High-Resolution Computed Tomography Imaging of Airway Disease in Infants with Cystic Fibrosis

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Rationale: The development of early lung disease in patients with cystic fibrosis (CF) remains poorly defined.

Objective: Determine whether asymptomatic infants with CF have evidence for changes in airway structure when assessed by high-resolution computed tomography, and whether airway structure correlates with airway function in this age group.

Methods: Thirteen infants with CF (8–33 mo) and 13 control infants (7–25 mo) were evaluated. Airway wall and lumen areas were measured from three 1-mm-thick cross-sectional images obtained from upper, middle, and lower lobes during a respiratory pause with the lungs inflated to an airway pressure of 20 cm H₂O. Lung tissue density was measured from images obtained during a respiratory pause at FRC. Forced expiratory flows were measured by the rapid thoracic compression technique in 11 infants with CF.

Results: Airway wall area increased more per unit increase in airway size, whereas airway lumen area increased less per unit increase in airway size in the CF than in the control group. Among infants with CF, a greater ratio of wall to lumen area correlated with lower airway function. In addition, lung density at relaxed (passive) FRC was lower for infants with CF than for control infants (0.38 vs. 0.43 g/ml; $p < 0.02$).

Conclusions: Our results indicate that infants with CF have thickened airway walls, narrowed airway lumens, and air trapping, when assessed by high-resolution computed tomography, and measurements of airway structure correlated with airway function.

Keywords: airway structure; high-resolution computed tomography; lung disease

Our understanding of the early pulmonary pathophysiology of cystic fibrosis (CF) has greatly expanded over the last two decades. Measurements of lung function have demonstrated the presence of airway obstruction in infants with CF without respiratory symptoms (1–4), and bronchoalveolar lavage has demonstrated that airway inflammation can be present even among infants with CF without respiratory symptoms (5, 6). Despite these advancements, our current knowledge about structural changes in the lungs of infants with CF is very limited and has primarily been obtained from autopsy studies. Lungs of newborns with CF have essentially normal histology; however, autopsied lungs from severely affected infants with CF can dem-

onstrate bronchiectasis as early as age 6 mo (7, 8). The availability of autopsied lungs of infants is currently very limited, and those obtained are most likely atypical of the general CF population. In adults and cooperative older children, high-resolution computed tomography (HRCT) has emerged as a powerful technique to assess lung structure *in vivo* (9, 10). Evaluations of adults with asthma, chronic obstructive pulmonary disease, or emphysema have demonstrated changes in lung structure on CT images, and quantitative measures of airway size, wall thickness, and parenchymal tissue density, as well as measures of pulmonary function have been consistent with histologic findings (11–15). Studies using CT imaging of older children and adults with CF have primarily used qualitative scoring systems (16–24) rather than quantitative methods of image analysis used in other respiratory diseases (11–15, 21, 25–30).

Respiratory motion artifact and the inability to obtain images at referenced lung volumes have been important limitations in the use of HRCT imaging and quantitative analysis in infants. Long and colleagues (31) have described a technique to induce a brief respiratory pause near total lung capacity (TLC) to obtain HRCT images in sedated infants. These investigators have also reported that infants with CF have increased airway wall thickness and dilated airway lumens when assessed using HRCT images (26). The purpose of our study was to evaluate whether quantitative measures of airway structure assessed by HRCT imaging correlate with measures of airway function in infants with CF, and whether these infants have evidence of air trapping when assessed by parenchymal tissue density measurement at FRC. Preliminary results of this study were presented as abstracts (32, 33).

METHODS

See the online supplement for more details regarding methods.

Subjects

Thirteen patients with CF aged between 3 mo and 2.5 yr were evaluated. These patients were clinically stable outpatients with no acute respiratory symptoms for at least 3 wk before evaluation. Thirteen control infants were recruited in the radiology department from patients undergoing CT imaging for nonrespiratory medical problems. The study was approved by our institutional review board, and informed consent was obtained from the parents.

HRCT Imaging and Analysis

Sedated infants (50–75 mg/kg chloral hydrate) breathed through a facemask and T-connection, which had a bias flow of 10 to 15 L/min. Manual occlusion of the expiratory portion augmented inspiratory effort to a lung volume at an airway pressure of 20 cm H₂O (V_{20}), which was set by a pressure relief valve; removal of the expiratory occlusion resulted in passive deflation. Several cycles of inflation–deflation inhibited inspiratory effort and resulted in a respiratory pause that persisted for at least several seconds. During the induced respiratory pauses near TLC and passive FRC, 1-mm-thick images (120 kV, 50 mA) were acquired at three anatomic locations: the top of the aortic arch, the lung

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hilum at the level of the carina, and approximately 1 cm above the diaphragm. The total radiation exposure was estimated to be 30 mrad.

Using custom software (EmphyxJ, Vancouver, BC, Canada), airway dimensions were analyzed only from the images obtained near TLC (34). Briefly, a seed point is placed in the airway lumen and rays are projected outwards in all directions. Using the x-ray attenuation values, the intersections of each ray with the internal and external sides of the airway wall were identified. The airway lumen and outer airway wall perimeters were obtained by connecting the endpoints of each of the rays as they transected the airway wall. The total airway area and the lumen airway were calculated as the areas within the outer and inner perimeters, respectively; the wall area was calculated as the difference between these two areas.

Lung tissue density was calculated from the images obtained near TLC and at passive FRC. The lung parenchyma was automatically segmented from the chest wall and large central blood vessels using CT values between $-1,000$ (air) and -200 Hounsfield units, as previously used by other investigators (35, 36). Lung density (g/ml) was calculated from the Hounsfield units of each voxel.

Airway Function

Airway function was measured in the subjects with CF using the raised-volume technique, as previously described (37). Forced expiratory flows were initiated from a lung volume at which the airway pressure was 30 cm H₂O and proceeded to residual volume. Jacket compression pressures were progressively increased until no further increases in the flow volume curve were obtained, and then three technically acceptable maneuvers were obtained. Forced expiratory flows were measured at 50 and 75% of expired volume (FEF₅₀, FEF₇₅), between 25 and 75% of expired volume (FEF₂₅₋₇₅), and at FEV_{0.5}. Values from the best curve (highest product of FVC and FEF₂₅₋₇₅) were expressed as *z* scores from a reference population evaluated in our laboratory (37). The *z* score is the difference between the measured and predicted value divided by the standard deviation for the normal infants.

Statistical Analysis

Demographic characteristics for infants with CF and control infants were compared using one-way analysis of variance, and categorical characteristics were compared with Fisher's exact test. In the analyses of differences in the airways between groups, repeated-measures analysis of variance was used to compare areas, as well as their ratios. The potential confounding effect of age and somatic size was not found to be significant and removed from the final analysis. Mean values for tissue density were compared using one-way analysis of variance. A *p* value of less than 0.05 was deemed statistically significant for all tests. SAS version 8.02 (SAS Institute, Inc., Cary, NC) was the software used for the repeated-measures analysis of variance.

RESULTS

Demographic data for infants with CF and control subjects are summarized in Table 1. There were no statistically significant differences between groups for age, weight, body length, and sex. The number of airways analyzed for the infants with CF and control subjects was not statistically different (mean, 8.4 [range, 3–21] vs. 9.5 [range, 4–19]; *p* > 0.80). The total airway

areas (lumen area + wall area) for each of the airways measured for the individual infants with CF and control subjects are illustrated in Figure 1. There was no significant difference between the two groups for this measure of airway size when assessed by repeated-measures analysis of variance (mean $\pm$ SE: 7.70 ± 0.61 vs. 7.54 ± 0.60 mm²; *p* > 0.85).

Repeated measurements of airway wall area and airway lumen area for 56 airways were obtained by a second observer, as well as repeated measurements by the same observer. The intraobserver, intraclass correlation coefficients for measurements of airway wall area and airway lumen area were 0.89 and 0.99, respectively. The interobserver intraclass correlation coefficients for measurements of airway wall area and airway lumen area were 0.78 and 0.96, respectively. The Bland-Altman plots illustrated that the scatter of differences between observations was more prominent for the smaller airways; however, there were no systematic differences between observations.

The individual measurements of lumen area versus total airway area for all of the airways measured from infants with CF and control subjects are illustrated in Figure 2. The effects on lumen area of total area and group (CF vs. control) and their interaction were analyzed. The lumen area was strongly correlated with the total area and increased as the total area increased (*p* < 0.0001). There was a significant interaction term that indicated that the relationship between the lumen area and the total area were different between the two groups (*p* < 0.0001); the CF group had a less steep slope so that the lumen area increased less for the CF than the control group with each unit increase in the total area. Because the interaction was significant, the significant group effect (*p* < 0.0001) identified from the model indicated that the two groups have different intercepts in their regression lines.

The individual measurements of wall area versus airway size for all of the airways measured from infants with CF and control subjects are illustrated in Figure 3. Wall area was strongly correlated with the total area and increased as the total area increased (*p* < 0.0001). The significant interaction term indicated that the relationship between the wall area and the total area was different between the two groups (*p* < 0.0001); the CF group had a steeper slope so that the wall area increased faster compared with the control group with each unit increase in the total area. Because the interaction was significant, the significant group effect (*p* < 0.0001) identified from the model indicated that the two groups had different intercepts in their regression lines.

TABLE 1. PATIENT DEMOGRAPHICS: CONTROL VERSUS CYSTIC FIBROSIS

	Age, mo Mean (range)	Sex	Weight, kg Mean (range)	Body Length, cm Mean (range)
Control subjects (n = 13)	14.7 (7–25)	7 M, 6 F	9.7 (6.8–12)	75.7 (67.5–82.7)
Subjects with cystic fibrosis (n = 13)	17.2 (8–33)	11 M, 2 F	9.8 (7.7–12.8)	74.5 (67.7–91.6)
<i>p</i> Value	0.28	0.20	0.85	0.65

Definition of abbreviations: F = female; M = male.

Figure 1. Total airway area (mm²) versus age (mo) for all of the individual airways measured from the individual control subjects (open squares) and subjects with cystic fibrosis (CF; solid circles). There was no significant difference in total airway area for the two groups (*p* > 0.85).

Figure 2. Lumen area (mm^2) versus total airway area (mm^2) for all airways measured from control subjects (open squares) and subjects with CF (solid circles). The CF group had a less steep slope, which means that the lumen area increased less for the CF than for the control group with each unit increase in the total area. CF: lumen area = $-0.197 + 0.133 \times \text{total area}$ control; lumen area = $-1.198 + 0.323 \times \text{total area}$.

The ratio of wall area to total airway area versus total airway area for all of the airways measured from infants with CF and control subjects are illustrated in Figure 4. The ratio of wall area to total area was strongly correlated with the total area and decreased as the total area increased ($p < 0.0001$). The significant interaction term indicated that the relationship between the ratio and the total area was different between the two groups ($p < 0.0001$); the CF group had a less negative slope so that the ratio decreased less compared with the control group with each unit increase in the total area. Because the interaction was significant, the significant group effect ($p < 0.001$) identified from the model indicated that the two groups had different intercepts in their regression lines.

Lung tissue density was analyzed in 13 infants with CF and

Figure 3. Wall area (mm^2) versus total airway area (mm^2) for all airways measured from control subjects (open squares) and subjects with CF (solid circles). The CF group had a steeper slope, which means that the wall area increased faster for the CF than control group with each unit increase in the total area. CF: wall area = $0.197 + 0.867 \times \text{total area}$ control; wall area = $1.198 + 0.677 \times \text{total area}$.

Figure 4. Wall area/total airway area versus airway size (mm^2) for all airways measured from control subjects (open squares) and subjects with CF (solid circles). The CF group had a less negative slope, which means the ratio decreased less for CF than control group with each unit increase in the total area. CF: wall area to total area ratio = $0.914 - 0.003 \times \text{total area}$ control; wall area to total area ratio = $0.960 - 0.013 \times \text{total area}$.

in 12 control infants; one control subject had motion artifact in the images obtained at FRC. Figure 5 illustrates the distributions of lung density within the images obtained from the lower lobes during a respiratory pause at FRC. The cumulative distributions of tissue density for the subjects with CF were shifted to the left and less dense compared with the distributions for the control subjects. The mean tissue densities at FRC were significantly lower for the infants with CF than for the control subjects in the lower and middle lobes, but not significantly different for the upper lobes (Figure 6). For HRCT images obtained at V_{20} , there were no significant differences for infants with CF and control subjects in tissue density measured in the lower, middle, or upper lobes ($p \geq 0.20$; see the online supplement).

Pulmonary function was measured in 11 of the 13 infants with CF; two subjects did not sleep and data were not obtained. The group of infants with CF demonstrated decreased airway function; the group's mean z scores were significantly ($p < 0.05$) less than zero for the following parameters: $\text{FEF}_{50} = -2.0$, $\text{FEF}_{75} = -1.6$, and $\text{FEV}_{0.5} = -2.1$; mean values for the coefficients of

Figure 5. Cumulative distributions of tissue densities measured from the high-resolution computed tomography images obtained from the lower lobes during respiratory pause at FRC. The subjects with CF (solid line) had significantly lower mean tissue densities than the control subjects (dashed line; $p < 0.01$).

Figure 6. Comparison of lung tissue density (mean + SE) for control and CF groups. At FRC, infants with CF had significantly lower lung tissue density than control infants in the lower ($p < 0.01$) and middle lobes ($p < 0.03$), but not significantly different for the upper lobes ($p > 0.55$).

variation for repeated measurements were 11, 18, and 3%, respectively. Among the infants with CF, there were significant negative correlations between the ratio of wall area to lumen area and the measures of airway function; the larger the ratio of wall area to lumen area, the lower or more negative the z score for airway function: $FEV_{0.5}$ ($r^2 = 0.66$, $p < 0.002$), FEF_{50} ($r^2 = 0.41$, $p < 0.002$), and FEF_{75} ($r^2 = 0.40$, $p < 0.002$). The relationship between the ratios of wall area to lumen area versus $FEV_{0.5}$ is illustrated in Figure 7.

DISCUSSION

Our study demonstrates that reduced airway caliber assessed from HRCT imaging in infants with CF correlates with lower airway function in this very young age group. Infants with CF had thicker airway walls and smaller airway lumens, which was associated with lower forced expiratory flows. In addition, the infants with CF demonstrated air trapping and lower tissue density at passive FRC.

This study obtained quantitative measures of the airways and the lung parenchyma from HRCT slices obtained from three different anatomic regions of the lung. Using a limited number of HRCT slices does not enable the specific airway generations to be identified and assumes that comparable airways are sampled at V_{20} from both the infants with CF and control infants. This method of sampling is similar to that used for morphometric measurements of isolated, fixed lungs *in vitro*; tissue slices are obtained from similar anatomic locations within the lung. We found no significant difference in the number of airways sampled for the infants with CF and control subjects. In addition, there

Figure 7. For infants with CF, the ratio of wall area to lumen area versus $FEV_{0.5}$, expressed as z score. Greater airway wall thickening was associated with lower airway function ($r^2 = 0.66$, $p < 0.002$).

was no significant difference between the two groups in the overall size of the airways measured at V_{20} . Last, we assessed airway size with the lung inflated to the same distending pressure in all subjects. Because we have previously reported that the elastic properties of the respiratory system does not differ between infants with CF and control subjects in this young age group (38), the degree of volume distention (V_{20}) should be similar for both groups of subjects in this study. Our finding that tissue density at V_{20} did not differ for the two groups is consistent with similar degrees of volume distention. Cumulatively, these findings strongly suggest that a comparable distribution of airways were examined from the infants with CF and control infants.

The airway wall areas adjusted for airway size were greater for the infants with CF than for the control subjects whether expressed as the absolute wall area (mm^2) or a percentage of total airway area. In addition, the airway lumen areas adjusted for airway size were smaller for the infants with CF than for control subjects whether expressed as an absolute lumen area (mm^2) or as a percentage of the total airway area. Thicker airway walls and smaller airway lumens in the infants with CF suggest that the airway wall has encroached on the airway lumen to produce airway narrowing for the subjects with CF. This interpretation would be supported by our finding that a higher ratio of wall to lumen area was associated with lower airway function among the infants with CF.

The thicker airway wall and the narrower airway lumen that we observed by HRCT imaging of the CF airways may be secondary to structural changes in the airway wall *per se* and/or mucosal secretions lining the lumen side of the airway wall. We are not able to discriminate between these two mechanisms and both are likely to occur secondary to the airway inflammation that is present even in asymptomatic infants with CF (5, 6, 39). We are aware of only one previous study that used quantitative airway measurements of HRCT images to assess patients with CF, and that study also evaluated infants (26). Long and coworkers (26) reported an increase in airway wall diameter in infants with CF, which is consistent with our current finding of an increased airway wall area. However, these investigators reported an increased diameter of the airway lumen in the infants with CF, which contrasts with our findings of a smaller airway lumen area. The average age of the subjects with CF evaluated by Long and coworkers was 2.4 yr (range, 2.5 mo to 5.5 yr), which is greater than the average age of 1.3 yr (range, 8 mo to 2.7 yr) evaluated in our study. Although we did not find that age was a significant factor among our infants with CF, we recruited relatively healthy outpatients with CF. The difference between the two studies in the findings of encroachment of the airway wall into the airway lumen versus dilation of the airway lumen may represent varying stages of CF-related airway disease early in life, as well as methodologic differences, such as distending airway pressure at which images were obtained, airway selection, software analysis, and whether airway measurements were referenced to the dimensions of the adjacent pulmonary blood vessel. Longitudinal studies will be required to define the progressive pathophysiology early in life.

We also found that parenchymal tissue density at FRC was lower for the infants with CF than for control infants. During the induced respiratory pause, the lung is at passive FRC, which is determined by the passive mechanical properties of the respiratory system. Therefore, measurements at this passive lung volume should accurately reflect hyperinflation secondary to airway obstruction, without the potential of an elevated lung volume secondary to the subject actively elevating end-expiratory lung volume during tidal breathing. We measured tissue density using a range of $-1,000$ (air) and -200 Hounsfield units, which is a similar range used by other investigators to quantify the lung parenchyma in patients with CF, as well as other lung diseases (29,

35, 36, 40). Our finding of decreased tissue density in infants with CF is consistent with findings previously reported in older children with CF with mild airway disease (36, 41). These older subjects with CF demonstrated air trapping at FRC and near residual volume by HRCT measurements, which also correlated with air trapping assessed by measurement of lung volumes. Although we did not measure lung volumes in our infants, lower tissue density at passive FRC in the infants with CF would be most consistent with air trapping. The airway narrowing present at V_{20} will become even more accentuated with decreasing lung volume and contribute to airway closure, decreased forced expiratory flows at low lung volumes, and air trapping at FRC; we were not able to obtain measurements of airway caliber at FRC because most of the airway lumens and airway walls were too small to resolve.

We also found that air trapping was not present uniformly throughout the lung of the infants with CF; air trapping was present in the slices from the lower and middle lobes, but not in the slice from the upper lobes. Our observation in infants with CF is consistent with recent findings in older children with CF with mild airway disease who demonstrated greater air trapping in the lower than in the upper lobes (20, 36, 41, 42). Although our lung slices sample only a limited portion of the lung, cumulatively these findings suggest that the earliest airway disease in subjects with CF may not occur in the upper lobes (36, 43).

Limitations of our study include the relatively small number of subjects, the limited number of CT slices used in the scanning protocol, and the relatively small number of airways evaluated. In addition, lung function measurements were not obtained in the control subjects, so that our correlations between structure and function were limited to the CF group. Obtaining lung function measurements in the control subjects would have required a second sedation, as well as an additional visit to the hospital. Larger studies, as well as longitudinal studies, will be required to assess the potential interactions related to age, sex, somatic size, and disease severity.

The risks of radiation exposure always remain a concern when using HRCT imaging, particularly in children. In this study, structural abnormalities were detected using HRCT imaging of the chest. Because CF is a genetic disease with high morbidity and mortality, the use of CT imaging in patients with CF may have a favorable risk-benefit ratio for assessing early lung disease and outcomes of interventions (44). Early intervention studies are required to determine whether the findings we observed by quantitative assessment of HRCT images are fixed or reversible in subjects with CF at this very young age. Several studies have demonstrated short-term improvement in the HRCT score of older children and adults with CF treated with intravenous antibiotics for an acute pulmonary exacerbation (45–48). Similarly, HRCT imaging has been used to demonstrate improvement in older children with CF treated with inhaled DNase (17). Quantitative analysis of the same airways before and after a therapeutic intervention would be ideal; however, this approach would probably require imaging the whole lung or large contiguous segments so that the same airways could be identified and followed longitudinally. Whole lung imaging could significantly increase the radiation dosage, which has become an area of increasing concern in pediatric CT imaging. Low-radiation-dose protocols for whole lung imaging may provide adequate resolution for qualitative scoring, but may not provide adequate resolution for quantitative measurements of the airways of interest in CF. Alternatively, measuring changes in lung tissue density at FRC, even from a limited number of lung slices, may be an effective index of generalized airway disease that would not require individual airways to be identified.

In conclusion, infants with CF have thickened airway walls and narrowed airway lumens when measured by HRCT images obtained at V_{20} . In addition, these early airway changes correlate with lower airway function measured from forced expiratory flows. Last, infants with CF have lower parenchymal tissue density at FRC, which suggests the presence of air trapping and diffuse airway disease.

Conflict of Interest Statement: T.M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.J.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.H.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.D.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.S.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.O.C. received \$2,500 in 2002 and £1,500 in 2003 for serving on an advisory board for GlaxoSmithKline (GSK). In addition, he is the coinvestigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project. A percentage of his salary between 2003 and 2006 (\$15,000/yr) derives from contract funds provided to a colleague, Peter D. Pare, by GSK for the development of validated methods to measure emphysema and airway disease using computed tomography. R.S.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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