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Association Between Airway Caliber Changes With Lung Inflation and Emphysema Assessed by Volumetric CT Scan in Subjects With COPD

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e-Appendix 1.

Methods

Study population

COPDGene (www.copdgene.org) is a multi-center study examining genetic and epidemiologic risk factors for COPD and smoking-related lung diseases in non-Hispanic white and African-American smokers.[1] From November of 2007 to October of 2009 the first 2500 smokers (with at least 10 pack years of smoking) between the ages of 45 and 80 were enrolled into COPDGene. For this study, we selected a subset of subjects based on GOLD (Global Initiative for Obstructive Lung Disease) stages of COPD[2] and CT phenotypes. These phenotypes were defined as AP or EP based upon CT measures of emphysema (<13 or ≥25%, respectively)[3]. Because of the limited number of subjects available with GOLD-4 stage and an AP, we first clustered all these subjects (N=23) into this group. Then, this group was age-, gender-, scanner brand-, and center-matched with GOLD-2-AP, GOLD-2-EP, and GOLD-4-EP groups (N=23 each group) and with a control group (N=46) with normal lung function and no emphysema on CT scans. Usually subjects were evaluated in 1 or 2 visits, in which the questionnaires and pulmonary functions tests were taken first and then CT scanning. In the present study, 118 out of 138 subjects had the date and time of both spirometry and of CT scanning available. In 96 subjects the spirometry was performed first and in 22 the CT

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scanning. The median (interquantile range) time between postbronchodilator spirometry and the following CT scanning was 78 (53-96) minutes.

Clinical and Physiologic Assessments

Demographic and clinical history data were collected with standardized instruments. Dyspnea was measured with the modified Medical Research Council Score.[4] Spirometry was performed at each center in accordance with American Thoracic Society/European Respiratory Society recommendations[5] with an ndd EasyOne™ spirometer (Zurich, Switzerland) before and 20 minutes after two puffs (180 mcg) of albuterol administration. The postbronchodilator forced expiratory volume in one second and forced vital capacity were expressed as percentages of predicted values using standardized prediction equations.[6] Exercise capacity was assessed with a standardized six-minute walk test.

Airway distensibility

W expressed airway distensibility as the ratio of absolute change in airway inner diameter (in mm) to the cubic root of absolute change in lung volume (in deciliters) from end tidal breathing to total full inspiration[7]. The ratio was calculated with whole-lung and lobar data sets and called global and *lobar* airway distensibility, respectively. Each ratio was calculated with the following formula:

Global airway distensibility:

$$\frac{\text{(Airway diameter [AD] of the 3rd /4th-AG at full inspiration - AD of the 3rd /4th-AG at end tidal breathing)}}{\text{(Whole-lung volume at full inspiration- Whole lung volume at end tidal breathing)}^{1/3}}$$

Airway diameters of the 3rd or 4th airway generations (AG) from the right upper lobe (RUL) apical bronchus (RB1) and the right lower lobe (RLL) posterior bronchus (RB10) were identified and matched on inspiratory and expiratory paired CT scans. We chose these two bronchi because their generally perpendicular orientation to the

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axial CT scanning plane. Then we measured all segments individually and averaged all 3rd-AG and 4th-AG diameter measurements. Measures of airway lumen area and total airway area and calculations of wall area percent were all performed following same steps as lumen diameters. Analyses using global airway distensibility were always performed with whole-lung emphysema measure.

Lobar airway distensibility for RUL:

$$\frac{\text{(Airway diameter [AD]of the RB1 3rd /4th-AG at full inspiration - AD of the RB1 3rd /4th-AG at end tidal breathing)}}{\text{(Volume of RUL at full inspiration - Volume of RUL at end tidal breathing)}^{1/3}}$$

Lobar airway distensibility for RLL:

$$\frac{\text{(Airway diameter [AD] of the RB10 3rd /4th-AG at full inspiration -AD of the RB10 3rd /4th-AG at end tidal breathing)}}{\text{(Volume of RLL at TLC - Volume of RLL at end tidal breathing)}^{1/3}}$$

An airway inner diameter was calculated for the 3rd and the 4th airway generations of RB1 and RB10 bronchi by averaging the three measures obtained in each segment; lobar volume changes for the RUL and RLL were used to calculate the denominator. Analyses using *lobar* airway distensibility always were performed with lobar emphysema data of RUL and RLL.

CT examination

Images acquisition parameters by scanner (Tables 1A and 1B) used by the subset of subjects of this study. Data were taken from the COPDGene website (www. copdgene.org).

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CT measures of emphysema and lung volumes

The lung volumes were calculated as volume of the lung mask minus the central airways for each CT scan by using Airway Inspector software as described elsewhere. RUL and RLL measures of volume and emphysema were obtained from the COPDGene Image Analysis Core (N=130). This data was obtained with VIDA software (Iowa City, IA). For the analyses looking at *lobar* airway distensibility, COPD patients within a GOLD stage were classified as EP or AP depending on whether their lobar emphysema value fell above or below the median lobar emphysema value, respectively. We used this approach because the groups using whole-lung or lobar emphysema were almost identical and thus comparable.

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e-Table 1A Inspiratory Volumetric Computed Tomography Protocol

Inspiratory CT

Scanner make	GE	GE	SIEMENS	SIEMENS
Scanner model	LS 16	VCT-64	Sensation-16	Sensation-64
Scan Type	Helical	VCT Helical	Spiral	Spiral
Rotation Time (s)	See mA	See mA	0.5	0.5
Det. Configuration	16 x 0.625	64 x 0.625	16 x 0.75	64 x 0.6
Pitch	1.375	1.375 mm	1.1	1.1
Speed (mm/rot)	13.75	13.75	13.2	21.1
kVp	120	120	120	120
mA	400 @ 0.5s	400 @ 0.5s	*Effective mAs:* 200	*Effective mAs:* 200
Dose modulation	Auto-mA off	Off	CARE Dose 4D off	CARE Dose 4D off
Reconstructions				
RECON1				
Algorithm	BONE	BONE	B46f	B46f
Thickness (mm)	0.625	0.625	0.75	0.75
Interval (mm)	0.625	0.625	0.5	0.5
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*
RECON 2				
Algorithm	Standard	Standard	B31f	B31f
Thickness (mm)	0.625	0.625	0.625	0.75
Interval (mm)	0.625	0.625	0.5	0.5
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*

* reconstruction field of view should encompass the widest diameter of the lung.

e-Table 1B Expiratory Volumetric Computed Tomography Protocol

Expiratory CT

Scanner make	GE	GE	SIEMENS	SIEMENS
Scanner model	LS 16	VCT-64	Sensation-16	Sensation-64
Scan Type	Helical	VCT Helical	Spiral	Spiral
Rotation Time (s)	See mA	See mA	0.5	0.5
Det. Configuration	16 x 0.625	64 x 0.625	16 x 0.75	64 x 0.6
Pitch	1.375	1.375 mm	1.1	1.1
Speed (mm/rot)	13.75	13.75	13.2	21.1
kVp	120	120	120	120
MA	100 @ 0.5s	100 @ 0.5s	*Effective mAs:* 50	*Effective mAs:* 50
Dose modulation	Auto-mA off	Off	CARE Dose 4D off	CARE Dose 4D off
Reconstructions				
RECON1				
Algorithm	BONE	BONE	B46f	B46f
Thickness (mm)	0.625	0.625	0.75	0.75
Interval (mm)	0.625	0.625	0.5	0.5
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*
RECON 2				
Algorithm	Standard	Standard	B31f	B31f
Thickness (mm)	0.625	0.625	0.75	0.75
Interval (mm)	0.625	0.625	0.5	0.5
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*

* reconstruction field of view should encompass the widest diameter of the lung.

Results

e-Table 2 Self-Reported Respiratory Treatment Across Study Groups.

Reported Treatment**	Control N=46	GOLD 2-AP N=23	GOLD 2-EP N=23	GOLD 4-AP N=23	GOLD 4-EP N=23
Short-Acting Bronchodilators, n (%)	6 (13)	10 (43)*	13 (57)*	18 (78)*	18 (78)*
Long-Acting Bronchodilators, n (%)	5 (11)	4 (17)	10 (43*)	13 (57)*	15 (65)*
Inhaled Corticosteroids, n (%)	0 (0)	1 (4)	2 (9)	8 (35)*	2 (9)†
Long-Acting β-Agonists plus Corticosteroids, n (%)	2 (4)	5 (22)	10 (43)*	11 (48)*	13 (57)*

**Short-Acting Bronchodilators: Albuterol, Ipratropium, Metaprotenerol, and Albuterol + Ipratropium; Long-Acting

Bronchodilators: Formoterol, Salmeterol, and Tiotropium; Inhaled Corticosteroids: Budesonide, Fluticasone, and

Triamcinolone; Long-Acting β- Agonists + Corticosteroids: Formoterol plus Budesonide and Salmeterol plus Fluticasone.

GOLD: Global Initiative for Obstructive Lung Disease; AP: airway-predominant CT subtype; EP: emphysema-predominant CT subtype.

*P <0.05 vs. controls; †P <0.05 vs GOLD 4- AP

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e-Table 3 CT lobar measures of volume, emphysema, and airway diameter (N= 130)

CT Measure	Control	GOLD 2-AP	GOLD 2-EP	GOLD 4-AP	GOLD 4-EP	All
Volume of RUL At End Tidal Breathing (ml)	610 ± 165	722 ± 207	1083 ± 319*†	1004 ± 235*	1231 ± 302*†	863 ± 335
Volume of RUL At Full Inspiration (ml)	1099 ± 249	1099 ± 282	1708 ± 497*	1304 ± 307	1551 ± 412*	1300 ± 415
Volume of RLL At End Tidal Breathing (ml)	639 ± 187	696 ± 208	806 ± 311	1055 ± 302*	1279 ± 318*	839 ± 345
Volume of RLL At Full Inspiration (ml)	1371 ± 358	1146 ± 298	1510 ± 417†	1342 ± 262	1670 ± 360*†	1396 ± 377
Emphysema of RUL (%)	1 ± 2	2 ± 1	36 ± 13*†	8 ± 5*	45 ± 12*†	15 ± 19
Emphysema of RLL (%)	1 ± 1	1 ± 1	20 ± 11*†	6 ± 3	38 ± 13*†	10 ± 15
Inner Diameter of RB1 3rd AG at End Tidal Breathing (mm)	3.86 ± 1.29	4.00 ± 1.16	4.35 ± 1.02	3.47 ± 1.05	4.10 ± 1.66	3.91 ± 1.27
Inner Diameter of RB1 4th AG at End Tidal Breathing (mm)	2.61 ± 0.62	2.78 ± 0.65	2.94 ± 0.58	2.44 ± 0.78	3.09 ± 0.87	2.75 ± 0.72

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Inner Diameter of RB10 3rd AG at End Tidal Breathing (mm)	3.62 ± 1.19	3.60 ± 0.93	3.60 ± 0.91	3.70 ± 1.14	3.75 ± 0.93	3.65 ± 1.05
Inner Diameter of RB10 4th AG at End Tidal Breathing (mm)	2.85 ± 1.04	2.94 ± 0.66	2.87 ± 1.01	2.84 ± 0.84	3.06 ± 0.76	2.93 ± 0.91

Data are presented as mean ± SD.

*P<0.05 vs. control; † P<0.05 vs. Airway-predominant CT subtype within a GOLD stage.

GOLD: Global Initiative for Obstructive Lung Disease; AP: airway-predominant CT subtype; EP: emphysema-predominant CT subtype. RUL: right upper lobe; RLL: right lower lobe; RB1: right upper lobe apical bronchus; RB10: right lower lobe posterior basal bronchus; AG: airway generation.

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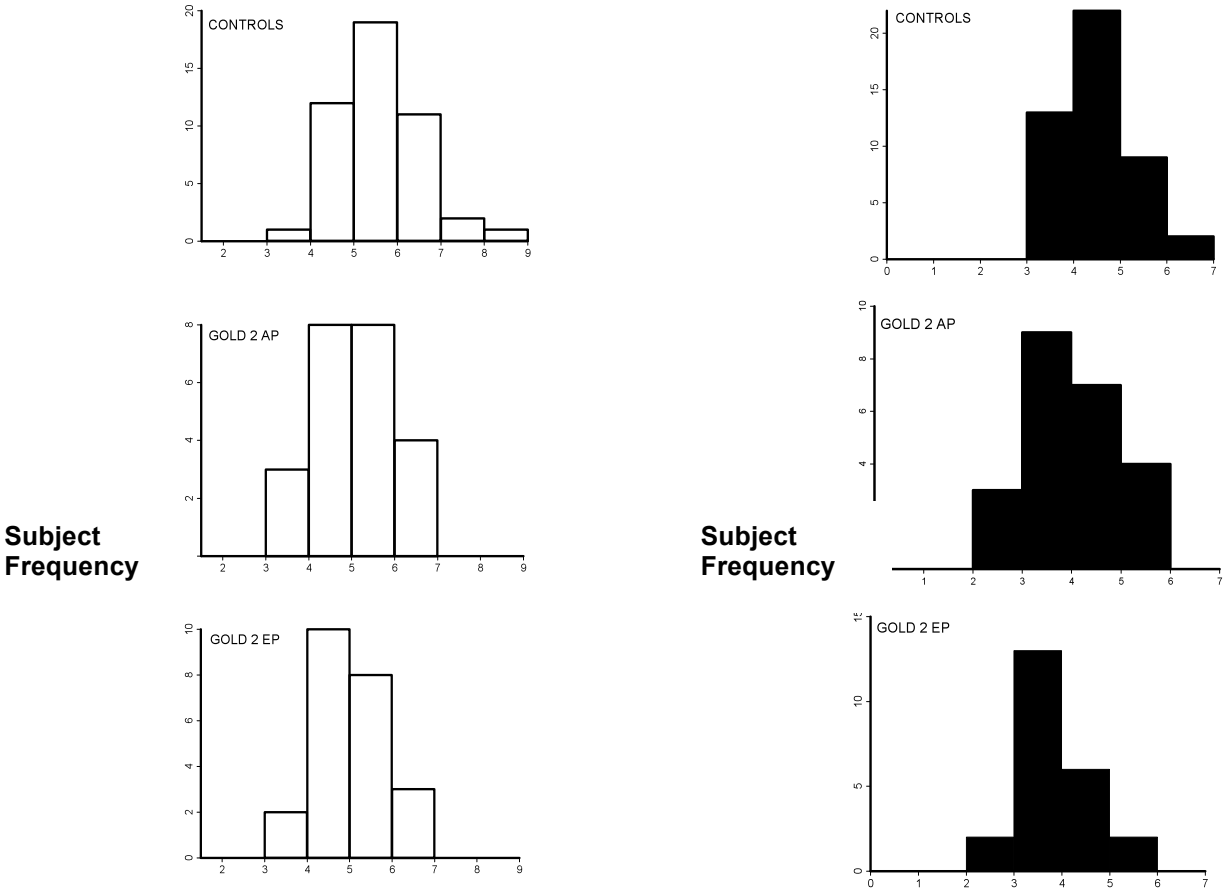

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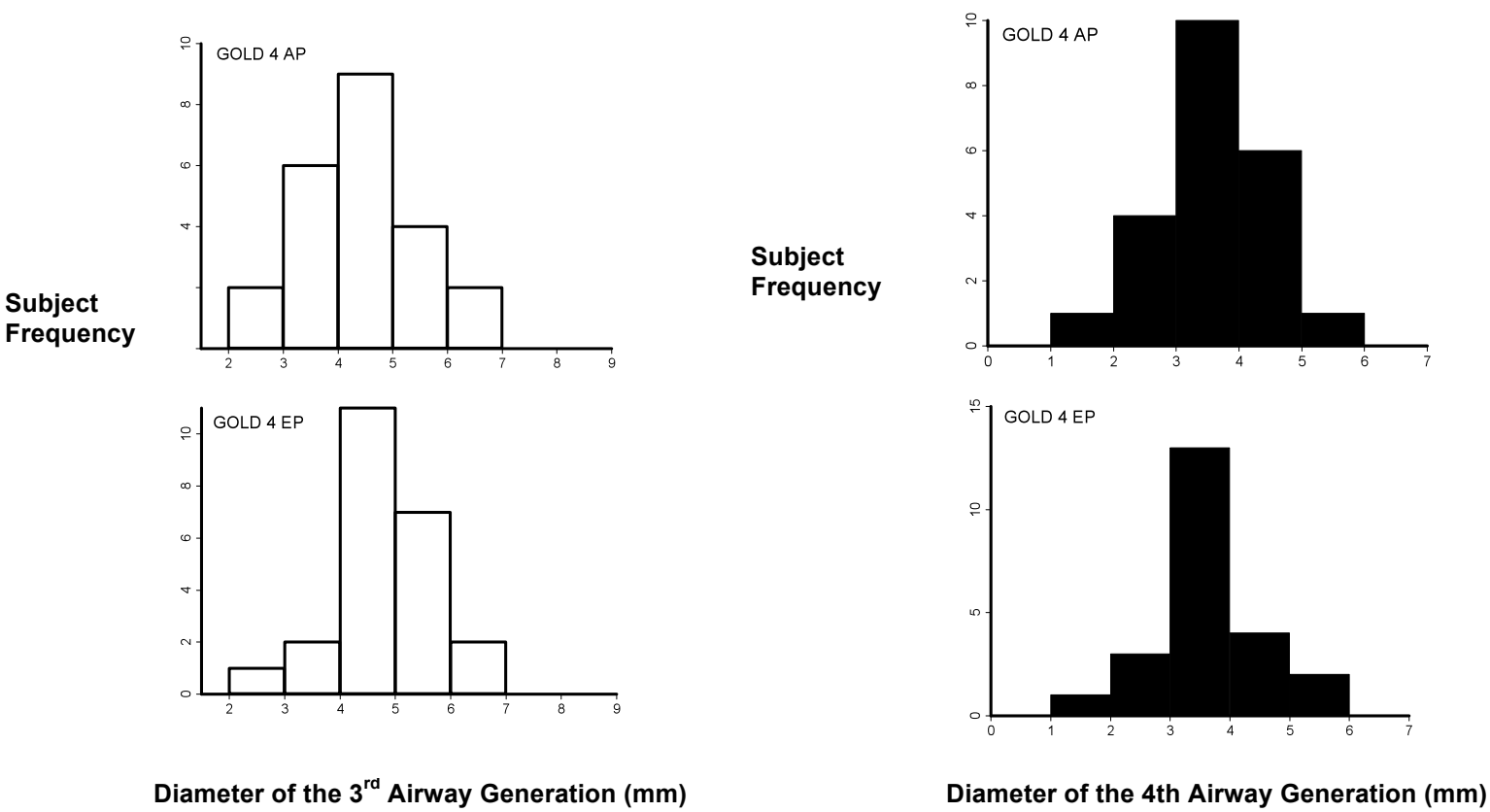

e-Figure 1 Distribution of inner diameter of the 3rd (open bars) and 4th (filled bars) airway generations across smokers with normal lung function and those with GOLD 2 and 4 COPD (airway-predominant [AP] and emphysema-predominant [EP]). GOLD: Global Initiative for Obstructive Lung Disease.

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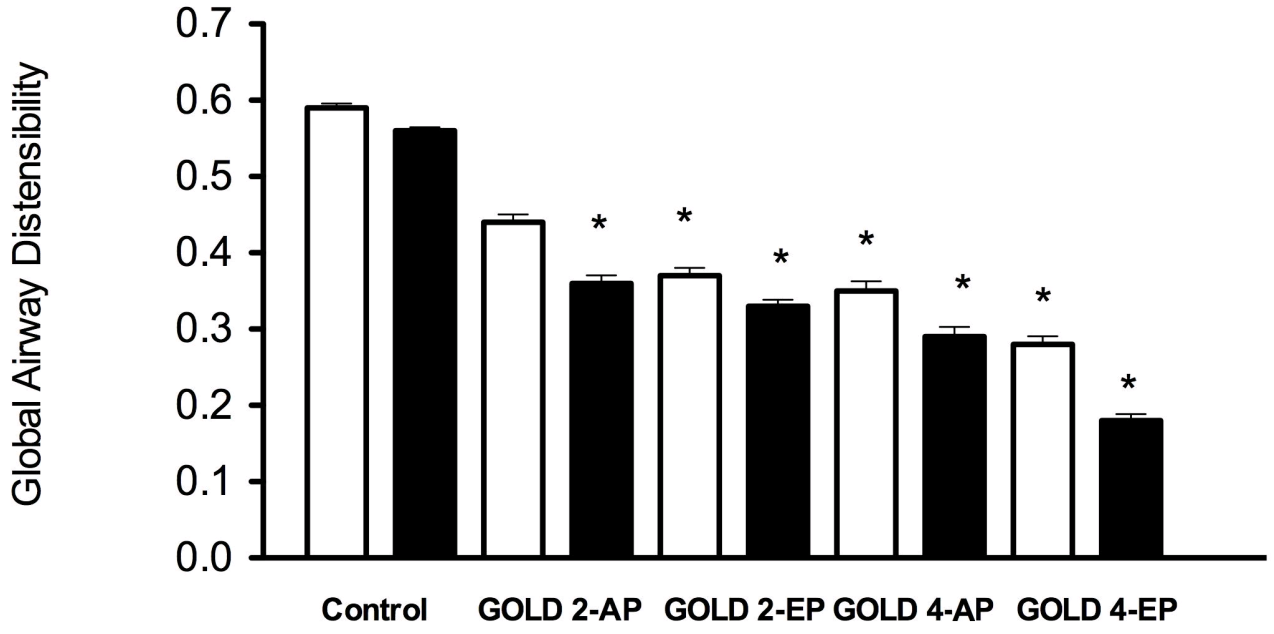

e-Figure 2 Global distensibility (mean ± SEM) of the 3rd (open bars) and the 4th (closed bars) airway generations from end tidal breathing to full inspiration by study group. Global distensibility was calculated using predicted rather than measured values for FRC and TLC. AP: airway-predominant CT subtype; EP: emphysema-predominant CT subtype; GOLD: Global Initiative for Obstructive Lung Disease. Global airway distensibility is defined in the methods section of this supplement.

*P<0.05 vs. control.

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e-Table 4 Correlation coefficients (r) between *lobar* airway distensibility and lobar emphysema.

Lobar Emphysema (%)	*Lobar* Airway Distensibility							
	Airway Generation of the RB1 Bronchus				Airway Generation of the RB10 Bronchus			
	3rd		4th		3rd		4th	
	r	P value	r	P value	r	P value	r	P value
Right Upper Lobe	-0.21	0.02	-0.46	<0.0001				
Right Lower Lobe					-0.19	0.04	-0.22	0.02

RB1: right upper lobe apical bronchus; RB10: right lower lobe posterior basal bronchus.

e-Table 5 Multivariate linear regression model for global and *lobar* airway distensibility of the 4th airway generation in the postbronchodilator cohort (N=73)

Model	Parameter Estimate	95% Confidence Interval	P value
Model 1 ***Global airway distensibility***			
Whole-lung Emphysema (%)	-0.004	-0.008, -0.0003	0.04
Wall Area Percent of the 4th AG at End Tidal Breathing	0.01	0.002, 0.02	0.02
Model 2 ***Right upper lobe airway distensibility***			
RUL Emphysema (%)	-0.003	-0.005, -0.002	0.0001
Wall Area Percent of the 4th AG of the RUL apical bronchus at End Tidal Breathing	0.003	-0.002, 0.007	0.22
Model 3 ***Right Lower Lobe Airway Distensibility***			
RLL Emphysema (%)	-0.003	-0.008, 0.002	0.29
Wall Area Percent of the 4th AG of the RLL posterior basal bronchus at End Tidal Breathing	0.004	-0.003, 0.02	0.09

Adjustment was done for age, gender, Body Mass Index, and pack years of smoking. Model R^2 was 0.33, 0.30, and 0.25 for global, right upper lobe, and right lower lobe airway distensibility, respectively. RUL: right upper lobe; RLL: right lower lobe; AG: airway generation.

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