Accurate Measurement of Small Airways on Low-Dose Thoracic CT Scans in Smokers

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Background: Partial volume averaging and tilt relative to the scan plane on transverse images limit the accuracy of airway wall thickness measurements on CT scan, confounding assessment of the relationship between airway remodeling and clinical status in COPD. The purpose of this study was to assess the effect of partial volume averaging and tilt corrections on airway wall thickness measurement accuracy and on relationships between airway wall thickening and clinical status in COPD.

Methods: Airway wall thickness measurements in 80 heavy smokers were obtained on transverse images from low-dose CT scan using the open-source program Airway Inspector. Measurements were corrected for partial volume averaging and tilt effects using an attenuation- and geometry-based algorithm and compared with functional status.

Results: The algorithm reduced wall thickness measurements of smaller airways to a greater degree than larger airways, increasing the overall range. When restricted to analyses of airways with an inner diameter < 3.0 mm, for a theoretical airway of 2.0 mm inner diameter, the wall thickness decreased from 1.07 ± 0.07 to 0.29 ± 0.10 mm, and the square root of the wall area decreased from 3.34 ± 0.15 to 1.58 ± 0.29 mm, comparable to histologic measurement studies. Corrected measurements had higher correlation with FEV₁, differed more between BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index scores, and explained a greater proportion of FEV₁ variability in multivariate models.

Conclusions: Correcting for partial volume averaging improves accuracy of airway wall thickness estimation, allowing direct measurement of the small airways to better define their role in COPD.

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Abbreviations: ANOVA = analysis of variance; BODE = BMI, airway obstruction, dyspnea, and exercise capacity; EI = emphysema index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ID = internal diameter; NLST = National Lung Screening Trial; PFT = pulmonary function test; Pi = internal perimeter; SRWA = square root of wall area; SRWA@ID2 = square root of wall area of a theoretical airway normalized at internal diameter = 2 mm; SRWA@Pi10 = square root of wall area of an airway normalized at internal perimeter = 10 mm; WA = wall area; WA% = wall area percent; WT = wall thickness; WT@ID2 = wall thickness of a theoretical airway normalized at ID = 2 mm; WT@Pi10 = wall thickness of an airway normalized at Pi = 10 mm

Using quantitative measurements of cross-sectional airway dimensions from transverse CT images, airway structure-function relationships can be investigated in vivo. CT scan measurements of airway wall thickness (WT) in smokers correlate with clinical measures, such as pulmonary function tests (PFTs),^{1–7} exercise capacity,⁸ and respiratory symptoms.^{9,10} Such airway measurements have been used in the study of COPD to explore differences related to age,¹¹ sex,^{11,12} phenotype,² genotype,¹³ familial aggregation,¹⁴ and outcome in lung volume reduction surgery.¹⁵

Airways < 2 to 3 mm in internal diameter (ID) represent the main site of airflow resistance in COPD.^{16,17}

Correlations between wall dimensions and PFTs increase as smaller, more peripheral airways are measured.^{4,8,18} However, CT scan measurements at this scale overestimate WT and underestimate lumen size. Because the CT scan number is a weighted average of the densities of the materials in an image voxel,¹⁹ one contributor to these errors is partial volume averaging. Small bronchi have WTs comparable to the typical 0.6- to 0.8-mm in-plane dimension of transverse lung CT image voxels and are bordered by air in the lumen and lung parenchyma. Additionally, differences in the angle or airway tilt lead to overestimation of airway WT on 2-dimensional transverse

images because of oblique sectioning of the airway wall.¹⁹⁻²⁴

An attenuation- and geometry-based method of correcting for partial volume averaging and tilt effects improves measurement accuracy for lung phantom polycarbonate tubes having an ID as small as 3 mm and a WT of 0.6 mm, dimensions approaching the range of the small airways.²² We hypothesized that applying this correction algorithm to measurements obtained on in vivo clinical CT scans reduces small airway WT overestimation, thereby improving accuracy and increasing the value of CT scan airway measurements in the study of airway remodeling in COPD. The purpose of this study was to determine the effects of the correction algorithm on in vivo transverse CT images by comparing corrected airway measurements to uncorrected measurements and to published ex vivo histologic measurements. Additionally, we assessed the effects of the corrections on correlations between small airway WT and parameters of pulmonary function.

MATERIALS AND METHODS

Subjects

Eighty-five National Lung Screening Trial (NLST) participants (NCT00047385) with three completed annual lung cancer screening chest CT scans at our institution were recruited to this study, which was part of a Washington University Human Research Protection Office-approved (approval number 2011019999) emphysema biomarkers investigation (NCT00757120)²⁵ that was not part of the NLST. The NLST enrolled individuals aged 55 to 74 years with a minimum smoking history of 30 pack-years.^{26,27}

CT Imaging

The preexisting low-radiation-dose (30 effective mAs) CT scans had been performed at our institution in full inspiration without contrast on either a hospital-based four-row scanner (SOMATOM Volume Zoom; Siemens AG) (21 subjects) or a 16-row scanner

(SOMATOM Sensation 16; Siemens AG) (35 subjects) or at an outpatient facility on a four-row scanner (SOMATOM Volume Zoom) (24 subjects). The images had been reconstructed as 2-mm-thick contiguous transverse sections at fields of view of 254 to 426 mm (median, 340 mm), corresponding to an in-plane resolution of 0.50 to 0.83 mm (median, 0.66 mm). A medium-smooth algorithm (B30f) was used for emphysema analysis, and a medium-sharp algorithm (B50f) was used for airway measurements.

Pulmonary Function Testing

PFTs were performed according to American Thoracic Society standards after obtaining written consent. Measurements obtained after bronchodilation with albuterol inhalation were compared with predicted values derived from reference equations.²⁸ The presence of airflow obstruction was defined as a postbronchodilator FEV₁/FVC < 0.70, and the severity was classified according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) spirometry criteria.

Measurement of Emphysema and Airway Dimensions

Emphysema was quantified as the percentage of all lung voxels having an attenuation < -950 Hounsfield units (ie, emphysema index [EI]) using Emphysema Profiler (VIDA Diagnostics, Inc) software.²⁹ B. A. L. and S. H. C. each performed measurements for the study and selected airways according to specified criteria. Each airway distal to lobar bronchi that was visible in cross-section on each CT image section was considered for measurement. Airways were excluded from measurement if the airway wall circumference appeared to be discontinuous as a result of inadequate resolution; if the ratio of the long to short axis of an ellipse fitting the lumen was > 2; or if abutting soft tissues, such as vessels or lymph nodes, obscured more than one-half of the outer wall circumference. Airways were measured in cross-section on transverse CT images using Airway Inspector (BWH and 3D Slicer contributors) software.³⁰ The phase congruency edge detection method was used to locate wall margins.^{30,31} Reported parameters include internal (lumen) perimeter (Pi) length, total airway area, mean WT, wall area (WA) (WA = total area - lumen area), and WA percent [WA% = 100 × (WA/total area)]. The ID was determined as ID = Pi/π, assuming circular airway cross-sections. Airway measurements were corrected for partial volume averaging and tilt using an algorithm²² that is summarized in e-Appendix 1.

Statistical Analysis

Regression coefficients derived from least-squares regression analysis were used to determine values for WT and the square root of the wall area (SRWA) of an airway normalized at Pi = 10 mm (WT@Pi10 and SRWA@Pi10). For comparison with published tissue measures, regression coefficients derived from a separate least-squares analysis using only airways with an ID < 3.0 mm were used to determine a value for the WT and SRWA of a theoretical airway normalized at ID = 2.0 mm (WT@ID2 and SRWA@ID2). Each subject's overall mean WA% was determined. Relationships among airway measurements, EI, and PFTs, were determined by Pearson correlation.

Using Student unpaired two-tailed *t* test, the FEV₁ and EI for subjects having < 20 measured airways with ID < 3.0 mm was compared with those having ≥ 20. GOLD stage and BMI, airway obstruction, dyspnea, and exercise capacity (BODE) index groups were compared using one-way analysis of variance (ANOVA). Correlations between the GOLD stages and the mean uncorrected and corrected values for WT@Pi10, SRWA@Pi10, WT@ID2, and SRWA@ID2 of subjects in each GOLD stage were determined using Spearman *p*. Subjects with normal spirometry were assigned

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a rank of 0, and subjects in GOLD stages 3 to 4 were combined and assigned a rank of 3. Analysis of covariance was used to determine the relationships of airway measurements and EI to PFTs, adjusting for sex, age, smoking pack-years, and smoking status. Statistical analyses were performed with Microsoft Excel (Microsoft Corporation) and SPSS (IBM) software. Results are reported as mean $\pm$ SD.

RESULTS

Subjects

Demographics, lung function, and emphysema severity are presented for 80 analyzable subjects (Table 1). Excessive image noise arising from obesity prevented quantitative CT scan analysis in five subjects. Subjects enrolled 3.1 ± 0.9 years (range, 1-5 years) after the latest NLST CT scan.

Airways Analyzed

A mean of 81 ± 68 (median, 67; range, 12-526) airway cross-sections with long:short axis ≤ 2 were measured per subject. The corresponding corrected Pi values were 9.7 ± 0.44 mm (median, 8.5 mm; range, 4.4-44.8 mm). Airways of ID < 3.0 mm used to determine WT@ID2 and SRWA@ID2 represented 58%

Table 1—Subject Demographic and Clinical Characteristics

Characteristic	Value
Age, y	65 $\pm$ 5
Sex	
Male	42 (52.5)
Female	38 (47.5)
Smoking status	
Current	22 (27.5)
Former	58 (72.5)
Emphysema index, %	12 $\pm$ 12
FEV ₁ , % predicted	85.5 $\pm$ 21
DLCO, % predicted	62 $\pm$ 17
Normal spirometry	40 (50)
GOLD stage	
1	15 (18.8)
2	20 (25.0)
3	4 (5.0)
4	1 (1.2)
BODE ^a index	
0	53 (70.7)
1	15 (20.0)
2	4 (5.3)
3	1 (1.3)
4	1 (1.3)
5	1 (1.3)

Data are presented as mean $\pm$ SD or No. (%). Normal spirometry, FEV₁/FVC $\geq 70\%$ predicted and FEV₁ $\geq 80\%$ predicted. BODE = BMI, airway obstruction, dyspnea, and exercise capacity; DLCO = diffusing capacity of the lung for carbon monoxide; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

^aData missing for five subjects who could not do a 6-min walk.

of all measurements. The corresponding corrected ID values were 2.2 ± 0.4 mm (median, 2.2 mm; range, 1.1-3.0 mm). Fifteen subjects had < 20 measurable airways with ID < 3.0 but did not differ significantly in age, FEV₁, smoking pack-years, or EI ($P = .30-.92$) from those with ≥ 20 .

Correction Algorithm Effects

Partial volume averaging and tilt corrections decreased individual airway WT, WA, and WA% measurements, with the smallest airways showing the greatest change (Fig 1). Corrections increased the range of WT and WA values, as illustrated for WT in a single subject in Figure 2. The degree to which correction reduced WT@Pi10 and SRWA@Pi10 and WT@ID2 and SRWA@ is shown in Table 2. The correction algorithm reduced the mean WA% from $72\% \pm 3.7\%$ (mean uncorrected Pi, 8.4 ± 1.4 mm) to $42\% \pm 7.6\%$ (mean corrected Pi, 9.4 ± 1.5 mm).

Correlations With Pulmonary Function

The correction algorithm increased correlations between airway dimensions and PFT parameters (Fig 3, Table 3). The correlations between the corrected WT@ID2 and expiratory airflow parameters were similar to those of the corrected WT@Pi10, whereas the correlations of corrected SRWA@ID2 were slightly lower than those for corrected SRWA@Pi10 (Table 3). Correlations with both residual volume % predicted and total lung capacity % predicted were greater for corrected than uncorrected WT@ID2 and SRWA@ID2. After corrections, the correlation between mean WA% and postbronchodilator FEV₁ % predicted increased from $r = 0.42$ ($P < .001$) to $r = 0.56$ ($P < .0001$). Correlations between emphysema severity and airway wall dimensions were positive and improved by applying the correction algorithm and

FIGURE 1. Change in WT resulting from partial volume and tilt corrections as a function of airway ID. WT values are means determined from all measured airways from all 80 subjects in each size range listed on the x-axis; error bars represent SDs. ID = internal diameter; WT = wall thickness.

FIGURE 2. Uncorrected and corrected measurements of WT plotted against Pi in a single subject. A, The corrections reduced the WT of an airway normalized at Pi = 10 mm from 1.15 to 0.52 mm and increased the correlation between Pi and WT from $r = 0.60$ to $r = 0.85$. B, The corrections reduced the WT of an airway normalized at an internal diameter of 2 mm (WT@Pi = 6.3 mm) from 1.05 to 0.24 mm and increased the correlation between Pi and WT from $r = 0.60$ to $r = 0.85$. Regression lines and equations are shown. Pi = internal perimeter. See Figure 1 legend for expansion of other abbreviation.

by limiting measurements to airways smaller than ID = 3 mm (Table 3).

Fifteen subjects had < 20 data points in the size range used to determine WT@ID2 and SRWA@ID2. Although excluding these subjects from the analysis produced minimal change in the mean uncorrected and corrected WT@ID2 and SRWA@ID2 values, correlations with most PFTs increased for both uncorrected and corrected measurements (see e-Appendix 1, e-Tables 1-4, e-Figs 1, 2).

Table 2—Uncorrected and Corrected Airway Wall Dimensions in 80 Subjects

Dimension	WTU, mm	WTC, mm	SRWAU, mm	SRWAC, mm
@Pi = 10 mm (ID = 3.2 mm)	1.18 ± 0.11	0.47 ± 0.15	4.13 ± 0.26	2.44 ± 0.43
@Pi = 6.3 mm (ID = 2 mm)	1.07 ± 0.07	0.29 ± 0.10	3.34 ± 0.15	1.58 ± 0.29

Data are presented as mean ± SD. C = corrected; ID = internal diameter; Pi = internal perimeter; SRWAC = square root of wall area corrected; SRWAU = square root of wall area uncorrected; WTC = wall thickness corrected; WTU = wall thickness uncorrected.

Airway Measurements and Clinical Disease Severity

As would be expected from the relationship between WT and FEV₁, each GOLD stage was associated with a statistically significant progressive increase in WT@Pi10 and SRWA@Pi10 and WT@ID2 and SRWA@ID2 compared with the other GOLD stages and patients with normal spirometry, which was greater for corrected values ($P < .001$ by ANOVA) than for uncorrected values ($P = .006-.05$ by ANOVA). Correlation is high ($r = 1.0$) and significant ($P < .05$) for the corrected mean airway dimensions and GOLD stage. Correlations are also high ($r = 0.8-1.0$) for all uncorrected measures and GOLD stage but not significant for the relationship between uncorrected SRWA@Pi10 or uncorrected WT@ID2 and GOLD stage. Additionally, an incremental increase in WT was found with increasing BODE index, which was statistically significant only for corrected values (Table 4).

Contribution of Airway Measurements to Airflow Obstruction

After adjusting for age, sex, smoking pack-years, and current vs former smoking status, multiple regression showed that EI was associated ($P < .0001$) with FEV₁ % predicted (model $R^2 = 0.36$, $P < .0001$). When parameters WT and SRWA were included in the models (one parameter per model), each parameter and EI were independently and significantly associated with FEV₁ % predicted. The proportion of variation in FEV₁ % predicted explained by the models (R^2) and, thus, the relative contribution of airway thickness to airflow obstruction were greater for corrected than for uncorrected airway measurements. Without and with airway measurement correction, the R^2 of the models for FEV₁ % predicted increased from 0.49 to 0.55 with inclusion of WT@Pi10, from 0.42 to 0.51 with WT@ID2, from 0.44 to 0.53 with SRWA@Pi10, and from 0.44 to 0.46 with SRWA@ID2 (all $P < .0001$).

DISCUSSION

Applying phantom-derived partial volume and tilt corrections to in vivo low-dose CT scans decreased measurements of airway WT. In addition, the corrected WT was more strongly associated with PFTs, emphysema, and clinical status. The corrected measurements approached ranges reported in histologic studies, suggesting that the algorithm improved accuracy.

In one study of mainly smokers with mildly impaired lung function,³² airways with ID = 1.94 mm had histologically measured mean WT of 0.3 mm, virtually identical to the present mean WT@ID2. Additionally, using a regression equation for a basement membrane

FIGURE 3. Scatter plots depict the relationship between CT scan airway measurements (uncorrected and corrected) and FEV₁. A, WT@Pi10. B, WT@ID2. Lines are regression lines. WT@ID2 = wall thickness of a theoretical airway normalized at internal diameter = 2 mm; WT@Pi10 = wall thickness at an airway normalized at internal perimeter = 10 mm.

perimeter length of 10 mm, the SRWA was 2.2 mm,³² which is highly consistent with the present SRWA@Pi10. Histologic studies³³⁻³⁵ limited to airways ≤ 2 mm in diameter found WT values smaller than the present WT@ID2 value of 0.29 mm, also supporting

an improvement in accuracy using the correction algorithm.

Histologic values for airway WA% have not been reported. However, the present mean corrected WA% values are approximately mid-range of those

Table 3—Correlations (r Values) Among WTU and WTC, Pulmonary Function, and Emphysema

Lung Function and Emphysema Severity Measures	@Pi10 (ID = 3.18 mm)				@ID2 (Pi = 6.28 mm)				EI
	WTU	WTC	SRWAU	SRWAC	WTU	WTC	SRWAU	SRWAC	
FVC, %	NS	NS	NS	NS	NS	NS	NS	NS	0.44 ^c
FEV ₁ , %	-0.35 ^a	-0.54 ^a	-0.22 ^b	-0.51 ^a	-0.31 ^c	-0.55 ^a	-0.32 ^c	-0.49 ^a	-0.59 ^c
FEF _{25%-75%} , %	-0.28 ^b	-0.52 ^a	-0.24 ^b	-0.50 ^a	-0.29 ^c	-0.51 ^a	-0.29 ^c	-0.47 ^a	-0.69 ^c
FEF _{75%} , %	-0.22 ^b	-0.44 ^a	NS	-0.43 ^a	-0.26 ^b	-0.43 ^a	-0.28 ^c	-0.38 ^a	-0.49 ^c
RV, %	0.36 ^a	0.47 ^a	0.34 ^c	0.43 ^a	0.35 ^c	0.52 ^a	0.40 ^a	0.50 ^a	0.50 ^c
TLC, %	NS	0.24 ^b	NS	0.22 ^b	NS	0.30 ^c	0.22 ^b	0.30 ^c	0.45 ^c
EI	NS	NS	-0.05 ^b	0.19 ^b	NS	0.30 ^c	NS	0.31 ^c	...

EI = emphysema index; FEF_{25%-75%} = forced expiratory flow, midexpiratory phase; FEF_{75%} = forced expiratory flow at 75% of FVC; NS = not significant; RV = residual volume; TLC = total lung capacity. See Table 2 legend for expansion of other abbreviations.

^a $P < .001$.

^b $P < .05$.

^c $P < .01$.

Table 4—Airway WT Stratified by BODE Index^a

Airway Dimension	BODE Score				P Value
	0 (n = 53)	1 (n = 15)	2 (n = 4)	3-5 merged (n = 3)	
Uncorrected WT@Pi10, mm	1.16 ± 0.10	1.21 ± 0.12	1.17 ± 0.07	1.33 ± 0.19	.048
Corrected WT@Pi10, mm	0.42 ± 0.13	0.55 ± 0.13	0.57 ± 0.07	0.66 ± 0.17	< .001
Uncorrected SRWA@Pi10, mm	4.11 ± 0.28	4.19 ± 0.26	4.09 ± 0.16	4.18 ± 0.15	.755
Corrected SRWA@Pi10, mm	2.32 ± 0.42	2.66 ± 0.34	2.68 ± 0.18	3.00 ± 0.44	.002
Uncorrected WT@ID2, mm	1.06 ± 0.07	1.10 ± 0.05	1.08 ± 0.04	1.13 ± 0.06	.106
Corrected WT@ID2, mm	0.26 ± 0.10	0.37 ± 0.08	0.38 ± 0.07	0.40 ± 0.07	< .001
Uncorrected SRWA@ID2, mm	3.31 ± 0.15	3.39 ± 0.14	3.34 ± 0.10	3.48 ± 0.23	.125
Corrected SRWA@ID2, mm	1.49 ± 0.27	1.78 ± 0.27	1.73 ± 0.19	1.88 ± 0.34	.001

Data are presented as mean ± SD. SRWA@ID2 = square root of wall area of a theoretical airway normalized at internal diameter = 2 mm; SRWA@Pi10 = square root of wall area of an airway normalized at internal perimeter = 10 mm; WT = wall thickness; WT@ID2 = wall thickness of a theoretical airway normalized at internal diameter = 2 mm; WT@Pi10 = wall thickness of an airway normalized at internal perimeter = 10 mm. See Table 1 and 2 legends for expansion of other abbreviations.

^aData missing for five subjects who could not do a 6-min walk.

obtained by Coxson et al³⁶ using in vivo optical coherence tomography for airways having CT scan measurements in the range of the present uncorrected measurements. In the Coxson et al study, the range of optical coherence tomography values was greater than the range of measured CT scan values, analogous to the difference in the ranges of corrected and uncorrected CT scan measurements we obtained.

Other COPD CT scan airway measurement studies, most using the full width at half maximum edge detection method, have reported a mean WT@Pi10 of 1.5 mm^{6,13} and mean SRWA@Pi10 ranging from 4.4 to 5.1 mm.^{6,7,9,11,12,14,37} The slightly lower uncorrected values in the present study probably resulted from differences in subject characteristics and image acquisition and analysis parameters and the high proportion of small airways measurements. The results for WT@ID2 and SRWA@ID2 suggest that an accurate and functionally significant characterization of the airways may be obtained by measuring the small airways only. Although the in-plane resolution of the CT scans is generally 0.5 to 0.8 mm, correction for partial volume averaging allows for subvoxel scale measurement and provides the ability to measure the small airways in vivo.

A wide variation was seen in the number of airways measured among subjects. We attribute this variation in part to individual subject differences in the numbers of airways meeting the measurability criteria of roundness and those excluded from measurement because the outer wall was obscured by adjacent vessels. A minimum number of airway measurements needed for reliable estimation of WT@Pi10 has not been established; however, although having fewer measurements in some individuals should increase the confidence limits for the WT@Pi10 of the group as a whole, it should not bias the group mean values in one direction or the other. Other investigators using the Pi10 approach have used a mean of 14; have

used a minimum of 3 points¹⁴; or, in most cases,^{6,9,12} have not reported the variability in the number of points measured. Nevertheless, the present uncorrected values are in the range of those in other studies that also obtained significant results, further supporting the general robustness of the technique.

Many of the results reported here illustrate the potential impact of improved airway measurement accuracy. For example, expiratory airflow obstruction in COPD is influenced by both airway remodeling and loss of tethering as a result of emphysema; the corrected CT scan measurements revealed a greater contribution of airway thickening compared with uncorrected measurements in the multivariable models. In contrast to the present uncorrected measurements and other CT scan studies showing a negative correlation between airway thickness and the amount of emphysema,^{6,10,14} the current corrected data show a mild positive correlation. The different result may be due to the lesser accuracy of uncorrected measurements and to differences in airway selection because some investigators excluded airways with Pi < 6 mm. The result agrees with previous histologic studies,³⁵ suggesting that emphysema and airway remodeling are associated processes and helping to rectify a discrepancy between CT scan and histologic studies.

Using multivariate models, other investigators have shown that increases in CT scan measures of emphysema and airway dimensions predicted higher BODE scores.³⁸ In the present study, uncorrected measurements indicated that airway thickness is unrelated to BODE score, whereas the corrected measurements demonstrated a relationship (Table 4). Finally, the increased accuracy of airway wall measurement should allow the evaluation of changes in WT with treatment over time to be made with greater reliability and efficiency. This technique would be applicable to investigation of longitudinal changes, but the sensitivity for detecting change over time will depend

on intrasubject variability, which has yet to be determined.

We calculated estimates of sample size needed for a clinical trial of a small airway-specific therapeutic agent in COPD based on corrected and uncorrected airway WT. The expected result of a successful antiinflammatory agent likely would be to decrease airway WT in symptomatic subjects with COPD (GOLD stage 2 and 3) toward the WT seen in normal control subjects. With corrected measurements, there is a substantial reduction in the number of subjects who would need to be enrolled in a phase 2 trial in order to detect a 25% or 50% reduction in WT toward the mean of normal control subjects (Table 5).

The amount of correction depends in part on the attenuation of the surrounding lung tissue,²² which in turn depends on radiation dose,³⁹⁻⁴¹ slice thickness,⁴²⁻⁴⁴ and reconstruction kernel.^{42,44,45} This technique was developed for use with scans acquired using the NLST protocol. Consequently, the correction factor determined by the algorithm and the amount of correction needed would be expected to vary if a different scan technique were used. Nevertheless, it is noteworthy that accurate and functionally relevant measurements were obtainable using a low-radiation-dose, two-dimensional technique. Also, given that the minimum number of airways required for sampling may be significantly below our rigorous approach, this indicates the potential to reduce radiation exposure even further by limiting the number of levels scanned, although this would require validation. The three-dimensional volumetric CT scan approach, while providing a more comprehensive assessment of airways in any orientation, requires thinner imaging sections than were used in this study at the expense of greater radiation exposure to ensure adequate signal to noise for full skeletonization and segmentation of the airway tree. The effect of the correction algorithm on multiplanar three-dimensional image analysis remains to be established.

Several limitations of this study are notable. First, the interval between CT scans and testing may have affected correlations between airway dimensions and

PFTs. This effect was likely small because most subjects had mild disease. Second, few subjects had severe COPD, limiting assessment of the relationship between airway thickness and higher BODE index levels. Third, the increased correlation between WT@ID2 and some PFT values after excluding 15 subjects with < 20 data points with ID < 3.0 mm suggests that the least-squares approach for characterizing small airway thickness may be less suitable for subjects with few measurable airways.

In summary, correction of WT overestimation produced more accurate measurements of the small airways that can be used to better understand the contribution of changes in WT to functional impairment, COPD symptoms, and disease progression. Although this study was limited to subjects with and at risk for COPD, the same principles for assessing airway WT should be appropriate for any disease of the small airways in which increased airway WT is a surrogate of inflammation or remodeling like asthma or bronchiolitis.

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Dr Lutey: contributed to the concept and design of the study; data acquisition and analysis; and drafting, critical review, and final approval of the manuscript.

Dr Conradi: contributed to the concept and design of the study; data acquisition and analysis; and drafting, critical review, and final approval of the manuscript.

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Dr Senior: contributed to the concept and design of the study; data acquisition and analysis; and drafting, critical review, and final approval of the manuscript.

Dr Gierada: contributed to the concept and design of the study; data acquisition and analysis; and drafting, critical review, and final approval of the manuscript.

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Table 5—Sample Sizes Needed to Detect Specified Changes in WT at P < .05

Airway Dimension	50% Change		25% Change	
	80% Power	90% Power	80% Power	90% Power
Corrected WT@Pi10	64	86	253	338
Uncorrected WT@Pi10	222	297	884	1,184

Change defined as percent of the difference in mean WT@Pi10 between subjects with GOLD stage 2 and 3 combined and subjects with normal spirometry (FEV₁/FVC ≥ 70% predicted and FEV₁ ≥ 80% predicted). See Table 1 and 4 legends for expansion of abbreviations.

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Additional information: The e-Appendix, e-Tables, and e-Figures can be found in the "Supplemental Materials" area of the online article.

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