CHEST

Original Research

GENETIC AND DEVELOPMENTAL DISORDERS

Automated CT Scan Scores of Bronchiectasis and Air Trapping in Cystic Fibrosis

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Background: **Computer analysis of high-resolution CT (HRCT) scans may improve the assessment of structural lung injury in children with cystic fibrosis (CF). The goal of this cross-sectional pilot study was to validate automated, observer-independent image analysis software to establish objective, simple criteria for bronchiectasis and air trapping.**

Methods: **HRCT scans of the chest were performed in 35 children with CF and compared with scans from 12 disease control subjects. Automated image analysis software was developed to count visible airways on inspiratory images and to measure a low attenuation density (LAD) index on expiratory images. Among the children with CF, relationships among automated measures, Brody HRCT scanning scores, lung function, and sputum markers of inflammation were assessed.**

Results: **The number of total, central, and peripheral airways on inspiratory images and LAD (%) on expiratory images were significantly higher in children with CF compared with control subjects. Among subjects with CF, peripheral airway counts correlated strongly with Brody bronchiectasis scores by two raters ($r = 0.86$, $P < .0001$; $r = 0.91$, $P < .0001$), correlated negatively with lung function, and were positively associated with sputum free neutrophil elastase activity. LAD (%) correlated with Brody air trapping scores ($r = 0.83$, $P < .0001$; $r = 0.69$, $P < .0001$) but did not correlate with lung function or sputum inflammatory markers.**

Conclusions: **Quantitative airway counts and LAD (%) on HRCT scans appear to be useful surrogates for bronchiectasis and air trapping in children with CF. Our automated methodology provides objective quantitative measures of bronchiectasis and air trapping that may serve as end points in CF clinical trials.**

CHEST 2014; 145(3):593–603

Abbreviations: ATV = air threshold value; CF = cystic fibrosis; FEF_{25-75} = midvolume forced expiratory flow; HRCT = high-resolution CT; HU = Hounsfield unit; ICC = intraclass correlation coefficient; LAD = low attenuation density; MMP = matrix metalloprotease; ROI = region of interest; RV = residual volume; TLC = total lung capacity

A thin-section CT scan, the best noninvasive tool for assessing bronchiectasis and structural lung injury, is commonly used to monitor cystic fibrosis (CF)-related lung disease because it provides morphologic information that is complementary to the functional information provided by lung function tests. Structural changes detected by CT scans often precede functional changes in children with CF,[1-5] and CT scanning may be a more sensitive method than measurement of lung function for detecting disease progression.[6,7] Furthermore, CT scanning is a potential outcome measure for CF clinical trials.[8,9]

To provide quantitative information, CT images must be converted into numeric data to allow statistical comparison between scans. Both qualitative visual scoring by expert readers and quantitative computer analysis have been used successfully to interpret CT scans in CF. In numerous studies, expert reader CT scan scores have been shown to correlate with other CF lung disease parameters, including clinical status and lung function.[10-17] Although expert visual scoring such as the Brody scoring system[16] includes more features of CF lung disease than can be evaluated by automated software, it is time consuming and limited by the number of expert readers available. In contrast, automated computer analysis does not require specially trained observers, avoids observer bias and variability, offers better standardization, and

is a more sensitive method for detecting subtle changes.[18-21]

The most studied metric of quantitative analysis from CT scans is air trapping.[22] Air trapping, a result of small airways obstruction, is indicated by areas of abnormally low lung attenuation on expiratory CT images. Air trapping has been quantified in CF and other lung diseases using a variety of lung-density approaches.[19,23-26]

Although air trapping is an important early indicator of peripheral airways disease in children with CF, the hallmark of airway pathology is bronchiectasis. The key feature of bronchiectasis on CT scanning is an enlarged airway lumen with bronchi that appear larger than the accompanying artery; however, this definition may underestimate the extent of airway damage.[27] Other radiographic findings include the failure of the larger airways to taper while progressing to the lung periphery and the identification of airways in the most peripheral areas of the lung, within 2 cm of the costal or paravertebral pleura.[28] Therefore, the number of visible airways, especially ones in the periphery, may be a surrogate of bronchiectasis on CT scans. There has been one previous report of counting visible airways in children with difficult-to-treat asthma.[29]

The objectives of this cross-sectional pilot study were to develop and validate automated, observer-independent image analysis software to quantify airway counts and the degree of air trapping on high-resolution CT (HRCT) scans in children with CF; to compare automated CT scan measures between children with CF and age-matched disease control subjects; and to examine relationships among automated CT scan measures, Brody CT scan scores, pulmonary function measures, and sputum markers of inflammation in children with CF.

Manuscript received March 11, 2013; revision accepted September 4, 2013.
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A prior abstract with preliminary data was presented at the 2006 North American Cystic Fibrosis Conference, November 2-5, 2006, Denver, CO, and part of this article has been presented in abstract form (Sagel SD, Swiercz W, Heltshe S, Kaess H, Anthony M. *Pediatric Pulmonology* 2006;41[S29]:387).
Funding/Support: This research was supported by the National Institutes of Health (NIH) [K23 RR018611] and by the NIH/National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Institute [Grant UL1 TR000154].
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DOI: 10.1378/chest.13-0588

Materials and Methods

Study Subjects

During routine outpatient clinic visits, we randomly recruited 35 children between the ages of 6 and 15 years who had CF. These children were studied during times of clinical stability, defined by both clinical impression and having had no hospitalizations or changes in antibiotic regimen during the 1 month prior to being studied. Twelve disease control subjects of similar ages who had undergone an HRCT scan for a variety of clinical indications (asthma, n = 4; chronic cough, n = 2; suspected interstitial lung disease, n = 2; exercise-induced dyspnea and/or hypoxia, n = 3; and pulmonary hypertension, n = 1) were identified. Inclusion criteria for the control group were having a similar age range to that of the CF group, CT scans showing no evidence of parenchymal or airways disease, and minimal air trapping on expiratory images. The criteria used for defining the control group did not include lung function or anthropometric measurements.

The protocol, No. 03-759, was approved by the Colorado Multiple Institutional Review Board, and informed consent was obtained from each of the subjects with CF, their parents, or both. Institutional approval was obtained to analyze deidentified HRCT scans from the control subjects.

Study Design

Each subject with CF underwent an HRCT scan of the chest, pulmonary function testing, and sputum induction during one outpatient clinic visit. All HRCT scans were performed between 2003 and 2005 on an Asteion S4 scanner (Toshiba Medical Systems Europe) using a pediatric protocol with a tube potential of 120 kVp, a current of 140 mA, and a 1-s scan time. Slice thickness was 1 mm, and scans were reconstructed with a high-frequency algorithm. The image matrix was 512 × 512 pixels, and the field of view was determined based on the subject's size. Inspiratory images were obtained at 10-mm intervals, extending from the lung apices to below the costophrenic angles, at full voluntary inspiration. During a breath hold after full voluntary exhalation, six equally spaced expiratory images were obtained. The total effective radiation dose was estimated to be $<$6.23 mSv, with variation based on patient size. The HRCT scans were evaluated independently by two individuals (rater 1 and rater 2) using the Brody scoring system[16] to generate overall lung disease scores and subscores (standardized, expressed as percent: 0% to 100%) for the presence and severity of bronchiectasis and air trapping.

Spirometry was performed according to American Thoracic Society guidelines[30,31] using a Sensormedics Vmax22 system (CareFusion). Lung volumes were obtained by plethysmography. The functional indexes measured included FEV_1, FVC, midvolume forced expiratory flow (FEF_{25-75}), total lung capacity (TLC), residual volume (RV), and RV/TLC. Percent predicted values were based on Wang et al[32] and Hankinson et al.[33]

Sputum was induced by having the subject inhale 3% hypertonic saline for six 2-min sessions, as described previously.[34] The sputum was collected into two containers, which were both transported on ice to the laboratory for processing within 20 min. One specimen was processed for quantitative cultures, according to the findings of a consensus conference on CF microbiology.[35] *Pseudomonas aeruginosa* and *Staphylococcus aureus* infection status was defined based on the result of this single sputum culture. The other specimen was processed for cytology and measurement