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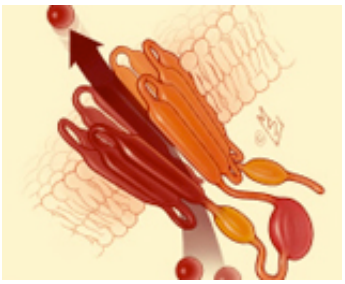

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Measurement of Early Lung Disease in Children With Cystic Fibrosis

In this Issue...

Significant advancements in the field of infant and preschool lung function testing, as well as computed tomography scanning of the chest, are now providing investigators and clinicians with an improved understanding of the early manifestations of cystic fibrosis (CF) lung disease. Sensitive outcome measures assessing early CF lung disease are critical, as new therapeutic agents are being developed for the youngest population. Certainly, the detection of early disease may lead to more aggressive management at a younger age, thereby improving long-term prognosis.

In this issue we focus on recent publications describing imaging and physiologic measures that are currently available to better demarcate early CF lung disease.

THIS ISSUE

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Guest Faculty Disclosures

Dr. Davis has disclosed no relationships with commercial supporters.

Dr. Pittman has disclosed no relationships with commercial supporters..

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The authors have indicated that there will be references to unlabeled or unapproved uses of drugs or products in this presentation.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

Newsletter:

- Describe the evolution of early lung disease in children with cystic fibrosis (CF)
- Discuss the techniques currently available for assessing lung function and disease in young children with CF
- Identify the structural and physiologic changes in the lungs of young children with CF

Podcast:

- Discuss the advantages and disadvantages of early physiologic and structural measurements available in the infant and preschooler with CF.
- Delineate the clinical and research utility of infant and preschool pulmonary function testing in the CF population.
- Discuss the clinical implications of structural abnormalities in the early CF lung.

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COMMENTARY

Identifying and tracking early cystic fibrosis (CF) lung disease has historically been difficult because of the lack of sensitive techniques that are easy to perform in a young child. Over the past 10 years, much progress has been made in this area, with CF clinicians now beginning to realize that airway disease begins early, often prior to the manifestation of clinical symptoms.[1] Focal, distal mucus plugging causes dilatation of the peripheral airways, as denoted by physiologic markers of hyperinflation and airway trapping. The CF clinician is often unable to detect these subtle changes because of the inability to auscultate airway abnormalities with his or her stethoscope, as well as a negative respiratory history reported by the parents.

In the older child, forced expiratory volume in 1 second (FEV_1), measured via spirometry, is used to track the progression of lung disease. In the preschooler, spirometry may be difficult to perform, since this technique requires active cooperation (this measure is clearly impossible to perform during infancy). Recent progress has led to use of a sedated lung function technique called raised volume rapid thoracoabdominal compression (RVRTC) in infancy to simulate adult-type measures. During the performance of this technique, the infant is sedated and forced expiratory maneuvers are initiated from an inflated lung volume. The lung parameters measured are similar to those used in classic spirometry, except that forced expiratory volume in 0.5 seconds ($FEV_{0.5}$) is assessed rather than FEV_1, since infants often cannot exhale for 1 full second. Published results using $FEV_{0.5}$ have demonstrated diminished lung function values in the CF population compared with healthy controls. Using pediatric-friendly procedures, spirometry in preschoolers has demonstrated effectiveness. In addition, simpler techniques have been developed to assist in the use of physiologic measures in the 3-to-5-year-old age-group. Standardization of the RVRTC technique and preschool lung function measurements have been published through a joint effort of the American Thoracic Society and the European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing,[2,3] thereby encouraging multicenter collaboration and dissemination of the procedures. The measurement of lung function during infancy and preschool years using these standardized techniques is addressed in articles by Kozlowska and colleagues, and Linnane and associates, reviewed in this issue.

In children with CF, the evaluation of structural damage through computed tomography (CT) scans of the chest has evolved over the past decade. Historically, chest radiographs have been used to assess progression of lung disease in the CF population; however, compared with conventional radiography, high-resolution computed tomography (HRCT) of the chest provides more detailed information on the regional distribution and severity of parenchymal and airway changes within the lung. In addition, a dichotomy between evidence of lung disease as presented on CT scans and physiologic markers of abnormality has been noted. Challenges in the young child include the need for sedation or anesthesia to perform the scan, as well as a respiratory motion artifact that often occurs. This artifact may lead to difficulty in interpreting subtle abnormalities of the airway

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and lung parenchyma noted in young children with CF. A controlled breathing technique developed by Long and coworkers[4] allows the infant's ventilation to be controlled non-invasively, thereby minimizing motion artifact and improving the quality of interpretation of chest CT findings. Certainly, a limitation associated with the use of CT scans is exposure to radiation, and dosing should be thoroughly reviewed with a pediatric radiologist. The articles by de Jong and colleagues, and Davis and associates, highlight the presence of early disease, even bronchiectasis, during infancy, and the dichotomy between structure and function.

Simple, yet sensitive techniques for the detection of early CF lung disease are ideal. The multiple-breath washout (MBW) technique uses inhalation of an inert gas (ie, sulfur hexafluoride; SF_6) to measure ventilation inhomogeneity. Subjects inhale a gas mixture containing an inert gas until the inhaled and exhaled concentrations of the gas are equal (washin phase). They then breathe room air until the exhaled concentration of the inert gas is below a certain threshold, typically 0.1% (washout phase). The lung function parameter, lung clearance index (LCI), is calculated as the cumulative expired volume in the washout phase divided by the functional residual capacity. A higher LCI implies increased ventilation inhomogeneity. MBW is currently being standardized for infants; the measure has great potential since it may be an early indicator of peripheral airway disease and may be used from infancy onward. The article by Aurora and coworkers outlines the sensitivity of MBW vs spirometry for the detection of early CF lung disease.

In conclusion, recent progress has shown that lung disease in children with CF begins early; however, the clinical manifestations are often silent. The physiologic and structural measures of disease described in this issue may serve as useful outcome measures for future clinical trials. Our current knowledge regarding early CF lung disease may lead to a more aggressive treatment approach in the youngest CF population.

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LUNG FUNCTION ABNORMALITIES FROM INFANCY THROUGH PRESCHOOL YEARS IN CHILDREN WITH CYSTIC FIBROSIS

Kozlowska WJ, Bush A, Wade A, et al; London Cystic Fibrosis Collaboration. **Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis.** *Am J Respir Crit Care Med.* 2008;178(1):42-49.

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Kozlowska and colleagues designed a prospective, longitudinal, case-control study to determine progression of lung disease in children with cystic fibrosis (CF) compared with healthy controls. Infant lung function testing, using the raised volume technique before 2 years of age and incentive spirometry between 3 and 5 years of age, were performed,

with a median of 3 lung function measurements per subject during the study period. Spirometric measures obtained included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) in preschoolers, forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}), forced expiratory volume in 0.5 seconds ($FEV_{0.5}$), and forced expiratory volume in 0.75 seconds ($FEV_{0.75}$). The latter 2 techniques are commonly used for infant and preschool lung function testing because of the shorter duration of exhalation required. Logistic regression was used to investigate the association between spirometric measures and clinical data, including height, weight, body mass index (by *z*-score), genotype, mode of presentation, wheeze on auscultation, recent cough, intravenous (IV) antibiotic use, and infection with *Pseudomonas aeruginosa*.

The study population included 48 children with CF and 33 healthy controls. Of the 48 subjects with CF, 22 (46%) had received at least 1 course of IV antibiotics (median, 1; range, 1 to 9) for respiratory exacerbation before 6 years of age. Six children presented for lung function testing with wheeze on auscultation but were otherwise asymptomatic; 6 had crackles on auscultation. A total of 37 children with CF were reported to have cough in the week prior to testing. By the completion of the study, 67% (32 of 48) of the children with CF had grown *P. aeruginosa* by deep pharyngeal culture at a median age of first growth of 1.4 years; 3 children grew mucoid *P. aeruginosa* strains. Of the 48 children with CF who were evaluated, 20 (42%) grew *Staphylococcus aureus* and 19 (39%) grew *Haemophilus influenzae*.

Within the multivariable linear regression model, height was the strongest predictor of all lung function measures. After adjustment for height, subjects with CF had mean reductions in $FEV_{0.75}$ and FEF_{25-75} of 7.5% (95% confidence interval [CI], 0.9, to 13.6) and 15.1% (95% CI, 3.6 to 25.3), respectively, compared with healthy controls, both of which were statistically significant ($p<0.05$). Reductions in FVC (2.6%), $FEV_{0.5}$ (4.3%), and FEV1 (7.1%) did not reach statistical significance in the overall population, although $FEV_{0.5}$ was a strong predictor of disease among infants. Positive *P. aeruginosa* culture prior to first lung function testing was associated with a further reduction in all lung function parameters except FEF_{25-75}; the presence of *P. aeruginosa* resulted in an additional mean reduction in FVC of 10.1% (95% CI, 4.0 to 15.9) and in $FEV_{0.75}$ of 9.0% (95% CI, 2.7 to 14.8) compared with healthy controls. The difference in lung function between *P. aeruginosa* -positive subjects and those who were *P. aeruginosa* -negative persisted regardless of culture clearance prior to testing. Wheeze on auscultation and cough in the week prior to testing were each independently associated with a reduction in $FEV_{0.5}$ and FEF_{25-75}.

This is the first prospective, longitudinal study using forced expiratory maneuvers to document the progression of lung disease in patients with CF vs healthy controls from infancy through the preschool years. CF was associated with a significant reduction in $FEV_{0.75}$ and FEF_{25-75} in the first 6 years of life, with larger reductions associated with a history of infection with *P. aeruginosa*, wheezing on auscultation, and cough in the week prior to testing. The authors suggest that because children with *P. aeruginosa* had similar lung function to those without *P. aeruginosa* prior to their first infection, this decline in lung function is a direct result of the infection itself. However, because subjects in this study were diagnosed by clinical symptoms, it is possible that significant lung damage had occurred prior to the study investigations. The fact that lung function was diminished regardless of current *P. aeruginosa* culture status is also of concern. These 2 observations leave open the possibility that *P. aeruginosa* is serving as a marker of more severe lung disease. Although $FEV_{0.5}$ was strongly correlated with the presence of lung disease in infancy, it was a poor predictor of disease in the preschool population. This may be related to differences in airway anatomy as children age, with $FEV_{0.5}$ representing central and peripheral airways in infants, but more predominantly central airways in older children. Evidence of decline in lung function in early childhood despite protocolized care of patients with CF, including aggressive management of infections, suggests that new therapies or more aggressive use of currently available treatments may be necessary to prevent early morbidity from CF lung disease.

PULMONARY FUNCTION TESTING IN INFANTS WITH CYSTIC FIBROSIS DIAGNOSED BY NEWBORN SCREENING

Linnane BM, Hall GL, Nolan G, et al; AREST-CF. **Lung function in infants with cystic fibrosis diagnosed by newborn screening.** *Am J Respir Crit Care Med.* 2008;178(12):1238-1244.

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Newborn screening for CF is now widely available in the United States, the United Kingdom, and Australia, allowing for the presymptomatic diagnosis of the disease. It has been shown that early diagnosis of CF by newborn screening improves nutritional status early in life; however, lung function in presymptomatic children with CF has not been evaluated. This study was designed to measure lung function via use of the raised volume rapid thoracoabdominal compression technique in infants with CF diagnosed by newborn screening. Values obtained were compared with those in healthy controls, and associations with pulmonary infection and inflammation (determined by bronchoalveolar lavage [BAL] performed within 24 to 48 hours after lung function testing) were investigated.

A total of 68 infants with CF and 49 healthy controls were studied using infant pulmonary function testing; 16 of the CF infants returned 1 year after their initial study visit for repeat lung function testing. Of the infants with CF, 96% had a diagnosis rendered or confirmed by newborn screening (immunoreactive trypsinogen/DNA). Half of the subjects with CF were homozygous for delta F508; an additional 46% were heterozygotes. The majority of infants (63%) were receiving prophylactic antibiotics at the time of evaluation. Height was similar between the CF infants and healthy controls; however, individuals in the CF group had lower mean body weight and body mass index *z*-scores.

After adjusting for gender, maternal smoking, and height, infants with CF had lower $FEV_{0.5}$ (-31.2 mL; 95% CI, -50.6 to -11.8) and forced expiratory flow at 75% of exhaled vital capacity (FEF75; -58 mL/s; 95% CI, -96.2 to -19.8) values than did healthy controls, corresponding to a 17.4% and 39.7% reduction in forced expiratory measures, respectively (differences in FVC were not statistically significant). The authors used data from healthy controls to create a predictive model for $FEV_{0.5}$ based on infant height, then generated $FEV_{0.5}$ *z*-scores for all infants in the study. The $FEV_{0.5}$, *z* -score in infants with CF decreased by 0.77 per year of age (95% CI, 0.41 to 1.14). Post hoc analysis revealed no difference in $FEV_{0.5}$ *z*-score between healthy controls and subjects with CF <6 months of age, whereas infants with CF >6 months of age had a mean *z* -score of -1.13, vs 0.02 in healthy controls (95% CI, -1.57 to -0.72). Similar differences between infants with CF and healthy controls were reportedly shown for FVC and FEF75, although the data are not included in the article. Whereas the majority of the data were cross-sectional, there was a decline in $FEF_{0.5}$ *z* -score of -0.73 (95% CI, -1.51 to 0.06), in FVC of -1.35 (95% CI, -2.52 to -0.17), and in FEF_{75} of -1.3 (95% CI, -2.27 to -0.33) in the 16 infants with CF who returned for lung function testing 1 year after their initial evaluation.

BAL fluid cultures grew *S. aureus* (17.8%), *H. influenzae* (8.9%), and *P. aeruginosa* (6.7%), as well as other pathogens (19.9%). Neither culture results nor inflammatory markers (total cell count, neutrophil percentage, free neutrophil elastase, or interleukin-8 [IL-8]) explained changes in lung function. Clinical symptoms, hospital admissions, and genotype also failed to show a significant association with diminished lung function.

This is the first study of lung function in infants with CF diagnosed by newborn screening. Despite optimized nutrition and early care, infants with CF appear to have significantly diminished lung function compared with healthy controls, which did not correlate with infection or inflammation as detected by BAL. Differences between CF infants and controls were first detectable after 6 months of age. Although the authors acknowledge

that the predominantly cross-sectional nature of this study is a significant limitation, it is important to note that the decline in $FEF_{0.5,}$ per year of age shown in the CF group as a whole (compared with healthy controls) was similar to that reported in the subgroup of CF infants in whom lung function testing was repeated 1 year later (0.77 vs 0.73, respectively). This study suggests that decline in lung function in children with CF may begin at a very early age, and there may be a "therapeutic window" in which lung function is relatively normal and thus interventions may have a maximum effect.

PROGRESSION OF STRUCTURAL AIRWAY DAMAGE ON COMPUTED TOMOGRAPHY IN CHILDREN WITH CYSTIC FIBROSIS

de Jong PA, Nakano Y, Hop WC, et al. **Changes in airway dimensions on computed tomography scans of children with cystic fibrosis.** *Am J Respir Crit Care Med.* 2005;172(2):218-224.

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It is believed that the airways of newborns with CF are structurally normal and that abnormalities develop progressively, beginning early in life. Computed tomography (CT) scanning may be more sensitive than pulmonary function testing (PFT) for the detection of airway abnormalities in children and adults with mild CF lung disease, and several published CT scoring systems are currently available. The composite CT score has the disadvantage of providing an overall value based on multiple structural findings; thus, following progression of composite CT scoring may mask particular patterns of structural change in the lungs of patients with CF. The authors measured airway wall thickening and bronchial dilatation in a cohort of CF subjects using 2 scans performed 2 years apart. Comparisons were made with CT scans from control subjects with normal lungs, and first and second scans from patients with CF were compared to assess the progression of structural airway disease. Among individuals with CF, measures of structural disease were also compared with changes in PFT parameters over time.

A total of 23 clinically stable children with CF were studied, with a mean age at first CT scan of 11.1 years (range, 4.0 to 15.9 years) and at second CT scan of 12.9 years (range, 6.2 to 17.9 years). Patients with CF were compared with control subjects (n = 21) without lung disease, who had a mean age at CT scan of 11.6 years (range, 3.6 to 17.2 years). Airway-artery pairs were identified, and measurements included airway wall area (WA), airway lumen area (LA), arterial area (AA), and airway wall thickness (AWT). AWT and the ratio of WA/AA were considered markers of airway wall thickening; LA/AA ratio was used to define bronchial dilatation. PFT data were available on 21 of the 23 subjects with CF; FEF_{25-75} data were assessed in 16 subjects. Mean FEV1 at the time of initial CT was 71% predicted (±16), FVC was 83% predicted (±16), and FEF_{25-75} was 54% predicted (±29).

The LA/AA ratio was 1.92 times higher in children with CF compared with healthy controls. Moreover, the WA/AA ratio was 1.45 times higher in children with CF compared with healthy controls. AWT changed significantly between the first and second CT scans (p=0.02), increasing by a mean of 0.03 mm in 2 years (no other airway measurements demonstrated a significant change over time). Four CT scoring systems (Brody, Helbich, Santamaria, and Bhalla [2-5]) all showed significant progression of airway damage over time, with a mean change over 2 years of 3% to 4% of the maximum score (P<.02). Within the composite CT scores, only the bronchiectasis score worsened significantly (P=.007). There was no significant change in PFT parameters over the 2 years between the first and second CT scans, except for an improvement in residual volume/total lung capacity of -12% (P=.03). AWT was the only measure that showed a significant (P=.002)

correlation with PFT data; for each 0.01-mm increase in AWT, FEF_{25-75} decreased by 0.45% predicted. LA/AA and WA/AA ratios did not correlate with global CT scoring, nor did they correlate with PFT.

This study shows a striking difference in bronchial dilatation and AWT (as measured by airway LA, and LA/AA and WA/AA ratios) on CT scans in children with CF compared with control subjects. Because airways with mucus plugging (potentially more damaged airways) were excluded from measurements and there was more mucus plugging on the second CT scan than on the first (20.5% of airway-artery pairs excluded vs 7.9%, respectively), changes in LA/AA and WA/AA ratios may be underestimated. Although these ratios did not appear to change over the 2-year time span, AWT and composite CT scores (driven predominantly by change in the bronchiectasis component) increased significantly. The lack of correlation between changes in bronchiectasis scoring and LA/AA ratio may have occurred because the bronchiectasis scores also reflect peripheral airways that were not included in LA/AA calculations (because of lack of visible arteries). Therefore, peripheral airway damage could be driving changes in the progression of bronchiectasis. The change in AWT was negatively correlated with FEF_{25-75} , suggesting that quantitative measures of AWT may be useful in assessing structural lung disease in patients with CF as an adjunct to the qualitative measures used as part of component scoring systems. This correlation may be associated with the impact of increased AWT on airflow, or AWT may serve as a marker for additional pathology, including small airway destruction. In this study, CT scans were more sensitive than PFT at tracking progression of lung disease, suggesting that CT scans may serve as useful outcome measures in future studies of children with CF.

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COMPUTED TOMOGRAPHY AND BRONCHOALVEOLAR LAVAGE FINDINGS IN EARLY CYSTIC FIBROSIS LUNG DISEASE

Davis, SD, Fordham LA, Brody AS, et al. **Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis.** *Am J Respir Crit Care Med.* 2007;175(9):943-950.

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Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR. **High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate.** *Pediatr Radiol* 1999;29:731–735.

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Davis and colleagues conducted a prospective study evaluating the sensitivity of high-resolution CT (HRCT) of the chest as an outcome measure in young children with CF. This study was designed to (1) identify regional distribution of CF lung disease during a pulmonary exacerbation in children <4 years of age; (2) correlate BAL cultures and inflammatory markers with areas of "greatest" and "least" disease on HRCT; and (3) determine the sensitivity of HRCT in detecting changes in airway disease following IV antibiotic therapy and intensified airway clearance.

A total of 17 children with CF aged 2 to 44 months scheduled to undergo clinically indicated bronchoscopy for pulmonary exacerbation were enrolled in the study. Each subject received chest x-ray (CXR) 1 to 2 days prior to bronchoscopy. On the day of bronchoscopy, a sedated, controlled-ventilation HRCT was performed, and lobes with the “greatest” and the “least” disease were identified qualitatively. These 2 lobes were then independently sampled by BAL, and the samples were sent for bacterial culture, cell count and differential, and IL-8 levels. Of the 17 individuals evaluated, 15 received IV antibiotics and intensified airway clearance (based on clinical assessment); 13 of them returned within 1 week of completion of intensified therapy for a second HRCT and CXR. Modified Brody HRCT scores (comprising bronchiectasis/bronchial dilatation, mucus plugging, peribronchial thickening, parenchymal lung disease, and hyperinflation subscores) were compared pre- and posttherapy, and regional changes were assessed. Brasfield CXR scores were also compared pre- and posttreatment.

The right lung consistently had a higher disease burden than did the left; the lobe identified as having the greatest disease on qualitative and quantitative (Brody scoring) evaluation was on the right in 100% and 82% of subjects, respectively. Similarly, the lobe with the least disease was on the left in 94% of subjects by qualitative evaluation and in 76% by quantitative evaluation ($p<0.01$). Total Brody score (all lobes) was significantly higher on the right than on the left. The total HRCT score improved significantly between visits 1 and 2 (pre- and posttreatment) ($p<0.01$), with significant improvements in subscores for hyperinflation and bronchiectasis/bronchial dilatation($p<0.01$ for both). The mean score for the lobe with the greatest disease showed significant improvement pre- and posttreatment ($p=0.002$), whereas the score for the lobe with the least disease did not change significantly. Brasfield scoring of plain CXRs was ≥20 (maximum score, 25) in all but 2 subjects and showed a trend toward improvement only between visits ($P=.06$). On BAL evaluation, IL-8 levels and neutrophil percentage were significantly higher in the lobe with the greatest vs the least disease ($p<0.01$ and $p=0.04$, respectively). Bacterial count and total cell count tended to be higher in the lobe with the greatest disease, but differences did not reach statistical significance. BAL cultures grew *S. aureus* (65%), *P. aeruginosa* (41%), *H. influenzae* (18%), and *Moraxella catarrhalis* (18%). Two subjects (1 with *P. aeruginosa* and *S. aureus*, 1 with *S. aureus* alone) grew organisms from the lobe identified as having the greatest disease but no organisms from the lobe with the least disease.

This is the first study to compare BAL findings and HRCT in the preschool age-group, and the first to compare HRCT findings pre- and posttherapy for pulmonary exacerbation in this population. Results demonstrate significant regional variation in airway inflammation, as evidenced by neutrophil percentages and IL-8 levels. Improvement in HRCT scoring following IV antibiotic therapy and intensified airway clearance suggests that HRCT is a sensitive outcome measure in this young population with relatively mild lung disease. Evidence of increased disease burden in the right lung may be secondary to gastroesophageal reflux disease with aspiration or to diminished clearance of secretions from the right lung compared with the left. Regional differences noted on both HRCT and BAL evaluation underscore the importance of performing multisite lavage in this population. Reversibility of HRCT findings, particularly hyperinflation, bronchiectasis, and bronchial dilatation in the lobe with the greatest disease, suggests that permanent lung disease in the preschool population may be prevented or delayed, and highlights the necessity of aggressive therapy for pulmonary exacerbations.

USE OF MULTIPLE-BREATH WASHOUT IN PRESCHOOL CHILDREN WITH CYSTIC FIBROSIS

Aurora P, Bush A, Gustafsson P; London Cystic Fibrosis Collaboration. **Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis.** *Am J Respir Crit Care Med.* 2005;171(3):249-256.

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Gustafsson PM, de Jong PA, Tiddens HA, Lindblad A. **Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis.** *Thorax* 2008;63:129-134.

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Identifying early CF lung disease has fueled interest in PFT methods that may be performed from infancy onward. Several techniques have been developed for the preschool age-group—preschool spirometry, plethysmography for the measurement of specific airway resistance, specific airway resistance (sRaw), and multiple-breath washout (MBW) measuring lung clearance index (LCI). Higher LCI and sRaw values are suggestive of airway disease, whereas lower $FEV_{0.5}$ and FEF_{25-75} values indicate obstructive airway disease. The study by Aurora and coworkers was designed to investigate the feasibility and sensitivity of each of these measures in a cohort of children with CF, aged 2 to 5 years, vs age-matched, healthy control subjects.

A total of 40 children with CF and 37 healthy controls were recruited for this study, with a mean age of 4.1 years (standard deviation [SD] 0.9) and 4.2 (SD 0.9) years, respectively. Of these children, 30 in each group were able to complete all 3 maneuvers (preschool spirometry, plethysmography, and MBW). The *z*-scores for $FEV_{0.5}$, FEF_{25-75}, FRC, and sRaw were calculated using reported data from the healthy control population. The authors also used healthy control subjects to generate a mean LCI for the healthy population, with an LCI >1.96 SD above the mean then classified as abnormal. There was no relationship between LCI and age in either the control or the CF population.

Children with CF had significantly higher mean LCI (9.61 vs. 6.89, respectively; P<.001) and sRaw (*z*-score 1.83 vs 0.00; P<.001) values, and significantly lower $FEV_{0.5}$ (*z*-score -0.76 vs 0.00; P< .05) values than did control subjects. Abnormal LCI values were observed in 73% (22 of 30) of children with CF; sRaw was abnormal in 47% (14 of 30), $FEV_{0.5}$ in 7% (2 of 30), and FEF_{25-75} in 13% (4 of 30) of children with CF. One child with an abnormal sRaw had a normal LCI; all other children with an abnormal sRaw, $FEV_{0.5}$, or FEF_{25-75} had abnormal LCI values as well. LCI was higher in CF subjects infected with *P. aeruginosa* than in uninfected individuals (10.77 vs 8.83, respectively); however, a comparison of only uninfected CF subjects vs healthy controls continued to show significant differences in all measured lung function parameters. There was no difference in other lung function parameters between *P. aeruginosa* -positive and *P. aeruginosa* -negative cohorts.

This is the first study to compare spirometry, measures of airway resistance, and LCI in a large cohort of preschool patients with CF. The authors demonstrated that MBW could be successfully performed by skilled operators in a majority of preschoolers. Results suggest that LCI measured by MBW may be more sensitive than plethysmography or spirometry for detection of CF lung disease, and is further affected by the presence of *P. aeruginosa* infection. The clinical relevance of these findings has yet to be determined; however, recent reports in older children have shown LCI to be more sensitive than spirometry for structural changes on CT,[2] suggesting that elevated LCI values may be a marker of early lung disease in children with CF. Because MBW is now being performed in infants, this

measurement may serve as a single airway function assessment that can be followed throughout a person's life.

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Learning Objectives

At the conclusion of this activity, participants should be able to:

Newsletter:

- Describe the evolution of early lung disease in children with cystic fibrosis (CF)
- Discuss the techniques currently available for assessing lung function and disease in young children with CF
- Identify the structural and physiologic changes in the lungs of young children with CF

Podcast:

- Discuss the advantages and disadvantages of early physiologic and structural measurements available in the infant and preschooler with CF.
- Delineate the clinical and research utility of infant and preschool pulmonary function testing in the CF population.
- Discuss the clinical implications of structural abnormalities in the early CF lung.

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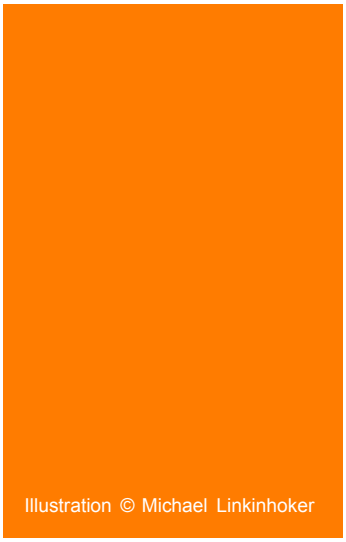

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