated with a steroid. Hiatt et al[44] demonstrated that FRC measured via helium dilution was increased in CF infants who had suffered from lower respiratory illnesses due to adenovirus or RSV.

There are several references for normative data for the gas dilution techniques and plethysmography.[46] The mean FRC value obtained via the gas dilution techniques for healthy children up to 18 months of age is 20–24 mL/kg. The mean plethysmographic FRC value for healthy children up to 1 year of age is 29–34 mL/kg.[1] Castile et al[29] published normative data on fractional lung volumes obtained via plethysmography and forced expiratory flow-volume maneuvers from a raised lung volume. These recent data were collected from 22 young children tested at 35 sessions (Fig. 3). More studies need to be conducted with healthy subjects to evaluate fractional lung volumes, as collected by Castile et al. Two recent publications by the ERS/ATS Task Force for Standards for Infant Respiratory Function Testing outlined recommendations for plethysmography and nitrogen washout techniques.[4,27]

Forced Expiratory Maneuvers

In older children and adults, forced expiratory flow (FEF) is measured as the subject exhales with a maximum effort from complete inhalation (TLC) to complete exhalation (RV). This type of testing is difficult with infants because they are unable to cooperate. Two techniques have been developed to measure forced expiratory maneuvers. In the first technique, the forced deflation method, the infant's lungs are inflated to 40 cm H_2O, then deflated with the use of negative pressure. This technique requires intubation and heavy sedation. Because of the complexity of this technique, it is limited to intensive care and surgical settings. This review will discuss the second technique, which was created by Adler and Wohl in 1978 and modified in the early 1980s.[47–49] The method allows FEF measurements in lightly sedated infants. The technique measures FEF from tidal breathing (not from full inhalation) and is therefore referred to as the partial expiratory flow technique. This approach became the standard technique for measuring infant lung function at several institutions and has been used both as a research tool and to aid in clinical decisions.[13,14,23,39,40,44–87] The main disadvantages of this technique are that (1) it is limited to the V_T range, (2) researchers are unsure if flow limitation is achieved, and (3) infants often do not exhale fully to RV. The partial expiratory flow technique has been recently modified to measure FEFs over a larger lung volume range.[29,88–105] This raised-volume technique more closely approximates adult spirometry. Similar to pulmonary function testing in adults, the raised-volume technique allows the infant to inhale to near TLC, and a forced expiratory maneuver is initiated from this elevated lung volume. The airway pressure used to establish an elevated lung volume is a normal physiologic pressure for these infants and toddlers. The forced expiratory maneuver ends when the infant reaches RV. At this point, forced expiratory maneuvers from a raised lung volume have been performed only in specialized laboratories (Fig. 4).

To perform a partial expiratory flow-volume maneuver, the sedated infant is placed in supine position and an inflatable jacket is wrapped around the infant's thorax. A face mask, attached to a circuit containing a pneumotachograph, is placed over the infant's nose and mouth. Tidal breathing is observed to ensure a stable FRC. Once the end-expiratory level is stable, the forced expiratory maneuver is initiated from end-inspiration of the tidal breath. To initiate the forced expiratory maneuver, a pressure reservoir inflates the jacket. Flow is measured via the pneumotachograph and, typically, the flow referenced to FRC (maximum flow at functional residual capacity [$\dot{V}_{maxFRC}$]) is analyzed. The maneuver to obtain a partial flow-volume curve is repeated at increasing jacket pressures until flow limitation is achieved. We assume flow limitation has occurred when flow no longer increases despite increasing jacket pressures. As stated above, the ability to reach flow limitation with this technique has been a controversial issue.[1,106]

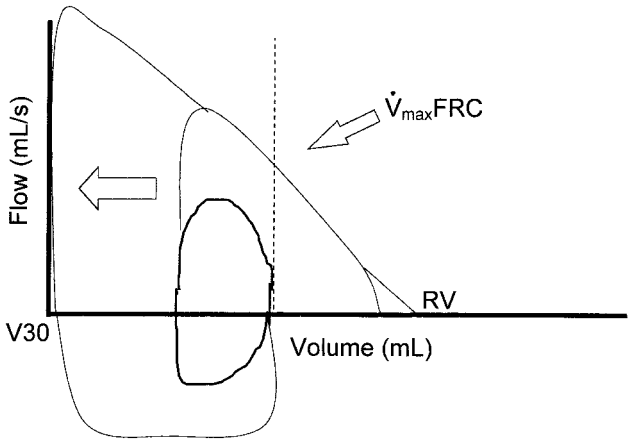

Fig. 4. Full expiratory flow-volume curves obtained with the raised-volume technique and a partial expiratory flow-volume curve. The 2 curves are overlaid. The smaller curve is the partial expiratory flow-volume curve. V30 is the point at which the infant's lungs are inflated to 30 cm H_2O, prior to the forced expiratory maneuver. $\dot{V}_{maxFRC}$ is maximum flow referenced to the end-expiratory part of the tidal breath (functional residual capacity [FRC]) on the partial expiratory flow-volume curve. The figure illustrates that the raised-volume technique measures flows over a much larger lung volume compared to the partial expiratory flow-volume curve. In addition, the infant completely exhales to residual volume during the raised-volume technique. During the partial expiratory maneuver, the infant inspires prior to reaching residual volume (RV).

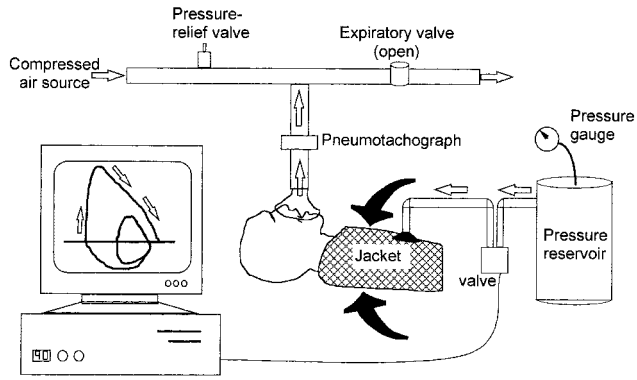

Fig. 5. Method for measuring a full expiratory flow-volume curve with a raised-volume technique during forced exhalation. Prior to forced exhalation the lung is inflated to a raised lung volume. To inflate the lungs, air is delivered from a compressed air source through an inspiratory circuit with a pressure-relief valve. Typically, the pressure-relief valve is set for 20–30 cm H_2O. The expiratory valve is closed during inflation. Once the inflation occurs, the expiratory valve is immediately opened and the infant passively exhales. The inspiration-exhalation cycles are repeated until the infant demonstrates a short respiratory pause. The infant is again inflated to the raised lung volume, and the forced expiratory maneuver is initiated from this raised lung volume. To initiate the forced expiratory maneuver, the jacket is inflated by opening the valve between the reservoir and the jacket. The forced expiratory maneuver is completed when the infant reaches residual volume. The flow-volume curve is displayed on the computer monitor.

To perform forced expiratory maneuvers from a raised lung volume,[89,106] an inflatable jacket is wrapped around the thorax of the sedated, supine infant. The face mask, attached to a circuit containing a pneumotachograph, is placed around the infant's nose and mouth. The infant's lung volume is increased to an airway pressure of 20–30 cm H_2O (V20 or V30) via the circuit attached to the face mask. The amount of pressure used to generate the increased lung volume depends on the research laboratory. During inflation maneuvers, the technician may apply gentle pressure to the cricoid cartilage to prevent air from passing down the esophagus into the stomach. After the infant's respiratory system is inflated to V20 or V30, the infant is allowed to passively exhale. These inspiratory-expiratory cycles are repeated until the infant exhibits a short respiratory pause. Once the short respiratory pause is noted, the infant's respiratory system is inflated to V20 or V30 again, and a forced expiratory maneuver is initiated from the elevated airway pressure by inflating the jacket that is wrapped around the infant's thorax. The forced maneuver proceeds until the infant reaches RV (Fig. 5). The maneuver to obtain FEF values from an elevated lung volume can be repeated at increasing jacket pressures, until flow limitation is achieved. Flow limitation occurs when flow no longer increases, despite increasing jacket pressures. Alternatively, if partial expiratory flow-volume curves have been collected, the pressure used to flow limit during these maneuvers can be applied to the jacket. At the end of the forced expiratory maneuver, tidal breathing is carefully monitored until it returns to a stable FRC. The difference between the volume at the end of the forced maneuver and the reestablished FRC is taken to be the ERV. RV is defined as the lung volume at the completion of the forced expiratory maneuver. FVC is the lung volume between V20 or V30 and RV. Flow at 50% and 75% of the forced expired volume (FEF_{50}, FEF_{75}) and flow between 25% and 75% (FEF_{25-75}) of the forced expired volume can be measured (Fig. 6). Forced expired volume in the first 0.4, 0.5, and 0.75 seconds ($FEV_{0.4}$, $FEV_{0.5}$, $FEV_{0.75}$) has also been analyzed. As described by Castile et al,[29] fractional lung volumes can be calculated from the FVC and ERV measured via the forced expiratory maneuver, and FRC measured via plethysmography.

The partial expiratory flow-volume maneuvers have improved our understanding of respiratory physiology, lung growth, and lung disease in infancy.[68] In the early 1980s, Taussig et al[48] evaluated newborn infants with the partial expiratory flow-volume maneuvers. They reported that size-corrected flows ($\dot{V}_{maxFRC}$/FRC) were higher in newborn infants than in older children. The authors concluded that the infant airways, though small, may be larger in neonates than in adults, relative to the size of their lungs. Tepper et al[18] later confirmed these findings by demonstrating that $\dot{V}_{maxFRC}$/FRC was higher in infants $<$ 12

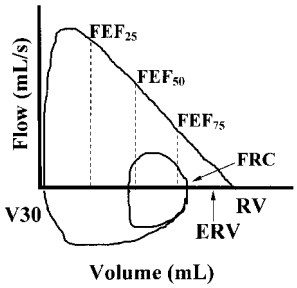

Fig. 6. Flow and volume variables that are analyzed on the flow-volume curve obtained from a raised lung volume. V30 is the lung volume at 30 cm H_2O. Forced vital capacity (FVC) is the lung volume between V30 and residual volume (RV). Expiratory reserve volume (ERV) is the lung volume between functional residual capacity (FRC) and RV. FEF_{25}, FEF_{50}, and FEF_{75} represent the forced expiratory flow at 25%, 50%, and 75%, respectively, of the FVC.

months old than in older infants. These same investigators also reported higher $\dot{V}_{maxFRC}$/FRC values in female infants than in male infants. However, Hanrahan et al[20] later collected normative data on 72 infants and did not find a difference in size-corrected flows between younger infants and older infants, nor between genders. A subsequent paper by Tepper and Reister[63] revealed normative data on partial expiratory flow-volume curves that is similar to the data published by Hanrahan et al. As in the Hanrahan report, there were no gender differences, but the size-corrected flows were not reported.

Several studies that used partial expiratory flow-volume curves have been conducted with infants suffering lung disease. $\dot{V}_{maxFRC}$ is lower in infants with recurrent wheezing,[56,73,78,82] bronchiolitis,[44,75,76,81,] tracheomalacia,[83,100] and CF.[44,84,85] Martinez et al[78] demonstrated that $\dot{V}_{maxFRC}$ measurements at $<$ 1 year of age were lower in infants who later developed transient early wheezing. The wheezing in these infants resolved by 6 years of age; however, $\dot{V}_{maxFRC}$ was still lower. Clayton et al[87] revealed a significant improvement in $\dot{V}_{maxFRC}$ in 17 CF infants tested at the beginning of hospitalization and prior to discharge. Studies evaluating the partial expiratory flow-volume curve have provided invaluable information about infant lung physiology and infant lung disease.

There have been several recent studies evaluating forced expiratory flow-volume curves from a raised lung volume in infants.[29,88–105] The advantages of this new technique are (1) flows are analyzed over a much larger lung volume than with partial expiratory flow-volume curves and (2) flow measurements are not referenced to a variable lung volume such as FRC. Since the infant's lungs are inflated to an absolute lung volume measured at 30 cm H_2O pressure, flow measurements are less variable than $\dot{V}_{maxFRC}$. Using this new technique, Feher et al[94] evaluated isovolume pressure-flow curves in healthy infants and demonstrated that flow limitation is obtained. Recently, Jones et al[95] obtained normative data evaluating forced expiratory maneuvers at an elevated lung volume measured at 30 cm H_2O, from 155 healthy infants at 2 separate centers. These results provide reference values for this new technique. In addition, Castile et al[29] recently published normative data on 22 children tested on 35 occasions, using the raised-volume technique. Recently, Ranganathan et al published data demonstrating that $FEV_{0.4}$ and maximum expiratory flow at 25% of FVC were significantly lower in CF infants than in controls.[104]

Turner et al,[97] the first investigators to publish data on this innovative technique, evaluated 26 normal infants and 27 wheezy infants. These investigators performed forced expiratory maneuvers from a raised lung volume versus partial flow-volume curves. The intrasubject variability was significantly lower with the forced expiratory maneuvers from a raised lung volume than with flows referenced to the V_T range. In addition, $\dot{V}_{maxFRC}$ was less sensitive at detecting decreased lung function than were forced expiratory measurements at an elevated lung volume (56% vs 71–89% sensitivity). Turner et al concluded that this new technique of measuring infant lung function was more sensitive at differentiating normal and wheezy infants and that the flow-volume curves were more reproducible than partial expiratory flow-volume curves. This same group of authors[96] reported that $\dot{V}_{maxFRC}$ did not detect lung disease in 12 CF infants compared to normal controls. However, $FEV_{0.5}$ and $FEV_{0.75}$ were significantly lower in the CF infants than in the controls. Turner et al concluded that forced expiratory maneuvers from a raised lung volume are more sensitive than partial expiratory flow-volume curves at detecting lung disease in CF infants.

In a study by Modl et al,[88] partial expiratory flow values were compared to measurements obtained at a raised lung volume. These authors also demonstrated that the raised volume measurements had significantly less intraindividual variability than partial expiratory flow values. More studies need to be conducted with infants suffering lung disease, to specifically compare the sensitivity of $\dot{V}_{maxFRC}$ versus the raised-volume technique.

There has been much progress in the evaluation of FEF in infants over the past several years. The ERS/ATS Task Force for Standards for Infant Respiratory Function Testing has been active at standardizing the raised-volume technique. Performing multicenter trials using a standardized method is critical for future studies.

As noted above, recent research in the field of infant lung function testing has led to a marked improvement in our understanding of infant physiology, control of breathing, and lung disease. Setting up an infant lung function laboratory requires intense training of the physician and technicians. Unlike spirometry in older children, this type of testing is much more difficult and time consuming. The infant must be continuously monitored during the study,

according to the institution's conscious sedation protocol. To perform adequate studies, there must be a full commitment from the physician and technicians involved in the testing. Following published standards is ideal for adequate data collection. Future multicenter studies will, hopefully, improve our understanding and management of airway disease in infants.

Spirometry in Preschool Children

Because spirometry requires cooperation, clinicians have often not attempted lung function testing in preschool children. Once children reach the age of 3 years, infant lung function testing is not possible because of the size of the child. In addition, children are not easily sedated at this age. Recent studies have demonstrated that preschool children are capable of performing flow-volume maneuvers. In 1994 Kanengiser and Dozer[107] collected data from preschool children conducting forced expiratory maneuvers before and after bronchodilator. The investigators evaluated the curves based on ATS criteria. The values for forced expiratory volume in the first second (FEV_1) met the ATS criteria in 56% of pre-bronchodilator maneuvers and 39% of post-bronchodilator maneuvers. In addition, 60% of these patients performed maneuvers with reproducible FVC values. The authors concluded that some preschool children could perform adequate forced expiratory maneuvers. Eigen et al[108] recently reported flow-volume data in 259 healthy preschool children. In these subjects, 82.6% produced technically acceptable flow-volume curves. These authors outlined techniques that helped the experienced technicians obtain acceptable data from these young children. The testing sessions were limited to 15 min. Peak flow, FVC, FEV_1 and $FEF_{25–75}$ were reported to have coefficients of variation for repeat measures of 7.8%, 2.5%, 2.7%, and 8.3%, respectively. In addition, the values of FVC and FEV_1 correlated well with values reported by Polgar and Promahhat[109] and Knudson et al[110] (Fig. 7). That study provides normative values in preschool children and illustrates that performing flow-volume maneuvers is possible with this age group. Marostica et al[111] recently published data demonstrating that CF children homozygous for the ΔF508 mutation had lower FVC and FEV_1 values than CF children with heterozygous mutations. This study revealed the potential benefit of spirometry in assessing the presence of lung disease in CF children between the ages of 3 and 6 years.

In a study by Crenesse et al,[112] spirometry was evaluated retrospectively in 355 preschool children referred to the laboratory for respiratory difficulties. Fifty-five percent of those children could perform forced expiratory maneuvers that met the ATS criteria of 2 acceptable curves with FVC or FEV_1 within 100 mL of each other. These authors also noted that 21% of these younger children

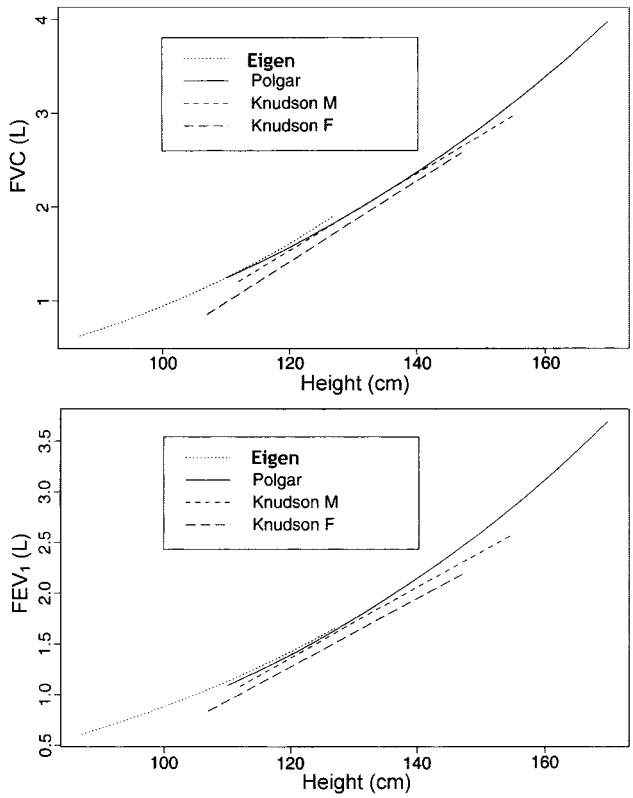

Fig. 7. Subject height versus forced vital capacity (FVC) and versus forced expiratory volume in the first second (FEV_1), from regression equations from Eigen et al, Polgar et al, and Knudsen et al (for males [M] and females [F]). Children with similar heights had FVC and FEV_1 values in good agreement. (From Reference 108, with permission.)

exhaled for ≤ 1 second. Based on that finding, the investigators concluded that measuring $FEV_{0.5}$ or $FEV_{0.75}$ may be more appropriate in this younger age group.

Achieving flow limitation is essential for technically adequate flow-volume curves. Jones et al[113] (Fig. 8) used a negative pressure technique to demonstrate flow limitation in preschool aged children. In that report, 10 healthy subjects naive to lung function testing were recruited for testing. The subjects performed spirometry with and without the application of negative pressure. For the negative pressure technique, –5 to –10 cm H_2O was applied to the opening of the airway during the expiratory part of the forced maneuver. The flow-volume curves with and without negative pressure technique were overlaid. Flow limitation was assumed if flow did not increase with the application of the negative pressure technique, and all 10 subjects demonstrated no increase in flow with the application of negative pressure. The negative pressure technique is a simple method that can be used to verify flow limitation.

The studies of preschool children demonstrate that spirometry is possible in this age group. Forced expiratory

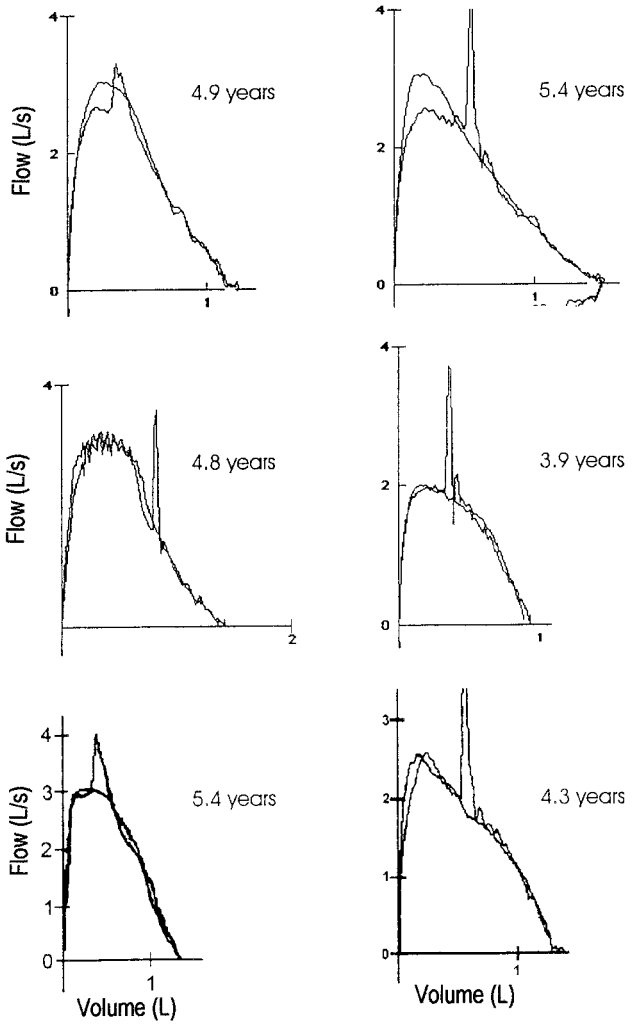

Fig. 8. Flow-volume curves obtained from 6 children (ages indicated next to curves) with and without the application of negative pressure. The best flow-volume curve without negative pressure is overlaid with the best flow-volume curve with negative pressure. Neither flow nor volume increased with the application of negative pressure, demonstrating that the subjects were flow-limited. (From Reference 113, with permission.)

maneuvers have the potential to improve our understanding and management of lung disease in these young children. In order to achieve reliable data in this age group, it is essential that well trained pediatric pulmonary technicians perform the maneuvers. More studies need to be conducted to evaluate this technique in healthy children and children with pulmonary disease.

Forced Oscillation Technique

The forced oscillation technique is a noninvasive method of assessing respiratory function. This technique was originally described in 1956 by DuBois et al.[114]

In the forced oscillation technique, pressure oscillations are transmitted to the patient's airway opening during normal tidal breathing. From the resultant flow and pressure changes, the impedance of the respiratory system is determined. The effective resistance and effective reactance of the respiratory system determine the impedance measurement. Reactance represents the inertial forces and compliance of the respiratory system. The resistance of the respiratory system is derived from the measurement of impedance. The pressure oscillations can be transmitted via single-frequency sine waves or multiple frequencies. A loudspeaker is typically used to transmit these superimposed oscillations.[2,115–117]

Normative data collected with the forced oscillation technique from healthy infants and children have been published;[118–121] however, the variability of the measurements was high. In addition, several investigators have evaluated the method with children suffering lung disease. In a study by Lebecque and Stanescu,[122] 45 asthmatic children (mean age 10 y) and 45 patients with CF (mean age 14 y) were evaluated using the forced oscillation technique and spirometry. Among the 45 asthmatic children, resistance measured via forced oscillation correlated with the FEV_1 results in 38 children. Twenty-one asthmatic children had low FEV_1 values and those values correlated with high resistance values. However, in the 45 CF children, resistance measured via forced oscillation correlated with FEV_1 in only 16 children. Resistance measurements did not detect severe obstructed airways in the CF patients. The authors concluded that respiratory system resistance measured via forced oscillation may detect disease in asthma, but is not reliable in CF (Fig. 9).

Malmberg et al[123] evaluated 49 children with histories of prematurity. Fifteen of the children did not have CLD and 34 did have CLD. These investigators reported that respiratory system resistance, measured via impulse oscillometry, was significantly higher in the children with CLD than in the children without CLD.

A study by Ducharme and Davis[124] compared the forced oscillation technique and spirometry with 150 children evaluated in an emergency room for asthma exacerbation. Reproducible data were obtained more often with the forced oscillation technique than with spirometry, especially in subjects < 6 years of age. In addition, FEV_1 correlated significantly with the respiratory resistance value measured via forced oscillation. Investigators[122,125] have also evaluated the effect of bronchodilators on the respiratory resistance value. The advantage of using the forced oscillation technique is that the bronchomotor tone is not affected by inspiring to TLC.

There are several advantages to the forced oscillation technique: it is simple, noninvasive, and performed during tidal breathing. Because of these advantages, the technique is suitable for infants and young children. However, there

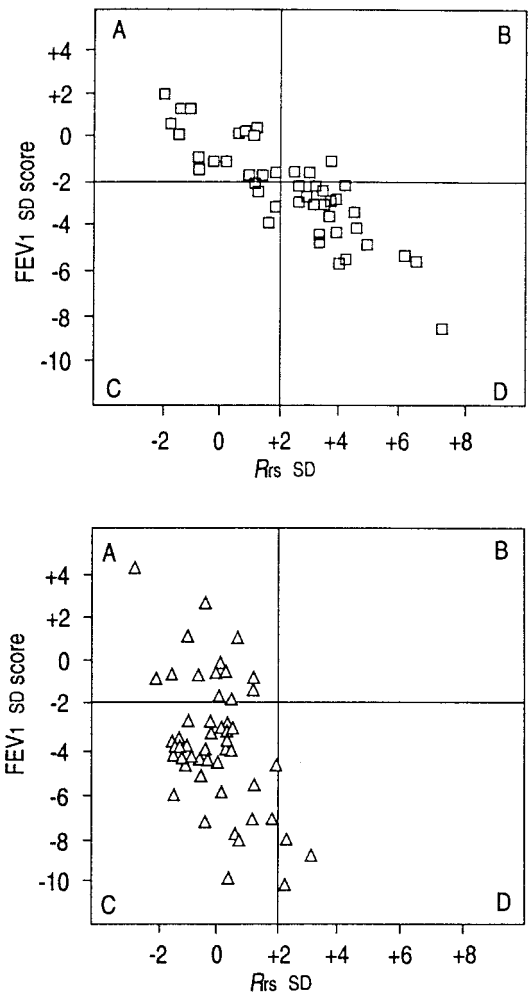

Fig. 9. Standard deviation scores from forced expiratory volume in the first second (FEV_1) versus standard deviation scores from respiratory system resistance (R_{rs}) measured via the forced oscillation technique with asthmatics (top) and cystic fibrosis subjects (bottom). Values are considered concordant in quadrants A and D. In general, R_{rs} correlated with FEV_1 in the asthmatic patients. In the cystic fibrosis patients R_{rs} did not correlate well with FEV_1. (From Reference 122, with permission.)

are several disadvantages. The published normative data in infants and children have wide variability. The resistance values may reflect upper airway measurements more than peripheral airways. Detecting early peripheral airway disease may be difficult with this technique. There are also different methods for performing the forced oscillation technique, so standardization has been difficult, and since different studies have used different methods, comparing data has been difficult. More research definitely needs to be conducted on forced oscillation.[115–117]

Interrupter Respiratory Resistance Technique

As with the forced oscillation technique, interrupter resistance (Rint) is a noninvasive technique that is simple to perform. To perform Rint, the patient's airway opening is briefly occluded during either the inspiratory or expiratory part of a tidal breath. During the occlusion, one assumes that the pressure at the airway opening equilibrates with the pressure in the alveoli. From this occlusion, resistance is calculated from the ratio of pressure change versus flow measured at the airway opening. Because this maneuver is simple and requires minimal cooperation, it is suitable for young children.[126–130]

Lombardi et al[126] published Rint reference values based on Rint testing of 284 healthy preschool children. The Rint measurements were performed with and without cheek support and during expiration and inspiration. The investigators reported no difference in Rint values whether or not the cheeks were supported. In addition, inspiratory and expiratory Rint values were not significantly different. Ninety-five percent of the 284 preschool children were capable of performing the technique.

In contrast to the study by Lombardi et al, Oswald-Mammosser et al[127] reported that Rint values were higher during expiration than during inspiration and that Rint values were lower when the cheeks were not supported than when the cheeks were supported. More studies need to be conducted with normal preschool children to assess these differences.

Merkus et al[128] recently published a study evaluating Rint with preschool children who had no respiratory symptoms and a group of children with mild respiratory symptoms. Asymptomatic children with mild respiratory disease had higher Rint values than healthy children, during both expiration and inspiration. The authors concluded that Rint was sensitive enough to detect mild airway disease. However, in the same study more symptomatic children with asthma or eczema had elevated Rint values during expiration but not during inspiration. The differences between the expiratory and inspiratory Rint values are not understood.

Phagoo et al[129] and Bridge et al[130] reported that Rint measurements could also detect a bronchodilator response in subjects with airway obstruction. The Rint maneuver has the potential to be a simple, noninvasive method for assessing airway disease; however, standardization and more Rint studies are needed with children suffering airway disease.

Exhaled Nitric Oxide

In 1991 Gustafsson et al[131] were the first investigators to detect exhaled NO. Since then, multiple studies have been conducted evaluating the role of this inflammatory marker in lower airway disease. NO is produced when L-arginine converts to L-citrulline. The enzyme NO synthase catalyzes this conversion using the cofactor, nicotinamide adenine dinucleotide phosphate (NADPH). NO syn-

thase is either calcium-dependent and constitutive or calcium-independent and inducible. The inducible form of NO synthase leads to the exhaled NO detected in the lower airways. Several inflammatory cytokines induce NO synthase, thus leading to the presence of exhaled NO in certain respiratory diseases. In the past, detection of lower airway inflammatory markers was mainly conducted via bronchoscopy and bronchoalveolar lavage. Measurement of exhaled NO is an attractive tool for evaluating lower airway disease in younger children, since it is noninvasive.[132–134] However, the technical aspects of measuring exhaled NO can be challenging with both adults and children.

In 1999 a committee of experts developed recommendations for measuring exhaled NO.[135] Exhaled NO can be measured either on-line or off-line. On-line testing refers to real-time, direct sampling of the exhaled gas. In off-line testing, the exhaled gas is collected in a receptacle and analyzed later. NO is measured in parts per billion, via chemiluminescence, a technique in which NO reacts with ozone to produce infrared radiation. Exhaled NO is produced in the upper and lower respiratory tract. In healthy subjects, exhaled NO is much lower in the lower respiratory tract than in the upper respiratory tract.[136,137] When measuring the NO that comes from the lower respiratory tract, potential sources of contamination include the gastrointestinal tract, the nose, and the atmosphere. NO is high in gastric samples; however, contamination from this source during exhaled NO measurements does not appear to occur because of the esophageal sphincters. The nose has a high level of exhaled NO, so this source of contamination must be eliminated to ensure accurate lower airway measurements. Exhaling against a set resistance closes the velum and can thus eliminate nasal contamination. To avoid ambient contamination, the technician must prevent the exhaled NO sample from mixing with the environment. For quality assurance, ambient NO should be measured during testing. Exhaled NO is also affected by the expiratory flow. Since exhaled NO is inversely related to the flow,[138,139] a constant flow should be used for all measurements. The subject should avoid a breath-hold during the maneuver, because a breath-hold can alter the results and lead to NO peaks.[137]

Several other factors can affect NO measurements, including age, spirometry, airway caliber, food, smoking, infection, and medications. In adults no change in NO measurements appears to come with age. However, one study of children found that exhaled NO increased with age.[140] Spirometry may reduce exhaled NO measurements; therefore, NO measurements should be conducted prior to performing flow-volume maneuvers. Since exhaled NO may change with bronchodilatation, it is critical to record the time of the last bronchodilator. The patient should not eat or drink for 1 hour prior to exhaled NO measurements, since water and/or nitrate-containing food may affect the results. Smoking can reduce exhaled NO, so the patient should not smoke for 1 hour prior to the maneuver. A smoking history should be documented for each patient. A respiratory infection can elevate exhaled NO values, so recent or current respiratory infections should be documented. In some cases, the exhaled NO measurement should be rescheduled if the patient has a respiratory infection. Finally, since medications such as steroids affect the results, all current medications should be listed for each patient.[135,138]

When performing on-line or off-line NO measurements one should refer to the guidelines and standards published in 1999.[135] For these maneuvers the patient inspires to TLC and then exhales immediately to avoid a breath-hold. In these recommendations the authors emphasize the importance of a constant flow. For adults and children a constant flow of 0.05 L/s is reasonable for on-line measurements. For adults and older children the recommended flow for off-line measurements is 0.35 L/s. In addition, to avoid nasal contamination the subject may exhale against a resistance set with a mouthpiece pressure of 5–20 cm H_2O. To ensure patient comfort the pressure should never be $>$ 20 cm H_2O. With adults and children $>$ 12 years old the NO plateau during on-line measurements should be at least 3 seconds. In children $<$ 12 years old this plateau should be at least 2 seconds. The authors also described the appropriate storage vessel for off-line measurements. With children unable to cooperate there is an on-line and an off-line tidal breathing maneuver in which the subject exhales against a set resistance (at least 2 cm H_2O with the off-line technique; at least 3–4 cm H_2O with the on-line technique). When performing multicenter studies that include NO measurements it is critical to follow the standardization recommendations to ensure quality data. Several different published studies have used different methods, which makes it difficult to compare results.

Multiple investigators have evaluated the utility of NO measurements in the clinical setting. Exhaled NO has been reported to be elevated in asthma, wheezy infants, upper respiratory tract infection, tuberculosis, and sarcoidosis.[139,141–144] Exhaled NO has been reported to be low in patients with CF, primary ciliary dyskinesia, and in smokers (Table 1).[139,145–147] In addition, there are reports revealing lower exhaled NO values in treated asthmatics than in untreated asthmatics.

In a study by Avital et al,[141] children between the ages of 2 and 7 years were evaluated for exhaled NO using the tidal breathing method. The children were divided into 4 groups: (1) mild, intermittent asthma, (2) moderate, persistent asthma treated with inhaled steroids, (3) nonasthmatic subjects with chronic cough and recurrent pneumonia, and (4) healthy subjects. The subjects with untreated mild asthma had significantly higher NO levels than the

Table 1. Exhaled Nitric Oxide Measurements

Increased Nitric Oxide	Decreased Nitric Oxide
Allergens	Menstruation
Air pollution	Smoking
Ozone	Alcohol
Nitrite-enriched food	Mouth washing
Asthma	Chronic cough (nonasthmatic)
Upper respiratory tract infection	Pulmonary hypertension
Allergic rhinitis	Primary ciliary dyskinesia
Tuberculosis	Cystic fibrosis
Influenza vaccine	
Bronchiectasis	
Ulcerative colitis	
Active pulmonary sarcoidosis	

(Adapted from Reference 139.)

other 3 groups. The authors concluded that NO measurements obtained via tidal breathing could be used to differentiate asthmatics not treated with steroids from asthmatics treated with steroids, healthy controls, and nonasthmatics with chronic cough.

A study by Visser et al[142] confirmed that children with untreated asthma had significantly higher NO levels than asthmatics treated with inhaled steroids. A study by Baraldi et al[143] evaluated the off-line exhaled NO technique with infants and young children with histories of (1) recurrent wheeze, (2) being a first time wheezer, and (3) no respiratory symptoms. The patients with recurrent wheeze were treated with steroids for exacerbation, and the NO measurements were repeated. The subjects with recurrent wheeze had significantly higher NO levels than healthy controls and first time wheezers, and the NO levels significantly dropped after steroid treatment. The authors concluded that inflammation is present at a young age and responds to steroids. Wildhaber et al[144] used a modification of the raised-volume technique to measure exhaled NO in infants. The modification included resistance to flow and the ability to increase jacket pressure to ensure constant flow during measurements. In that study the wheezy infants had significantly higher NO values than healthy controls. Interestingly, the $FEV_{0.5}$ did not significantly correlate with the NO values. More studies need to be conducted with infants and young children because this group often is unable to perform forced expiratory maneuvers without sedation.

In a study by Lundberg et al[145] exhaled NO was measured in healthy children, asthmatics, and CF patients. The values from the CF subjects were similar to the controls, whereas the asthmatics had higher NO levels. In addition, the CF children had lower nasal NO levels than the controls or the asthmatics. The lower NO levels in the CF population may be due to the thick mucus that CF causes, which may prevent diffusion of the NO into the airway lumen. Another study by Lundberg et al[146] measured nasal NO from 4 children with Kartagener syndrome and reported almost complete absence of NO, compared to healthy controls. Karadag et al[147] clarified these results in a larger group of patients with primary ciliary dyskinesia. These patients also had low NO levels in the lower airways; however, there was some overlap with healthy controls. The nasal NO levels were better than the lower airway values for discriminating the primary ciliary dyskinesia patients from the control group. When evaluating for primary ciliary dyskinesia, nasal NO measurements may be a useful tool.

In conclusion, measurement of exhaled or nasal NO may prove useful for assessing lower airway disease. The recommendations for nasal NO measurements were also published in 1999.[135] Method standardization, appropriate reference values, and correlation with other forms of lung function testing are critical, especially for multicenter trials.

Exhaled Carbon Monoxide

Recent studies have evaluated the utility of exhaled carbon monoxide as a marker of lower airway disease. Carbon monoxide is produced during the catalytic conversion of heme to biliverdin. During this conversion, heme oxygenase converts heme to biliverdin. During the conversion, carbon monoxide and iron are produced. Biliverdin reductase then catalyzes biliverdin to bilirubin. There are 3 different isoforms of heme oxygenase. Heme oxygenase 1 is the inducible form that leads to the production of exhaled carbon monoxide. Cytokines, oxidants, endotoxins and NO are known to induce heme oxygenase 1 and, thus, production of exhaled carbon monoxide. This catalytic reaction occurs as a protection against oxidant stress. Because of the factors that induce exhaled carbon monoxide, the measurement of exhaled carbon monoxide has been studied with regard to lower airway disease.[132,148,149]

As with exhaled NO measurement, the technical aspects of measuring exhaled carbon monoxide are important. Exhaled carbon monoxide is measured in parts per million.[132] Ambient carbon monoxide should be measured when analyzing exhaled carbon monoxide. In addition, it is critical to ask the patient whether he or she has an upper respiratory tract infection before beginning an exhaled carbon monoxide measurements, because such infections can increase the exhaled carbon monoxide level.[150] As with exhaled NO measurements, standardization of the technique for measuring exhaled carbon monoxide is important.

Zayasu et al[151] published a study documenting that exhaled carbon monoxide was higher in untreated asthmatics than in controls and asthmatics treated with inhaled steroids. In addition, the exhaled carbon monoxide levels correlated with eosinophils, a marker of inflammation.

Uasuf et al[152] reported that exhaled carbon monoxide was higher in children with persistent asthma treated with inhaled steroids than in controls and subjects with infrequent, episodic asthma. However, there was overlap between the asthmatics and the control subjects.

In a recent study by Zanconato et al[148] 30 asthmatic children were evaluated by measuring exhaled NO and carbon monoxide during asthma exacerbations. Exhaled NO and carbon monoxide were evaluated before and after a 5-day prednisone burst. Both exhaled NO and carbon monoxide were significantly higher in the asthmatics than in the controls; however, the carbon monoxide levels did have some overlap with the healthy controls. After the prednisone burst, exhaled NO significantly decreased. Exhaled carbon monoxide decreased after the prednisone burst, but the decrease was not significant. The authors concluded that exhaled carbon monoxide is less inhibited by steroids than is exhaled NO.

Paredi et al[149] evaluated exhaled carbon monoxide and NO in 29 CF patients and 15 controls. The investigators reported that exhaled carbon monoxide was significantly higher in the CF patients than in the controls, but exhaled NO was not higher in the CF patients, as had been reported in other studies. The authors concluded that exhaled carbon monoxide may be a sensitive marker of lower airway disease and oxidative stress. Another report[153] documented that exhaled carbon monoxide is higher in CF patients experiencing a CF exacerbation than in controls and that the carbon monoxide level decreases after treatment. More studies need to be conducted to evaluate the utility of exhaled carbon monoxide in the management of CF adults and children.

There are far fewer studies of exhaled carbon monoxide than of exhaled NO. At this point there are no published standards for measuring exhaled carbon monoxide. Standards need to be published and more research is needed to evaluate carbon monoxide as a tool for detecting and monitoring lower airway disease.

Summary

Over the last few years, there has been much progress in diagnostic testing of lung function in infants and children. Infant lung function testing is beginning to expand from a purely research tool into the clinical setting. Studies with preschool children indicate that this age group can produce technically acceptable flow-volume curves. Forced oscillation and Rint are diagnostic tools that are noninvasive and simple, and thus suitable for young children. In addition, exhaled NO and carbon monoxide measurements may be used to evaluate and help manage lower airway disease. Despite the large number of published studies, more studies, especially multicenter trials, are needed to evaluate these techniques. For all these measurements, adherence to standards is critical to perform large multicenter trials, through which the clinical utility of these techniques can be more adequately assessed.

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Discussion

Kercsmar: You commented about the difficulty of using infant pulmonary function testing in multicenter trials, and that they haven't been done much. I think the Pediatric Pulmonary and Cardiovascular Complications of Vertically-Transmitted Human Immunodeficiency Virus study (the P2C2 study)[1] was a multicenter trial that used pulmonary function ($\dot{V}_{maxFRC}$) as one of the outcomes. And I think they had incredible difficulty training the centers, standardizing the data, and even trying to analyze the data, which took a lot of statistical manipulation. Can you comment on that?

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1. Colin AA, Sunil Rao J, Chen XC, Hunter JM, Hanrahan J, Hiatt P, et al. Forced expiratory flow in uninfected infants and children born to HIV-infected mothers. Am J Respir Crit Care Med 2001;163(4):865–873.

Davis: That was a multicenter effort to evaluate cardiovascular and respiratory outcome measures in children born to mothers infected with HIV. Two recent publications from that group evaluated (1) the effect of the compression technique on compliance, resistance, and time constant measures[1] and (2) flows referenced to tidal breathing in children born to mothers infected with HIV.[2] In the study by Platzker et al, the investigators reported decreases in compliance and time constant measures produced by the compression technique, which were more marked in infants infected with HIV. The investigators concluded that the order of performing the different types of infant lung function maneuvers should be standardized when comparing values from different visits.

In the study by Colin et al, 5 centers participated and there were differences in flow referenced to FRC ($\dot{V}_{maxFRC}$), between the centers, among the subjects studied. All the subjects had been exposed to HIV but were not infected. These differences may be due to maternal smoking, socioeconomic status, or racial or ethnic factors. Because of the differences among the 5 centers, interpretation of the data was difficult.

The P2C2 study demonstrated the importance of standardization in performing multicenter trials, using infant lung function testing as an outcome measure. All centers need to be taught how to perform infant lung function tests and interpret data in a standardized fashion. There has been no multicenter study using the raised-volume technique in infants. For future trials, standardization is critical.

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Hansell: I am curious about a practical matter. Why did you pick 30 cm H_2O pressure as opposed to simply looking at a flow-volume curve and waiting until you achieved as much tidal volume as you could—in other words, when you get to the point on the pressure curve that no more volume is going in to get a TLC? Is that not a maneuver you could perform on an infant in that situation? Why not just keep increasing the pressure until you see no more volume?

Davis: Of course it would be optimal for each infant to be inflated to TLC prior to the forced expiratory maneuver. The 30 cm H_2O inflation pressure is well tolerated by the infants, but if you go above that pressure, leaks around the mask can occur, leading to technical difficulties. Higher inflation pressures also add risk to the procedure, so to avoid additional risk, 30 cm H_2O has been used in the United States. Investigators in Australia use only 20 cm H_2O.[1,2]

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Wagener: With patients suffering RSV bronchiolitis, is there clinical value in pulmonary function testing those infants before and after bronchodilators to see if bronchodilators make a difference?

Davis: That's a good question. Infant lung function testing has been reported to demonstrate a response or lack of a response to bronchodilators in patients infected with RSV. Derish et al evaluated flow referenced to FRC ($\dot{V}_{maxFRC}$) in 25 infants mechanically ventilated for sequelae of RSV.[1] In that study, flow at FRC significantly increased after administration of albuterol in the majority of the patients. However, 3 patients suffered significantly decreased flow at FRC. In a study by Hammer et al, infant lung function tests were also performed in patients ventilated for sequelae of RSV.[2] Those authors performed a forced deflation technique, and lung volume was measured via the nitrogen washout technique in the infected infants. Fifty percent of the infants with obstructive lung disease had no response to albuterol. In both these studies, infant lung function testing helped delineate the infants with RSV who responded to albuterol from the subjects who did not respond.

REFERENCES

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Black: A European study[1] that used that technique documented a bronchodilator response in infants with bronchiolitis. I had not been acquainted with the technique, and I was a little shocked when I read the methods section. They purported to show bronchodilator response in a portion, but not all, of the RSV infants they tested.

REFERENCE

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Davis: Since you mentioned that you were shocked when you read the methods section, I would like to reiterate that this technique is safe when performed by experienced personnel. When setting up a laboratory, it is critical that the personnel receive extensive training.