Airway Wall Thickness Assessed Using Computed Tomography and Optical Coherence Tomography

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Rationale: Computed tomography (CT) has been shown to reliably measure the airway wall dimensions of medium to large airways. Optical coherence tomography (OCT) is a promising new micron-scale resolution imaging technique that can image small airways 2 mm in diameter or less.

Objectives: To correlate OCT measurements of airway dimensions with measurements assessed using CT scans and lung function.

Methods: Forty-four current and former smokers received spirometry, CT scans, and OCT imaging at the time of bronchoscopy. Specific bronchial segments were identified and measured using the OCT images and three-dimensional reconstructions of the bronchial tree using CT.

Measurements and Main Results: There was a strong correlation between CT and OCT measurements of lumen and wall area ($r = 0.84$, $P < 0.001$, and $r = 0.89$, $P < 0.001$, respectively). Compared with CT, OCT measurements were lower for both lumen and wall area by 31 and 66%, respectively. The correlation between FEV₁% predicted and CT and OCT measured wall area (as percentage of the total area) of fifth-generation airways was very strong ($r = -0.79$, $r = -0.75$), but the slope of the relationship was much steeper using OCT than using CT ($y = -0.33x + 82$, $y = -0.1x + 78$), indicating greater sensitivity of OCT in detecting changes in wall measurements that relate to FEV₁.

Conclusions: OCT can be used to measure airway wall dimensions. OCT may be more sensitive at detecting small airway wall changes that lead to FEV₁ changes in individuals with obstructive airway disease.

Keywords: chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction, in most cases caused by inhalation of toxic particles, such as cigarette smoke (1, 2). It is well known that, in the susceptible host, chronic exposure to these particles causes an exaggerated inflammatory response

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Computed tomography is widely used to quantify airways in subjects with chronic obstructive pulmonary disease. Optical coherence tomography (OCT) is a new micron-scale resolution optical imaging method used in studies of the eye, gastrointestinal tract, and preneoplastic bronchial lesions.

What This Study Adds to the Field

OCT can be used to measure airway wall dimensions. OCT may be more sensitive at detecting small airway wall changes that lead to FEV₁ changes in individuals with obstructive airway disease.

that remodels the wall of the small airway, ultimately resulting in nonreversible airflow limitation (3, 4). Remodeling of the small airways is believed to occur early in the disease process and worsens with disease progression. The “gold standard” for assessing small airway disease is morphometry of resected lung tissue, but the invasiveness of this approach precludes its use in clinical studies. With the advent of high-resolution computed tomography (CT), and the development of multislice CT scanning techniques, CT has become a very popular technique for the noninvasive assessment of airway disease in COPD (5–8). Although there have been considerable improvements in the resolution of CT images over the past decade, CT scans are still limited by a pixel size of approximately 0.5 mm, which makes the measurement of small airways in particular prone to errors (9, 10). Moreover, there is growing concern regarding radiation-related cancer risks associated with repeated CT scanning, although the overall risk appears to be small (11–13).

A new noninvasive technique called optical coherence tomography (OCT) is gaining credibility as a thoracic imaging tool (14–17). Although similar in principle to B-type ultrasound, OCT uses near-infrared light instead of sound waves and does not require a transducing medium. A detector is used to collect back-scattered and reflected waves from the tissues, which are then compared with a reference beam using an interferometer (14). Due to the use of low coherence light, OCT can produce images with resolution in the range of 5 to 15 μm (14–17).

The hypothesis for this pilot study was that *in vivo* measurements of airway wall dimensions obtained using OCT would correlate with CT measurements of airway wall dimensions. Furthermore, we also evaluated if a correlation exists between OCT measures of airway wall area and FEV₁ and how this compares to similar measurements made using CT.

Some of the results of these studies have been previously reported in the form of an abstract (18).

METHODS

Subjects

Forty-four current and former smokers participating in two ongoing National Cancer Institute (NCI)-sponsored lung cancer chemoprevention trials were enrolled in this investigation before treatment with any chemopreventive agent. All subjects gave written, informed consent to participate in study. The study was approved by the Clinical Ethics Review Board of the British Columbia Cancer Agency and the University of British Columbia.

Spirometry

Spirometry was conducted using a flow-sensitive spirometer (Presto Flash Portable Spirometer, version 1.2; Spacelab Burdick, Inc., Deerfield, WI) according to American Thoracic Society recommendations (19). The FEV₁ and FVC were recorded in liters and as a percentage of predicted values using standardized prediction equations (20).

CT Imaging and Measurements

Contiguous 1-mm-thick CT images ("b35f," 120 kVp, 215 mA, 0.5-s rotation time) were acquired at suspended full inspiration while the subject was supine using a Siemens Sensation 16 multislice scanner (Siemens Medical Solutions, Erlangen, Germany). CT scans were analyzed using Pulmonary Workstation 2.0 software (VIDA Diagnostics, Iowa City, IA). Briefly, the CT scans were reformatted into three-dimensional images (Figure 1) and the airway lumen (Ai), total airway area (Ao), airway wall area (Aaw), and wall area percentage (WA%) defined as $(Ao - Ai)/Ao \times 100\%$ were measured at cross-section to the central axis of the airway as previously described (21). Additional detail on the method for making these measurements is provided in the online supplement.

OCT Imaging and Measurements

Bronchoscopy was performed using the Onco-LIFE device (Novadaq Technologies, Inc., Richmond, BC, Canada) under local anesthesia and conscious sedation (22). The design of the OCT system and measurement of the airways are further outlined in the online supplement. Briefly, a small optical probe (Pentax SOCT-PR-150300; Pentax Corp., Tokyo, Japan) with an outer diameter of 1.5 mm and a depth of focus of 2 mm was inserted through the biopsy channel of the bronchoscope and advanced in 5-mm increments until the catheter fit snugly into a small airway with a luminal diameter similar to the outer diameter of the OCT probe. Low coherence light with a bandwidth of 50 nm was split evenly, half toward the bronchial surface via a fiber-optic catheter and half toward a moving mirror. Light was then reflected both from within the tissue and from the mirror, and an interference image was created and stored as a digital video file. Airways were manually measured using ImageJ software (National Institutes of Health, Bethesda, MD) (Figure 2).

Statistical Analysis

The relationships between OCT-based and CT-based measurements of airway dimensions were assessed using Pearson correlation analysis and linear regression modeling. A Bland-Altman plot was used to compare the difference in the measurements and the limits of agreement (bias $\pm$ 2 SD of bias) between the paired OCT and CT measurements of the same airway (23). The trend of the relationship was determined after smoothing the data using the locally weighted least squares (LOWESS) technique (24). A Z test was used to compare two slopes of different ordinal least square models. A *P* value less than 0.05 was considered statistically significant.

RESULTS

There were 44 subjects in this study. The baseline characteristics of the study participants are shown in Table 1.

Relationship between OCT- and CT-based Measurements of Wall Area

To compare between OCT and CT, 22 matched airways were analyzed, which included 18 third-generation airways and 4

fourth-generation airways (see online supplement for more details). For OCT assessments, the mean Ai (airway luminal area) was 8.4 ± 4.6 mm² (mean $\pm$ SD) and the mean Aaw (airway wall area) was 7.5 ± 2.8 mm², whereas for CT, the mean Ai was 12.5 ± 6.1 mm² and the mean Aaw was 22.7 ± 8.5 mm². There was excellent correlation between OCT- and CT-based estimations of Ai ($r = 0.89$, $P < 0.001$), Aaw ($r = 0.84$, $P < 0.001$), and WA% (see Figure 3). In general, the CT measurements of Ai were consistently larger than those acquired using OCT (see online supplement for more details).

Table 2 summarizes the relationship between OCT- and CT-based measurements of various components of airway dimension from linear regression models. In all these analyses, OCT-based values were included as the "independent" variables (*x* axis) and the CT-based values were the "dependent" variables (*y* axis). All components of the airway dimension were increased with CT- compared with OCT-based assessments.

Relationship between OCT- and CT-based Measurements with FEV₁% Predicted in the Third- and Fifth-Generation Airways

To determine whether or not OCT- and CT-based measurements of airways correlated with the subject's FEV₁% predicted, we measured Ai and Aaw from the third- and fifth-generation airways separately. The Ai of the third-generation airways was 10.9 ± 5.7 mm² and Aaw was 8.3 ± 2.2 mm² for OCT-based measurements, whereas the Ai was 20.0 ± 7.5 mm² and Aaw was 30.3 ± 8.0 mm² for CT-based measurements. The Ai of the fifth-generation airways was 3.3 ± 0.33 mm² and Aaw was 4.1 ± 1.5 mm² for OCT-based measurements, whereas the Ai was 5.4 ± 1.7 mm² and Aaw was 12.8 ± 3.7 mm² for CT-based measurements.

FEV₁% predicted did not correlate significantly with the airway measurements of the third-generation airways regardless of whether CT or OCT was used (see Figure 4A). However, in the fifth-generation airways, we observed a significant negative correlation for both CT-based ($r = -0.79$, $P < 0.001$) and OCT-based ($r = -0.75$, $P < 0.001$) measurements of WA% (Figure 4B). However, the slope of OCT measurements was significantly steeper than that for CT-based measurements (P for the slope difference < 0.0001), indicating greater discriminative power (i.e., sensitivity) of OCT in detecting lung function changes. Representative matched CT and OCT airways for a subject with normal FEV₁ (118% predicted) and low FEV₁ (52%) are shown in Figure 5. The WA% measured using CT was only 5% different (69 vs. 74%) but 29% different (43 vs. 72%) using OCT. The subepithelial structure was denser in the airway from the subject with low FEV₁ in keeping with increase in collagen deposition with the airway remodeling process.

DISCUSSION

The most important finding of this study is that, although there is a very good correlation between CT and OCT measurements of airway wall dimensions, OCT appears to be a more sensitive method for discriminating the changes in the more distal airways of subjects with a range of expiratory airflow obstruction. OCT-based measurements of WA%, which estimates airway wall thickness (corrected for the size of the airway), in the fifth-generation airway were more sensitive to changes in subjects' lung function, as assessed by FEV₁% predicted than were CT-based measurements on the same airways. Neither OCT- nor CT-based measurements in the large (third-generation) airways were associated with FEV₁. This is not surprising because the primary site of airflow obstruction is the small peripheral airways (4).

Figure 1. A screen shot of the Pulmonary Workstation 2.0 software (VIDA Diagnostics, Iowa City, IA) showing a multiplanar reformat of the right lateral basal segmental bronchus. The longitudinal section of the reformatted airway is shown in (A), and the cross-section of the airway at right angles to the center line of the airway segment at the location of the *yellow dotted line* in (A) is shown in (B). (C) The three-dimensional reconstruction of the airway tree, with the path of airway in (A) highlighted in *blue*. (D) An internal view of the airway at the level of (B). Measurements of the airway dimensions are automatically calculated for each segment of the airway path (between airway branch points) as indicated by the *red lines* at the level of the inferior lobar bronchus in (A).

It is well known that the chronic airflow limitation seen in people with COPD is related to a combination of the loss of elastic recoil pressure due to emphysema and increased resistance in the small airways. The exact contribution of these mechanisms to COPD is believed to be under genetic control, and the ability to noninvasively phenotype individuals into those whose airflow limitation is due to airway remodeling ver-

sus emphysema is of great interest. CT scans have been proposed as an ideal method to phenotype subjects because both lung density changes due to emphysema and airway wall dimensions can be measured (7). However, it has been noted that CT has many problems associated with airway wall measurements, and its sensitivity in predicting FEV_1 is suboptimal. Nakano and colleagues originally published results that showed

Figure 2. Optical coherence tomography images of a third-generation airway (A) and a fifth-generation airway (B), which were compared with pulmonary function. The internal perimeter (Pi) and outer perimeter (Po) of the airway wall was manually traced using ImageJ software (National Institutes of Health, Bethesda, MD), and the lumen area (Ai) and wall area (Aaw) were calculated using these boundaries.

TABLE 1. SUMMARY OF BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS

Variable	Values
Age, yr	60.1 (6.8)
Female	15 (34.1%)
Male	29 (65.9%)
Current smokers	5 (11.4%)
Ex-smokers	39 (88.6%)
Smoking history, pack-years	45.6 (13.3)
Years of quitting	7.6 (6.0)
Height, cm	173 (10)
Weight, kg	81.1 (13.7)
FEV ₁ , L	2.8 (0.9)
FEV ₁ % predicted	83.2 (18.9)
FVC, L	3.9 (1.1)
FVC% predicted	94 (16)
FEV ₁ /FVC	70.0 (8.5)

For continuous variables, data are shown as mean (SD), and for binary variables, data are shown as number (% of column totals).

that FEV₁ was correlated with both low attenuating areas on CT (emphysema) and WA% of the apical segmental bronchus (7). Hasegawa and coworkers recently were unable to show this correlation between FEV₁ and third-generation airways, but by tracking the airways out to the sixth generation, they were able to show a modest correlation with FEV₁ (6). These findings make intuitive sense because it is well established that the major site of airflow limitation is in the small airways (3, 4). Therefore, the association between airway wall dimensions and FEV₁ should be stronger in smaller airways, especially in subjects with severe airflow obstruction. Furthermore, our data show that, although there is a significant correlation with FEV₁, the slope is not sufficiently steep to detect subtle (but likely clinical relevant) changes in FEV₁. It is possible that CT is not very sensitive to differences in FEV₁ because of suboptimal resolution of small airways as the limits of CT resolution are approached (10). OCT is a new, relatively noninvasive technique for measuring airway wall dimensions. Because the resolution of OCT is between 5 and 15 μ m (14, 16, 17), this will provide greater spatial resolution and hence more accuracy to wall measurements of small airways.

Figure 3. The relationship between percentage of airway wall area (WA%) estimated by computed tomography (CT) and that by optical coherence tomography (OCT).

TABLE 2. COMPARISON OF AIRWAY DIMENSIONS BETWEEN MEASUREMENTS MADE BY OPTICAL COHERENCE TOMOGRAPHY AND COMPUTED TOMOGRAPHY USING LINEAR REGRESSION MODELING*

	Intercept (95% CI)	Slope (95% CI)
Airway luminal area, mm ²	2.61 (−0.01 to 5.24)	1.17 (0.90 to 1.44)
Total airway area, mm ²	6.26 (−0.17 to 12.69)	1.79 (1.41 to 2.16)
Airway wall area, mm ²	3.46 (−2.36 to 9.28)	2.56 (1.83 to 3.29)
Wall area, % [†]	0.48 (0.37 to 0.60)	0.34 (0.11 to 0.57)

Definition of abbreviation: CI = confidence interval.

* Regression modeling was performed with optical coherence tomography (OCT)-based values as independent variables and computed tomography (CT)-based values as dependent variables. Thus, the intercepts represent CT-based values when OCT-based measurements are set at zero. The slope indicates the change in CT-based values for every 1-unit change in OCT-based measurements.

[†] Percentage of total airway area that is wall (i.e., measure of wall thickness adjusted for size of the airway).

The data from the present study show that there is a very good correlation between CT and OCT measurements of airway dimensions. Previous studies suggest that, compared with histologic measurements of small airways, which is the current gold standard, CT-based measurements tend to overestimate wall thickness and underestimate lumen area (10). The CT measure-

Figure 4. The relationship between percentage of wall area of a third-generation airway (A) and a fifth-generation airway (B) as estimated by computed tomography (CT) (open circles) and by optical coherence tomography (OCT) (closed diamonds) and FEV₁% predicted. The slope of the regression line for the OCT is different from that of the CT ($P < 0.0001$).

Figure 5. Images of fifth-generation airways obtained using computed tomography (CT) (A, B) and optical coherence tomography (OCT) (C, D). The airways in (A) and (C) were obtained from a subject with normal FEV₁ (118% predicted) and in (B) and (D) are obtained from a subject with an FEV₁ of 52% predicted. The percentage of wall area measured using CT is only 5% different (69 vs. 74%) but 29% different (43 vs. 72%) using OCT. The green dotted arrow in the CT images (A, B) represents the orientation of the longitudinal plane of the reformatted airway path from which the cross-sectional image is obtained (see Figure 1).

ments of A_i are larger across all airway sizes, suggesting that increased lung volume during the CT scan compared with bronchoscopy may increase the lumen area. However, the change in WA will be minimal across the breathing cycle because it is a solid structure, which makes its dimensions harder to change. The relative difference in the WA measurements is largest in the small airways and least in the large (see online supplement). This suggests that, as the airway approaches the resolution of the CT scanner (i.e., as the pixel size of the CT image becomes larger than the airway of interest), the superior resolution of OCT becomes very important. Although newer CT airway algorithms may be able to measure airways with submillimeter resolution (21, 25), CT is still limited by the resolution of the CT scanner, which is approximately 0.5 mm. The current data indicate that, in all cases, OCT-based measurements of airway dimensions were smaller than those obtained on CT scans and, although we do not have histologic confirmation of the airway dimensions, we believe that OCT-based measurements of wall thickness may be more accurate in assessing remodeling changes in the small conducting airways because of the increased resolution of OCT compared with CT. This may explain why WA% values obtained on OCT were more responsive to changes in FEV₁ than were those generated from CT scans. Figure 5 shows images of airways obtained from a subject with normal FEV₁ and low FEV₁ and it is obvious from the data and the image that OCT can measure the differences in airway wall thickness in these fifth-generation airways. OCT may therefore be superior to CT in assessing the “small airway” phenotype of COPD and in evaluating disease progression over time and the effects of novel drugs on small airway remodeling of COPD.

The other major advantage of OCT is that there is no radiation exposure associated with this procedure. Although the risk of radiation-related cancer is low with CT scans, there is growing concern in the public regarding safety of CT scans (11). The use of OCT eliminates this risk. The disadvantage, however, is that OCT requires bronchoscopy.

There are limitations to the current study. First, although the distribution of FEV₁ values was heterogeneous, we only had two

subjects whose FEV₁ was below 50% of predicted. Thus, the accuracy of detecting remodeling changes in the airways with OCT in patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 3 and 4 disease requires further studies. Second, as the subjects in this study underwent only one bronchoscopic session, we could not evaluate the reproducibility of OCT measurements over time. However, it is important to further evaluate the use of OCT in combination with genomic or protein biomarker studies that require a bronchoscopic procedure to retrieve bronchial cells and bronchoalveolar lavage fluid to improve our understanding of the pathogenesis of airway diseases such as COPD and asthma as well as the effect of therapeutic intervention, especially novel treatments.

In summary, the present study suggests that OCT is a more sensitive tool in detecting airway wall remodeling in current and former smokers compared with CT scans, which raises the possibility that OCT could be used to study airway changes *in vivo* in patients with COPD and assess therapeutic potential of novel airway therapies.

Conflict of Interest Statement: H.O.C. received \$11,000 in 2005 and \$4,800 in 2006 and 2007 for serving on an advisory board for GlaxoSmithKline (GSK). In addition, H.O.C. is the co-investigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project. H.O.C. has three contract service agreements with GSK to quantify the CT scans in subjects with COPD and a service agreement with Spiration, Inc., to measure changes in lung volume in subjects with severe emphysema. A percentage of H.O.C.’s salary between 2003 and 2006 (\$15,000/yr) derives from contract funds provided to a colleague, Peter D. Paré, by GSK for the development of validated methods to measure emphysema and airway disease using CT. H.O.C. is the co-investigator (D. Sin, principal investigator) on a Canadian Institutes of Health-Industry (Wyeth) partnership grant. There is no financial relationship between any industry and the current study. B.Q. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.D.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.X. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

1. Celli BR, Snider GL, Heffner J, Tiep B, Ziment I, Make B, Braman S, Olsen G, Phillips Y; Committee of the Scientific Assembly on Clinical Problems. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society statement. *Am J Respir Crit Care Med* 1995;152:S77-S120.
2. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;163:1256-1276.
3. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645-2653.
4. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278:1355-1360.
5. 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.
6. Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, Ito Y, Betsuyaku T, Nishimura M. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:1309-1315.
7. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Pare PD, Hogg JC, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102-1108.
8. Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, Nishimura K, Itoh H, Izumi T. Airway wall thickness in asthma assessed by computed tomography: relation to clinical indices. *Am J Respir Crit Care Med* 2000;162:1518-1523.
9. King GG, Müller NL, Whittall KP, Xiang QS, Paré PD. An analysis algorithm for measuring airway lumen and wall areas from high-resolution computed tomographic data. *Am J Respir Crit Care Med* 2000;161:574-580.
10. Nakano Y, Whittall KP, Kalloger SE, Coxson HO, Pare PD. Development and validation of human airway analysis algorithm using multidetector row CT. *Proc SPIE* 2002;4683:460-469.
11. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277-2284.
12. de Gonzalez AB, Kim KP, Samet JM. Radiation-induced cancer risk from annual computed tomography for patients with cystic fibrosis. *Am J Respir Crit Care Med* 2007;176:970-973.
13. de Jong PA, Mayo JR, Golmohammadi K, Nakano Y, Lequin MH, Tiddens HA, Aldrich J, Coxson HO, Sin DD. Estimation of cancer mortality associated with repetitive computed tomography scanning. *Am J Respir Crit Care Med* 2006;173:199-203.
14. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, et al. Optical coherence tomography. *Science* 1991;254:1178-1181.
15. Armstrong JJ, Leigh MS, Sampson DD, Walsh JH, Hillman DR, Eastwood PR. Quantitative upper airway imaging with anatomic optical coherence tomography. *Am J Respir Crit Care Med* 2006;173:226-233.
16. Hanna N, Saltzman D, Mukai D, Chen Z, Sasse S, Milliken J, Guo S, Jung W, Colt H, Brenner M. Two-dimensional and 3-dimensional optical coherence tomographic imaging of the airway, lung, and pleura. *J Thorac Cardiovasc Surg* 2005;129:615-622.
17. Whiteman SC, Yang Y, Gey van Pittius D, Stephens M, Parmer J, Spiteri MA. Optical coherence tomography: real-time imaging of bronchial airways microstructure and detection of inflammatory/neoplastic morphologic changes. *Clin Cancer Res* 2006;12:813-818.
18. Coxson HO, Quiney B, Sin DD, McWilliams AM, Mayo JR, Lam S. Airway wall thickness assessed using computed tomography and optical coherence tomography [abstract]. *Am J Respir Crit Care Med* 2008;177:A563.
19. Crapo RO, Hankinson JL, Irvin C, MacIntyre NR, Voter KZ, Wise RA; Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Standardization of spirometry: 1994 update. American Thoracic Society Statement. *Am J Respir Crit Care Med* 1995;152:1107-1136.
20. Crapo R. Spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659-664.
21. Tschirren J, Hoffman EA, McLennan G, Sonka M. Intrathoracic airway trees: Segmentation and airway morphology analysis from low-dose CT scans. *IEEE Trans Med Imaging* 2005;24:1529-1539.
22. Lam S, leRiche JC, McWilliams A, Macaulay C, Dyachkova Y, Szabo E, Mayo J, Schellenberg R, Coldman A, Hawk E, et al. A randomized phase IIb trial of Pulmicort Turbuhaler (budesonide) in people with dysplasia of the bronchial epithelium. *Clin Cancer Res* 2004;10:6502-6511.
23. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;8:307-310.
24. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc* 1979;74:829-836.
25. 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.