Tsuneo Yamashiro[1,2]
Shin Matsuoka[3]
Raúl San José Estépar[4]
Mark T. Dransfield[5]
Alejandro Diaz[6,7]
John J. Reilly[8]
Samuel Patz[1]
Sadayuki Murayama[2]
Edwin K. Silverman[6,9]
Hiroto Hatabu[1]
George R. Washko[6]

Quantitative Assessment of Bronchial Wall Attenuation With Thin-Section CT: An Indicator of Airflow Limitation in Chronic Obstructive Pulmonary Disease

Keywords: airway wall attenuation, airway wall thickness, chronic obstructive pulmonary disease, CT, pulmonary emphysema

DOI:10.2214/AJR.09.3653

Received September 9, 2009; accepted after revision February 2, 2010.

E. K. Silverman received an honorarium for a talk on COPD genetics in 2006, grant support for two studies of COPD genetics (2004–2009), and consulting fees (2005–2009) from GlaxoSmithKline; an honorarium from Wyeth for a talk on COPD genetics in 2004; an honorarium from Bayer HealthCare for a symposium at the European Respiratory Society meeting in 2005; and honoraria for talks in 2007 and 2008 and consulting fees in 2008–2009 from AstraZeneca.

Supported by NIH grant 1K23HL089353-01A1 and a grant from the Parker B. Francis Foundation.

This study was conducted with data provided by the National Lung Screening Trial.

[1]Center for Pulmonary Functional Imaging, Brigham and Women's Hospital, Boston, MA.

[2]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan. Address correspondence to T. Yamashiro (clatsune@yahoo.co.jp).

[3]Department of Radiology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan.

[4]Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, MA.

[5]Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama, Birmingham, AL.

[6]Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, MA.

[7]Pontificia Universidad Catolica de Chile, Santiago de Chile, Chile.

[8]Department of Medicine, University of Pittsburgh, Pittsburgh, PA.

[9]Channing Laboratory, Brigham and Women's Hospital, Boston, MA.

AJR 2010; 195:363–369

0361–803X/10/1952–363

OBJECTIVE. The purpose of this study was to evaluate the relation between bronchial wall attenuation on thin-section CT images and airflow limitation in persons with chronic obstructive pulmonary disease.

SUBJECTS AND METHODS. One hundred fourteen subjects (65 men, 49 women; age range, 56–74 years) enrolled in the National Lung Screening Trial underwent chest CT and prebronchodilation spirometry at a single institution. At CT, mean peak wall attenuation, wall area percentage, and luminal area were measured in the third, fourth, and fifth generations of the right B_1 and B_{10} segmental bronchi. Correlations with forced expiratory volume in the first second of expiration (FEV_1) expressed as percentage of predicted value were evaluated with Spearman's rank correlation test.

RESULTS. The peak wall attenuation of each generation of segmental bronchi correlated significantly with FEV_1 as percentage of predicted value (B_1 third, $r = -0.323$, $p = 0.0005$; B_1 fourth, $r = -0.406$, $p < 0.0001$; B_1 fifth, $r = -0.478$, $p < 0.0001$; B_{10} third, $r = -0.268$, $p = 0.004$; B_{10} fourth, $r = -0.476$, $p < 0.0001$; B_{10} fifth, $r = -0.548$, $p < 0.0001$). The correlation coefficients were higher in peripheral airway generations. Wall area percentage and luminal area had similar significant correlations. In multivariate analysis to predict FEV_1 as percentage of predicted value, the coefficient of determination of the model with the combination of percentage of low-attenuation area (< –950 HU) and peak wall attenuation of the fifth generation of the right B_{10} was 0.484; the coefficient of determination with percentage of low-attenuation area and wall area percentage was 0.40.

CONCLUSION. Peak attenuation of the bronchial wall measured at CT correlates significantly with expiratory airflow obstruction in subjects with chronic obstructive pulmonary disease, particularly in the distal airways.

The clinical application of CT-based quantitative assessments of the morphologic features of the airway wall in persons with chronic obstructive pulmonary disease (COPD) has been the subject of numerous investigations [1–10]. Some of the most common imaging-based indexes of airway disease used in those studies are wall area percentage, which is the percentage of the total cross-sectional area of the airway occupied by the airway wall, and luminal area, which is the cross-sectional area of the airway lumen. Both of these metrics are believed to reflect the chronic remodeling process characterized by airway wall thickening and luminal occlusion occurring in the distal small airways. The evidence to support this belief is based on the direct relation of these indexes to airway remodeling found at histologic examination [3, 11] and their relation to spirometric measures of expiratory airflow [1–3, 6, 10]. Hasegawa and colleagues [1] refined such observations by finding that wall area percentage and luminal area from the distal airways, typically the fifth or sixth generations of the bronchial tree, have stronger correlations with airflow limitation than those from the proximal airways. Replication of such findings has led to the consensus that quantitative assessment of the wall area percentage and luminal area of the distal fifth and sixth airway generations results in the strongest correlation with lung function in persons with COPD [6, 10].

In a previous study [12] we found that mean peak attenuation of the airway wall, defined as the peak attenuation on the density curve, can also be used as a CT-based airway index of COPD. Measurements of the

luminal area from the segmental bronchi in the right upper lobe yielded significant correlations with forced expiratory volume in the first second of expiration (FEV_1 expressed as percentage of predicted value [hereafter, FEV_1%]). In thin-walled structures, such as the distal bronchi, peak wall attenuation is expected to represent both wall density and wall thickness and to be a sensitive CT airway index for predicting airflow limitation, which is similar to wall area percentage. The investigation did not, however, explore generation-based measurements of peak wall attenuation and their tendency to correlate with lung function. We therefore hypothesized that peak wall attenuation of the distal bronchi would show stronger correlation with FEV_1% than peak wall attenuation of the proximal bronchi in a manner similar to wall area percentage and luminal area. The aims of the current study were, first, to compare peak wall attenuation with other airway indexes, including luminal area and wall area percentage, in evaluating airflow limitation across multiple airway generations and, second, to investigate whether airflow limitation is more closely related to peak wall attenuation of the distal airways than to peak wall attenuation of the proximal airways.

Subjects and Methods

The study and manuscript were reviewed and approved according to the procedures outlined in the NLST/LSS Publications, Presentations, and Associated Studies Working Group's Review Procedures and Authorship Guidelines. This study also received approval from the institutional review boards at our institutions.

Subjects

Subjects were eligible to participate in the National Lung Screening Trial, which is a multicenter randomized trial in which annual chest radiographs are compared with CT scans for early detection of lung cancer among current and former smokers. A full description of the trial is available at the National Lung Screening Trial Website [13]. In brief, approximately 50,000 subjects were enrolled in the trial, provided they were 55–74 years old and had a minimum cigarette smoking history of 30 pack-years. Detailed exclusion criteria from the National Lung Screening Trial are shown at the Website. For example, persons who had a history of lung resection, lung cancer, or an acute respiratory infection requiring treatment with antibiotics in the previous 12 weeks were not included in the trial.

At a single institution, 304 subjects, who provided additional informed consent, performed optional prebronchodilation spirometry according to the American Thoracic Society standards [14]. The spirometric results were expressed as percentage of predicted value and used to classify the subjects' conditions according to the modified Global Initiative for Chronic Obstructive Lung Disease criteria for disease severity [15, 16]. All subjects were assigned to one of five groups (smokers with normal lung function and those with Global Initiative for Chronic Obstructive Lung Disease stage I, stage II, stage III, or stage IV disease). According to the National Lung Screening Trial protocol, subjects with stage III or IV disease were eventually assigned to one group (stage III and IV) because of the small number of subjects with stage IV disease.

To standardize the scanning protocol for this study, 46 subjects who underwent CT with different tube currents were initially excluded. Among the other 258 subjects, 129 subjects, or one half of the eligible cohort, were randomly selected without investigators' knowledge of clinical information. Fifteen subjects were secondarily excluded from the study for the following reasons: severe image noise caused by obesity (eight subjects), pulmonary fibrosis (three subjects), image artifact due to subject's motion or previous surgical procedure (two subjects), and atelectasis in the targeted lobe (two subjects). Consequently, 114 subjects (65 men, 49 women; age range, 56–74 years) were included in the study.

Thin-Section CT

All 114 subjects underwent imaging with a 4-MDCT scanner (Light Speed QX/i, GE Healthcare) at full inspiration without receiving contrast medium. Images were obtained at 120 kV and 60 mA. The scanning field of view ranged from 27 to 42 cm, depending on the subject's body habitus. The exposure time was 0.9 seconds and the matrix size was 512 × 512 pixels. Images were contiguously reconstructed with a 2.5-mm slice thickness and the standard algorithm.

Airway Analysis

Airway analysis was performed on transverse images with free open-source software (Airway Inspector, Brigham and Women's Hospital) as described previously [12]. Using a lung window setting (width, 1,000 HU; level, –450 HU), one chest radiologist (8 years of experience) identified the upper apical segmental bronchus (B_1) and the posterior basal segmental bronchus (B_{10}) in the right lung, where a segmental bronchus is defined as the third-generation airway. These bronchi were chosen because in the long axis they are generally perpendicular to the imaging plane and circular in appearance in the standard axial imaging plane. After identification of the third-generation airway, the more peripheral fourth and fifth generations were identified on the same trunk of the bronchus. In each generation, a measured point (bronchus) was selected on the image that was peripherally next to the branching point of the generation. Ultimately, three generations (third to fifth) on both the right B_1 and B_{10} were measured in all subjects. Only airways in which the ratio of the long and short axes was less than 2 were included in this investigation.

Airway measurement was performed semiautomatically with the software, and peak wall attenuation, wall area percentage, and luminal area were measured with the full-width at half-maximum method [11, 17, 18]. Peak wall attenuation is defined as the mean value of the peak attenuation values on the density curves used in the full-width at half-maximum method. Figure 1 shows an example of the measurement of peak wall attenuation. All analyses were performed without investigators' knowledge of the subjects' clinical information.

Reproducibility of Airway Analysis

Intraobserver error was tested by having the radiologist measure peak wall attenuation, wall area percentage, and luminal area of the right B_1 twice in 15 subjects, who were randomly selected from among the 114 subjects. The second measurement was performed 2 months after the first session. To evaluate interobserver error, the radiologist and another chest radiologist (18 years of experience) independently measured the same indexes of the right B_1 in 15 randomly selected subjects. Intraobserver and interobserver reproducibility were assessed by Bland-Altman analysis [19].

CT Densitometry

Emphysema was evaluated on the basis of low-attenuation area (< –950 HU). The software used for the airway analysis was used to segment the lung parenchyma from the chest wall and the hilum, and the volumes of both the lung parenchyma and low-attenuation area were automatically calculated [12, 16]. The percentage of low-attenuation area of the whole lung was obtained by dividing the total low-attenuation area volume by the total parenchymal volume.

Statistical Analysis

All statistical analyses were performed with JMP 7.0 software (SAS Institute). Data were expressed as mean ± SD. Linear regression analysis and Spearman's rank correlation analysis were used to estimate the relation between measured CT indexes and FEV_1%. Multiple regression analysis with FEV_1% as the dependent outcome was performed to evaluate the relative contributions of the airway and emphysema indexes. Values of $p < 0.05$ were considered statistically significant.

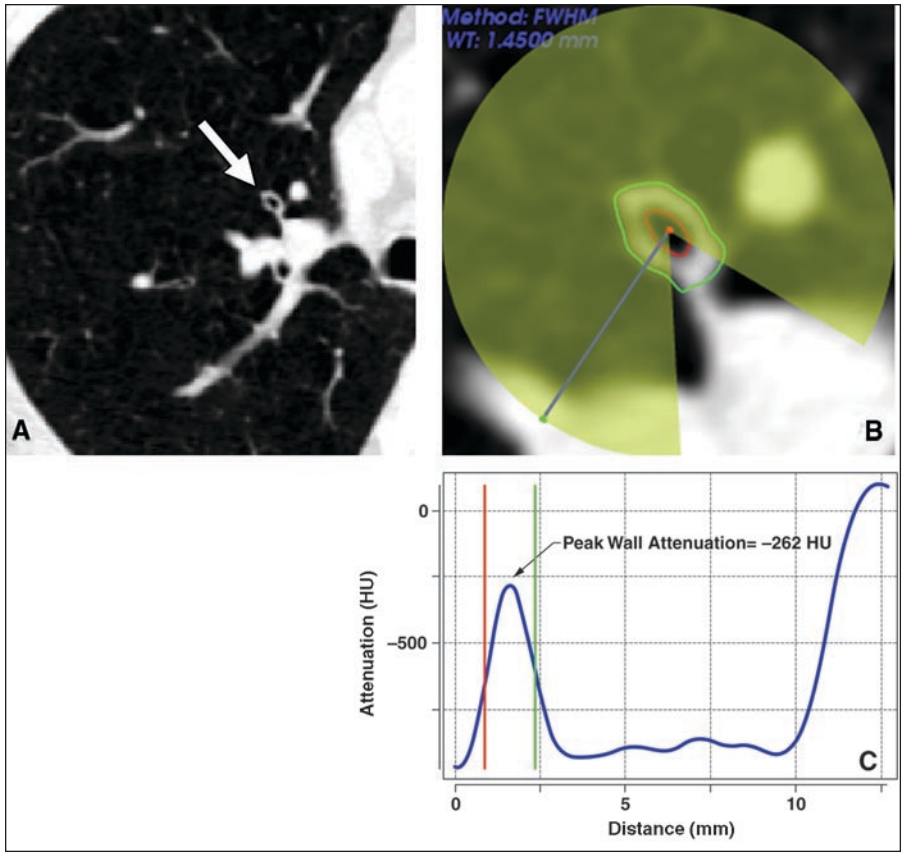

Fig. 1—64-year-old woman with chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease stage III; FEV_1%, 38% of predicted value).
A, CT image shows fourth generation of right upper apical segmental bronchus (B_1) (*arrow,* **A**).
B, CT image shows airway measurement performed with sector measurement method to exclude adjacent vascular and interstitial component (*yellow*).
C, Single intensity curve based on full-width at half-maximum (*blue line,* **B**) shows peak wall attenuation is –262 HU. Final mean peak wall attenuation is different from this value and automatically calculated by averaging values from all rays in sector.

Results

Subject Characteristics

A summary of the subjects' clinical information is shown in Table 1. Smoking index had an inverse correlation with FEV_1% (r = –0.304, p = 0.001). According to the modified Global Initiative for Chronic Obstructive Lung Disease staging, the 114 subjects were in the following four groups: 37 smokers with normal lung function, 19 patients with stage I disease, 40 patients with stage II disease, and 18 patients with stage III and IV disease.

Prevalence of Emphysema

The mean percentage of low-attenuation area was 7.0% ± 7.3%. Percentage of low-attenuation area had significant negative correlation with FEV_1% (r = –0.460, p < 0.0001) (Table 1).

Reproducibility of Airway Measurements

The results of the reproducibility of airway analysis are shown in Table 2. Plots of the average of and difference between the measurements of peak wall attenuation are shown in Figure 2. These values were used to evaluate intraobserver and interobserver reproducibility. For each plot, the mean difference did not appreciably deviate from zero, and the limits of agreement were small. In addition, no relation was observed between measurement error and the value of peak wall attenuation.

Airway Measurements and Correlations With Lung Function

The results of the CT measurements of the airways, including peak wall attenuation, wall area percentage, and luminal area, are shown in Table 3. Mean peak wall attenuation decreased with peripheral progression of the generations of bronchial segments. Correlations between measured airway indexes and FEV_1% are shown in Table 4. The peak wall attenuation of all generations showed significant correlation with FEV_1% (B_1 third generation, r = –0.323, p = 0.0005; B_1 fourth generation, r = –0.406, p < 0.0001; B_1 fifth generation, r = –0.478, p < 0.0001; B_{10} third generation, r = –0.268, p = 0.004; B_{10} fourth generation, r = –0.476, p < 0.0001; B_{10} fifth generation, r = –0.548, p < 0.0001). Furthermore, the correlation coefficients increased with distal progression from the third through fifth generations in both the right B_1 and the right B_{10} (Figs. 3 and 4). Like peak wall attenuation, wall area percentage and luminal area had significant correlation with FEV_1% (Table 4). The correlation coefficients of wall area percentage and luminal area also were greater with distal progression of the airways from the third through the fifth generations in both the right B_1 and the right B_{10}.

Correlations Among Airway Indexes

Table 5 shows the correlations among peak wall attenuation, wall area percentage, and luminal area in both B_1 and B_{10}. Overall, strong correlations were found between wall area percentage and luminal area. Weak or insignificant correlations were found between peak wall attenuation and luminal area and between peak wall attenuation and wall area percentage.

TABLE 1: Summary of Clinical Information and Pulmonary Function Results

Characteristic	Mean ± SD	Range	Correlation With FEV_1 as Percentage of Predicted Value
Age (y)	62 ± 5	56–74	–0.331[b]
Smoking index (pack-years)	64 ± 32	30–207	–0.304[c]
Forced vital capacity (L)	3.7 ± 0.9	1.8–5.9	0.245[c]
FEV_1 (L)	2.3 ± 0.8	0.7–4.3	—
FEV_1 as percentage of predicted value	75 ± 21	30–119	—
FEV_1/FVC ratio (%)	64 ± 14	27–92	—
Percentage of low-attenuation area (< –950 HU)	7.0 ± 7.3	0.6–35.9	–0.460[a]

Note—FEV_1 = forced expiratory volume in the first second of expiration. Dash [—] indicates not applicable.
[a] p < 0.0001.
[b] p < 0.001.
[c] p < 0.01.

TABLE 2: Reproducibility of Airway Measurements

Measurement	Mean Difference ± SD	Limits of Agreement
Intraobserver error		
Peak wall attenuation (HU)	1.90 ± 12.76	–23.63 to 27.43
Wall area percentage	0.13 ± 1.55	–2.96 to 3.22
Luminal area (mm^2)	0.35 ± 1.15	–1.94 to 2.64
Interobserver error		
Peak wall attenuation (HU)	9.31 ± 14.95	–20.58 to 39.20
Wall area percentage	0.72 ± 1.68	–2.63 to 4.07
Luminal area (mm^2)	–0.13 ± 1.44	–3.03 to 2.77

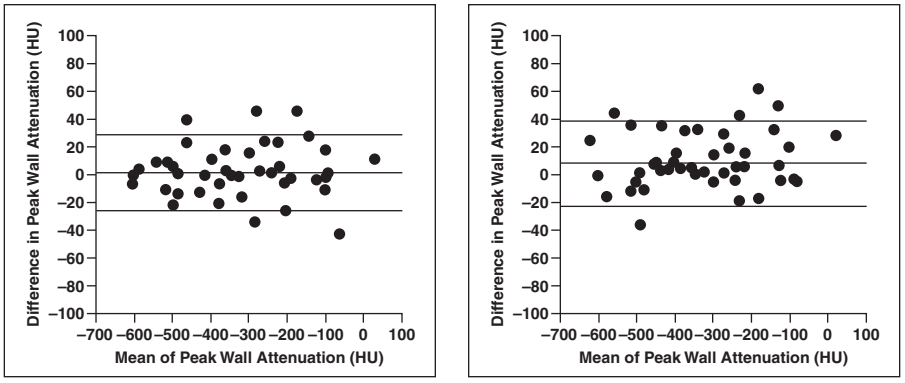

Fig. 2—Intraobserver and interobserver error for measurement of peak wall attenuation.
A and **B,** Scatterplots show intraobserver (**A**) and interobserver (**B**) error for measurement of peak wall attenuation with Bland-Altman analysis. Means and differences of two measurements are plotted. Mean difference does not appreciably deviate from zero, and limits of agreement are small. There is no obvious relation between measurement error and peak wall attenuation.

TABLE 3: CT Measurements of the Airways

Airway Segment and Generation	Peak Wall Attenuation (HU)		Wall Area Percentage		Luminal Area (mm^2)	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
B_1						
Third	–240 ± 122	–525 to 97	72 ± 7	53–84	16.1 ± 7.3	3.8–40.2
Fourth	–410 ± 132	–712 to –15	77 ± 6	62–87	7.4 ± 3.3	1.9–21.9
Fifth	–545 ± 104	–711 to –249	84 ± 4	68–92	3.6 ± 1.9	1.2–12.0
B_{10}						
Third	–303 ± 120	–623 to 38	73 ± 6	54–89	15.8 ± 7.2	4.6–40.5
Fourth	–457 ± 121	–676 to –165	78 ± 6	62–90	8.1 ± 3.3	2.0–17.9
Fifth	–541 ± 119	–737 to –164	83 ± 5	68–94	4.2 ± 2.0	1.1–10.6

Multivariate Analysis

Multivariate analysis was performed with an airway index and percentage of low-attenuation area to predict FEV_1% (Table 6). In total, six models were analyzed, each of which consisted of one of the fifth-generation airway indexes (peak wall attenuation, wall area percentage, or luminal area) and percentage of low-attenuation area. In each multivariate model, both the airway index and percentage of low-attenuation area were significant independent predictors of FEV_1%. The model including both the percentage of low-attenuation area and the peak wall attenuation of the right B_{10} had the highest coefficient of determination with FEV_1% ($R^2 = 0.484$).

Discussion

In this study, we found that peak wall attenuation can be used as another quantitative CT index for airway disease in persons with COPD. The correlative strength of these measurements with airflow limitation increases when the assessment is made in the more peripheral airway generations. These observations show that peak wall attenuation is a useful airway index, similar to more dimensional indexes such as wall area percentage and luminal area. Peak wall attenuation also may be more robust than these dimensional indexes, at least for the CT protocol used in this study.

CT analysis of the bronchi has increasingly been the subject of investigation of respiratory diseases such as asthma and COPD [1–10, 20–22]. In 2000, Nakano and colleagues [2] reported that wall area percentage, luminal area, and the ratio of wall thickness to the total cross-sectional area of the bronchus were related to FEV_1% in a cohort of persons with COPD. In accordance with this concept, Hasegawa and colleagues [1] undertook 3D CT assessment of the morphologic features of the airways in the third through sixth generations in persons with COPD. In that report, wall area percentage and luminal area were predictors of the degree of expiratory airflow obstruction, and the strength of these correlations increased with successively peripheral airway generations. Although such relations between lung function and the morphologic features of the central airways have not been consistently observed [4, 8], the tendency of the more peripheral airway generations to act as stronger predictors of lung function has been replicated [6, 10].

The basis for the correlations between peak wall attenuation and lung function in persons with COPD remains theoretic, but it may be attributable to concomitant changes in airway wall thickness and density that have been observed in persons with chronic inflammatory conditions involving the airways [23, 24]. Persons with relapsing polychondritis involving the tracheobronchial tree have been found to have airways with increased attenuation on CT scans [24]. In COPD, several pathologic studies have revealed that the mural remodeling process observed is associated with degeneration of the bronchial cartilage, fibrosis, smooth-muscle hypertrophy, calcification, and epithelial metaplasia, which can lead to excessive mucus secretion and luminal occlusion [25–27]. Although histopathologic examination was not performed in our study, we currently hypothesize that these airway changes, including mural fibrosis and calcification, would increase airway wall thickness and density in COPD, which may be detectable on CT images as a quantifiable change in airway wall

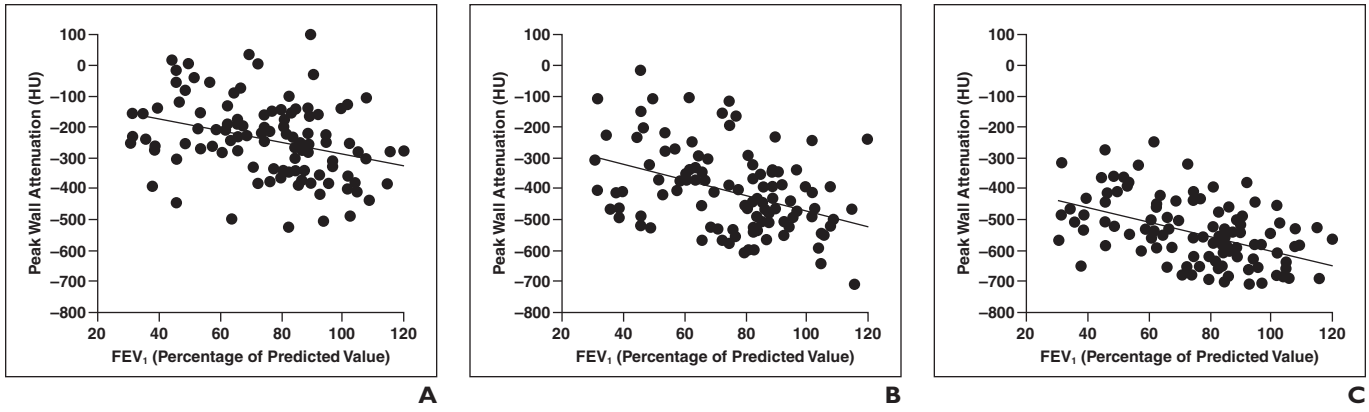

Fig. 3—Correlation between peak wall attenuation and forced expiratory volume in first second of expiration expressed as percentage of predicted value (FEV_1) in right B_1 segment.
A–C, Scatterplots show peak wall attenuation of each generation has significant negative correlation with FEV_1. Correlation coefficient increases with peripheral progression from third generation ($r = 0.323$, $p = 0.0005$) (**A**) through fourth generation ($r = -0.406$, $p < 0.0001$) (**B**) to fifth generation ($r = -0.478$, $p < 0.0001$) (**C**).

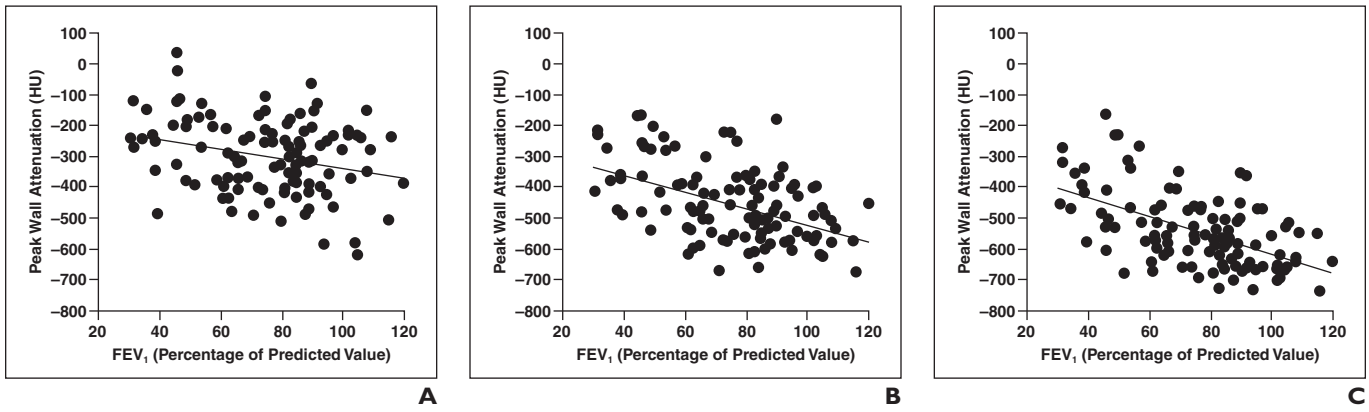

Fig. 4—Correlation between peak wall attenuation and forced expiratory volume in first second of expiration expressed as percentage of predicted value (FEV_1) in right B_{10} segment.
A–C, Scatterplots show that as in right B1 measurements, peak wall attenuation of each generation has significant negative correlation with FEV_1. Correlation coefficient increases with distal progression from third generation ($r = -0.268$, $p = 0.004$) (**A**) through fourth generation ($r = -0.476$, $p < 0.0001$) (**B**) to fifth generation ($r = -0.548$, $p < 0.0001$). Peak wall attenuation of fifth generation had highest correlation among overall airway measures in this study.

attenuation. However, because no tissue was available for histopathologic examination in our study cohort, these conjectures cannot be confirmed and the results of this study must be considered observational.

Although peak wall attenuation had the highest correlations with FEV_1% in both univariate and multivariate analyses in our study, the superiority of peak wall attenuation measurement over wall area percentage or luminal area measurements was not clearly found. We believe, however, that peak wall attenuation would be a unique, alternative airway index and would have potential for future CT-based airway analysis of COPD. As shown in Table 5, the correlations between peak wall attenuation and wall area percentage or luminal area are weaker than the correlation between wall area percentage and luminal area. It is already known that the thickness of thin structures, such as distal airways, often is overestimated with the full-width at half-maximum method, resulting in overestimation of wall area percentage and underestimation of luminal area [11, 12, 17, 18]. We contend, however, that measurement of peak wall attenuation represents a combination of the contrast reduction observed in thin-walled structures similar in size to the point spread function of the CT scanner [28] and possible changes in airway wall density, such as fibrosis and calcification. Results of previous studies [12, 29–32] support such a hypothesis and further suggest the optimal application of measurement of peak wall attenuation of such small thin-walled structures because differences in the thickness of the measured structures would be detected as differences in peak wall attenuation. Thus peak wall attenuation is expected to be more sensitive than wall area percentage in determining not only true airway wall density but also wall thickness of the distal airways. In the current study, because of the lower spatial resolution of CT, we did not conduct further airway assessments in the more distal airways, such as the sixth and seventh generations. Although we believe peak wall attenuation would be a more reliable airway index than wall area percentage and luminal area in the peripheral airways, future study focusing on the more distal airways is needed for evaluating the utility of peak wall attenuation measurement in comparisons with wall area percentage and luminal area.

There were limitations to this study. First, the CT data were not optimal for the quantitative assessments of airway wall structure owing to both the inherent noise associated with the low radiation dose and the CT protocol itself. Compared with the previous analyses in which isotropic voxel data were used with a voxel size of 0.625 mm [1, 6, 10], our CT

TABLE 4: Correlations Between CT Airway Indexes and Forced Expiratory Volume in the First Second of Expiration Expressed as Percentage of Predicted Value

Airway Segment and Generation	Peak Wall Attenuation		Wall Area Percentage		Luminal Area	
	r	*p*	*r*	*p*	*r*	*p*
B_1						
Third	−0.323	0.0005	−0.371	< 0.0001	0.284	0.002
Fourth	−0.406	< 0.0001	−0.399	< 0.0001	0.305	0.001
Fifth	−0.478	< 0.0001	−0.464	< 0.0001	0.408	< 0.0001
B_{10}						
Third	−0.268	0.004	−0.408	< 0.0001	0.282	0.002
Fourth	−0.476	< 0.0001	−0.451	< 0.0001	0.362	< 0.0001
Fifth	−0.548	< 0.0001	−0.475	< 0.0001	0.492	< 0.0001

TABLE 5: Correlations Among CT Airway Indexes

Airway Segment and Generation	Combination of Airway Indexes		
	Peak Wall Attenuation and Wall Area Percentage	Peak Wall Attenuation and Luminal Area	Wall Area Percentage and Luminal Area
B_1			
Third	0.193[d]	−0.094	−0.743[a]
Fourth	0.238[d]	0.084	−0.817[a]
Fifth	0.304[c]	0.093	−0.855[a]
B_{10}			
Third	0.337[b]	0.143	−0.674[a]
Fourth	0.441[a]	−0.321[b]	−0.836[a]
Fifth	0.460[a]	−0.340[b]	−0.854[a]

[a] $p < 0.0001$.
[b] $p < 0.001$.
[c] $p < 0.01$.
[d] $p < 0.05$.

images were reconstructed with a 2.5-mm thickness, and the measured bronchi were not always perpendicular on the images. Furthermore, fields of view were not standardized in this study, resulting in various pixel sizes among the subjects. Both the partial volume effect from the larger slice thickness and the lower spatial frequency of the reconstruction algorithm might have biased our airway measurements, particularly dimensional indexes such as wall area percentage and luminal area, toward overestimation or underestimation of true wall characteristics. A similar bias in measurements of peak wall attenuation also is difficult to predict. We cannot speculate whether our observations would be reproducible in different CT protocols. Further investigation is required to determine the relative influence of these processes on measurements of peak wall attenuation.

The second limitation was that the anatomic heterogeneity inherent in airway remodeling in persons with airway disease was not fully investigated in this study. In the earlier study, large variability and heterogeneity of the airway dimensions were reported in patients with asthma and in animal models [20, 33]. Matsuoka and colleagues [9] found that serial changes in airway dimensions, including luminal area and wall area percentage, are frequently observed in healthy persons. These findings suggest the potential difficulty in assuming that limited point measurements in the bronchi represent the whole airway tree and that results of a single measurement are reproducible in the same patient. Although we found significant correlations using peak wall attenuation and other indexes, it is still questionable whether the observed changes in the airway wall are uniform throughout the tracheobronchial tree.

Third, in measurement of thin-walled objects such as the distal airways, peak wall attenuation is influenced by wall thickness (owing to the point spread function of the CT scanner) and wall density [12, 31, 32]. Peak wall attenuation, particularly in the distal airways, therefore differs from the actual density of the bronchial wall. Although we believe that peak wall attenuation is an appropriate term to represent the peak attenuation of the density curve in the full-width at half-maximum method, it should be acknowledged that measured peak wall attenuation is a theoretic

TABLE 6: Results of Multivariate Analysis of Airway and Emphysema Indexes for Prediction of Forced Expiratory Volume in the First Second of Expiration Expressed as Percentage of Predicted Value

Model	R^2	Parameter Estimate (Airway Index)	Parameter Estimate (Percentage of Low-Attenuation Area)
Right upper lobe			
Peak wall attenuation (fifth-generation B_1) and percentage of low-attenuation area	0.390	−0.09	−117.00
Wall area percentage (fifth-generation B_1) and percentage of low-attenuation area	0.369	−1.88	−114.65
Luminal area (fifth-generation B_1) and percentage of low-attenuation area	0.346	4.05	−123.06
Right lower lobe			
Peak wall attenuation (fifth-generation B_{10}) and percentage of low-attenuation area	0.484	−0.09	−124.04
Wall area percentage (fifth-generation B_{10}) and percentage of low-attenuation area	0.400	−1.94	−121.12
Luminal area (fifth-generation B_{10}) and percentage of low-attenuation area	0.407	4.68	−118.17

Note—In all models, both airway and emphysema indexes are significant predictors of forced expiratory volume in the first second of expiration expressed as percentage of predicted value ($p < 0.0001$).

value and does not solely reflect the density of the targeted bronchial wall. It can be predicted that use of an experimental model with a very small field of view would allow depiction of the distal airway walls with multiple pixels and direct measurement of the density of airway walls in each pixel. However, such an experimental model cannot be applied to whole-lung CT and is therefore difficult to use in large CT studies of COPD. Furthermore, results of previous studies [31, 32] have suggested that the size of the field of view does not greatly influence peak wall attenuation, particularly when a standard kernel is used.

The results of this study show that peak wall attenuation is another airway index for evaluating airway abnormalities in COPD and is comparable to other airway indexes for predicting airflow limitation. As is observed with the use of wall area percentage or luminal area, FEV_1% is more closely related to the peak wall attenuation of the distal airways, such as the fifth generation of bronchi, than that of the proximal airways. In the multivariate analysis, the combination of percentage of low-attenuation area and peak wall attenuation of the fifth generation in the right B_{10} showed the highest correlation with FEV_1%. Additional investigation with optimal CT protocols is required to determine the utility of peak wall attenuation in prediction of lung function.

Acknowledgments

The authors thank Alba Cid, Kerianne R. Panos, Junichi Tokuda, and Sung-Hee Shin for important suggestions.

References

1. Hasegawa M, Nasuhara Y, Onodera Y, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173:1309–1315
2. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. *Am J Respir Crit Care Med* 2000; 162:1102–1108
3. Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 2005; 171:142–146
4. Lee YK, Oh YM, Lee JH, et al. Quantitative assessment of emphysema, air trapping, and airway thickening on computed tomography. *Lung* 2008; 186:157–165
5. Berger P, Perot V, Desbarats P, Tunon-de-Lara JM, Marthan R, Laurent F. Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. *Radiology* 2005; 235:1055–1064
6. Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Nakajima Y. Airway dimensions at inspiratory and expiratory multisection CT in chronic obstructive pulmonary disease: correlation with airflow limitation. *Radiology* 2008; 248:1042–1049
7. Ohara T, Hirai T, Sato S, et al. Longitudinal study of airway dimensions in chronic obstructive pulmonary disease using computed tomography. *Respirology* 2008; 13:372–378
8. Ohara T, Hirai T, Sato S, et al. Comparison of airway dimensions in different anatomic locations on chest CT in patients with COPD. *Respirology* 2006; 11:579–585
9. Matsuoka S, Kurihara Y, Nakajima Y, Niimi H, Ashida H, Kaneoya K. Serial change in airway lumen and wall thickness at thin-section CT in asymptomatic subjects. *Radiology* 2005; 234:595–603
10. Hasegawa M, Makita H, Nasuhara Y, et al. Relationship between improved airflow limitation and changes in airway calibre induced by inhaled anticholinergic agents in COPD. *Thorax* 2009; 64:332–338
11. de Jong PA, Muller NL, Pare PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. *Eur Respir J* 2005; 26:140–152
12. Washko GR, Dransfield MT, San Jose Estepar R, et al. Airway wall attenuation: a biomarker of airway disease in subjects with COPD. *J Appl Physiol* 2009; 107:185–191
13. National Cancer Institue Website. National Lung Screening Trial. http://www.cancer.gov/nlst. Accessed April 22, 2010
14. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS task force: standardisation of spirometry. *Eur Respir J* 2005; 26:319–338
15. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176:532–555
16. Dransfield MT, Washko GR, Foreman MG, San Jose Estepar R, Reilly J, Bailey WC. Gender differences in the severity of CT emphysema in COPD. *Chest* 2007; 132:464–470
17. Nakano Y, Whittall KP, Kalloger SE, et al. Development and validation of human airway analysis algorithm using multidetector row CT. *Proc SPIE* 2002; 4683:460–469
18. Kim N, Seo JB, Song KS, Chae EJ, Kang SH. Semi-automatic measurement of the airway dimension by computed tomography using the full-width-half-maximum method: a study on the measurement accuracy according to the CT parameters and size of the airway. *Korean J Radiol* 2008; 9:226–235
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1:307–310
20. Paganin F, Vignola AM, Seneterre E, Bruel JM, Chanez P, Bousquet J. Heterogeneity of airways obstruction in asthmatic patients using high-resolution computed tomography. *Chest* 1995; 107[3 suppl]:145S–146S
21. Boulet L, Belanger M, Carrier G. Airway responsiveness and bronchial-wall thickness in asthma with or without fixed airflow obstruction. *Am J Respir Crit Care Med* 1995; 152:865–871
22. Okazawa M, Müller N, McNamara AE, Child S, Verburgt L, Paré PD. Human airway narrowing measured using high resolution computed tomography. *Am J Respir Crit Care Med* 1996; 154:1557–1562
23. Coxson HO, Quiney B, Sin DD, et al. Airway wall thickness assessed using computed tomography and optical coherence tomography. *Am J Respir Crit Care Med* 2008; 177:1201–1206
24. Behar JV, Choi YW, Hartman TA, Allen NB, Page McAdams H. Relapsing polychondritis affecting the lower respiratory tract. *AJR* 2002; 178:173–177
25. Kim V, Rogers TJ, Criner GJ. New concepts in the pathobiology of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5:478–485
26. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350:2645–2653
27. Haraguchi M, Shimura S, Shirato K. Morphometric analysis of bronchial cartilage in chronic obstructive pulmonary disease and bronchial asthma. *Am J Respir Crit Care Med* 1999; 159:1005–1013
28. Shuping RE, Judy PF. Resolution and contrast reduction. *Med Phys* 1978; 5:491–496
29. Reinhardt JM, D'Souza ND, Hoffman EA. Accurate measurement of intrathoracic airways. *IEEE Trans Med Imaging* 1997; 16:820–827
30. Saba OI, Hoffman EA, Reinhardt JM. Maximizing quantitative accuracy of lung airway lumen and wall measures obtained from X-ray CT imaging. *J Appl Physiol* 2003; 95:1063–1075
31. Dougherty G, Newman D. Measurement of thickness and density of thin structures by computed tomography: a simulation study. *Med Phys* 1999; 26:1341–1348
32. Newman DL, Dougherty G, al Obaid A, al Hajrasy H. Limitations of clinical CT in assessing cortical thickness and density. *Phys Med Biol* 1998; 43:619–626
33. Brown RH, Zerhouni EA, Mitzner W. Variability in the size of individual airways over the course of one year. *Am J Respir Crit Care Med* 1995; 151:1159–1164