ORIGINAL ARTICLE

Comparison of spatially matched airways reveals thinner airway walls in COPD. The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS)

Benjamin M Smith,[1,2] Eric A Hoffman,[3] Dan Rabinowitz,[4] Eugene Bleecker,[5] Stephanie Christenson,[6] David Couper,[7] Kathleen M Donohue,[1] Meilan K Han,[8] Nadia N Hansel,[9] Richard E Kanner,[10] Eric Kleerup,[11] Stephen Rennard,[12] R Graham Barr[1,13]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2014-205160).

For numbered affiliations see end of article.

Correspondence to
Dr Benjamin M Smith, Presbyterian Hospital 9E Room 109, Columbia University Medical Center, 630 West 168th St, New York, NY 10032, USA; benjamin.m.smith@mcgill.ca

Received 22 January 2014
Revised 22 May 2014
Accepted 26 May 2014
Published Online First 13 June 2014

ABSTRACT

Background COPD is characterised by reduced airway lumen dimensions and fewer peripheral airways. Most studies of airway properties sample airways based upon lumen dimension or at random, which may bias comparisons given reduced airway lumen dimensions and number in COPD. We sought to compare central airway wall dimensions on CT in COPD and controls using spatially matched airways, thereby avoiding selection bias of airways in the lung.

Methods The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) recruited smokers with COPD and controls aged 50–79 years and 40–80 years, respectively. COPD was defined by current guidelines. Using CT image data, airway dimensions were measured for all central airway segments (generations 0–6) following 5 standardised paths into the lungs. Case-control airway comparisons were spatially matched by generation and adjusted for demographics, body size, smoking, CT dose, per cent emphysema, airway length and lung volume.

Results Among 311 MESA COPD participants, airway wall areas at generations 3–6 were smaller in COPD compared with controls (all $p<0.001$). Among 1248 SPIROMICS participants, airway wall areas at generations 1–6 were smaller (all $p<0.001$), and this reduction was monotonic with increasing COPD severity ($p<0.001$). In both studies, sampling airways by lumen diameter or randomly resulted in a comparison of more proximal airways in COPD to more peripheral airways in controls ($p<0.001$) resulting in the appearance of thicker walls in COPD ($p<0.02$).

Conclusions Airway walls are thinner in COPD when comparing spatially matched central airways. Other approaches to airway sampling result in comparisons of more proximal to more distal airways and potentially biased assessment of airway properties in COPD.

Key messages

What is the key question?
- Are airway walls thicker or thinner in COPD?

What is the bottom line?
- Airway walls are thinner in COPD when comparing spatially matched central airways.

Why read on?
- We demonstrate that techniques commonly used to study airway wall properties in COPD, such as sampling airways based upon lumen diameter or at random, results in a biased comparison of more proximal airways in COPD to more peripheral airways in controls.

INTRODUCTION

COPD is defined by persistent airflow limitation and is a leading cause of morbidity and mortality in the USA and globally.[1] Understanding the pathophysiology of COPD requires understanding of the relationship between airway structure and function. Airflow limitation is determined in part by the resistive properties of the tracheobronchial tree, which is a three-dimensional branching structure.[2] Weibel's classic study of human lung morphometry demonstrated that airway dimensions vary according to the spatial location within the tracheobronchial tree.[3] Therefore, it is likely that the study of airway properties in COPD requires accurate anatomical localisation and comparison of spatially equivalent airways in order to provide unbiased results.[4]

Studies accounting for spatial differences in airway dimensions on pathological section or CT have consistently demonstrated reduced airway lumen dimensions and fewer peripheral airways in COPD.[5–12] Multiple histological and CT studies have reported thicker airway walls in COPD.[10 12–17] However, these studies sampled airways either based upon lumen diameter or randomly within the identified airways in the lung. If COPD is characterised by reduced airway lumen size and fewer distal airways, such sampling is likely to lead to a comparison of more proximal airways in cases of COPD

Linked

▶ http://dx.doi.org/10.1136/thoraxjnl-2014-206118
▶ http://dx.doi.org/10.1136/thoraxjnl-2014-206188

CrossMark

To cite: Smith BM, Hoffman EA, Rabinowitz D, *et al*. *Thorax* 2014;**69**:987–996.

compared with controls. Such a comparison may introduce a selection bias that would yield erroneous conclusions of thickened airway walls in COPD.

In order to avoid selection bias in the study of airways in COPD, our objective was to compare central airway wall dimensions in COPD and controls that were matched spatially by generation number and anatomical name (eg, lobar bronchi, segmental bronchi) in two multicentre case-control studies of COPD, one of milder disease recruited predominantly from the general population and the other of more severe disease recruited predominantly from the subspecialist setting. In addition, we repeated the analyses of airway walls using potentially biased approaches, that is, sampling airways by lumen diameter or randomly. Finally, we examined the implications of reduced airway lumen calibre and number in COPD for the validity of the Pi10, a derived measure commonly used to study wall thickness in COPD.[5 12 15–18]

Preliminary results were presented in abstract form.[19]

METHODS

Study participants

The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited cases of COPD and controls predominantly from MESA, a population-based prospective cohort study of subclinical atherosclerosis, a non-overlapping lung cancer screening study, and the outpatient community at Columbia University Medical Center. Participants were 50–79 years of age with ≥10 pack-year smoking history (see web supplement for Additional Details and References). Exclusion criteria were clinical cardiovascular disease, stage IIIb–V chronic kidney disease, asthma prior to age 45 years, prior lung resection, contraindication to MRI, and pregnancy.

The Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) is recruiting participants 40–80 years of age with >20 pack-year smoking history with COPD and controls with >20 pack-year smoking history, as well as never smokers.[20] Exclusion criteria include other chronic lung diseases except asthma (eg, sarcoidosis, interstitial lung disease), body mass index (BMI) >40 kg/m^2, prior lung resection, metal in the chest (eg, pacemaker) and pregnancy. The present analysis was performed on the first 1278 current or former smokers completing the baseline evaluation.

Study protocols were approved by the institutional review board of participating institutions and by the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

Chest CT acquisition and analysis

All participants in both studies underwent full-lung thoracic CT on 64-slice or 128-slice helical scanners (120 kVp, 0.625–0.75 mm slice thickness, 0.5 s rotation time). Scans were acquired with milliamperes (mA) set by BMI to maintain a consistent volume CT dose index (6.1 mGy, 7.6 mGy, 11.4 mGy, respectively). Images were obtained at suspended full inspiration. Airway dimensions were assessed at a single reading centre for both studies blinded to other participant information.

The central airway tree was identified using Apollo Software (VIDA Diagnostics, Coralville, Iowa). Airways were labelled anatomically from trachea to subsegmental bronchi along five prespecified paths: RB1, RB4, RB10, LB1 and LB10. Segmentation and labelling were visually verified by a dedicated image analyst and all labelled airways were assigned a generation number based upon the number of branch points from the trachea, which was assigned generation 0. Cross-sectional airway wall area and wall thickness, as well as lumen area, diameter and perimeter were measured perpendicular to the local airway segment's long axis using a subvoxel resolution algorithm in the Apollo Software, within an image plane, and measurements were averaged along the middle third of each labelled airway segment. Airway length was measured as the distance between branch points.

Per cent wall area was calculated for each airway as the ratio of wall area to the sum of wall and lumen area, multiplied by 100. Pi10 was calculated by regressing the square-root wall area on internal perimeter of included airways to predict the square-root wall area of a single hypothetical airway with internal perimeter of 10 mm. A Pi10 was calculated for each participant using all measured airways, as well as using airways from each generation with five or more airways. Airway counts were determined by software summing all visually-confirmed airway segments detected along the five prespecified paths and stratified by lumen diameter. Intraclass correlation coefficients for reproducibility of airway measure in the MESA COPD Study were 0.79–0.99, 0.74–0.99 and 0.78–0.96 for wall area, lumen area and airway count, respectively (see web supplement tables E1–E2).

Lung volumes were quantified from segmented lung images. Per cent emphysema-like lung was defined as the percentage of total voxels within the lung field <−950 Hounsfield units (per cent emphysema$_{-950HU}$).

Spirometry

Postbronchodilator spirometry was performed following American Thoracic Society recommendations on a dry-rolling-sealed spirometer in MESA COPD and a pneumotachograph spirometer in SPIROMICS. Predicted spirometry values were calculated using Hankinson reference equations.[21] COPD was defined as postbronchodilator ratio of FEV_1/FVC less than 0.7 and spirometric severity as mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), severe ($30\% \leq FEV_1 < 50\%$ predicted) and very severe ($FEV_1 < 30\%$ predicted).[1] Controls had a postbronchodilator $FEV_1/FVC > 0.7$ and a FVC above the lower limit of normal.

Anthropometry and other covariates

Age, gender and race-ethnicity were self-reported, and height and weight were measured following standardised protocols. Smoking history was assessed using standard questionnaire items; current smoking status was confirmed with urine or plasma cotinine levels in MESA COPD.

Statistical analysis

The MESA COPD and SPIROMICS data were examined separately because the former recruited predominantly from the general population with milder disease, and the latter recruited from the subspecialist setting with more severe disease. Dichotomous variables are presented as proportions and continuous variables as means with SD unless otherwise indicated.

The primary analysis compared central airway wall areas among participants with COPD to controls stratified spatially by generation number. All airways in the prespecified paths of a given generation were included in the analyses. Within-generation generalised estimating equations with exchangeable covariance matrix structure and robust SEs were used to account for multiple airway measures per participant[22]; and linear regression to adjust for age, gender, height, BMI-determined CT dose, race-ethnicity, current smoking status, airway length, per cent emphysema$_{-950HU}$, and lung volume achieved at CT. Height and lung volume were included to normalise body size and to account for lung

hyperinflation and depth of inspiration at CT, which may influence airway wall dimensions.[23] Sensitivity analyses modelled per cent predicted FEV_1 and FVC, and stratified by anatomical name as an alternate method of comparing spatially matched airways, and by COPD severity. Airway lumen areas and per cent wall areas were also compared according to COPD status by generation number adjusting for the same covariates.

To assess the potential bias of alternative sampling methods, secondary analyses compared airway wall areas in COPD and controls selected based upon airway lumen diameter, as well as randomly sampled (n=15 airways) from each participant, and adjusting for the same covariates. Comparison of the spatial location of airways sampled by these methods according to COPD status was assessed using the χ^2-test. The number of observed airways within lumen diameter strata was compared according to COPD status. Finally, Pi10 was calculated for each participant using all airways, as well as for airways from each generation, and compared with respect to COPD status. Calculation of Pi10 required five or more airway wall measures per participant; therefore, Pi10 was not calculated for generations 0–2.

All calculations were performed using SAS V.9.3 (Cary, North Carolina, USA) with a hypothesis testing α level of 0.05.

RESULTS

Of 329 participants enrolled in the MESA COPD Study, 311 had visually confirmed spatial mapping of the tracheobronchial tree. Similarly, 1248 of the 1278 SPIROMICS participants had visually confirmed mapping of the tracheobronchial tree. Participants included in the analyses were similar to those with incomplete measures except for differences in severity of airflow obstruction (see web supplement table E3).

Clinical characteristics of included participants by COPD status are summarised in table 1. The MESA COPD Study participants had a mean age of 68±7 years with 37±24 pack-years of smoking. Forty-seven per cent of participants had COPD that was predominantly moderate in severity. The SPIROMICS sample had a mean age of 65±9 years, 50±24 pack-years of smoking and more severe COPD. In both studies, the prevalence of white race-ethnicity and number of pack-years of smoking were greater among participants with COPD compared with controls.

The number of detectable airways with lumen diameter between 2.5 mm and 4.0 mm was reduced in COPD compared with controls in both studies (table 1), and this difference was independent of age, gender, height, BMI-determined CT dose, race-ethnicity, smoking status, airway length, per cent $emphysema_{-950HU}$ and lung volume ($p<0.001$).

Central airway lumen size was significantly smaller in COPD compared with controls in both cohorts, and this was independent of covariates (see web supplement table E4). Consistent observations were made for per cent predicted FEV_1 and FVC (see web supplement table E5).

Airway wall areas in COPD: spatially matched central airways

Table 2 summarises mean airway wall areas according to airway generation number and differences between COPD and controls. In the MESA COPD Study, generation 4–6 airway wall areas were significantly smaller in COPD compared with controls in crude comparisons ($p\leq0.01$ for all). In adjusted comparisons (figure 1), these differences remained statistically significant ($p<0.001$ for all), and extended to generations 1 and 3 ($p\leq0.005$ for both). Similar associations between airway wall area and COPD status were obtained when matching by anatomical name (see web supplement table E6), or using airway wall thickness instead of wall area (see web supplement table E7).

In SPIROMICS, generations 4 to 6 airway wall areas were significantly smaller in COPD compared with controls (table 2). In adjusted comparisons, these differences were observed at generations 1 through 6 (table 2), and remained statistically significant with matching by anatomical name (see web supplement table E6), or using airway wall thickness (see web supplement table E7). Compared with controls, greater COPD severity was associated with monotonically thinner airway wall areas from generations 0 to 6 in SPIROMICS (figure 2).

Similar associations were observed between airway wall area and per cent predicted FEV_1 and FVC in both cohorts (see Web supplement table E8).

Per cent wall area was significantly greater in COPD compared with controls in both cohorts, and independent of covariates (see web supplement table E9). Consistent observations were made using per cent predicted FEV_1 and FVC (see web supplement table E10). These associations, when combined with the above observations of smaller airway wall and lumen dimensions in COPD, imply proportionally smaller lumen area compared with wall area.

Airway wall areas in COPD assessed with alternative approaches to airway sampling

When airways were selected according to lumen diameter in the MESA COPD Study, a significantly greater proportion of proximal airways in COPD compared with controls was observed for airways 2.5–4.0 mm in diameter (global χ^2: $p<0.001$). Similar results were observed for airways of lumen diameter 4.0–5.5 mm, and 5.5–7 mm (global χ^2: $p\leq0.01$ for both) in the MESA COPD Study. In SPIROMICS, a greater proportion of proximal airways in COPD compared with controls were observed for airways of lumen diameter 2.5–4.0 mm, 4.0–5.5 mm, 5.5–7.0 mm, 7.0–8.5 mm and 8.5–10.0 mm (global χ^2: $p<0.001$ for all).

In MESA COPD and SPIROMICS, airways selected based upon lumen size yielded associations of greater wall area in COPD in unadjusted and adjusted comparisons for airways of lumen diameter 2.5–4.0 mm, 4.0–5.5 mm and 5.5–7.0 mm ($p<0.001$ for all; table 3).

When 15 airways were selected randomly from the observed airways for each participant, a significantly greater proportion of proximal airways were selected in COPD cases compared with controls in MESA COPD and SPIROMICS (global χ^2: $p\leq0.01$ for both). Analyses using these airways sampled randomly from observed airways also resulted in larger wall areas in COPD compared with controls (table 4).

Pi10 in COPD

Achieving an unbiased comparison of Pi10 when the spatial distribution of sampled airways differs requires that the ratio of square-root wall area to lumen perimeter is similar across the sampled range of generations. In MESA COPD and SPIROMICS, however, significant differences in this ratio were observed (Kruskal-Wallis: $p<0.001$ for both).

Hence, calculation of Pi10 among spatially matched airways should yield an unbiased estimate of the Pi10. Indeed, spatial matching by generation number resulted in significantly smaller Pi10 in COPD compared with controls for generations 4–6 in MESA COPD ($p<0.03$ for all) and SPIROMICS ($p\leq0.01$ for all; figure 3).

In contrast, calculating Pi10 from all measured airways yielded results suggesting increased wall dimensions in COPD

Table 1 Characteristics of participants included in airway dimensions analysis

	MESA COPD		SPIROMICS	
	No COPD N=166	COPD N=145	No COPD N=438	COPD N=810
Age—year	68±7	68±7	61±10	66±8
Male—%	54	66	46	59
Race-ethnicity—%				
White	45	62	70	84
Black	25	28	26	12
Other	30	10	5	5
Height—cm	167±9	171±9	170±10	171±10
Weight—kg	80±17	80±19	83±18	80±17
Smoking status—%				
Former	77	67	54	68
Current	23	33	46	32
Pack-years	32±19	44±32	43±21	54±25
Per cent predicted FEV_1	100±16	74±19	95±14	62±23
FEV_1/FVC	78±5	58±11	87±5	51±13
COPD GOLD severity—%				
Mild ($FEV_1 \geq 80\%$ predicted)	–	39	–	24
Moderate ($50\% \geq FEV_1 < 80\%$ predicted)	–	47	–	44
Severe ($30\% \geq FEV_1 < 50\%$ predicted)	–	12	–	23
Very severe ($FEV_1 < 30\%$ predicted)	–	1	–	9
Lung volume at CT—L	4.2±1.1	4.8±1.2	5.3±1.2	6.3±1.4
Per cent $emphysema_{-950HU}$—median (IQR)	1.2 (1.8)	4.5 (7.7)	0.9 (1.7)	6.9 (14)
No. of airways per participant—median (1st, 3rd quartile)				
Lumen diameter>11.5 mm	2 (2, 3)	2 (2, 3)	2 (2, 3)	2 (2, 3)
10.0 mm<lumen diameter≤11.5 mm	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (0, 2)
8.5 mm<lumen diameter≤10.0 mm	2 (1, 2)	2 (1, 2)	2 (1, 3)	2 (1, 2)*
7.0 mm<lumen diameter≤8.5 mm	3 (2, 4)	3 (2, 3)*	3 (2, 4)	3 (2, 4)*
5.5 mm<lumen diameter≤7.0 mm	4 (3, 5)	4 (2, 5)*	3 (2, 5)	3 (2, 4)*
4.0 mm<lumen diameter≤5.5 mm	7 (6, 10)	7 (5, 8)*	8 (6, 10)	6 (4, 8)*
2.5 mm<lumen diameter≤4.0 mm	28 (20, 38)	19 (14, 27)*	34 (24, 44)	20 (15, 28)*
Lumen diameter—mm				
Generation 0	16.0±2.3	16.5±2.6	16.7±2.4	16.4±2.5
Generation 1	12.0±1.9	12.0±1.9	12.6±2.1	12.3±2.0
Generation 2	8.5±1.6	8.4±1.6	8.8±1.5	8.6±1.6
Generation 3	6.1±1.5	5.7±1.5*	6.3±1.6	6.0±1.6*
Generation 4	4.4±1.4	4.1±1.3*	4.7±1.7	4.3±1.5*
Generation 5	3.2±1.0	3.0±1.0*	3.4±1.0	3.1±1.0*
Generation 6	2.6±0.9	2.5±1.0*	2.7±0.9	2.5±0.8*

Plus-minus values are means±SD.
*P<0.05 for comparison between COPD and controls of airway lumen diameter (Student t test) or number of airways per participant (Pearson's χ^2-test).
GOLD, Global Initiative for chronic Obstructive Lung Disease; HU, Hounsfield units; MESA, Multi-Ethnic Study of Atherosclerosis; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study.

compared with controls in MESA COPD and SPIROMICS ($p<0.001$ for both; figure 3).

DISCUSSION

In two independent studies of smokers, COPD was associated, on average, with significantly smaller airway wall areas on CT compared with controls when central airways were matched spatially based on generation number or anatomical name. Analysis of airways sampled on lumen diameter or sampled randomly from observed airways resulted in a comparison of more proximal airways in COPD compared with controls, thus introducing a selection bias and suggesting larger wall areas in COPD. Results for the Pi10 were similar. In addition to the observed reduction of airway wall thickness, these results suggest that studies of airway wall morphology, histology and genomics should compare spatially matched airways in COPD cases compared with controls.

The present study is the first to compare commonly used airway sampling techniques to study airway wall dimensions in COPD. Consistent with our observation, the COPDGene Study also observed significantly smaller central airway wall areas when comparing anatomically matched airway segments.[24] In contrast, several studies have suggested thicker walls in COPD.[10 12–17 25] We suspect these associations may have been biased, however, due to sampling from different locations in the tracheobronchial tree depending on disease status, a bias that we replicate in the current study. Airway wall and lumen dimensions, as well as the ratio of square-root wall area to lumen perimeter, differ significantly by generation number,[3] which, we found, results in a differential spatial distribution of airways by COPD status when airways are sampled by lumen diameter or

Table 2 Airway wall area according to COPD status stratified by generation number in the MESA COPD study and SPIROMICS

	Airway generation number						
MESA COPD	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Unadjusted mean airway wall area in mm^2							
COPD	179.1	109.3	75.7	45.1	27.9	17.3	13.7
No COPD	168.0	106.9	73.3	45.4	29.4	19.1	14.9
Difference (95% CI)	11.1 (2.3 to 20.3)	2.4 (−3.2 to 8.4)	2.3 (−1.1 to 5.9)	−0.4 (−2.1 to 1.4)	−1.6 (−2.7 to −0.4)	−1.7 (−2.5 to −0.9)	−1.2 (−1.7 to −0.6)
p Value	0.01	0.41	0.19	0.68	0.01	<0.001	<0.001
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT							
COPD	171.3	103.6	73.0	43.5	27.2	16.9	13.2
No COPD	174.5	110.0	75.8	46.5	30.0	19.8	15.3
Difference (95% CI)	−3.2 (−9.8 to 3.7)	−6.4 (−10.7 to −2.0)	−2.8 (−5.6 to 0.1)	−3.0 (−4.5 to −1.4)	−2.8 (−3.8 to −1.6)	−2.9 (−3.6 to −2.1)	−2.0 (−2.7 to −1.4)
p Value	p=0.36	p=0.005	p=0.06	p<0.001	p<0.001	p<0.001	p<0.001
	Airway generation number						
SPIROMICS	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Unadjusted mean airway wall area in mm^2							
COPD	181.3	113.5	75.7	44.9	29.0	17.7	13.3
No COPD	173.5	112.0	76.7	46.8	31.3	20.0	14.9
Difference (95% CI)	7.8 (3.5 to 12.2)	1.5 (−1.9 to 5.0)	−1.0 (−3.0 to 1.1)	−1.9 (−2.9 to −0.9)	−2.3 (−2.9 to −1.6)	−2.4 (−2.8 to −2.0)	−1.6 (−1.9 to −1.4)
p Value	<0.001	0.40	0.36	<0.001	<0.001	<0.001	<0.001
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT							
COPD	177.0	97.4	67.4	40.8	25.6	16.5	14.0
No COPD	180.6	102.4	72.3	43.9	28.1	18.7	16.1
Difference (95% CI)	−3.6 (−7.2 to 0)	−5.1 (−7.8 to −2.2)	−4.9 (−6.6 to −3.2)	−3.1 (−3.9 to −2.3)	−2.5 (−3.1 to −1.9)	−2.2 (−2.6 to −1.8)	−2.1 (−2.4 to −1.8)
p Value	p=0.049	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Mean values and differences, along with 95% CI and p values were estimated using linear regression with generalised estimating equations.
BMI, body mass index; HU, Hounsfield units; MESA, Multi-Ethnic Study of Atherosclerosis; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study.

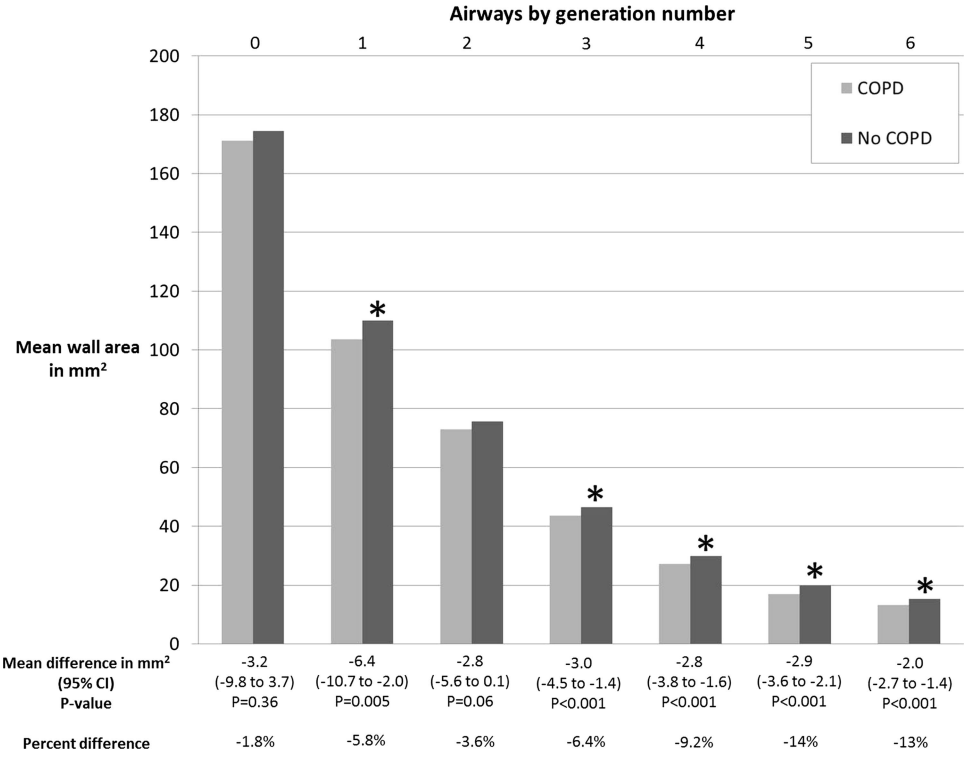

Figure 1 Airway wall area according to COPD status stratified by generation number in the MESA COPD Study. *p<0.05 for within-generation comparison of mean wall area between participants with no COPD to those with COPD. Mean values and differences adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT. MESA, Multi-Ethnic Study of Atherosclerosis; HU, Hounsfield units; BMI, body mass index.

randomly. Applying these biased sampling techniques in the present study yielded results suggesting thicker airway walls in COPD.

Wall-lumen ratio measures (eg, per cent wall area) have been reported to be increased in COPD,[6–8 23] which has been interpreted by some as evidence that airway wall thickening encroaches upon and narrows airway lumens in COPD. Without comparing absolute airway dimensions, this inference assumes that total airway calibres are similar in COPD and controls. However, consistent with the COPDGene cohort,[24] we show that wall and lumen areas are reduced in COPD compared with controls, although the difference is greater in lumen size, a finding which is likely of greater physiological importance to airflow limitation.

The mechanism underlying the observed smaller wall areas in COPD was not the primary focus of this paper. However, differences in lung volume due either to COPD-related hyperinflation or submaximal inspiration at the time of CT do not appear to explain our findings.[23] Smaller wall areas in COPD were consistently observed with adjustments for lung volume achieved at CT, as well as airway-specific length, suggesting that the airways were not merely stretched and therefore thinner.

Other potential mechanisms include regression of airway smooth muscle resulting from reduced wall tension, apoptosis or replacement fibrosis resulting from chronic airways inflammation, or reduced bronchial vascular volume.[26 27] We did not assess airway wall histology in the present study. Therefore, some components of the airway wall may be increased in

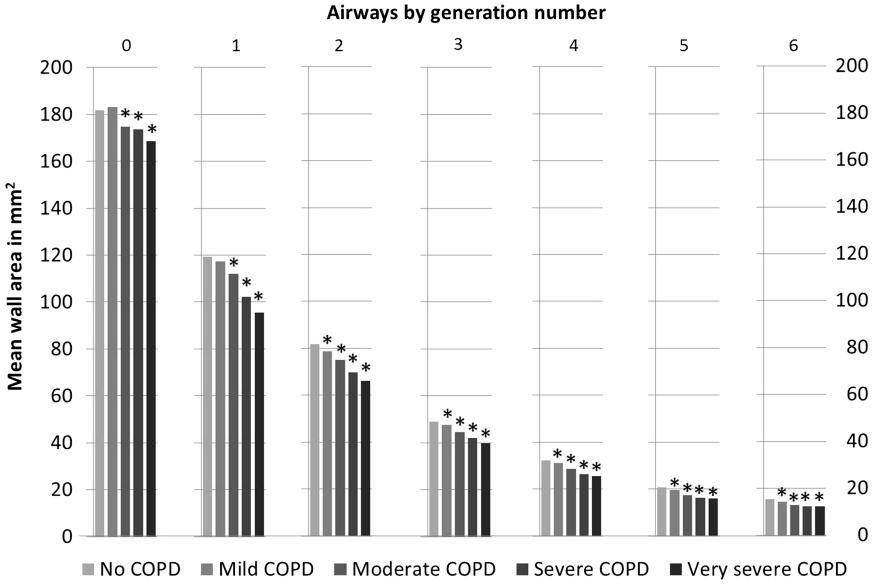

Figure 2 Airway wall areas according to COPD severity stratified by generation number in SPIROMICS. *p<0.05 for within-generation comparison of airway wall area between participants with no COPD to those with the COPD severity indicated. Mean values and differences adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT. SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study; HU, Hounsfield units; BMI, body mass index.

Table 3 Airway wall area according to COPD status stratified by lumen diameter strata in SPIROMICS and the MESA COPD study

	Lumen diameter strata in mm						
MESA COPD	**>11.5**	**>10.0 to 11.5**	**>8.5 to 10.0**	**>7.0 to 8.5**	**>5.5 to 7.0**	**>4.0 to 5.5**	**>2.5 to 4.0**
Unadjusted mean airway wall area in mm^2							
COPD	149.7	96.4	81.1	65.5	50.9	35.1	20.4
No COPD	144.4	92.6	78.5	62.0	46.8	32.7	19.7
Difference (95% CI)	5.3 (−0.2 to 10.9)	3.8 (−0.6 to 8.4)	2.6 (−0.1 to 5.5)	3.5 (1.6 to 5.5)	4.1 (2.9 to 5.4)	2.4 (1.6 to 3.2)	0.7 (0.4 to 1.1)
p Value	0.06	0.09	0.06	<0.001	<0.001	<0.001	<0.001
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose, and lung volume at CT							
COPD	141.9	93.6	78.2	64.9	50.6	34.9	22.0
No COPD	147.1	93.8	78.1	62.5	46.8	32.7	21.6
Difference (95% CI)	−5.2 (−10.1 to −0.2)	−0.2 (−4.4 to 4.3)	0.1 (−2.7 to 3.0)	2.3 (0.5 to 4.2)	3.8 (2.5 to 5.2)	2.2 (1.3 to 3.0)	0.4 (0.1 to 0.7)
p Value	p=0.04	p=0.9426	p=0.96	p=0.01	p<0.001	p<0.001	p=0.003
	Lumen diameter strata in mm						
SPIROMICS	**>11.5**	**>10.0 to 11.5**	**>8.5 to 10.0**	**>7.0 to 8.5**	**>5.5 to 7.0**	**>4.0 to 5.5**	**>2.5 to 4.0**
Unadjusted mean airway wall area in mm^2							
COPD	150.8	96.3	78.8	63.1	48.7	33.9	18.8
No COPD	145.6	94.1	77.6	61.6	46.2	32.1	18.6
Difference (95% CI)	5.2 (2.5 to 8.0)	2.2 (−0.3 to 4.6)	1.2 (−0.2 to 2.7)	1.5 (0.5 to 2.4)	2.5 (1.8 to 3.2)	1.7 (1.4 to 2.1)	0.3 (0.1 to 0.5)
p Value	<0.001	0.08	0.09	0.003	<0.001	<0.001	<0.001
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose, and lung volume at CT							
COPD	145.6	95.0	78.0	62.8	48.7	33.6	18.9
No COPD	146.1	94.5	78.2	62.8	47.0	32.2	18.6
Difference (95% CI)	−0.5 (−3.5 to 2.5)	0.6 (−2.1 to 3.3)	−0.2 (−1.8 to 1.3)	0.0 (−1.1 to 1.0)	1.7 (0.9 to 2.5)	1.4 (1.0 to 1.8)	0.2 (0.1 to 0.4)
p Value	p=0.74	p=0.68	p=0.77	p=0.97	p<0.001	p<0.001	p=0.01

Mean values and differences, along with 95% CI and p values were estimated using linear regression with generalised estimating equations.
BMI, body mass index; HU, Hounsfield units; MESA, Multi-Ethnic Study of Atherosclerosis; SPIROMICS Subpopulations and Intermediate Outcome Measures in COPD Study.

Table 4 Airway wall areas according to COPD status from 15 randomly selected airways per participant

MESA COPD	Fifteen randomly selected airways per participant
Unadjusted mean airway wall area in mm^2	
COPD	19.9
No COPD	18.2
Difference (95% CI)	1.7 (0.6 to 2.7)
p Value	0.001
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT	
COPD	18.8
No COPD	17.7
Difference (95% CI)	1.2 (0.1 to 2.2)
p Value	0.02
SPIROMICS	**Fifteen randomly selected airways per participant**
Unadjusted mean airway wall area in mm^2	
COPD	17.7
No COPD	17.0
Difference (95% CI)	0.7 (0.2 to 1.2)
p Value	0.003
Mean airway wall area in mm^2 adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT	
COPD	17.7
No COPD	17.1
Difference (95% CI)	0.5 (0.1 to 1.0)
p Value	0.02

Mean values and differences, along with 95% CI and p values were estimated using linear regression with generalised estimating equations.
BMI, body mass index; HU, Hounsfield units; MESA, Multi-Ethnic Study of Atherosclerosis; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study.

COPD.[5 25] Finally, we present differences in means, which suggests that most people with COPD have thinner airways but does not rule out the possibility of a subset having thicker airway walls.

Our analyses did not include many airways less than 2 mm in lumen diameter, a threshold below which many believe the excess airways resistance arises in COPD.[28 29] This was due in part to CT resolution,[9] as well as the technical demands of

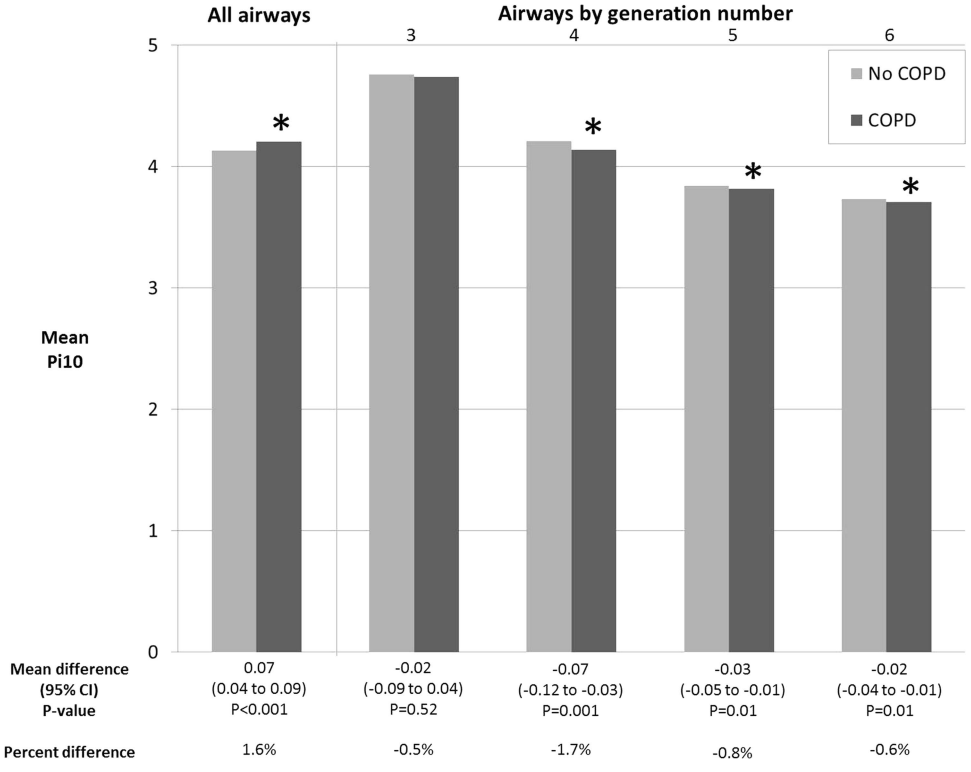

Figure 3 Pi10 according to COPD status in SPIROMICS. *p<0.05 for comparison of mean Pi10 between participants with no COPD to those with COPD. Calculation of Pi10 required five or more airways per participant; therefore, Pi10 was not computed for generations 0–2. Mean values and differences adjusted for age, gender, height, race-ethnicity, smoking status, airway length, per cent emphysema$_{-950HU}$, BMI-determined CT dose and lung volume at CT. SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study; HU, Hounsfield units; BMI, body mass index.

visually confirmed spatial mapping of the tracheobronchial tree to the sixth generation in large studies. However, the classic studies[28 29] that describe airways less than 2 mm as the predominant site of resistance in COPD may have been subject to the same bias described here: comparison of peripheral and central resistance when a fixed-diameter catheter may have wedged more proximally in COPD could bias inferences related to the site of airways obstruction. Central airways likely also contribute to airways resistance in COPD, as demonstrated by Yanai[29] and Macklem.[30] Nevertheless, histological confirmation of fewer and thinner central airways, as well as a method of spatially matching peripheral airways is needed.

Alternative approaches to matching airways in COPD based on histological characteristics (eg, membranous,[18] cartilaginous[5] or terminal bronchioles[9]) were not addressed in this paper. However, these histologically defined airways span multiple generations,[3] thus bias resulting from sampling of more proximal airways with similar histological characteristics in COPD cannot be excluded.

Airway segments occluded by mucous may have gone undetected by the imaging software. We do not believe such a sampling bias contributed to our findings, however, given the association between increasing COPD severity and thinner walls was also observed in proximal airways (eg, main stem and lobar bronchi) where complete mucous occlusion is unlikely and spatial mapping reproducibility was excellent.[31]

In summary, in two independent studies of smokers, COPD was associated with significantly less airway wall thicknesses throughout most of the central tracheobronchial tree when comparing spatially matched airways. Sampling airways by lumen diameter or randomly resulted in differential spatial distributions by COPD status and introduced selection bias in the study of airway wall properties, as did the use of the Pi10. Studies of airway morphometry, histology and genomics in COPD should spatially match airways to avoid potentially large selection bias due to comparison of proximal-to-peripheral airways.

Author affiliations
[1]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York, USA
[2]Department of Medicine, McGill University, Montreal, Canada
[3]Departments of Radiology, Medicine and Biomedical Engineering, University of Iowa, Iowa City, Iowa, USA
[4]Department of Statistics, Columbia University, New York, New York, USA
[5]Department of Medicine, Wake Forest University, Winston-Salem, North Carolina, USA
[6]Department of Medicine, University of California San Francisco, San Francisco, California, USA
[7]Deparment of Biostatistics, University of North Carolina Chapel Hill, Chapel Hill, North Carolina, USA
[8]Department of Medicine, University of Michigan, Ann Arbor, Michigan, USA
[9]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[10]Department of Medicine, University of Utah, Salt Lake City, Utah, USA
[11]Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA
[12]Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA
[13]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, USA

Contributors BMS contributed to the study concept and design, data analysis and interpretation, manuscript drafting and revising, as well as final approval. EAH contributed to study design, data acquisition and analysis, manuscript revising and final approval. DR contributed to the study concept, data analysis, manuscript revising and final approval. MKH, SC and EK contributed to data acquisition, manuscript revising and final approval. KMD contributed to data interpretation, manuscript revising and final approval. EB, DC, REK and SR contributed to study design, data acquisition, manuscript revising and final approval. RGB contributed to study concept and design, data collection, acquisition and analysis, manuscript revising, as well as final approval.

Funding NIH/NHLBI R01-HL093081, R01-HL077612, R01-HL075476, N01-HC95159-HC95169, HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN2682009000019C and HHSN268200900020C; Fonds de la recherche en santé Québec.

Competing interests Authors have completed the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest.

Ethics approval National Heart Lung and Blood Institute (NHLBI) and all participating institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data used in the present study are from two ongoing prospective cohort studies of COPD. Persons interested in using data from these studies should contact the corresponding author or visit the study websites.

REFERENCES

1 Vestbo J, Hurd SS, Agusti AG, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–65.
2 Fishman AP, Macklem PT, Mead J, *et al*. *Mechanics of breathing. Handbook of physiology*. Bethesda, MD: American Physiological Society, 1986:2 v. (xxv, 784p.).
3 Weibel ER. *Morphometry of the human lung*. Berlin: Springer, 1963.
4 Hsia CC, Hyde DM, Ochs M, *et al*. An official research policy statement of the American Thoracic Society/European Respiratory Society: standards for quantitative assessment of lung structure. *Am J Respir Crit Care Med* 2010;181:394–418.
5 Tiddens HA, Pare PD, Hogg JC, *et al*. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med* 1995;152:260–6.
6 Nakano Y, Muro S, Sakai H, *et al*. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):1102–8.
7 Berger P, Perot V, Desbarats P, *et al*. Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. *Radiology* 2005;235:1055–64.
8 Hasegawa M, Nasuhara Y, Onodera Y, *et al*. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:1309–15.
9 McDonough JE, Yuan R, Suzuki M, *et al*. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;365:1567–75.
10 Matsuoka S, Kurihara Y, Yagihashi K, *et al*. Airway dimensions at inspiratory and expiratory multisection CT in chronic obstructive pulmonary disease: correlation with airflow limitation. *Radiology* 2008;248:1042–9.
11 Diaz AA, Valim C, Yamashiro T, *et al*. Airway count and emphysema assessed by chest CT imaging predicts clinical outcome in smokers. *Chest* 2010;138:880–7.
12 Bosken CH, Wiggs BR, Pare PD, *et al*. Small airway dimensions in smokers with obstruction to airflow. *Am Rev Respir Dis* 1990;142:563–70.
13 Kim WD, Ling SH, Coxson HO, *et al*. The association between small airway obstruction and emphysema phenotypes in COPD. *Chest* 2007;131:1372–8.
14 Hogg JC, Chu F, Utokaparch S, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–53.
15 Kim WJ, Silverman EK, Hoffman E, *et al*. CT metrics of airway disease and emphysema in severe COPD. *Chest* 2009;136:396–404.
16 Patel BD, Coxson HO, Pillai SG, *et al*. Airway wall thickening and emphysema show independent familial aggregation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;178:500–5.
17 Grydeland TB, Dirksen A, Coxson HO, *et al*. Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. *Am J Respir Crit Care Med* 2010;181:353–9.
18 Kuwano K, Bosken CH, Pare PD, *et al*. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;148:1220–5.
19 Airway wall thinness and COPD: analysis of spatially comparable airways. The MESA COPD Study. *European Respiratory Society Congress*; 8 September 2013, Barcelona, Spain, 2013.
20 Couper D, Lavange LM, Han M, *et al*. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014;69:491–4.
21 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. *population.* Am J Respir Crit Care Med 1999;159:179–87.
22 Liang KY, Zeger SL. Regression analysis for correlated data. *Annu Rev Public health* 1993;14:43–68.
23 Diaz AA, Bartholmai B, San Jose Estepar R, *et al*. Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD. *Respir Med* 2010;104:1145–51.
24 Washko GR, Diaz A, Kim V, *et al*. Computed tomographic measures of airway morphology in smokers and never-smoking normals. *J Appl Physiol* 2014;116:668–73.
25 Tiddens HA, Bogaard JM, de Jongste JC, *et al*. Physiological and morphological determinants of maximal expiratory flow in chronic obstructive lung disease. *Eur Respir J* 1996;9:1785–94.

26 Cosio M, Ghezzo H, Hogg JC, *et al*. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med* 1978;298:1277–81.
27 Thurlbeck WM, Pun R, Toth J, *et al*. Bronchial cartilage in chronic obstructive lung disease. *Am Rev Respir Dis* 1974;109:73–80.
28 Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278:1355–60.
29 Yanai M, Sekizawa K, Ohrui T, *et al*. Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure. *J Appl Physiol (1985)* 1992;72:1016–23.
30 Macklem PT, Fraser RG, Brown WG. Bronchial Pressure Measurements in Emphysema and Bronchitis. *J Clin Invest* 1965;44:897–905.
31 Montaudon M, Berger P, de Dietrich G, *et al*. Assessment of airways with three-dimensional quantitative thin-section CT: in vitro and in vivo validation. *Radiology* 2007;242:563–72.