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Gender Differences of Airway Dimensions in Anatomically Matched Sites on CT in Smokers

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Abstract

Rationale and Objectives—There are limited data on, and controversies regarding gender differences in the airway dimensions of smokers. Multi-detector CT (MDCT) images were analyzed to examine whether gender could explain differences in airway dimensions of anatomically matched airways in smokers.

Materials and Methods—We used VIDA imaging software to analyze MDCT scans from 2047 smokers (M:F, 1021:1026) from the COPDGene® cohort. The airway dimensions were analyzed from segmental to subsubsegmental bronchi. We compared the differences of luminal area, inner diameter, wall thickness, wall area percentage (WA%) for each airway between men and women, and multiple linear regression including covariates (age, gender, body sizes, and other relevant confounding factors) was used to determine the predictors of each airway dimensions.

Results—Lumen area, internal diameter and wall thickness were smaller for women than men in all measured airway (18.4 vs 22.5 mm^2 for segmental bronchial lumen area, 10.4 vs 12.5 mm^2 for subsegmental bronchi, 6.5 vs 7.7 mm^2 for subsubsegmental bronchi, respectively $p < 0.001$). However, women had greater WA% in subsegmental and subsubsegmental bronchi. In multivariate regression, gender remained one of the most significant predictors of WA%, lumen area, inner diameter and wall thickness.

Conclusion—Women smokers have higher WA%, but lower luminal area, internal diameter and airway thickness in anatomically matched airways as measured by CT scan than do male smokers. This difference may explain, in part, gender differences in the prevalence of COPD and airflow limitation.

Keywords

Airway dimensions; CT scan; Gender differences; Smoker

INTRODUCTION

Smoking is a major risk factor for chronic obstructive pulmonary disease (COPD) and airflow obstruction. However, only a minority of smokers develop COPD, and the relationship between smoking history and the severity of airflow obstruction is weak (1). Thus, there is a new appreciation that COPD may be a heterogeneous disorder of smoking with many phenotypes (2). Some of the factors that are associated with the severity of airflow obstruction include: age, height, race, gender, genetic susceptibility, air pollution, and airway dimensions (3–7). Within the past several decades, there has also been a

demographic shift in gender distribution of individuals with COPD. In 2000 there were more women diagnosed with COPD than men in the United States (8). Some have postulated that women may be more susceptible to the damaging effects of smoking and may be at greater risk of smoking-induced lung function impairment (4, 9–11).

Besides spirometry, chest CT has recently been used as a valuable tool to assess lung damage from smoking. Advances in CT imaging have permitted more detailed analysis of airway dimensions (12). It has been suggested that these CT measurements has potential power to represent histological dimension changes in the airway (13, 14). Although CT measurements of airway dimensions are predominantly of medium-sized airways, they could be representative of the degree of remodeling in small airways determined by pathology (13). Aysola et al. (14) reported that the airway thickness on endobronchial biopsy samples from individuals with asthma and healthy subjects correlated with wall area percentage (WA %).

Histologically, Martinez et al. (15) reported that women exhibited smaller airway lumens with disproportionately thicker airway walls than men in patients with severe COPD. Three other publications (7, 16, 17) that reported sex differences associated with CT airway thickness found that female smokers did not show increased wall thickness compared to men; however, a recent publication found that the square root of the wall thickness of a hypothetical airway of internal perimeter of 10 mm (SQRTWA@pi10) was higher in men than women (16).

None of these studies has reported gender difference of anatomically matched, specified airway wall. Furthermore, most studies used only a single population of subjects for airway measurement. To overcome these limitations and to evaluate whether there are gender differences in airway dimensions even when including confounding variables, we used the COPDGene® (the Genetic epidemiology of COPD) cohort (http://www.copdgene.org/) (18) to determine whether gender could explain the differences in airway dimensions of anatomically matched airways in smokers.

MATERIALS AND METHODS

Study Populations

The COPDGene® Study is an ongoing multicenter investigation of the genetic epidemiology of smoking-related lung disease (18). The first 2,047 smokers with quantitative CT data from the COPDGene® cohort were included in this study. All subjects were studied after obtaining the consent of study under protocols approved by local Institutional Review Board (IRB) and with guidelines recommended by the National Institutes of Health. Subjects were men and women; non-Hispanic whites or African-Americans aged 45 to 80 years with a smoking history of at least 10 pack years.

Previously proposed exclusion criteria (18) were applied in the cohort (18): exclusion criteria are a pregnant woman, a history of other lung disease except asthma (e.g., pulmonary fibrosis, extensive bronchiectasis, cystic fibrosis), previous surgical excision of at least one lung lobe (or lung volume reduction procedure), active cancer under treatment, suspected lung cancer (large or highly suspicious lung mass), metal in the chest, recent exacerbation of COPD treated with antibiotics or steroids, recent eye surgery, MI, other cardiac hospitalization, recent chest or abdominal surgery, inability to use albuterol, multiple self-described racial categories, history of chest radiation therapy, and first- or second-degree relative already enrolled in the study. Smokers who have an unclassified pattern by GOLD (Global initiative for chronic Obstructive Lung Disease) criteria on spirometry, denoted as GOLD U (normal FEV1/FVC but reduced FEV1) and GOLD 0 (smokers with

normal spirometry) are eligible for the study. Each subject underwent a spirometry and multi-detector CT (MDCT). The COPDGene® cohort includes nineteen clinical centers in the United States (18) (see center and investigator list in Acknowledgments).

Quantitative CT Analysis

Analysis of COPDGene cohort using VIDA software—In COPDGene® study, all MDCT (at least 16 detector channels) of the chest used a tube potential of 120 kVp and an effective mAs of 200 (Supplemental Tables S1-A, B and C) (18). Submillimeter near isotropic MDCT scans without contrast were acquired at end inspiration. The images were reconstructed with slice thicknesses of 0.625, 0.75 or 0.9 mm depending on the CT manufacturer (General Electric Medical Systems, Siemens and Philips) (18). The optimal reconstruction kernel for a given model of CT scanner for the VIDA software program was used to segment the lungs, lobes and airway tree. The image matrix size was 512 × 512 pixels, and the pixel sizes ranged from x: 0.55 to 0.78 mm, y: 0.55 to 0.78. Other detailed CT protocols were the same with the previous report (18).

Airway dimensions were measured using automated, quantitative software that was designed to label and quantify the bronchial tree (Pulmonary Workstation+ VIDA Diagnostics; Iowa City, IA. www.vidadiagnostics.com, Supplemental Figure 1) (19, 20). These airways were as follows: right upper apical segmental, subsegmental and subsubsegmental brochi, right middle lateral segmental, subsegmental and subsubsegmental bronchi, right posterior basal segmental, subsegmental and subsubsegmental bronchi, left upper apical segmental, subsegmental and subsubsegmental bronchi, left superior lingular segmental, subsegmental and subsubsegmental bronchi, and left posterior basal segmental, subsegmental and subsubsegmental bronchi.

These airway indices were measured from the centerline to the airway edge in each slice of the 3D image set. Reported airway dimensions represented the average of all the measurements collected along the middle third of each individual airway segment. For each individual, the segmental, subsegmental and subsubsegmental airway data were averaged to provide a mean value for each level of branching. Structural measurements of airway dimensions included the lumen area (Ai), inner diameter, airway wall thickness, wall area percentage (WA%) and SQRTWA@pi10 in each anatomically matched airway. The perimeters of the airway lumen and of the adventitia subtended two areas: Ai (luminal area) and Ao (total area). WA% was calculated as (Ao – Ai)/Ao × 100. SQRTWA@pi10 was calculated for each subject by fitting a linear relationship between Pi and SQRTWA of each measured bronchus (16, 21).

For determining the extent of emphysema, quantitative densitometric analysis was performed with VIDA and areas of CT emphysema were defined as low attenuation areas (LAA) [<–950 Hounsfield units, HU]. Then, the percentage of LAA (LAA% −950HU) was determined for the entire lung. Region growing of airway tree was performed by research assistants under the training and supervision of the Imaging core of the COPDGene® study (list in Acknowledgements). The stability of CT measurements for each scanner is monitored by monthly scanning using a custom COPDGene phantom (18).

Statistical Analysis

Gender differences were evaluated using *t*-tests for continuous variables and χ^2 tests for categorical variables. Data that were not normally distributed (e.g., LAA% −950 HU and packs years of smoking (PYs)) were also analyzed after log transformation. Regression analysis was used to determine predictors of WA%. Multivariate analysis was performed using linear regression models for WA% adjusted for subject's age, sex, height, weight,

PYs, race, smoking status (current/former smoker), LAA% −950HU and total lung capacity (TLC% predicted) to adjust demographic and body size differences, and confounding factors that could affect WA%. Clinical centers and CT scanner types were also included as a variable to adjust those differences in multicenter COPDGene® cohort. Correlations between lung function (FEV_1% pred.) and airway parameters were determined using parametric testing methods with Pearson correlation coefficients. P values less than 0.05 were considered statistically significant. Statistical software (SPSS, version 17.0; Chicago, IL) was used for analysis.

RESULTS

Demographics, smoking history and lung function for the 2047 COPDGene® subjects who were included in the study are shown in Table 1. Subjects were predominantly White, but there were no ethnic differences between genders (Caucasian 78.0% in male, 77.3% in female, p = 0.706). Subjects had a heavy smoking history and PYs was higher in males (M:F, 49.9: 42.1 PYs, p < 0.01). Current smokers were more frequently male (M:F, 42.8% : 36.6%, p = 0.004). Height and body weight were smaller in women. There were no significant differences in lung function between genders and mean FEV_1% (pred.) results (M:F, 72.5%: 73.9%) were consistent with GOLD stage II disease (812 smokers without evidence of airway obstruction, 146 smokers with GOLD-I, 486 smokers with GOLD-II, 294 smokers with GOLD-III, 158 smokers with GOLD-IV, and 151 smokers with GOLD U).

Most airway measurements (inner diameter, wall thickness and lumen area) were lower in women compared to men (Table 2 and Supplemental Figs. 2A and 2B). The numbers of obtainable measurements were slightly decreased as the bronchial branches go more distal (n = 2043 for segmental bronchi, 2040 for subsegmental, 2033 for subsubsegmental). However, women had higher WA% in the subsegmental and subsubsegmental bronchi. In subgroup analyses using subjects with or without airflow obstruction, gender differences of airway dimensions were consistent (Supplemental Table S2-A and B). SQRTWA@pi10 was not significantly different between men and women (Supplemental Table S3).

Emphysema (LAA% < −950 HU) was more extensive and CT measured lung volume (TLC % predicted) was lower in men than women (Supplemental Table S3). Univariate analysis was used to determine which factors might be associated with WA% for different airways (Supplemental Table S4). There were significant associations between WA% and most variables (age, gender, race, pack-years, smoking status, height, weight, emphysema score, TLC, study center, and scanner type). Male gender (t ratios −7.8, −12.2), height (t ratios −10.4, −13.3) and LAA% (t ratios 9.1, 7.9) were stronger predictors than other variables in subsegmental and subsubsegmental bronchi while body weight and TLC% were more powerful in segmental bronchi compared to other variables.

In multivariate analysis including all of these variables (Table 3: shown for several key variables, and Supplemental Table S5 shown for all variables), PYs, smoking status (current smoker), height, weight and TLC% showed consistent and significant associations with WA % from all airways, from segmental to subsubsegmental bronchi. Male gender was negatively associated with subsegmental and subsubsegmental WA% (t = −3.47, −6.9; p = 0.001, <0.001, repectively) while there was no significant associations between gender and segmental WA%.

Among the above variables, height, LAA% and TLC% were more powerful predictors than other demographic predictors in the subsegmental and subsubsegmental paths. In multivariate analysis for other airway parameters such as lumen area and wall thickness

(Table 4: shown for several key variables, Supplemental Table S6, S7-A and B), gender was one of the significant and powerful determinants for each quantitative CT parameter. However, gender was not a significant predictor of SQRTWA@pi10 in the multivariate analysis. WA%, lumen area and SQRTWA@pi10 were significantly correlated with FEV_1% predicted (Table 5).

DISCUSSION

Computed tomography is becoming a useful, non-invasive tool to evaluate the airway dimensions. There are several different investigational methods used to express the morphologic characteristics of airway wall. These include the two most frequently used metrics: WA% and SQRTWA@Pi10 (21–23). It should be noted that these two metrics are not directly measured, but are derived from other airway measurements. Directly measured metrics include luminal area, inner diameter and wall thickness. These computational differences have led to different investigators reporting apparently paradoxical conclusions regarding gender differences and have led to confusion in interpretation of CT derived airway measurement. For example, WA% is a deceptive measure of wall thickness because as airways become smaller, the WA% becomes larger (24).

Thus, WA% is affected not only by airway thickness, but also by airway size. SQRTWA@Pi10 is a useful method to correct for differences in airway size; however, the concept of a hypothetical airway is less relevant when one can measure actual airways that have been anatomically matched. Using the SQRTWA@Pi10 also discounts the importance of airway size on airflow. We speculated that this is why WA% and luminal area had better correlation with FEV_1 (% predicted) than SQRTWA@Pi10 (Table 5).

To our knowledge, this report is the largest investigation of airway dimensions measured by MDCT and the only report of gender differences in airway dimensions classified according to bronchial branching order. A novel finding is that in anatomically matched sites, especially in distal airways such as subsegmental and subsubsegmental bronchi, female smokers have higher WA% compared to male smokers. However, they have lower luminal area, airway thickness, and internal diameter of airway in anatomically matched airways than do male smokers. The significance of reduced luminal area in women is particularly important to physiology because the smaller size of women's lungs is associated with lower flow rates (25).

Furthermore, airflow limitation in COPD is more closely related to the dimensions of the distal (small) airways than proximal (large) airways (23). The diameters of subsubsegmental bronchi in our study were around 3 mm, which is thought to be more representative of airflow limitation (26). Thus, the direct measurement of anatomically matched airway lumen also has an important physiologic relevance to airflow. The smaller lumen area and the higher WA% of these distal airways in women could explain why women have a higher prevalence of COPD and may also explain gender differences in the presentation and pathophysiology of airflow obstruction and COPD.

SQRTWA@Pi10 is a hypothetical airway parameter that is obtained by fitting a linear relationship between Pi and SQRTWA (21). Other studies (7, 16, 17) have come to different conclusions from our results; namely that airways are thicker in men compared to women in terms of SQRTWA@Pi10. In our study, there were no significant differences of SQRTWA@Pi10 between genders. In the subgroup analysis according to GOLD stage, there was significant difference of SQRTWA@Pi10 between genders (men : women, 3.84 : 3.80 mm, $p = 0.02$) only among severe COPD (GOLD 3 and 4) like the other previous report (7). But, the differences of SQRTWA@Pi10 between genders are very small. In the other

studies (7, 16, 17), the differences of SQRTWA@Pi10 between genders (around 0.2–0.3mm) were also very small.

We postulated that these small differences could be easily obscured by other hidden confounding factors such as different airway measurement algorithm in each study. In contrast to SQRTWA@Pi10, women had the higher WA% in the subsegmental and subsubsegmental paths through all GOLD stages. Thus, in regarding whether airways are thicker in women compared to men, it is important to consider which definitions of airway dimensions are reported. However, further study will be needed to clarify these discrepancies and its contribution to clinical relevance, and to evaluate which airway parameter could be more important to clinical settings.

The other major difference between this study and the recently published studies of airway measurements (7, 16, 17) is the methodology for determining airway wall thickness. Most publications have used the Full-Width-At-Half-Maximum (FWHM) method to measure the dimensions. We used an optimal surface algorithm (VIDA) to determine airway boundaries. The results from VIDA have showed better subpixel accuracy for the inner border and equivalent results for the outer wall border compared with those of the FWHM method (20). The segmentation algorithm of VIDA retrieves a significantly higher count of airway branches compared with a commonly used region growing segmentation algorithm (20). However, the numbers of obtainable measurements were decreased as the branches go more distal. This suggests that some difficulties including reproducibility are still remained to measure airway dimensions especially in the small airways with the VIDA software even though this is a more updated and automatically operated software that has been validated previously (28).

Also, long-term reproducibility should be validated in a longitudinal future study using VIDA. But, a strength of this study includes the large sample of airway measurements with averaging data for each generational path. The problem of reproducibility of the measurements could be weakened, at least, to some extent by averaging the values of each different airway from a large number of subjects. Furthermore, parallel imaging analyses of LAA% were done using Airway Inspector (www.airwayinspector.org) and 3D Slicer (http://www.slicer.org/) for all subjects and, airway dimensions were also measured using 3D slicer for more than 80 subjects. The results of gender differences from 3D slicer were similar to VIDA's (data not shown).

A secondary finding in this study was that age, smoking (status and amount), body sizes (height and weight), emphysema and other various factors affect airway measurements. Smoking status, body sizes and TLC% showed significant associations with WA% from all the airways. Gender effects for WA% were present in the subsegmental and subsubsegmental paths, not in the segmental bronchi. Among the variables for WA%, height, LAA% and TLC% were more powerful predictors than other demographic predictors in the subsegmental and subsubsegmental paths. For other airway parameters, gender is one of the powerful predictors for luminal area and wall thickness, but not for SQRTWA@Pi10. This suggests that each variable could affect different airway metrics with different intensity and different location, and this might be associated with the heterogeneity of COPD and the importance of airway measurements in anatomically matched sites.

There were small gender differences (around 1%) in WA% that could affect the small physiologic relevance. However, the small changes in each variable should be considered to better understand the heterogeneity of COPD because the factors of airflow obstruction and COPD are multifactorial. Additionally, gender differences in WA% were exaggerated in current smokers with COPD (Supplemental Table S8). This could suggest that women's

airway may be more susceptible than men's to the airway damaging effects of current smoking. However, to clarify these heterogeneous relationships between each airway parameter and other variables, and smoking effects in gender, a longitudinal study is needed in the future.

We found other sources of variability in airway wall measurements including clinical center, CT scanner type, and location of airways. However, the magnitudes of gender effect for luminal area (t ratio, around 7.2, Table 4) and wall thickness (t-ratio, around 7.2, Table 4) in all airway paths were higher than those of CT scanner type (t-ratio, around 1.0, data not shown) or clinic center (t-ratio, around 2.0, data not shown). The magnitudes of gender effect for WA% in subsegmental and subsubsegmental paths were also higher than they were for scanner or center. This suggests gender differences are consistent irrespective of scanner type or clinic center. However, center or scanner type could affect the quantitative measurements as a noise to some extent.

These findings indicate that gender is just one factor for airway wall, that a complex background of airway dimensions exists and that failure to take into account other clinical variables may weaken any observed differences in CT derived airway wall measurements. The most likely explanations for gender differences in airways are biological and environmental determinants (30). Several studies suggest that genetic interactions may be important to the gender differences and CT phenotypes associated with COPD (4, 31, 32). However, the precise mechanism and determinants of gender differences on airway dimension remains unknown. This study also suggests that other causes of variability in airway measurements need further investigation.

The limitations of this study are similar to those of the parent study (COPDGene®). First, it is cross-sectional and may not account for changes in airway dimension over time. Second, nonsmokers were not included. Thus, we cannot fully evaluate the effects of smoking per se on airway dimensions. Additionally, a fundamental limitation of airway measurements is the spatial resolution (voxel size: x, y, z = slice thickness) of the underlying CT image data. For example, for a CT acquisition field-of-view of 35 cm, typical for the COPDGene® cohort, the 512 × 512 image size translates to an x, y pixel dimension of 0.68 mm. Slice thickness (z) ranged from 0.625 to 0.9 mm depending on the CT scanner manufacturer. Therefore, to have two pixels on a feature of interest (e.g., an airway lumen or airway wall) as suggested from Nyquist sampling theory would require a feature of approximately 1.37 mm size or greater (33).

Airway wall thickness may be near the spatial resolution limit in subsegmental and subsubsegmental airways in the COPDGene cohort. This requires further study and comparison to CT phantom results. Note that larger field-of-view dimensions and larger slice thicknesses will further decrease spatial resolution. These technical issues may explain, at least in part, the variation of airway dimensions by clinical center and scanner type. Last, we used a convenience cohort from COPDGene cohort that was obtained to look for genetic factors in COPD. The cohort is a heterogeneous mix of individuals with varied smoking histories and a range of airflow obstruction. It was not ideally recruited to answer the question about gender differences. More studies will be needed only for gender differences of airway dimensions to confirm these differences.

In conclusion, female smokers have disproportionately higher WA%, but lower luminal area and airway thickness in anatomically matched sites, subsegmental and subsubsegmental bronchi as measured by CT scan than do male smokers. This difference may explain, in part, gender differences in the heterogeneity of COPD and airflow obstruction. Awareness of the

gender difference in airway dimensions should be considered in future investigations of airway related disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

COPD	chronic obstructive pulmonary disease
FEV_1% pred.	% Predicted Forced Expiratory Volume in 1 Second
LAA%	percentage of low attenuation areas
SQRTWA@pi10	square root of the wall area at a airway internal perimeter of 10 mm
WA%	percentage of wall area

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Table 1

Subject characteristics*

	Men (n = 1021)	Women (n = 1026)	P-value
Age (yr)	61.7 ± 9.3	61.7 ± 9.1	0.968
Caucasian (%)	78.0	77.3	0.706
Pack years smoking	49.9 ± 29.3	42.1 ± 24.5	<0.001‡
Current smoker (%)	42.8	36.6	0.004†
Height, cm	176.4 ± 72	162.9 ± 6.4	<0.001‡
Body weight, Kg	88.4 ± 18.5	75.9 ± 18.6	<0.001‡
FEV_1%pred(postBD)	72.5 ± 27.9	73.9 ± 26.7	0.229
GOLD 0§	98.4 ± 11.9(*n*, 389)	97.6 ± 12.0(*n*, 423)	0.339
GOLD 1	91.1 ± 9.4(*n*, 82)	92.3 ± 10.4(*n*, 64)	0.464
GOLD 2	64.6 ± 8.6(*n*, 245)	63.4 ± 8.5(*n*, 241)	0.108
GOLD 3	39.1 ± 5.8(*n*, 150)	40.2 ± 5.7(*n*, 144)	0.116
GOLD 4	22.0 ± 4.5(*n*, 91)	21.9 ± 4.7(*n*, 67)	0.916
GOLD U¶	70.7 ± 6.6(*n*, 64)	70.2 ± 8.0(*n*, 87)	0.675

*Data are reported as mean ± SD unless otherwise indicated.

†P-values are indicated as follows: ******p < 0.05.

‡p < 0.001.

§GOLD 0

¶GOLD U denote smokers with normal spirometry, and smokers with normal FEV_1/FVC but reduced FEV_1(%pred), respectively.

Table 2

Mean CT airway parameters at each level of bronchial branching by gender*

Site of airway	Airway parameter†	Men	Women	P-value
Segmental bronchi	Inner diameter	5.3 ± 0.7	4.8 ± 0.6	<0.001
(M:F, 1019:1024)	Lumen area (mm^2)	22.5 ± 6.5	18.4 ± 4.8	<0.001
	Wall Sickness	1J ± 0.2	1.5 ± 0.2	<0.001
	WA%	61.2 ± 3.4	61.3 ± 3.2	0.411
Subsegmental bronchi	Inner diameter	3.9 ± 0.5	3.6 ± 0.5	<0.001
(M:F, 1017:1023)	Lumen area (mm^2)	12.5 ± 3.4	10.4 ± 2.8	<0.001
	Wall Sickness	1.5 ± 0.2	1.4 ± 0.2	<0.001
	WA%	63.9±2.7	64.8 ± 2.6	<0.001
Subsubsegmental bronchi	Inner diameter	3.1 ± 0.4	2.8 ± 0.3	<0.001
(M:F, 1014:1019)	Lumen area (mm^2)	7 J ± 1.9	6.5 ± 1.6	<0.001
	Wall Sickness	1.5 ± 0.2	1.4 ± 0.2	<0.001
	WA%	66.7 ± 2.1	67.8 ± 1.9	<0.001

*Data are reported as mean ± SD (mm) unless otherwise indicated. Histograms of segmental and subsegmental airway dimensions are shown in Supplemental Figures 2A and 2B.

†Airway parameter: WA% = percentage of wall area.

Table 3

Multivariate regression analysis of predictors of generational WA%

Site	Variables	Estimates	Std. Error	*t*	Adjusted R Square	P-value
Segmental Bronchi	Male gender	0.162	0.187	0.867	0.207	0.386
	PYs	0.012	0.003	4.556		<0.001
	Current smoker	0.921	0.161	5.737		<0.001
	Height, cm	−0.084	0.01	−8.291		<0.001
	Weight, kg	0.041	0.004	10.269		<0.001
	LAA% −950HU	0.072	0.008	9.149		<0.001
	TLC%	−0.031	0.005	−6.511		<0.001
Subsegmental bronchi	Male gender	−0.514	0.148	−3.47	0.247	0.001
	PYs	0.008	0.002	4.16		<0.001
	Current smoker	0.747	0.127	5.877		<0.001
	Height, cm	−0.072	0.008	−8.994		<0.001
	Weight, kg	0.018	0.003	5.62		<0.001
	LAA% −950HU	0.085	0.006	13. 692		<0.001
	TLC%	−0.031	0.005	−9.176		<0.001
Subsubsegmental bronchi	Male gender	−0.794	0.115	−6.928	0.268	<0.001
	PYs	0.007	0.002	4.43		<0.001
	Current smoker	0.586	0.098	5.951		<0.001
	Height, cm	−0.051	0.006	−8.174		<0.001
	Weight, kg	0.006	0.002	2.429		0.015
	LAA% −950HU	0.066	0.005	13. 647		<0.001
	TLC%	−0.031	0.003	−10.544		<0.001

Table 4

Multivariate regression analysis of predictors of luminal area of subsegmental bronchi, wall thickness of subsegmental bronchi and SQRTWA@pi10

Parameters	Variables	Estimates	Std. Error	*t*	Adjusted R2	Sig.
Lumen area*	Male gender	1.307	0.l82	7.177	0.247	<0.001
	PYs	−0.009	0.002	−3.542		<0.001
	Current smoker	−0.736	0.l56	−4.702		<0.001
	Height, cm	0.084	0.0l	8.527		<0.001
	Weight, kg	0.002	0.004	0.387		0.699
	LAA% −950HU	−0.092	0.008	−12.075		<0.001
	TLC%	0.029	0.005	6.247		<0.001
Wall thickness*	Male gender	0.071	0.0l	7.345	0.33	<0.001
	PYs	<0.001	0	0.683		0.495
	Current smoker	−0.0l4	0.008	−1.658		0.097
	Height, cm	<0.001	0.00l	−0.737		0.46l
	Weight, kg	0.003	0	16.335		<0.001
	LAA% −950HU	<0.001	0	0.884		0.377
	TLC%	0.00l	0	−1.918		0.055
SQRTWA@pi10	Male gender	0.002	0.007	0.253	0.197	0.8
	PYs	0.00l	0	2.l5l		0.032
	Current smoker	0.03	0.006	4.654		<0.001
	Height, cm	−0.002	0	−4.797		<0.001
	Weight, kg	0.00l	0	8.749		<0.001
	LAA% −950HU	0.002	0	6.795		<0.001
	TLC%	−0.002	0	−9.4l5		<0.001

*Lumen area, Wall thickness and WA% in subsegmental bronchi. The results in other airway sites, segmental and subsubsegmental bronchi (Supplemental Tables S7-A and B), were similar as above.

Table 5

Correlations between airway dimensions and FEV_1 (% predicted)

Airway parameters†	r	P-value
SQRTWA@pi10	−0.301	<0.001
Segmental WA%	−0.502	<0.001
Subsegmental WA%	−0.557	<0.001
Subsubsegmental WA%	−0.510	<0.001
Segmental Ai	0.395	<0.001
Subsegmental Ai	0.465	<0.001
Subsubsegmental Ai	0.393	<0.001

†Airway parameters: SQRTWA@pi10 = square root of the wall area at a airway internal perimeter of 10 mm. WA% (or Ai) = mean wall area percentage (or lumen area).