Quantitative CT Measures of Bronchiectasis in Smokers

Alejandro A. Diaz, MD, MPH; Thomas P. Young, BSc; Diego J. Maselli, MD; Carlos H. Martinez, MD, MPH; Ritu Gill, MD, MPH; Pietro Nardelli, PhD; Wei Wang, PhD; Gregory L. Kinney, PhD; John E. Hokanson, PhD; George R. Washko, MD; and Raul San Jose Estepar, PhD

BACKGROUND: Bronchiectasis is frequent in smokers with COPD; however, there are only limited data on objective assessments of this process. The objective was to assess broncho-vascular morphology, calculate the ratio of the diameters of bronchial lumen and adjacent artery (BA ratio), and identify those measurements able to discriminate bronchiectasis.

METHODS: We collected quantitative CT (QCT) measures of BA ratios, peak wall attenuation, wall thickness (WT), wall area, and wall area percent (WA%) at matched fourth through sixth airway generations in 21 ever smokers with bronchiectasis (cases) and 21 never-smoking control patients (*control* airways). In cases, measurements were collected at both *bronchiectatic* and *nonbronchiectatic* airways. Logistic analysis and the area under receiver operating characteristic curve (AUC) were used to assess the predictive ability of QCT measurements for bronchiectasis.

RESULTS: The whole-lung and fourth through sixth airway generation BA ratio, WT, and WA% were significantly greater in bronchiectasis cases than control patients. The AUCs for the BA ratio to predict bronchiectasis ranged from 0.90 (whole lung) to 0.79 (fourth-generation). AUCs for WT and WA% ranged from 0.72 to 0.75 and from 0.71 to 0.75. The artery diameters but not bronchial diameters were smaller in *bronchiectatic* than both *nonbronchiectatic* and *control* airways ($P < .01$ for both).

CONCLUSIONS: Smoking-related increases in the BA ratio appear to be driven by reductions in vascular caliber. QCT measures of BA ratio, WT, and WA% may be useful to objectively identify and quantify bronchiectasis in smokers.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00608764; URL: www.clinicaltrials.gov.

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FOR EDITORIAL COMMENT SEE PAGE 1204

ABBREVIATIONS: AATD = alpha-1 antitrypsin deficiency; AUC = area under the receiver operating characteristic curve; BA ratio = ratio of the diameters of bronchial lumen and adjacent artery; CCC = concordance correlation coefficients; %LAA-950 = attenuation areas below -950 Hounsfield units; PWA = peak wall attenuation; QCT = quantitative CT; WA = wall area; WA% = wall area percent; WT = wall thickness

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Diaz and Washko and Mr Young), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Division of Pulmonary Diseases & Critical Care (Dr Maselli), University of Texas Health Science Center, San Antonio, TX; Division of Pulmonary & Critical Care Medicine (Dr Martinez), University of Michigan Health System, Ann Arbor, MI; Division of Sleep Medicine (Drs Gill, Nardelli, and San Jose Estepar) and Department of Radiology (Dr Wang), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and the Colorado School of

Public Health (Drs Kinney and Hokanson), University of Colorado-Denver, Aurora, CO.

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CORRESPONDENCE TO: Alejandro A. Diaz, MD, MPH, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115; e-mail: adiaz6@partners.org

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Bronchiectasis is a pathological enlargement of the airways.¹ Several studies suggest that bronchiectasis in subjects with COPD is frequent and associated with longer hospital stays and higher risk for death.²⁻⁵ The diagnosis of this condition is made on the basis of visual identification of an airway whose diameter is greater than of the adjacent artery (the BA ratio) and a lack of airway tapering on CT scans or lung tissue.⁶⁻⁸

There is an extensive body of literature focused on the clinical associations and prognostic value of visual detection of bronchiectasis on CT scans,^{2,3,6,9} but only a small number of CT studies in children have reported quantitative CT (QCT) measures of the disease.^{10,11} Despite the high prevalence of bronchiectasis in patients with COPD (up to 56% in some series),^{2,3,5} we are not aware of published investigations focused on QCT measures of BA ratio and airway morphology to detect bronchiectasis in smokers. Unlike more severe forms of bronchiectasis found in cystic fibrosis and alpha-1

antitrypsin deficiency (AATD),¹² bronchiectasis in non-AATD COPD is typically more subtle,^{2,5,13} which limits adoption of universal visual standards for disease detection. Our goal was to determine objective metrics of bronchovascular morphology for the detection of bronchiectasis. Using data from the COPDGene Study,¹⁴ we examined measures of airway morphology such as the peak wall attenuation (PWA, a measure of wall attenuation),^{15,16} wall thickness (WT), wall area (WA), the WA percent ([WA%] = total bronchial area – WA/total bronchial area × 100),¹⁷ bronchial and artery calibers, and the BA ratio. We included metrics of the vasculature since an increased bronchial lumen or a decreased arterial caliber could both result in a BA ratio >1, which is a commonly used threshold to define bronchiectatic dilation of the airway.^{11,18} Finally, we explored the relationship between oxygen saturation and artery diameters made on the basis of a prior study demonstrating increased BA ratios in people living in altitude.¹⁸

Methods

Study Cohort

The COPDGene Study was designed to assess the genetic and epidemiological determinants of COPD.¹⁴ Smokers (10 or more pack-years) who were 45 to 80 years old were recruited to this study. Subjects with active pulmonary disease other than COPD and asthma were excluded and subjects who had an acute respiratory disease episode (ie, new or increase in respiratory symptoms) within a month before enrollment were also excluded. A subset of never-smoking control patients (N = 108) with normal pulmonary function tests and no history of pulmonary diseases were also included. All subjects provided written informed consent to participate in the study. The institutional review board at each participating clinical center approved the COPDGene study, and the Partners HealthCare Research Committee (2007P-000554) approved the current study.

Study Design

A convenience sample of bronchiectasis cases was identified by visually reviewing approximately 300 serially acquired CT scans from the COPDGene cohort. A pulmonologist with experience in lung imaging identified 25 subjects with bronchiectasis using the criteria described in e-Appendix 1. The presence or absence of bronchiectasis in this cohort was adjudicated by a second pulmonologist. Concordant diagnoses of bronchiectasis were made in 21 subjects, which then became the final cohort of cases. Control subjects (N = 21) were randomly chosen from non-smoking control patients.

CT Analysis

Lung Volume and Emphysema: COPDGene imaging protocols are provided in e-Appendix 1.¹⁴ Total lung volume at full inspiration was used as a radiologic measure of total lung capacity and was expressed as % of predicted values.¹⁹ Emphysema was measured as percent of low attenuation areas below -950 Hounsfield units (%LAA-950).²⁰

Bronchiectasis Scoring: Inspiratory CT scans were visually scored (restricted to bronchiectasis subjects) by a third pulmonologist who agreed with the other 2 readers on the presence of bronchiectasis in all selected CT scans. The bronchiectasis score sheet is shown in e-Table 1. The mean bronchiectasis CT score was used for analysis.

Bronchovascular Bundle Measurements: A trained analyst with 3 years of experience in lung imaging performed the CT measures of the bronchovascular bundle.^{18,21} Note that airway types are here named (and italicized) as *control* (from nonsmoking subjects), *nonbronchiectatic*, and *bronchiectatic* (the 2 latter are from bronchiectasis subjects). BA ratios and airway morphology measurements were collected and matched on the basis of generations. In control patients, we used anatomically matched sites in the right upper lobe apical bronchus and the right lower lobe basal posterior bronchus.²² In bronchiectasis subjects, we measured 1 of the affected bronchial paths per lobe (range, 1-4). *Nonbronchiectatic* airways were also measured in an unaffected lobe remote from the visually determined pathologic airways. All measurements were manually at the midpoint of one airway branch of the fourth, fifth, and sixth generations and adjacent pulmonary artery.²² The bronchial lumen and artery diameters were measured at both the longest and shortest axes using a Slicer digital ruler. Measures of PWA, WA, WT, and WA % were performed as described previously.²³ Bronchial lumen and artery diameters as well as the BA ratios were computed using an average of the long and short cross sectional axes for each generation and whole lung. Intra- and inter-analysts reproducibility assessment is described in the e-Appendix 1.^{21,23}

Clinical and Physiologic Assessments: Demographic and clinical data with standardized questionnaires including a modified adult respiratory questionnaire were collected (questionnaires are available at www.COPDGene.org).¹⁴ We used the question, “Do you usually bring up phlegm from your chest on getting up, or first thing in the morning?” to evaluate sputum production. Spirometric measures of lung function were performed before and after the administration of albuterol according to

American Thoracic Society recommendations. Postbronchodilator FEV₁ and FVC are expressed as percent of predicted values.²⁴ Resting oxygen saturation was assessed by pulse oximetry on room air.²⁵

Statistical Analysis: Measurements are presented as mean $\pm$ SD. Comparisons between control patients and cases and pairwise comparisons across *control*, *nonbronchiectatic*, and *bronchiectatic* airway types were performed using Wilcoxon rank sum test. Spearman correlation coefficients were used to test the relationships between QCT measurements and demographic, spirometric measures of lung function, and %LAA-950. To assess the ability of QCT metrics to predict visual bronchiectasis we used generalized linear mixed model (SAS

procedure GLIMMIX), which allows accounting for repeated measurements. The generalized linear mixed model predicted probabilities were then used to perform logistic models. Model building was performed using all subjects and QCT measures from both *bronchiectatic* and *nonbronchiectatic* airways. These models provided the C statistic, which measures the area under the receiver operating characteristic curve (AUC) for QCT measurements. The added value of QCT measurements was tested as a change in AUC using χ^2 tests. The reproducibility of the measurements was assessed using concordance correlation coefficients (CCC) and Bland-Altman analysis.^{26,27} Software SAS 9.4 (SAS Institute) was used to perform the analysis. A *P* value $<.05$ was considered significant.

Results

The characteristics of the control and bronchiectasis subjects are shown in Table 1. Compared with control patients, bronchiectasis subjects were older and had lower FEV₁, FVC, FEV₁/FVC ratio, and resting oxygen saturation as well as higher predicted total lung capacity percent and %LAA-950. Thirty-eight percent of bronchiectasis subjects usually had sputum production first thing in the morning. No control subject reported

this symptom. There were no other significant differences between these 2 groups.

The mean CT score in subjects with bronchiectasis was 7.7 of 40 possible points with an average of 4.7 (range, 1-11) number of bronchopulmonary segments involved. Eighty-one percent of bronchiectasis subjects had COPD. The intra-analyst CCC for both BA ratio and wall thickness was 0.92. Corresponding values for

TABLE 1] Characteristics of Control Patients and Bronchiectasis Subjects

Characteristics	Bronchiectasis Subjects (n = 21)		Control Subjects (n = 21)		<i>P</i>
	Mean ± SD or %		Mean ± SD or %		
Age, y	69.6	± 7.7	64.4	± 5.5	.03
Men	43.0		52.0		.76
Non-Hispanic whites	86.0		100.0		.23
BMI, kg/m ²	26.5	± 4.5	28.3	± 5.4	.23
Pack-years smoked, No.	45.9	± 23.7	...	...	...
Current smoking status	14.0		...	...	...
Sputum production in the morning	38.0		0		.002
FEV ₁ , L	1.5	± 0.8	3.0	± 0.6	<.0001
FVC, L	2.8	± 0.9	3.8	± 0.8	.004
FEV ₁ /FVC, %	53.0	± 16.0	80.0	± 4.0	<.0001
FEV ₁ , % predicted	62.3	± 30.4	106.9	± 10.1	<.0001
FVC, % predicted	85.3	± 25.3	100.9	± 7.9	.04
Spirometric COPD	81.0		...	...	...
TLC, L	5.9	± 1.2	5.5	± 1.2	.39
TLC, % predicted	104	± 13	94	± 10	.02
Resting oxygen saturation, %	94	± 1	97	± 1	.0007
%LAA-950	12.8	± 10.0	2.1	± 1.6	.0002
CT bronchiectasis score	7.7	± 5.1	...	...	...

%LAA-950 = percent of low attenuation areas below -950 Hounsfield units.

inter-analyst CCC were 0.87 and 0.78. The Bland-Altman analysis showed no pattern of intra- and inter-analyst systematic bias across the range of measurements for both metrics ($P > .05$ for both metrics).

BA Ratios/Airway Morphology Measurements

Generally, patients with bronchiectasis had an increased BA ratio, WT, and WA% in the aggregated whole lung measures and in the generation-specific comparisons to control patients. The exception to this was in the sixth-generation measures of WT and WA%, in which such trends did not reach statistical significance (Table 2). There were no differences in PWA and WA between control patients and cases; therefore, subsequent analyses excluded these airway measures.

The BA ratios were 1.43 (fourth generation) to 1.62 (sixth generation) times greater in *bronchiectatic* than *control* airways. When the bronchovascular analysis was limited to the 21 subjects with bronchiectasis, the BA ratios and WT were consistently higher in *bronchiectatic* than the *nonbronchiectatic* airways (Table 2). The differences in BA ratios for whole-lung and fourth through sixth generations between *bronchiectatic* and *control* airways remained significant when age was accounted for ($P < .004$ for all differences). To explore the relative contribution of bronchial and vessel sizes to the BA ratio, we examined the mean bronchial lumen and arterial diameters across airway types. The whole-lung and fourth- through sixth-generation mean vessel diameters were smaller in *bronchiectatic* than in *nonbronchiectatic* and *control* airways (Fig 1). For most of the airway generations and whole-lung, there were no significant differences in the mean bronchial lumen across airway types (Table 2).

The BA ratios measured in the *bronchiectatic* airways were directly correlated with CT score (whole-lung $r = 0.51$, sixth-generation $r = 0.53$; $P = .02$ for both), whereas neither the WT or WA% were related with CT score at any airway generation ($P > .16$). The BA ratio, WT, and WA% were inversely related with the FEV₁ (r range, -0.30 [fourth-generation WT] to -0.68 [fourth-generation WA%]) and FEV₁/FVC (r range, -0.34 [sixth-generation WA%] to -0.62 [fourth-generation WA%]). The BA ratios (r range, 0.40 - 0.42) and WA% (r range, 0.36 - 0.39) and fifth-generation WT ($r = 0.31$) were significantly and directly related to %LAA-950. There was no association between the measures of bronchovascular morphology and either age or TLC (e-Table 2). Whole-lung WT was related with sputum production in the morning (OR, 1.30; 95% CI,

1.10-1.53; $P = .002$) as well as WT at generations 4 (OR, 1.27, 95% CI, 1.08-1.49; $P = .004$), 5 (OR, 1.15; 95% CI, 1.04-1.28; $P = .008$), and 6 (OR, 1.22; 95% CI, 1.07-1.40; $P = .002$). The BA ratios and WA% were not associated with this symptom. In the entire cohort, oxygen saturation was directly related to artery diameter for the whole lung ($r = 0.47$, $P = .002$) and generations 4 ($r = 0.38$, $P = .01$), 5 ($r = 0.42$, $P = .006$), and 6 ($r = 0.47$, $P = .002$).

Predictive Ability of BA Ratio, WT, and WA%

The AUCs for BA ratio and WT to predict visually ascertained *bronchiectatic* airways are shown in Table 3. AUC values for BA ratios, WT, and WA% ranged from 0.79 (fifth generation) to 0.90 (whole lung), 0.68 (sixth generation) to 0.75 (fourth generation), and 0.71 (fifth generation) to 0.75 (fourth generation), respectively. Compared with a model using the BA ratio alone, a model with the addition of WT or WA% nonsignificantly increased the AUC at variable magnitudes (eg, increase in AUC was 0.11 for fifth-generation WA%, $P = .053$). Similarly, when sex, age, or FEV₁% predicted were added to the model with whole-lung BA ratio, the modest increases in the AUCs did not reach statistical significance ($P > .18$ for all comparisons).

Discussion

In this study, we evaluated QCT measures of the BA ratio as well as assessments of airway and vascular morphology in ever smokers with mild bronchiectasis and never smoking control patients. The BA ratios, WT, and WA% were greater in *bronchiectatic* than *control* airways and were able to discriminate bronchiectatic and nonbronchiectatic airways. Further, those with an increased BA ratio had lower expiratory airflows and worse airflow obstruction. Finally, it appears that the elevated BA ratio in subjects with mild bronchiectasis is due to reductions in the caliber of the adjacent pulmonary artery rather than dilation of the airway.

Bronchiectasis and COPD appear to share common pathogenic mechanisms including genetics and environmental. AATD might lead to the development of both processes.²⁸ Similarly, respiratory infections early in life are likely triggers for airway inflammation leading to the development of both diseases.^{29,30} Regardless of the mechanisms involved in disease pathogenesis, the diagnosis of COPD is made on the basis of obstructive physiology, whereas bronchiectasis is a structural diagnosis. In this study, we demonstrated that the BA ratios were greater in smokers with mild bronchiectasis

TABLE 2] QCT Measures of BA Ratio and Airway Morphology by Airway Type

QCT Measurement	Control Subjects		Bronchiectasis Subjects				Comparison	
	Airway Type							
	Control Patients		Nonbronchiectatic		Bronchiectatic		Bronchiectatic vs Nonbronchiectatic	Bronchiectatic vs Control Patients
	Mean	± SD	Mean	± SD	Mean	± SD	<i>P</i>	<i>P</i>
BA ratio								
Whole-lung	0.71	± 0.10	0.67	± 0.20	1.07	± 0.28	.0001	<.0001
Generation								
4	0.75	± 0.10	0.77	± 0.25	1.07	± 0.26	.003	<.0001
5	0.71	± 0.12	0.63	± 0.20	0.95	± 0.28	.001	.0002
6	0.66	± 0.14	0.61	± 0.21	1.20	± 0.49	<.0001	.0001
PWA								
Whole-lung	−434	± 68	−524	± 103	−462	± 132	.14	.31
Generation								
4	−347	± 91	−458	± 115	−412	± 129	.36	.10
5	−417	± 86	−517	± 174	−441	± 143	.051	.30
6	−539	± 87	−612	± 129	−536	± 157	.15	.95
WT								
Whole-lung	1.23	± 0.05	1.22	± 0.08	1.30	± 0.08	.02	.006
Generation								
4	1.24	± 0.06	1.21	± 0.09	1.30	± 0.10	.003	.02
5	1.23	± 0.06	1.22	± 0.10	1.31	± 0.11	.02	.02
6	1.22	± 0.05	1.22	± 0.09	1.28	± 0.10	.08	.054
WA								
Whole-lung	25.1	± 8.8	18.1	± 3.9	22.9	± 9.3	.42	.16
Generation								
4	27.0	± 4.8	21.2	± 4.8	24.1	± 10.5	.31	.14
5	22.7	± 3.6	17.4	± 4.1	22.6	± 8.4	.33	.41
6	20.3	± 4.8	14.7	± 3.9	23.7	± 16.1	.49	.45
WA%								
Whole-lung	54	± 4	59	± 7	60	± 6	.15	.001
Generation								
4	50	± 7	55	± 9	58	± 6	.12	.0003
5	54	± 5	58	± 10	61	± 7	.18	.002
6	58	± 5	64	± 12	62	± 8	.48	.10
Airway lumen diameter								
Whole-lung	3.59	± 0.70	2.93	± 0.82	3.37	± 0.88	.09	.31
Generation								
4	4.69	± 0.86	4.00	± 1.00	4.05	± 1.06	.55	.02
5	3.46	± 0.82	2.81	± 0.82	3.20	± 1.04	.15	.30
6	2.61	± 0.70	1.99	± 0.89	2.91	± 0.99	.003	.54

BA ratio = ratio of the diameters of bronchial lumen and adjacent artery; PWA = peak wall attenuation; QCT = quantitative CT; WA = wall area; WA% = wall area percent; WT = wall thickness.

Figure 1 – Artery diameters by airway type. The boxplots show the whole-lung and fourth- through sixth-generation mean artery diameters for control, nonbronchiectatic, and bronchiectatic airways. * $P < .001$ for control vs bronchiectatic airways; ^ $P < .05$ for nonbronchiectatic vs bronchiectatic airways.

than control patients, which is consistent with prior investigation in a cohort of cystic fibrosis children with bronchiectasis, where the BA ratio was almost 2 times greater in bronchiectatic airways.¹¹ The difference in the BA ratio we observed between cases and control patients

was significant but smaller in magnitude, likely because of the more mild nature of the airway pathology present in the smoking cohort. The smaller differences in the measures between cases and control patients may also be due to the nature of the CT images in COPDGene. Unlike prior studies, we used volumetric CT data, which reduces the bias in overestimation of airway size,³¹ which in turn may lead to more accurate comparisons between control patients and cases. The volumetric images also allowed us to demonstrate that the discriminatory ability of the BA ratio varied by airway generation.

Although an elevated BA ratio was able to differentiate a normal from bronchiectatic airway identified by visual inspection, the increase in the ratio was not due to increases in airway lumen size but rather reductions in caliber of the adjacent pulmonary artery. We found progressive decrements in artery size from control to nonbronchiectatic and then to bronchiectatic airways. This trend was consistent across the range of airway generations examined. There was no such trend in airway lumen size. Potential explanations for this finding include systematic differences in innate vessel size, tobacco smoke-induced vascular damage, and smoking-related vasoconstriction. Although Santos et al³² have demonstrated smoking-related pulmonary vascular remodeling in subjects without COPD, Kim et al¹⁸ demonstrated greater BA ratios in subjects living in altitude compared with that of those living at sea level. This latter group thought that their finding was due to hypoxia at high altitude, which leads to vasoconstriction. In our cohort, we looked at the relationships between oxygen saturation at rest and artery diameters and found they were directly correlated across all airway generations, supporting that vasoconstriction might contribute to the observed increase in BA ratio. More research is needed to elucidate the interplay between the mechanisms proposed. Independent of the cause, this finding suggests that the BA ratio may be more indicative of bronchovascular remodeling rather than a mere reflection of airway caliber. This finding also leads to the question of whether the arteries accompanying the airway are an appropriate reference to define bronchial dilation in bronchiectasis as discussed by de Jong et al.¹¹

We found that the %LAA-950 was directly related to the BA ratio. We have previously demonstrated that emphysema is associated with pruning of the distal vasculature and decreases in vascular cross sectional areas.^{33,34} This suggests that the increase in BA ratio in

TABLE 3] AUC and OR for Bronchiectasis^a

QCT Measurement	AUC	95% CI	OR	95% CI	P
BA ratio					
Whole-lung	0.90	0.81-0.99	1.11	1.05-1.18	.0002
Generation					
4	0.83	0.72-0.94	1.06	1.03-1.10	.0002
5	0.79	0.65-0.93	1.06	1.06-1.10	.0004
6	0.89	0.80-0.98	1.08	1.04-1.13	.0005
WT					
Whole lung	0.74	0.61-0.87	1.14	1.05-1.24	.002
Generation					
4	0.75	0.62-0.88	1.12	1.04-1.20	.003
5	0.72	0.58-0.86	1.10	1.03-1.17	.006
6	0.68	0.52-0.84	1.10	1.02-1.18	.01
WA%					
Whole lung	0.73	0.58-0.87	1.12	1.02-1.23	.02
Generation					
4	0.75	0.63-0.88	1.11	1.02-1.20	.01
5	0.71	0.57-0.85	1.10	1.02-1.19	.02
6	0.55	0.39-0.71	1.02	0.95-1.08	.63

AUC = area under the receiver operating characteristic curve. See Table 2 legend for expansion of other abbreviations.

^aModels included cases, control patients, and all airway types.

emphysematous lungs is likely the result of smaller arteries. We believe that our results in this cohort of smokers bring up a complex interaction between smoking, COPD, bronchiectasis, emphysema, and pulmonary vasculature, and more research is warranted to disentangle them.

Bronchiectatic airways were thicker and had a greater WA% than control patients. Although the difference in WT was small (0.06-0.09 mm), it was highly statistically significant and similar in magnitude to previous reports comparing WT in children with and without cystic fibrosis-associated bronchiectasis.¹¹ These observed differences in airway morphology are likely from mural inflammation and the remodeling characteristic of bronchiectasis. These metrics were also predictive of lung function. We believe that the findings together support the ability of QCT measures to objectively identify and quantify bronchiectasis.

There are limitations to our investigation that should be noted. First, we used a small, convenience sample of mainly non-Hispanic white men who were smokers with COPD to identify bronchiectasis cases. This method of sampling may limit the generalizability of the results. It might be felt that lung pathology is an ideal gold standard with which to compare objective CT data. In absence of such a

gold standard, our in vivo assessment is consistent with results obtained from explanted lungs from patients with cystic fibrosis in which the cumulative lumen diameter of visible airways was greater in patients than control patients.³⁵ Early work also demonstrated that 87% of pathological-proven bronchiectasis was made visually on CT scan.⁸ We believe that objective measurements that are concordant with the visual diagnosis of the disease provide a solid foundation to further develop less biased approaches to quantify bronchiectasis. Further, this study did not objectively quantify other important radiographic features of *bronchiectatic* airways such as the lack of bronchial tapering, which becomes relevant when the bronchovascular bundles are not orthogonal to the axial plane.

In summary, we have demonstrated that in smokers, the BA ratios, WT, and WA% appear to be able to discriminate the presence of bronchiectasis and that the increased BA ratio observed in bronchiectatic airways may be due to reductions in the cross sectional area of the adjacent pulmonary vasculature. Using the BA ratio in smoking bronchiectasis requires careful interpretation because it might be sensitive to changes in pulmonary arteries. Further investigation is needed to disentangle the interactions among smoking, COPD, bronchiectasis, emphysema, and pulmonary vasculature.

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

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