

Pulmonary Function Testing in Young Children

Hugo Escobar · Terrence W. Carver Jr.

© Springer Science+Business Media, LLC 2011

Abstract Pulmonary function testing (PFT) is of great importance in the evaluation and treatment of respiratory diseases. Spirometry is simple, noninvasive, and has been the most commonly used technique in cooperative children, obtaining reliable data in only a few minutes. The development of commercially available equipment as well as the simplification of previous techniques that now require minimal patient cooperation applied during tidal breathing have significantly stimulated the use of PFT in younger children. Tidal breathing techniques such as impulse oscillometry, gas dilution, and plethysmography have permitted previously unobtainable PFT in children 2 to 5 years of age. The purpose of this review is to help clinicians become familiar with available PFT techniques used in young children by discussing their general principles, clinical applications, and limitations.

Keywords Lung function · Pulmonary function testing · Children · Pediatric · Spirometry · Impulse oscillometry · Plethysmography · Gas dilution · Nitrogen washout · Lung clearance index · Airway resistance · Specific airway resistance · Tidal breathing · Bronchoprovocation · Bronchodilator

Introduction

Pulmonary function testing (PFT) is a fundamental tool used to evaluate respiratory problems in infants, children, and adults. Children 2 to 5 years old present special challenges for PFT, including difficulty with short attention span, cooperation with techniques, and fear of the equipment used. The development of commercially available equipment that in the past was only available in research laboratories, as well as simplification of techniques that now can be applied during tidal breathing and require minimal patient cooperation have significantly stimulated the use of PFT in younger children in clinical settings. The following review is intended to briefly review spirometry and to help clinicians become familiar with these newer techniques used in younger children.

Spirometry

Spirometry requires more cooperation than many of the PFTs that will be discussed; however, 95% of 8- to 9-year-old children were able to yield adequate data [1]. During properly performed spirometry, a patient achieves reproducible airflow limitation, and by comparing a patient to reference values or to himself or herself over time, the clinician can obtain information regarding the patient's pulmonary status.

The primary measurements of spirometry include the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and forced expiratory flow (FEF), with FEF 25% to 75% most commonly representing that particular portion of the FVC curve [2]. The FVC is the total volume of air that can be exhaled, and the volume of air that is expired during the first second is termed the FEV₁. For

H. Escobar (✉) · T. W. Carver Jr.
Pediatric Pulmonary Department, The Children's Mercy Hospitals
and Clinics, University of Missouri-Kansas City,
2401 Gillham Road,
Kansas City, MO 64108, USA
e-mail: hescobar@cmh.edu

T. W. Carver Jr.
e-mail: twcarver@cmh.edu

healthy individuals, the FEV₁ contains the majority of air in the FVC, and typically both are measured in liters. Flow, defined as the rate of air movement, is typically recorded as liters per second. PFTs are generally interpreted as normal, obstructed, restricted, or as a pattern of mixed obstruction and restriction [3–5]. Although disease processes are often thought of in these distinct categories, many diseases may fit into more than one category.

Typically a patient begins the forced expiratory maneuver from total lung capacity with full inflation of the lungs and ends at residual volume (RV) when no more air can be squeezed out of the chest [2]. Younger patients can deliver this volume faster than adults, and evaluation of the FEV_{0.4}, FEV_{0.5}, or FEV_{0.75} may be necessary [3, 6]. Patients are usually studied in a standing or seated position to optimize lung function. The speed of inspiration and length of the end-inspiratory pause is important in the maneuver, and consistency in effort should minimize the variability of the viscoelastic properties of the lung and chest wall tissues [7]. Maximal airflow will be proportional to elastic recoil and inversely related to the airways' resistance [8].

Requirements, External Quality Standards, and Purpose of Testing

Because of the smaller volumes involved with children's PFTs, equipment should include minimal dead space, low resistance, and software programs that elicit the child's cooperation [3]. Reproducibility of the maneuver is often a marker of accuracy; therefore, quality and standardizing laboratory methods encourage reproducible results [1]. Clinicians and guiding organizations such as the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have attempted to improve quality and reproducibility through official statements often delineating requirements and clinical standards for testing [2–5, 9]. PFT is often used to differentiate health from disease and to differentiate potential causes of a patient's symptom [10]. Evaluation of bronchial hyperreactivity through clinical challenges also may be helpful [10]. Longitudinal PFTs may be utilized to evaluate lung function in epidemiologic studies such as changes due to aging or personal habits such as smoking [11]. Evaluating the pulmonary effects of medications for efficacy and for unwanted effects, including toxicity such as cancer, chemotherapy, or radiation, also may be helpful [10, 11].

Interpretation

Patients are often compared with healthy population data or with themselves over time. Reference values become least accurate at the extremes of age and height for age [3, 9, 12]. Height is the most important predictive variable for lung

function, followed by race [12]. Comparing a patient with himself or herself over time removes the limitations of comparing the patient with a reference population that may be dissimilar to the patient and to statistical anomalies [10]. Most laboratories use 80% of predicted or less as a definition of an abnormal test [9, 10]. When comparing an individual with himself or herself during longitudinal testing, a minimum change from baseline for significance has been defined by some as $\pm 10\%$ for FVC and FEV₁, and $\pm 25\%$ for FEF 25% to 75% [10], but this may be an overestimate based on others' data [12]. Most lung function data are normally distributed or can be transformed so that 90% of "normal" values can be defined within the range of mean ± 1.65 SD, and 95% within ± 1.96 SD [3]. Using regression lines has been suggested as a more accurate means of distinguishing normal from abnormal [9, 13].

Appropriate repeatability is defined as at least two acceptable curves, with the second highest FVC and FEV₁ within 0.1 L or 10% of the highest value, whichever is greater [3]. Severity classification of the FEV₁ can be important, and the interpretive strategy set out by the ATS/ERS task force suggests mild abnormalities being greater than 70%, moderate 60% to 69%, moderately severe 50% to 59%, severe 35% to 49%, and very severe less than 35% of predicted values [5].

Evidence of airway obstruction may also be recognized by the spirometry flow-volume loop, with different patterns of abnormalities for fixed obstruction, variable extrathoracic obstruction, and variable intrathoracic airway obstruction [5].

Clinical Applications

Examples of Diseases with Obstructive Lung Disease

Children with wheezing in the first 3 years of life have a relatively benign prognosis, and these transient early wheezing children had abnormally low PFT initially, with these abnormalities on pulmonary function preceding any lower respiratory tract illness [14]. Those in this group were theorized to have congenitally smaller airways that predisposed them to wheezing in early life, and despite the fact that they no longer were wheezing by 6 years of age, the patients' PFTs remained abnormal compared with children who had never wheezed. This dataset was updated when the children were 16 years of age [15]. Again, these children continued to have lower levels of lung function at the ages of 11 and 16 years relative to those who had never wheezed. Hereditary of asthma, female gender, atopy, inhalant allergens, IgE level at 9 months of age, exposure to tobacco smoke, viral infection, and early animal exposure have been shown to have important effects on lung function and bronchial hyperresponsiveness [6, 14–22].

Patients with bronchiolitis obliterans (BO) have been shown to have abnormal PFT, most often obstruction with FEV₁ as low as 19% [23–25]. Progressive abnormalities in the PFTs with an annual rate of decline of −1.01% for FEV₁ and −1.04% for FEV 25% to 75% have been reported [26].

Patients born prematurely and below normal birth weights often have long-term health issues [27]. These patients show severe reductions in flow at low lung volumes consistent with peripheral airways obstruction and resultant air trapping at a mean chronological age of 2 years [28]. Their data suggested the lung function changes in bronchopulmonary dysplasia were not fully explained by the prematurity alone. Respiratory function was evaluated in children 8 to 9 years of age who were born prematurely at extremely low birth weights, and substantial reductions in respiratory function variables were found, reflecting airflow and evidence of air trapping, especially for those with bronchopulmonary dysplasia as compared with normal birth weight children [29]. Reduced lung function at 6 to 8 years of age in children born prematurely was related to severity of bronchopulmonary dysplasia [30]. Some have found that bronchopulmonary dysplasia is associated with higher RV percentage predicted only [31].

Although patients with cystic fibrosis are known to have lung disease even at a young age, the relationship between lung function and clinical indicators of disease was inconsistent [32•], suggesting that spirometry does not give the complete picture.

Examples of Diseases with Restrictive Lung Disease

Neuromuscular patients are often at risk of respiratory complications, scoliosis, and subsequent perioperative complications [33, 34]. Neuromuscular patients with an inspired vital capacity of less than 1.1 L or a peak cough flow of less than 160 L/min are at high risk of chest infection [35, 36]. Patients at the highest risk of respiratory failure are indicated by inspiratory force of less than 20 cm of water [35]. Subjective cough assessment has been found to be relatively less sensitive for cough strength than objective measurements of maximal expiratory pressure [37]. As expected, patients with neuromuscular respiratory weakness have decreased maximal inspiratory and expiratory pressure compared with healthy individuals [29].

Examples of Diseases with Obstructive and/or Restrictive Lung Disease

Spathopoulos et al. [38] studied the effect of obesity on PFTs on school-aged children in Greece and found that obese children defined by body mass index percentile or body mass index z-score were characterized by a reduction in most spirometric measurements. In a separate study by

Sidoroff et al. [39], children who were overweight had associated decreased FEV₁/FVC ratio and reduced flow in small airways, but no restriction. These authors had chosen to study children who had been hospitalized for wheezing between the ages of 1 and 23 months, so their data may not be extrapolable to the more general obese population.

Garty et al. [40] evaluated PFTs in children with progressive systemic sclerosis and found that 92% had abnormal tests, although only 61% had clinical respiratory disease and 54% had radiographic abnormalities [40]. The PFT abnormalities were divided, with the majority having restrictive defects.

Impulse Oscillometry

Impulse oscillometry (IOS) is a noninvasive method that allows the measurement of airway mechanics (resistance [R] and reactance [X]) with minimal patient cooperation. IOS is a modification of the forced oscillatory technique (FOT) initially described in 1956 by DuBois et al. [41]. While the patient is sitting and breathing tidally, sound pressure waves (oscillations) are applied to the airway (mouth) at different frequencies (typically 5–30 Hz). The resulting pressure and flow changes on the tidal breaths are recorded and analyzed as airway impedance (R+X) [3]. Resistance reflects the factors limiting the flow of air in the airways, whereas reactance reflects the energy generated by the movement of air in the airways and is determined by the elastic properties of the lung tissue and the inertance forces.

Resistance and reactance are measured over the different oscillatory frequencies. Faster frequencies (~20 Hz) are dampened in the larger airways, providing resistance information about the central airways. Lower frequencies can travel more distally into the smaller airways, providing information about the entire pulmonary system (small and large airways). In healthy individuals, airway resistance remains unchanged at the different oscillatory frequencies (frequency independent), but in small airway disease, changes in resistance and reactance at slow frequencies (5 Hz) are noted. Large airway disease shows altered resistance at all the frequencies. Reactance is not significantly changed by upper airway alterations. Debate remains regarding multiple aspects of IOS, including the best indicators for airway obstruction (resistance vs reactance), the ability of IOS to identify patients with stable asthma, and the best indicators to follow patients over time.

Clinical Applications

IOS is most helpful in diseases with airway involvement (upper and/or lower) to determine the degree of flow

limitation for diagnosis or treatment. IOS is effort independent and therefore useful in preschool children and other patients with difficulties performing spirometry. Asthma patients have been found to have a baseline elevation in resistance at 5 Hz (R5Hz) as compared with controls [42, 43]; however, the same elevation has not been found by other authors, especially among children with well-controlled asthma [44–46].

Multiple studies have shown that improvement after bronchodilator testing in R5Hz by IOS correlates well with a significant response by spirometry or plethysmography [42, 47, 48]. Initial pre- and postbronchodilator studies suggested that an increase in R5Hz by 40% was needed to distinguish asthmatic from nonasthmatic children [44]. Most recent studies suggest that a change in R5Hz by 30% to 35% is enough to be considered a positive test [42, 47, 48].

When IOS has been used in bronchoprovocation testing (eg, methacholine, mannitol), authors have found that lower doses are required to induce a measurable bronchoconstriction, and testing is also less demanding on patients as compared with spirometry [49, 50]. Bronchoprovocation studies with FOT identified that a 20% decrease in FEV₁ (PC₂₀) correlated with a 40% increase in resistance at 6 Hz [51]. Subsequent studies did not find a positive correlation between resistance and a positive methacholine challenge by spirometry. Importantly, one of the studies did not use spirometry to compare with IOS [52], and in the other study, airway resistance was measured at only two different methacholine concentrations and not the complete methacholine series [53]. Reactance (X), instead of resistance, and specifically reactance at 5 Hz (X5Hz) is a better indicator of methacholine-induced bronchoconstriction by IOS [54]. In the two most recent studies, the authors determined that a change in X5Hz by 70% to 80% has 68% to 80% sensitivity and 82% to 83% specificity to detect patients with asthma. In this same study, spirometry was found to have 74% sensitivity and 89% specificity [43]. Mannitol challenge has been recognized by the International Olympic Committee [55], and the US Food and Drug Administration has approved this challenge to diagnose asthma and exercise-induced bronchoconstriction [56]. In the only report of mannitol challenge comparing spirometry and IOS, a positive test by spirometry (15% decrease in FEV₁) correlated with a 25% increased resistance at 5 Hz by IOS. There was no significant change in R20Hz, which led the authors to hypothesize that mannitol acts mostly on the peripheral airways [57].

Gas Dilution

Gas dilution is a noninvasive method used to measure lung volumes not measured by spirometry. In patients with

abnormal spirometry, lung volumes are important as an adjunct to confirm obstructive or restrictive patterns. One of the most important measurements obtained by gas dilution is the functional residual capacity (FRC). FRC is the combination of RV and the expiratory reserve volume (ERV). FRC is of great importance because it is the volume of intrathoracic gas at which the elastic forces of the lung (pulling inward) and the elastic properties of the chest wall (pulling outward) are in equilibrium. Since expiration is normally a passive maneuver, FRC is the volume of intrathoracic gas at the end of a normal, nonforced expiration [58].

Gas dilution techniques are based on the determination of helium or nitrogen (N₂) as a tracer gas (sulfur hexafluoride [SF₆] gas is limited to a few specialized centers and is not commercially available in the United States). The technique is performed as a single or multiple breath test. Multiple breath washout (MBW) test requires minimal cooperation from the patient and can be performed on small infants [59].

In the multiple breath helium washout method, the child breathes from a circuit connected to a reservoir of a gas with an initial known concentration and volume of helium. After a few breaths from the closed system, the intrathoracic (initially no helium) and the closed circuit concentration of helium equilibrate, and FRC can be calculated from the new helium concentration. Different from helium MBW, the system in the N₂ washout method is open, and the exhaled gas is not stored (simplifying the equipment). With this method, the patient starts breathing room air (known concentration of N₂) through a face mask or a mouth piece, and once the patient is breathing at a regular rate and pattern, the inhaled gas is switched to 100% oxygen. The concentration of N₂ and the volume of exhaled gas are measured until the concentration of N₂ is less than 2% of the starting concentration [3]. Because the initial N₂ concentration is known and the total exhaled N₂ volume was measured, FRC can then be calculated.

$$\text{FRC} = \frac{\text{volume of N}_2 \text{ washed out}}{\text{initial fractional N}_2 \text{ concentration} - 0.02}$$

Both of the above techniques measure gas coming from ventilated areas of the lung (communicating open airways) and cannot measure gas trapped distal to obstructed airways, and thereby underestimate FRC in patients with significant obstructive diseases.

Clinical Applications

In general, restrictive diseases (interstitial lung disease, muscle weakness) will have a decreased FRC. Obstructive diseases (asthma, bronchiolitis obliterans, and cystic fibrosis) will have an elevated FRC mainly due to increased residual volume. Lung volume by MBW has allowed

clinicians to identify significant air trapping in patients too young to perform conventional PFTs [59] or with obstructive diseases that spirometry does not detect [60]. MBW has been demonstrated to be an important tool in evaluating the effects of medications on preterm neonates, including measuring response to bronchodilator [61], outcomes of infants taking diuretics [62], or in the analysis of the effects of systemic steroids on lung function later in life [63].

Additional information that can be obtained by N₂ washout is the lung clearance index (LCI). The LCI requires equipment capable of measuring (or calculating) the concentration of N₂ and the exhaled volume of air on a breath-by-breath basis. Commercially available devices calculate N₂ concentration by the carbon dioxide and oxygen substitution method. The LCI can be understood as the number of lung turnovers (or functional residual capacities) needed to decrease the concentration of N₂ to less than 2% of the initial concentration [64•].

LCI = cumulative added exhaled gas volumes until N₂ is < 2%/FRC

The LCI is independent of age, weight, and height. In addition, it has very good within-test repeatability (coefficient of variation [CV] = 5.1%) and is highly reproducible (CV=4.1%), making it a great tool to follow lung function over time [64•].

The small airways (<2 mm diameter in adults) account for less than 10% of the airway resistance, making spirometry (and specifically FEV₁) insensitive to changes in these areas [65•]. Because the tracer gas (helium, N₂, SF₆) comes from all ventilated areas (including the small airways), LCI can be considered an index of ventilation distribution that is possibly more sensitive than FEV₁ to detect peripheral airway obstruction.

When young children with cystic fibrosis were evaluated by LCI, spirometry, and plethysmography, LCI was able to identify more patients with airway abnormalities than the other two techniques; LCI was elevated in 73% of the cases, whereas specific airway resistance (sRaw) was increased in 47% and spirometry was abnormal in just 13% of the cases [66]. Similarly, LCI was more sensitive (85%–94%) than FEV₁ (19%–26%) to detect abnormalities on pulmonary function in children with cystic fibrosis who had early changes on high-resolution CT; even more a normal LCI almost completely excluded abnormalities on these patients [67]. Asthma and wheezing are very common in children, and the ability to measure ventilation abnormalities in young children can facilitate the differentiation of the different asthma phenotypes. When children with viral-induced wheezing were compared with children who had episodes of wheezing associated with multiple other factors (eg, dust, smoke, exercise), it was noted that the LCI was able to differentiate between the two groups. In

children with nonviral wheezing, the LCI was significantly elevated as compared with children with viral-induced wheezing. The LCI of children with viral-induced wheezing was not different from that of the control group [68]. These findings are of great interest because there is some evidence that children with viral-induced wheezing may not benefit from systemic corticosteroids [69], and identification of these children may decrease systemic steroid use.

Plethysmography

Total body plethysmography is the gold standard to measure airway resistance. Airway resistance is an indicator of a limitation in the access of air into the lungs that results in airflow changes. Body plethysmography is measured with an individual enclosed in a sealed chamber (plethysmograph). In infants, the plethysmograph is the size of a baby incubator, and in older children, it is similar in size to a telephone booth. Airway resistance is dependent on lung volume (increased lung volume will decrease airway resistance). To minimize the effects of lung size, airway resistance is adjusted for lung volume and is reported as sRaw, which allows an age- and size-independent resistance value that can be compared between individuals and longitudinally as the child grows [70]. Measurements of lung volumes are based on Boyle's law (if temperature is kept constant in an enclosed system, pressure [p] and volume [V] are inversely proportional).

$$p_1V_1 = p_2V_2 \text{ [71].}$$

Once the plethysmograph is closed, pressure and flow are measured while the patient breathes at a constant rate and pattern; after a few breaths and once the temperature has equalized, an airway occlusion is created at the level of the mouthpiece at the end of expiration. Pressure changes at the mouth level and inside the chamber are recorded as the patient continues to make inspiratory and expiratory breathing efforts, then the occlusion is released and the patient is asked to breathe to a total lung capacity. Because the initial volume of the plethysmograph is known and pressure inside the body box and at the mouth level (respiratory pressure) was recorded, intrathoracic gas volume can then be calculated. Additionally, from the resulting pressure and flow curves, airway resistance is obtained [72].

Cooperation to perform this maneuver can be difficult in young children. A simplified method has been described by Bisgaard and Nielsen [73]. In the simplified method, sRaw is measure directly without the need to obtain lung volumes. During this technique, the patient is

placed inside a plethysmograph while breathing at a normal rate and pattern through a face mask. As the child's chest expands on inhalation and contracts on exhalation, it creates pressure changes inside the chamber that are recorded. As the child breathes, a pneumotachograph measures flow changes. Pressure and flow changes are then plotted (resistance loop), and sRaw can be calculated as the slope of the resistance loop. This technique is better tolerated in young children, with good sRaw repeatability (CV=11%) [70].

Clinical Applications

The use of sRaw has focused on evaluation of young children with suspected airway dysfunction that cannot be measured by spirometry. Among children with infantile wheezing, differentiating various asthma phenotypes can be challenging. In a cohort study of children younger than 3 years of age, it was found that children who had never wheezed but were atopic or had a family history of atopy had significant elevations in sRaw ($P=0.001$) as compared with children without any personal or family history of atopy [74]. In a different study, the same authors evaluated children with a history of wheezing, and children with increased sRaw at 3 years of age were more likely to continue wheezing 2 years later [75]. Viral infections are very common in children, and rhinovirus infection in infancy has been associated with persistent wheezing [76]. Children with tissue biopsy-confirmed lower airway rhinovirus infection have been found to have abnormal airway resistance in 86% of the cases, as compared with 56% of children with limited upper airway infection [77]. Findings from the previously described studies suggest that plethysmography, and specifically sRaw, can identify specific populations at risk of persistent wheezing.

When lung function pre-and postbronchodilator was measured in children younger than 5 years old, sRaw was found to be better than IOS and the interrupter resistance technique in distinguishing between asthmatic and healthy children [42]. A decrease in sRaw by 25% after bronchodilator was identified with a sensitivity of 66% and a specificity of 81% to distinguish asthmatic from healthy children.

Among patients with asthma, sRaw has been used to evaluate the effect of different medications. In a study of asthmatic children 3 to 5 years old, leukotriene receptor antagonists were found to have a protective effect against bronchoconstriction. Patients on leukotriene inhibitors had a 17% increase in sRaw by cold air inhalation, as compared with a 46% increase in the control group [78].

Different from the gas dilution techniques' limitations, plethysmography measures all the intrathoracic air, including air trapped behind occluded airways. Thus, the

difference between FRC by plethysmography and FRC by gas dilution can be used as a measure of airway obstruction. In a study of children scheduled to have corrective surgery for idiopathic scoliosis, moderate to severe air trapping was found in 46% by FRC by plethysmography or helium dilution, while just 7% of the patients met criteria for airway obstruction by spirometry [79], showing that plethysmography and helium dilution techniques can detect airway dysfunction that was missed by spirometry alone.

In a very interesting application, one study identified plethysmography as an important evaluation of postinfectious BO. When children with BO from two different countries were analyzed by spirometry and plethysmography, the authors found that the combination of a decrease in FEV₁, FEF_{25%-75%}, increased sRaw, and elevated RV was a common pattern in children with BO. Furthermore, when used together, the four results were better for diagnosis, evaluation of dysfunction, and progression of obstruction than any result alone [80•].

Tidal Breathing Analysis

For young patients who cannot produce a maximal expiratory flow maneuver, analyzing tidal breathing as a measure of airway obstruction has been used [3]. In patients with airway obstruction, a rapid rise in flow reaching a peak earlier in exhalation was found, suggesting that inspiratory muscle activity ends abruptly at the beginning of exhalation in order to maximize airflow and time for exhalation [81]. These authors suggest that time to maximal air flow to total expiratory time values less than 32% may be defined as abnormal. Similar data have been seen in infants [82], and interestingly, they theorized two principal breaking mechanisms, diaphragmatic and laryngeal.

Conclusions

Although spirometry has been the most frequently used PFT, many newer techniques show promise in examining lung function, especially in younger and less cooperative children. Clinicians will need to gain further experience, and more research will be needed to define more clearly the usefulness of these newer forms of PFT.

Disclosure Dr. Carver has received honoraria for serving on speakers' bureaus from Merck & Co. and AstraZeneca and has had travel/accommodations expenses covered/reimbursed (for speaker training) by Merck & Co.

Dr. Escobar reported no potential conflicts of interest relevant to this article.

The authors thank Donna M Moore and Nicole Curless for the administrative assistance.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

- Kanner RE, Schenker MB, Munoz A, et al. Spirometry in children. Methodology for obtaining optimal results for clinical and epidemiologic studies. *Am Rev Respir Dis*. 1983;127(6):720–4.
- Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(3):1107–36.
- Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. 2007;175(12):1304–45.
- Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis*. 1991;144(5):1202–18.
- Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948–68.
- Pike KC, Rose-Zerilli MJ, Osvald EC, et al. The relationship between infant lung function and the risk of wheeze in the preschool years. *Pediatr Pulmonol*. 2011;46(1):75–82.
- D'Angelo E, Prandi E, Milic-Emili J. Dependence of maximal flow-volume curves on time course of preceding inspiration. *J Appl Physiol*. 1993;75(3):1155–9.
- Pfaff JK, Morgan WJ. Pulmonary function in infants and children. *Pediatr Clin North Am*. 1994;41(2):401–23.
- Pattishall EN. Pulmonary function testing reference values and interpretations in pediatric training programs. *Pediatrics*. 1990;85(5):768–73.
- Mueller GA, Eigen H. Pulmonary function testing in pediatric practice. *Pediatr Rev*. 1994;15(10):403–11.
- Crapo RO. Pulmonary-function testing. *New Engl J Med*. 1994;331(1):25–30.
- Dockery DW, Berkey CS, Ware JH, et al. Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. *Am Rev Respir Dis*. 1983;128(3):405–12.
- Knudson RJ, Slatin RC, Lebowitz MD, et al. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis*. 1976;113(5):587–600.
- Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *New Engl J Med*. 1995;332(3):133–8.
- Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*. 2005;172(10):1253–8.
- Britton J, Martinez FD. The relationship of childhood respiratory infection to growth and decline in lung function. *Am J Respir Crit Care Med*. 1996;154(6 Pt 2):S240–5.
- Jedrychowski W, Maugeri U, Perera FP, et al. Early wheeze as reported by mothers and lung function in 4-year-olds. Prospective cohort study in Krakow. *Pediatr Pulmonol*. 2010;45(9):919–26.
- Goksor E, Amark M, Alm B, et al. The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. *Acta Paediatr*. 2007;96(7):1030–5.
- Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, et al. Lung function and bronchial hyper-responsiveness 11 years after hospitalization for bronchiolitis. *Acta Paediatr*. 2007;96(10):1464–9.
- Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, et al. Wheezing due to rhinovirus infection in infancy: bronchial hyperresponsiveness at school age. *Pediatr Int*. 2008;50(4):506–10.
- Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. *Thorax*. 1998;53(10):884–93.
- Stein RT, Holberg CJ, Sherrill D, et al. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. *Am J Epidemiol*. 1999;149(11):1030–7.
- Aguerre V, Castanos C, Pena HG, et al. Postinfectious bronchiolitis obliterans in children: clinical and pulmonary function findings. *Pediatr Pulmonol*. 2010;45(12):1180–5.
- Mattiello R, Sarria EE, Mallol J, et al. Post-infectious bronchiolitis obliterans: can CT scan findings at early age anticipate lung function? *Pediatr Pulmonol*. 2010;45(4):315–9.
- Zhang L, Irion K, Kozakewich H, et al. Clinical course of postinfectious bronchiolitis obliterans. *Pediatr Pulmonol*. 2000;29(5):341–50.
- Cazzato S, Poletti V, Bernardi F, et al. Airway inflammation and lung function decline in childhood post-infectious bronchiolitis obliterans. *Pediatr Pulmonol*. 2008;43(4):381–90.
- Hack M, Schluchter M, Andreias L, et al. Change in prevalence of chronic conditions between childhood and adolescence among extremely low-birth-weight children. *JAMA*. 2011;306(4):394–401.
- Filbrun AG, Popova AP, Linn MJ, et al. Longitudinal measures of lung function in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2011;46(4):369–75.
- Szeinberg A, Marcotte JE, Roizin H, et al. Normal values of maximal inspiratory and expiratory pressures with a portable apparatus in children, adolescents, and young adults. *Pediatr Pulmonol*. 1987;3(4):255–8.
- Brostrom EB, Thunqvist P, Adenfelt G, et al. Obstructive lung disease in children with mild to severe BPD. *Respir Med*. 2010;104(3):362–70.
- Kitchen WH, Olinsky A, Doyle LW, et al. Respiratory health and lung function in 8-year-old children of very low birth weight: a cohort study. *Pediatrics*. 1992;89(6 Pt 2):1151–8.
- Gangell, CL, Hall GL, Stick SM, et al. Lung function testing in preschool-aged children with cystic fibrosis in the clinical setting. *Pediatr Pulmonol*. 2010;45(5):419–33. *This article provides a nice review of various PFT techniques used in young cystic fibrosis patients.*
- Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest*. 1997;112(4):1024–8.
- Mehta S. Neuromuscular disease causing acute respiratory failure. *Respir Care*. 2006;51(9):1016–21. discussion 1021–3.
- O'Donohue Jr WJ, Baker JP, Bell GM, et al. Respiratory failure in neuromuscular disease. Management in a respiratory intensive care unit. *JAMA*. 1976;235(7):733–5.
- Dohna-Schwake C, Ragette R, Teschler H, et al. Predictors of severe chest infections in pediatric neuromuscular disorders. *Neuromuscul Disord*. 2006;16(5):325–8.
- Szeinberg A, Tabachnik E, Rashed N, et al. Cough capacity in patients with muscular dystrophy. *Chest*. 1988;94(6):1232–5.
- Spathopoulos D, Paraskakis E, Trysianis G, et al. The effect of obesity on pulmonary lung function of school aged children in Greece. *Pediatr Pulmonol*. 2009;44(3):273–80.
- Sidoroff V, Hyvarinen M, Piippo-Savolainen E, et al. Lung function and overweight in school aged children after early childhood wheezing. *Pediatr Pulmonol*. 2010, Dec 30 (Epub ahead of print).
- Garty BZ, Athreya BH, Wilmott R, et al. Pulmonary functions in children with progressive systemic sclerosis. *Pediatrics*. 1991;88(6):1161–7.

41. Dubois AB, Brody AW, Lewis DH, et al. Oscillation mechanics of lungs and chest in man. *J Appl Physiol*. 1956;8(6):587–94.
42. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med*. 2001;164(4):554–9.
43. Kim HY, Shin YH, da Jung W, et al. Resistance and reactance in oscillation lung function reflect basal lung function and bronchial hyperresponsiveness respectively. *Respirology*. 2009;14(7):1035–41.
44. Hellinckx J, De Boeck K, Bande-Knops J, et al. Bronchodilator response in 3–6.5 years old healthy and stable asthmatic children. *Eur Respir J*. 1998;12(2):438–43.
45. Olaguibel JM, Alvarez-Puebla MJ, Anda M, et al. Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children. *J Investig Allergol Clin Immunol*. 2005;15(2):102–6.
46. Harrison J, Gibson AM, Johnson K, et al. Lung function in preschool children with a history of wheezing measured by forced oscillation and plethysmographic specific airway resistance. *Pediatr Pulmonol*. 2010;45(11):1049–56.
47. Marotta A, Klennert MD, Price MR, et al. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. *J Allergy Clin Immunol*. 2003;112(2):317–22.
48. Song TW, Kim KW, Kim ES, et al. Utility of impulse oscillometry in young children with asthma. *Pediatr Allergy Immunol*. 2008;19(8):763–8.
49. Weersink EJ, vd Elshout FJ, van Herwaarden CV, et al. Bronchial responsiveness to histamine and methacholine measured with forced expirations and with the forced oscillation technique. *Respir Med*. 1995;89(5):351–6.
50. Broeders ME, Molema J, Hop WC, et al. Bronchial challenge, assessed with forced expiratory manoeuvres and airway impedance. *Respir Med*. 2005;99(8):1046–52.
51. Duiverman EJ, Neijens HJ, Van der Snee-van Smaalen M, et al. Comparison of forced oscillometry and forced expirations for measuring dose-related responses to inhaled methacholine in asthmatic children. *Bull Eur Physiopathol Respir*. 1986;22(5):433–6.
52. Wilson NM, Bridge P, Phagoo SB, et al. The measurement of methacholine responsiveness in 5 year old children: three methods compared. *Eur Respir J*. 1995;8(3):364–70.
53. Bailly C, Crenesse D, Albertini M. Evaluation of impulse oscillometry during bronchial challenge testing in children. *Pediatr Pulmonol*. 2011.
54. Klug B, Bisgaard H. Measurement of lung function in awake 2–4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. *Pediatr Pulmonol*. 1996;21(5):290–300.
55. Fitch KD, Sue-Chu M, Anderson SD, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22–24, 2008. *J Allergy Clin Immunol*. 2008;122(2):254–60. 260 e1-7.
56. Thompson CA. FDA approves mannitol bronchial-challenge test kit. *Am J Health Syst Pharm*. 2010;67(22):1886.
57. Horsman TA, Duke RK, Davenport PW. Airway response to mannitol challenge in asthmatic children using impulse oscillometry. *J Asthma*. 2009;46(6):600–3.
58. West JB. *Respiratory physiology: the essentials*. 8th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. ix, 186 p.
59. Morris MG, Gustafsson P, Tepper R, et al. The bias flow nitrogen washout technique for measuring the functional residual capacity in infants. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. *Eur Respir J*. 2001;17(3):529–36.
60. Gustafsson PM, Johansson HJ, Dahlback GO. Pneumotachographic nitrogen washout method for measurement of the volume of trapped gas in the lungs. *Pediatr Pulmonol*. 1994;17(4):258–68.
61. Yuksel B, Greenough A. Airways resistance and lung volume before and after bronchodilator therapy in symptomatic preterm infants. *Respir Med*. 1994;88(4):281–6.
62. Kao LC, Durand DJ, McCrea RC, et al. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr*. 1994;124(5 Pt 1):772–81.
63. Merz U, Peschgens T, Kusenbach G, et al. Early versus late dexamethasone treatment in preterm infants at risk for chronic lung disease: a randomized pilot study. *Eur J Pediatr*. 1999;158(4):318–22.
64. • Fuchs SI, Eder J, Ellemunter H, et al. Lung clearance index: normal values, repeatability, and reproducibility in healthy children and adolescents. *Pediatr Pulmonol*. 2009;44(12):1180–5. *The authors presented normal values and specific data on LCI for healthy children.*
65. • Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. *Respiration* 2009;78(3): 339–55. *This is an excellent review about the general principles of the gas dilution technique.*
66. Aurora P, Bush A, Gustafsson P, et al. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med*. 2005;171(3):249–56.
67. Gustafsson PM, De Jong PA, Tiddens HA, et al. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. *Thorax*. 2008;63(2):129–34.
68. Sonnappa S, Bastardo CM, Wade A, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol*. 2010;126(3):519–26 e1-7.
69. Panickar J, Lakhnypaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *New Engl J Med*. 2009;360(4):329–38.
70. Klug B, Bisgaard H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2–7 years. *Pediatr Pulmonol*. 1998;25(5):322–31.
71. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J*. 2005;26(3):511–22.
72. Dubois AB, Botelho SY, Comroe Jr JH. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J Clin Invest*. 1956;35(3):327–35.
73. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest*. 2005;128(1):355–62.
74. Lowe L, Murray CS, Custovic A, et al. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet*. 2002;359(9321):1904–8.
75. Lowe LA, Simpson A, Woodcock A, et al. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med*. 2005;171(3):231–7.
76. Lemanske Jr RF, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol*. 2005;116(3):571–7.
77. Malmstrom K, Pitkaranta A, Carpen O, et al. Human rhinovirus in bronchial epithelium of infants with recurrent respiratory symptoms. *J Allergy Clin Immunol*. 2006;118(3):591–6.

78. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. *Am J Respir Crit Care Med.* 2000;162(1):187–90.
79. Boyer J, Amin N, Taddonio R, et al. Evidence of airway obstruction in children with idiopathic scoliosis. *Chest.* 1996;109(6):1532–5.
80. • Mattiello R, Mallol J, Fischer GB, et al. Pulmonary function in children and adolescents with postinfectious bronchiolitis obliterans. *J Bras Pneumol.* 2010;36(4): 453–9. *This article presented lung function findings of the largest sample of patients with postinfectious BO.*
81. van der Ent CK, Brackel HJ, van der Laag J, et al. Tidal breathing analysis as a measure of airway obstruction in children three years of age and older. *Am J Respir Crit Care Med.* 1996;153(4 Pt 1):1253–8.
82. Seddon PC, Davis GM, Coates AL. Do tidal expiratory flow patterns reflect lung mechanics in infants? *Am J Respir Crit Care Med.* 1996;153(4 Pt 1):1248–52.