Title

Pulmonary Arterial Pruning and Longitudinal Change in Percent Emphysema and Lung Function The Genetic Epidemiology of COPD Study

Journal

CHEST Journal, 160(2)

ISSN

0012-3692

Authors

Pistenmaa, Carrie L
Nardelli, P
Ash, SY
et al.

Publication Date

2021-08-01

DOI

10.1016/j.chest.2021.01.084

Peer reviewed

CHEST

Pulmonary Arterial Pruning and Longitudinal Change in Percent Emphysema and Lung Function

The Genetic Epidemiology of COPD Study

*Carrie L. Pistenmaa, MD; P. Nardelli, PhD; S. Y. Ash, MD; C. E. Come, MD; A. A. Diaz, MD; F. N. Rahaghi, MD, PhD; R. G. Barr, MD, DrPH; K. A. Young, PhD; G. L. Kinney, PhD; J. P. Simmons, MD; R. C. Wade, MD; J. M. Wells, MD; J. E. Hokanson, PhD; G. R. Washko, MD; and R. San José Estépar, PhD; for the COPDGene Investigators**

BACKGROUND: Pulmonary endothelial damage has been shown to precede the development of emphysema in animals, and vascular changes in humans have been observed in COPD and emphysema.

RESEARCH QUESTION: Is intraparenchymal vascular pruning associated with longitudinal progression of emphysema on CT imaging or decline in lung function over 5 years?

STUDY DESIGN AND METHODS: The Genetic Epidemiology of COPD Study enrolled ever smokers with and without COPD from 2008 through 2011. The percentage of emphysema-like lung, or "percent emphysema," was assessed at baseline and after 5 years on noncontrast CT imaging as the percentage of lung voxels < –950 Hounsfield units. An automated CT imaging-based tool assessed and classified intrapulmonary arteries and veins. Spirometry measures are postbronchodilator. Pulmonary arterial pruning was defined as a lower ratio of small artery volume (< 5 mm^2 cross-sectional area) to total lung artery volume. Mixed linear models included demographics, anthropomorphics, smoking, and COPD, with emphysema models also adjusting for CT imaging scanner and lung function models adjusting for clinical center and baseline percent emphysema.

RESULTS: At baseline, the 4,227 participants were 60 ± 9 years of age, 50% were women, 28% were Black, 47% were current smokers, and 41% had COPD. Median percent emphysema was 2.1 (interquartile range, 0.6-6.3) and progressed 0.24 percentage points/y (95% CI,

ABBREVIATIONS: BV5 = volume of pulmonary vessels less than 5 mm^2 in cross-sectional area; BV5a = volume of pulmonary arteries less than 5 mm^2 in cross-sectional area; COPDGene = Genetic Epidemiology of COPD; HU = Hounsfield units; PD15 = lung density at the 15th percentile; percent emphysema$_{-950}$ = percentage of lung volume with attenuation < –950 Hounsfield units; TBVa = total arterial volume of interparenchymal vessels

AFFILIATIONS: From the Department of Medicine (C. L. Pistenmaa, S. Y. Ash, C. E. Come, A. A. Diaz, F. N. Rahaghi, and G. R. Washko), the Department of Radiology (P. Nardelli and R. San José Estépar), Brigham and Women's Hospital, Boston, MA; the Departments of Medicine and Epidemiology (R. G. Barr), Columbia University, New York, NY; the Department of Epidemiology (K. A. Young, G. L. Kinney, and J. E. Hokanson), Colorado School of Public Health, University of Colorado, Denver, CO; and the Department of Medicine (J. P. Simmons, R. C. Wade, and J. M. Wells), University of Alabama at Birmingham, Birmingham, AL.

This article was presented as an abstract at American Thoracic Society International Conference, May 21, 2019, Dallas, TX.

FUNDING/SUPPORT: This study was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health [Grants K23 HL141651, R01 HL116931, R01 HL116473, U01 HL089897, and U01 HL089856]. The COPDGene Study is also supported by the COPD Foundation through contributions made to an industry advisory board comprising AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Siemens, and Sunovion.

*Collaborators from the COPDGene Investigators are listed in the Acknowledgments.

CORRESPONDENCE TO: Carrie L. Pistenmaa, MD; email: cpistenmaa@bwh.harvard.edu

DOI: https://doi.org/10.1016/j.chest.2021.01.084

0.22-0.26 percentage points/y) over 5.6 years. Mean FEV_1 to FVC ratio was 68.5 ± 14.2% and declined 0.26%/y (95% CI, −0.30 to −0.23%/y). Greater pulmonary arterial pruning was associated with more rapid progression of percent emphysema (0.11 percentage points/y per 1-SD increase in arterial pruning; 95% CI, 0.09-0.16 percentage points/y), including after adjusting for baseline percent emphysema and FEV_1. Arterial pruning also was associated with a faster decline in FEV_1 to FVC ratio (−0.04%/y per 1-SD increase in arterial pruning; 95% CI, −0.008 to −0.001%/y).

INTERPRETATION: Pulmonary arterial pruning was associated with faster progression of percent emphysema and more rapid decline in FEV_1 to FVC ratio over 5 years in ever smokers, suggesting that pulmonary vascular differences may be relevant in disease progression.

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

CHEST 2021; 160(2):470-480

KEY WORDS: emphysema; imaging; longitudinal; lung function; pulmonary circulation

COPD is a globally important disease and a leading cause of death.[1,2] Significant heterogeneity exists in the characteristics of COPD, including emphysema,[3] which is defined on pathologic examination as permanent airspace dilation and also can be measured on CT scan as the percentage of emphysema-like lung, or "percent emphysema."[4] Percent emphysema has been associated with greater lung function decline, hospitalizations, and mortality in those with COPD.[5-7]

Pulmonary vascular endothelial damage has been implicated as an early step in the pathogenesis of COPD and emphysema.[8-10] The pulmonary vasculature regulates perfusion to optimize gas exchange and transports essential cellular mediators to the lung parenchyma (eg, neutrophils, cytokines, and lung progenitor cells).[11] In animal models, vascular endothelial growth factor receptor blockade causes endothelial apoptosis, emphysema, and pruning of pulmonary arteries.[12] In humans, a loss of pulmonary capillaries is evident on pathologic sections of emphysematous lung,[13,14] and a lower pulmonary microvascular perfusion on contrast-enhanced MRI was associated with greater percent emphysema in the Multi-Ethnic Study of Atherosclerosis COPD Study.[15] In the Genetic Epidemiology of COPD (COPDGene Study), a higher degree of pulmonary vascular pruning (a lower ratio of volume of vessels < 5 mm^2 in cross-sectional area to total lung vessel volume) on noncontrast CT scan was found in those with more advanced COPD and with more emphysema.[16] However, it is unknown whether differences in the parenchymal pulmonary vasculature contribute to the progression of emphysema and COPD.

We recently developed techniques to classify pulmonary arteries and veins on noncontrast CT imaging.[17] Therefore, we sought to test the hypothesis that pulmonary arterial pruning, measured as a decrease in the ratio of small artery volume to total pulmonary arterial volume on noncontrast CT imaging, would be associated with a faster progression of percent emphysema and decline in lung function measured over 5 years in the COPDGene Study.

Methods

Study Design and Participants

The COPDGene Study is a longitudinal observational study designed to evaluate genetic contributors to COPD (ClinicalTrials.gov Identifier: NCT000608764). Current and former smokers with at least a 10-pack-year history with and without COPD were enrolled at 21 clinical centers in the United States from 2008 through 2011.[18] Participants self-identified as non-Hispanic White or Black and were between 45 and 80 years of age at enrollment. The major exclusion criteria were significant lung disease other than COPD or asthma, major lung surgery (lobar resection, lung volume reduction surgery, or transplantation), and an exacerbation in the prior month treated with antibiotics or steroids. Those enrolled at baseline were invited to return for the 5-year follow-up visit (from 2012 through 2016), and the 10-year follow-up visit is ongoing. All participants provided written informed consent, and institutional review board approval was obtained at all sites. The full protocol is available at www.copdgene.org.

CT Imaging Measurements

Noncontrast CT scan of the chest was performed at full inspiration (total lung capacity) at baseline and the 5-year follow-up visit using the COPDGene Study protocol, with a smooth reconstruction kernel (Bf31 for Siemens scans, Bone for GE scans) and 0.45- to 0.9-mm slice thickness, depending on the scanner manufacturer.[18] Quantitative assessment of lung parenchyma (CT scan densitometry)

was performed at a single center blinded to other participant information using automated software that includes lobar segmentation (Thirona). The percent emphysema was calculated as the percentage of lung volume with attenuation < –950 Hounsfield units (percent emphysema$_{-950}$). Percent emphysema$_{-950}$ also was calculated for each lobe. Secondary analyses used lung density at the lower 15th percentile (PD15) adjusted for percent predicted total lung volume (ie, sponge model to account for different degree of inhalation on CT scans),[19] based on healthy participants in a population-based study undergoing CT scan.[20] Per convention, PD15 values are reported as the Hounsfield units plus 1,000 to reflect lung density in grams per liter.

Assessment of the pulmonary vasculature was performed using the Chest Imaging Platform (www.chestimagingplatform.org) after lung and lobe segmentation,[21] with 3-dimensional vascular reconstruction using a scale-space particle method.[22,23] Arterial and venous vessels then were separated by a deep learning technique (Fig 1), with mean accuracy of 93.6% when compared with manual artery-vein segmentation.[17] The total arterial volume of interparenchymal vessels (TBVa) and total venous volume of interparenchymal vessels in the lung were calculated for each participant, as were volume of pulmonary arteries less than 5 mm^2 in cross-sectional area (BV5a) and the volume of pulmonary veins less than 5 mm^2 in cross-sectional area. BV5a was correlated with histologic assessment of vessel volume ($r = 0.50$, $P = .04$)[24] and overall BV5 was found to correlate with pulmonary perfusion by scintigraphy, including on a regional basis within the lung ($r = 0.87$, $P < .001$).[25] The main exposure of interest is a decrease in the relative volume of small pulmonary vessels, which we term "pruning," with pulmonary arterial pruning being a decrease in BV5a to TBVa ratio and pulmonary venous pruning being a decrease in volume of pulmonary veins less than 5 mm^2 in cross-sectional area per total venous volume of interparenchymal vessels.

Pulmonary artery and aorta diameters were measured at the bifurcation of the pulmonary artery on baseline inspiratory CT scans by two reviewers using the OsiriX MD DICOM Viewer version 11.0 (Pixmeo SARL), as described previously.[26-28]

Lung Function and Covariates

Participant race, sex, educational attainment, current smoking status, smoking history, and diagnosis of diabetes were self-reported and categorized as in Table 1. Height and weight were measured according to standard techniques. Spirometry was performed using the EasyOne Spirometer (ndd) following a standardized protocol and quality review; postbronchodilator values are used in all analyses.[18,29] COPD classification followed the Global Initiative for Chronic Obstructive Lung Disease categories based on FEV_1 percent predicted for those with COPD with a postbronchodilator FEV_1 to FVC ratio of < 0.7.[30]

Statistical Analysis

Participant characteristics are shown stratified by quintile of vascular pruning for descriptive purposes (highest quintile has the greatest pruning, ie, lowest small arterial to total lung vessel volume [BV5a/TBVa]). Analyses used a mixed linear regression model with a random intercept to assess the interaction between time and baseline vascular variables (all treated continuously). For emphysema, results are shown unadjusted, adjusted for CT imaging scanner, and the full model is adjusted for baseline age, sex, race, education, time-varying height, weight, and smoking status. In lung function analyses, the base model adjusted for baseline age, sex, race, education, and time-varying height, weight, smoking status, and pack-years of smoking, and a full model also adjusted for percent emphysema$_{-950}$ and clinical center. For analyses of percent change in FEV_1, the outcome was log-transformed. All analyses were adjusted for COPD status given the case-control study design. Nonlinearity was assessed using quintiles of BV5 per total blood volume of intraparenchymal vessels in the linear models.

Additive interactions were assessed between arterial pruning and age, sex, race, BMI, smoking status, COPD, baseline emphysema, CT imaging scanner manufacturer, and pulmonary artery to aorta ratio

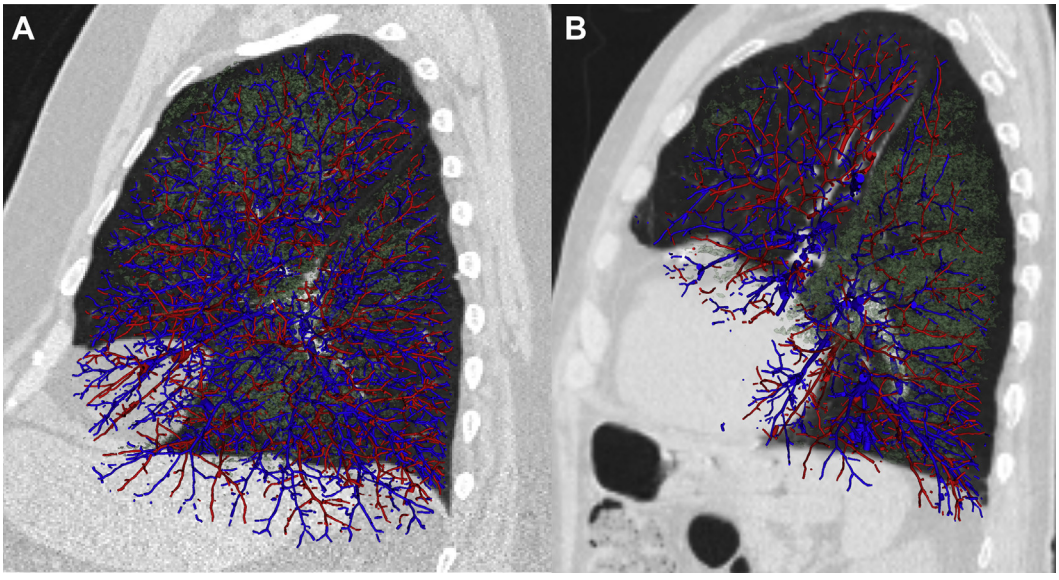

Figure 1 – *A, B, Pulmonary arteries and veins defined by a deep learning technique in selected participants with Global Initiative for Chronic Obstructive Lung Disease 2 COPD without pruning of small arteries (volume of pulmonary arteries less than 5 mm^2 in cross-sectional area [BV5a] per total arterial volume of interparenchymal vessels [TBVa] ratio > 50th percentile) (A) and pruning of small arteries (BV5a per TBVa < 50th percentile) (B). Vessels are a 3-dimensional reconstruction with 2-dimensional CT image for anatomic landmarks. Blue = artery; green overlay = emphysematous lung areas; red = vein.*

TABLE 1] Baseline Characteristics by Quintile of Pulmonary Arterial Pruning[a]

Characteristic	Quintile 1 (n = 845)	Quintile 2 (n = 846)	Quintile 3 (n = 845)	Quintile 4 (n = 846)	Quintile 5 (n = 845)
	Less Pruning → More Pruning				
Age, y	59.8 ± 7.8	60.1 ± 8.4	60.0 ± 8.7	59.8 ± 9.1	59.3 ± 9.4
Male sex	29.1	45.7	53.3	59.1	62.4
Race	…	…	…	…	…
Non-Hispanic White	87.5	77.9	74.6	66.8	54.7
Black	12.5	22.1	25.4	33.2	45.3
Height, cm	166.9 ± 8.5	169.2 ± 9.4	171.5 ± 9.5	170.8 ± 10.0	171.8 ± 9.5
BMI, kg/m^2	26.5 ± 4.6	28.4 ± 5.0	29.5 ± 6.1	29.6 ± 6.2	31.7 ± 7.0
Education	…	…	…	…	…
High school or less	22.8	31.2	32.0	36.4	45.5
Some college	29.0	26.1	29.6	28.3	26.3
College or more	48.2	42.7	38.4	35.3	28.2
Smoking status	…	…	…	…	…
Former smoker	54.6	56.4	52.5	52.4	47.3
Current smoker	45.4	43.6	47.5	47.6	52.7
Pack-years	38.7 ± 20.2	41.3 ± 22.8	42.9 ± 23.5	45.6 ± 26.1	44.9 ± 24.9
Lung function	…	…	…	…	…
GOLD stage	…	…	…	…	…
1, $FEV_1 > 80\%$	15.3	10.6	8.1	6.2	4.3
2, $50\% < FEV_1 < 80\%$	14.2	18.9	20.8	22.7	22.8
3-4, $FEV_1 < 50\%$	1.9	3.9	11.8	17.2	25.0
Normal (FEV_1 to FVC ratio ≥ 0.7, FVC ≥ LLN)	62.7	57.9	49.6	41.5	28.5
Abnormal, nonobstructive (FVC < LLN, FEV_1 to FVC ratio ≥ 0.7)	5.9	8.7	9.7	12.4	19.4
FEV_1, L	2.6 ± 0.7	2.5 ± 0.8	2.4 ± 0.9	2.2 ± 0.9	2.0 ± 0.8
FEV_1, percent predicted	91.7 ± 17.2	86.7 ± 18.6	80.7 ± 21.7	75.0 ± 23.5	67.6 ± 23.0
FEV_1 to FVC ratio	0.72 ± 0.09	0.72 ± 0.11	0.69 ± 0.14	0.66 ± 0.16	0.65 ± 0.16
Percent emphysema$_{-950}$	2.0 (0.7-5.3)	2.2 (0.7-5.5)	2.1 (0.6-6.2)	2.2 (0.6-7.4)	1.8 (0.4-8.3)
Lung density at the lower 15th percentile adjusted for lung volume, g/L	88.4 ± 20.8	87.5 ± 21.0	86.9 ± 24.9	85.2 ± 28.0	87.0 ± 32.2
Total lung volume on CT scan, L	5.60 ± 1.20	5.57 ± 1.30	5.63 ± 1.41	5.54 ± 1.42	5.19 ± 1.45
Small artery volume (BV5a), mL	110.7 ± 25.5	107.0 ± 25.1	102.3 ± 24.5	95.5 ± 23.1	82.0 ± 21.4
Small venous volume (BV5v), mL	66.8 ± 13.8	66.4 ± 12.9	64.7 ± 12.9	61.2 ± 13.2	54.4 ± 14.5
Total lung arterial volume (TBVa), mL	158.9 ± 37.1	167.7 ± 39.3	171.1 ± 41.1	173.3 ± 41.7	177.2 ± 41.8
Total venous volume of interparenchymal vessels, mL	106.4 ± 21.2	108.5 ± 21.7	108.2 ± 22.4	106.0 ± 23.3	102.1 ± 25.4
BV5a per TBVa (lower values reflect arterial pruning)	0.70 ± 0.03	0.64 ± 0.01	0.60 ± 0.01	0.55 ± 0.02	0.46 ± 0.05
BV5v per TBVv (lower values reflect venous pruning)	0.63 ± 0.04	0.61 ± 0.04	0.60 ± 0.05	0.58 ± 0.05	0.53 ± 0.07
Pulmonary artery diameter to aorta diameter ratio	0.79 ± 0.11	0.82 ± 0.11	0.83 ± 0.12	0.85 ± 0.12	0.88 ± 0.12

Data are presented as percentage, mean SD, or median (interquartile range). BV5a = volume of pulmonary arteries less than 5 mm^2 in cross-sectional area; BV5v = volume of pulmonary veins less than 5 mm^2 in cross-sectional area; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LLN = lower limit of normal; percent emphysema$_{-950}$ = percentage of lung volume with attenuation < –950 Hounsfield units; TBVa = total arterial volume of interparenchymal vessels; TBVv = total venous volume of interparenchymal vessels

[a]Highest quintile has the most pruning, that is, the lowest BV5a per TBVa.

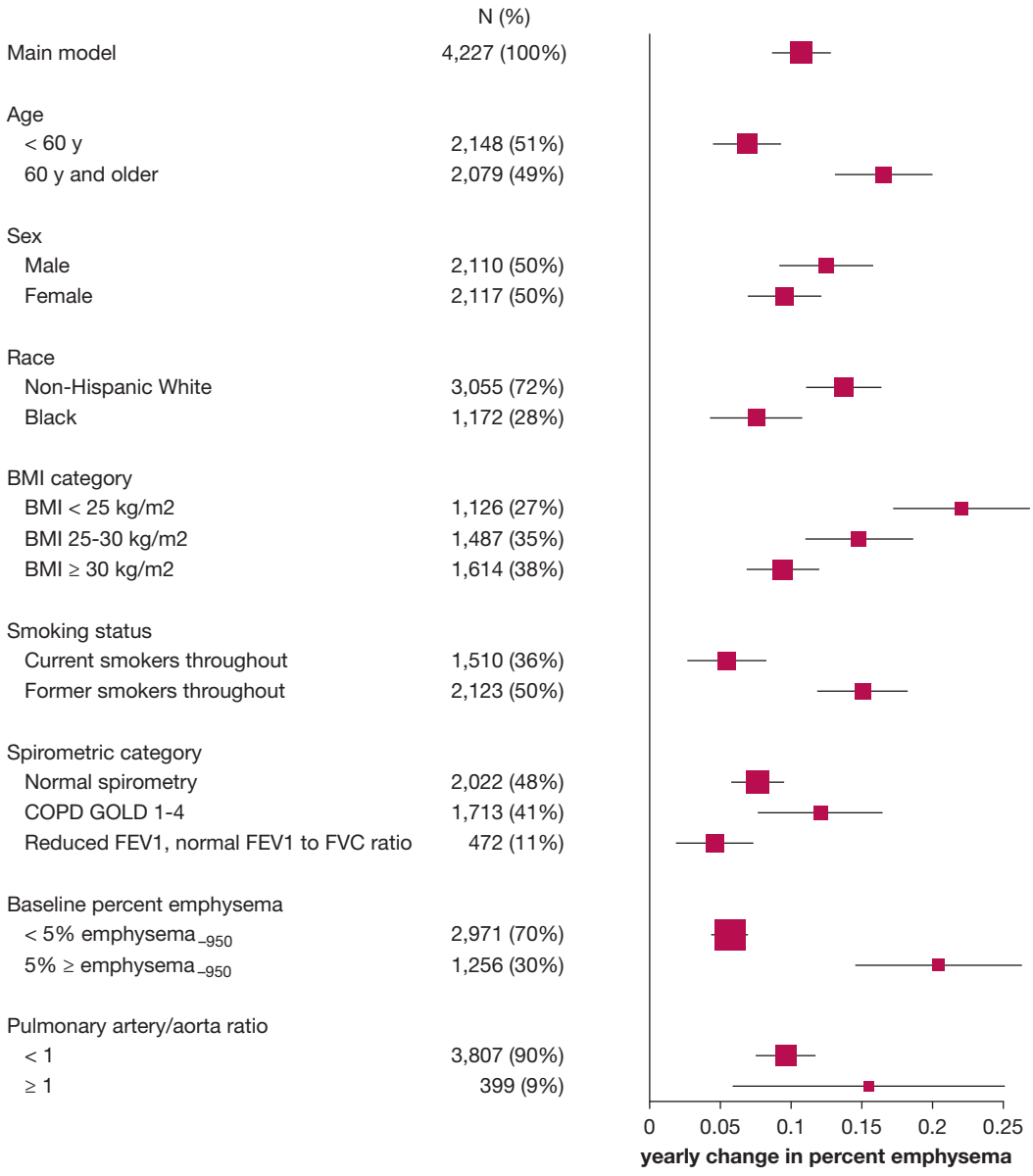

Figure 2 – *Stratified analyses of the mean difference in yearly progression of percentage of lung volume with attenuation < –950 Hounsfield units (percent emphysema$_{-950}$) for a 1-SD increase in arterial pruning (decrease in volume of pulmonary arteries less than 5 mm^2 in cross-sectional area per total arterial volume of interparenchymal vessels). Model adjusts for baseline age, sex, race, education, and COPD status and time-varying height, weight, and smoking status, except when stratified by the variables. Three-way interaction P values for age, race, BMI category, smoking status, and spirometric category and baseline percent emphysema were < .001; P = .015 for sex; and P = .145 pulmonary artery diameter to aorta diameter ratio (P = 0.064 for CT imaging scanner manufacturer; not shown). GOLD = Global Initiative for Chronic Obstructive Lung Disease.*

for change in percent emphysema$_{-950}$ (all categorized as shown in Fig 2). For lung function analyses, interactions were assessed for age, sex, race, smoking status, and COPD category, as well as baseline FEV_1 for the FEV_1 analyses. Further analyses for percent emphysema used lobar measures of vascular pruning and emphysema, and sensitivity analyses were adjusted for potential confounders: baseline percent emphysema$_{-950}$, percent predicted FEV_1, time-varying pack years, cigarettes smoked within 24 h, self-reported diabetes, oxygen saturation, and pulmonary artery to aorta ratio. Additional analyses excluded those scanned on a different CT imaging scanner at the two visits (45%), with more than 20% change in CT scan lung volume between scans (13%), with a CT scan lung volume of < 80% or > 120% predicted (23%), and where smoking status changed during follow-up (14%). For percent emphysema, alternate measures of vascular pruning also were assessed: the ratio of small vessel volume to lung volume on CT scan and small vessel volume (BV5a or volume of pulmonary veins less than 5 mm^2 in cross-sectional area) and total lung vessel (arterial or venous) volume as separate terms in the model. We also evaluated lobe-specific measures and used PD15 corrected for CT scan lung volume as an alternate lung density outcome.[19] For lung function, sensitivity analyses excluded outliers in the change in FEV_1: those with the

greatest gain (> 90 mL/y, n = 50) and greatest loss (> 180 mL/y, n = 45), and adjusting for baseline lung function parameters. Those missing covariates for the main analyses were not included. All analyses were performed in SAS version 9.4 software (SAS Institute) and R software (R Foundation for Statistical Computing). *P* values were two-sided, and a value of less than .05 was considered significant.

Results

Of the 10,263 ever smoking participants enrolled at baseline, a total of 6,409 participants returned for the 5-year follow-up visit (62%, or 65% of those living). At baseline, 9,541 participants had percent emphysema measures and 7,970 (84%) had valid pulmonary vascular measures; of these, 4,227 had 5-year percent emphysema measures and 4,449 had baseline and 5-year lung function measures. Compared with those in the current analyses, baseline participants not included were more likely to be Black, to be men, to be current smokers with COPD, to show more percent emphysema, and to show more arterial pruning (e-Table 1).

At baseline, the 4,227 participants included in the emphysema analyses were a mean of 60 ± 9 years of age, 50% were women, 72% were non-Hispanic White, and 28% were Black; 47% were current smokers and 41% had COPD. Those with the most pulmonary arterial pruning (quintile 5 in Table 1) were more likely to be men, Black, and current smokers with greater height and weight, lower educational status, lower lung function, and greater mean percent emphysema. The median baseline percent emphysema$_{-950}$ was 2.1 (interquartile range, 0.6-6.3), and mean progression was 0.24 percentage points/y (95% CI, 0.22-0.26 percentage points/y) over an average of 5.6 years. Mean baseline FEV_1 was 2330 ± 830 mL, with an average decline of 2.0%/y (95% CI, –1.9 to –2.1 %/y) and 37.6 mL/y (95% CI, –39.1 to –36.1 mL/y). Mean FEV_1 to FVC ratio was 68.5 ± 14.2%, with an average decline of 0.26%/y (95% CI, –0.30 to –0.23 %/y).

Percent Emphysema

Pulmonary arterial pruning was associated with a faster progression of percent emphysema$_{-950}$ in the main model (0.11 percentage points/y per 1-SD increase in arterial pruning; 95% CI, 0.09-0.13 percentage points/y) (Table 2). Pulmonary venous pruning also predicted faster progression of percent emphysema$_{-950}$, although results were of lower magnitude (0.03 percentage points/y per 1-SD increase in venous pruning; 95% CI, 0.01-0.05 percentage points/y) (Table 2). Results were similar when restricted to the right upper lobe and right lower lobe (e-Table 2).

Additional adjustment for baseline percent emphysema$_{-950}$ increased the magnitude of the results, whereas adjustment for baseline percent predicted FEV_1 attenuated them; with inclusion of both of these measures, the results were of similar magnitude and significance as the main model (Fig 3). With adjustment for pack years, cigarettes smoked within

TABLE 2] Predicted Yearly Change in Percent Emphysema$_{-950}$ by Quintile of Vascular Pruning[a]

Variable	Quintile of Vascular Pruning Less Pruning → More Pruning					Mean Difference per Year per 1-SD Greater Pruning (95% CI)[b]	*P* Value[b]
	1	2	3	4	5		
Arterial vessels (BV5a/TBVa)							
Unadjusted	Reference	**0.10**	**0.23**	**0.37**	**0.46**	0.19 (0.17-0.21)	< .001
Scanner adjusted	Reference	0.05	**0.15**	**0.23**	**0.29**	0.12 (0.10-0.14)	< .001
Main model	Reference	0.05	**0.13**	**0.22**	**0.25**	0.11 (0.09-0.13)	< .001
Venous vessels (BV5v/TBVv)							
Unadjusted	Reference	0.02	**0.06**	**0.12**	**0.23**	0.08 (0.06-0.11)	< .001
Scanner adjusted	Reference	0.003	0.03	**0.06**	**0.12**	0.04 (0.02-0.06)	< .001
Main model	Reference	0.01	0.03	**0.06**	**0.10**	0.03 (0.01-0.05)	< .001

The main model adjusts for baseline age, sex, race, education, and time-varying height, weight, smoking status, and scanner terms. All models adjust for COPD status. Boldface values indicate that the quintile was significantly different from the reference group ($P < .05$). BV5a = volume of pulmonary arteries less than 5 mm^2 in cross-sectional area; BV5v = volume of pulmonary veins less than 5 mm^2 in cross-sectional area; percent emphysema$_{-950}$ = percentage of lung volume with attenuation < –950 Hounsfield units; TBVa = total arterial volume of interparenchymal vessels; TBVv = total venous volume of interparenchymal vessels.

[a]Highest quintile has the most pruning, that is, the lowest BV5a per TBVa.

[b]Effect estimate and *P* value are from a model with a continuous independent variable.

24 h, diabetes, oxygen saturation, and pulmonary artery to aorta ratio, the results essentially were unchanged (Fig 3). Also, little variation was found when limiting the analysis to those with a repeat CT scan on the same scanner, with < 20% change in lung volume between the two CT scans, with CT scan lung volume between 80% and 120% predicted, and those without change in smoking status during follow-up (Fig 3). In stratified analyses, the association was of lower magnitude in those younger than 60 years, women, Black people, obese individuals, current smokers, those with a reduced FEV_1 and preserved FEV_1 to FVC ratio, and those with less than 5% emphysema at baseline ($P < .01$ for each interaction); however, in each subcategory, pulmonary arterial pruning was associated significantly with faster emphysema progression (Fig 2).

Results when using the ratio of small vessel volume to total CT scan lung volume were of lower magnitude, but remained statistically significant (e-Table 3). When adjusting for small vessel volume and total lung vessel volume separately, results were similar to those using their ratio as the primary exposure (e-Table 4). In addition, using PD15 adjusted for CT scan lung volume as the outcome instead of percent $emphysema_{-950}$ showed very similar results (e-Table 5).

Lung Function

Pulmonary arterial pruning was associated with a more rapid decline in FEV_1 to FVC ratio (–0.04%/y per 1-SD increase in arterial pruning; 95% CI, –0.08 to –0.001%/y; $P = .042$) (e-Table 6). After excluding outliers and adjusting for baseline FEV_1 to FVC ratio, results were of greater magnitude (e-Fig 1). No significant interactions were identified in the association between pulmonary arterial pruning and decline in FEV_1 to FVC ratio.

Pulmonary arterial pruning was associated with a more rapid percent decline in FEV_1 (0.18%/y per 1-SD increase in arterial pruning; 95% CI, –0.27 to –0.08%/y; $P < .001$) (e-Table 7). However, results were in the opposite direction when looking at absolute change in FEV_1, with a slower decline in FEV_1 by 2.4 mL/y per 1-SD increase in arterial pruning (95% CI, 0.7-4.1 mL/y; $P = .005$) (e-Table 8). After excluding outliers, the association for percent FEV_1 was of greater magnitude and absolute FEV_1 was attenuated, and after adjusting for baseline FEV_1, both results were nonsignificant (e-Fig 1). Interactions by spirometric category were

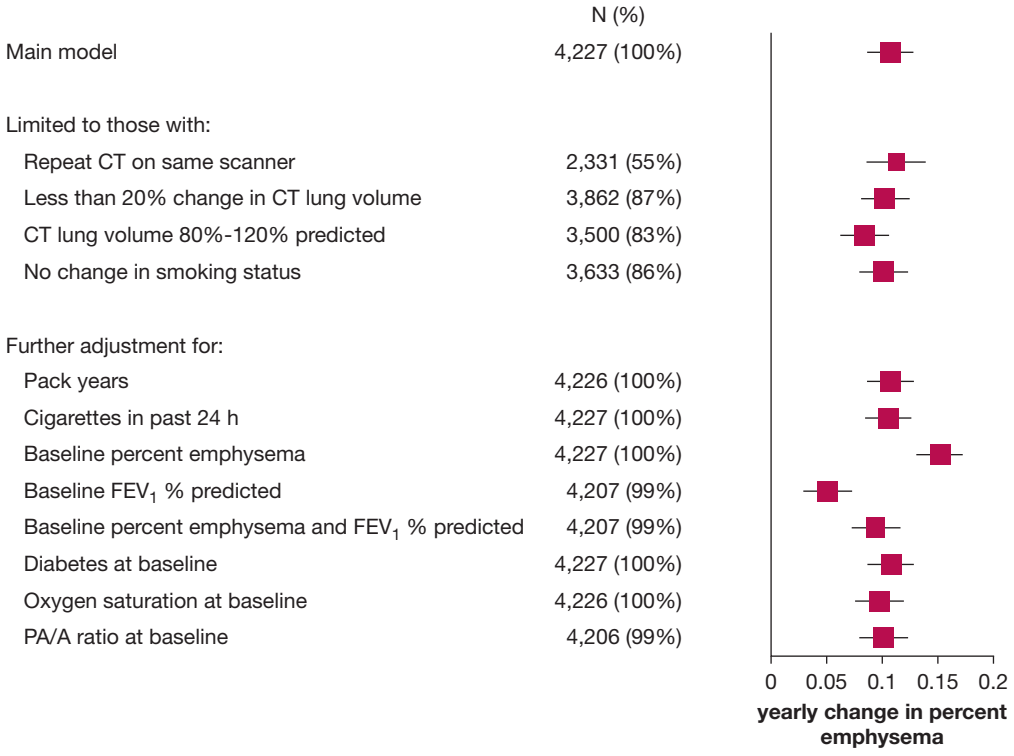

Figure 3 – *Sensitivity analyses of the mean difference in yearly progression of percentage of lung volume with attenuation < –950 Hounsfield units for a 1-SD increase in arterial pruning (decrease in volume of pulmonary arteries less than 5 mm^2 in cross-sectional area per total arterial volume of interparenchymal vessels). Model adjusts for baseline age, sex, race, education, and COPD status and time-varying height, weight, smoking status, and scanner terms. PA/A = pulmonary artery diameter to aorta diameter ratio.*

present for both percentage change and absolute change in FEV_1, and the most divergent findings were in those with COPD (e-Table 9). In addition, results for absolute change in FEV_1 differed by baseline FEV_1 ($P = .079$ for interaction), whereas those for percentage FEV_1 did not (e-Table 9). No significant associations were found between pulmonary venous pruning and change in any measure of lung function.

Discussion

A higher degree of pulmonary arterial pruning was associated with a faster longitudinal progression of percent $emphysema_{-950}$ over 5 years in ever smokers in the COPDGene Study. These results were consistent using alternate measures of vascular pruning and PD15 instead of percent emphysema, and when limited to those with both CT scans obtained with the same scanner. Over the same period, pulmonary arterial pruning was associated with a faster decline in FEV_1 to FVC ratio. Together, these results suggest that in smokers, pulmonary arterial structure may be relevant in the progression of emphysema and COPD.

Pulmonary vascular differences have been demonstrated in COPD, with a loss of pulmonary capillaries seen in excised emphysematous lung specimens compared with control specimens.[13,14] Imaging studies also have found reduced pulmonary microvascular perfusion on MRI and vascular pruning on CT imaging in COPD and emphysema.[15,16,31,32] In 74 participants with COPD, Saruya et al[33] found a moderate correlation ($r = -0.46$) between an increase in percent emphysema and decrease in volume of small vessels ($< 5\ mm^2$) over 3 years on axial CT scan slices; however, this was not replicated in another study by the same group.[34] In the present study, we found that baseline vascular, particularly arterial, differences on CT imaging were associated with a faster longitudinal progression of percent emphysema and loss of lung function that was robust to adjustment for multiple covariates.

Pulmonary vascular pruning may be the result of vascular injury, pulmonary vasoconstriction, or hyperinflation and gas trapping with compression of the vessels. Although this study cannot determine the cause, several potential mechanisms may link vascular pruning to progression of percent emphysema or decline in lung function. First, vascular pruning may impede the augmentation of pulmonary blood flow usually seen in infection, resulting in fewer cellular mediators to fight infection and aid in resolving lung injury.[11,35] Second, pulmonary vascular pruning may reflect endothelial dysfunction or activation, leading to increased recruitment of inflammatory cells.[36] Third, arterial pruning may impact capillary blood flow directly, leading to a slower transit of neutrophils or activated platelets through the pulmonary vasculature, leading to more inflammation.[37-40] Further evaluation of the vasculature, and these potentially related pathways, may lead to a better understanding of disease progression.

We found interactions in almost every category for the effect of arterial pruning on the progression of percent emphysema, with greater magnitude results in those with more emphysema, older individuals, and former smokers, and lower magnitude results in women, obese individuals, and Black people. It is not unexpected to see faster emphysema progression in those with more baseline emphysema, because it may reflect disease susceptibility and may be a similar relative increase, and this also may explain the greater magnitude results seen in older participants. Stronger associations in former smokers compared with current smokers may be the result of acute changes in lung attenuation with smoking[41,42] or differences in the pulmonary vasculature, because current smokers and those with greater air pollution exposures show an increase in the volume of smaller pulmonary vessels instead of the decrease seen in emphysema and COPD.[43,44] The interactions by sex and obesity may relate to pulmonary vascular disease, which is more common in women and obese individuals,[45,46] and emphysema progression, which was found to be faster in women and slower in obese individuals.[47] Racial differences also have been described in pulmonary hypertension and in the extent of emphysema.[20,48] At baseline less arterial pruning was seen in women, and more was seen in obese individuals and Black people. However, more work is needed to understand fully how these factors relate to pulmonary arterial pruning and to modify the relationship between pruning and emphysema progression.

Results for FEV_1 differed when assessed by percentage and absolute change, and both results were nonsignificant after adjusting for baseline FEV_1, leading us to interpret an overall null result for FEV_1. The most divergent results were in those with COPD and those with a low baseline FEV_1 and in participants who have

more arterial pruning and a smaller absolute change in FEV_1 compared with those with normal lung function. Although it is used less commonly, percentage change in FEV_1 has been reported to be more reliable than absolute change,[49] and our findings for FEV_1 to FVC ratio, where FEV_1 is normalized to FVC, are more consistent with results for percentage change in FEV_1.

Although this was a large prospective observational study of smokers with and without COPD, is has several limitations. First, noncontrast CT scan measures of the pulmonary vasculature do not include the microvasculature, and it is an aggregate measure of the entire lung or lobe. Further, the lower ratio (BV5a to TBVa) that we call "pruning" may reflect loss, narrowing, or decreased filling of smaller vessels, or even proximal vessel dilation. Nonetheless, BV5a has been correlated with small vessels on histologic analysis and BV5 was correlated with pulmonary perfusion by scintigraphy.[24,25] We found very similar results in analyses in which BV5a was normalized to the total lung volume instead of TBVa, and also when evaluating BV5a by itself while adjusting for TBVa. Adjusting for pulmonary artery to aorta ratio showed no significant impact on our results, suggesting that proximal artery dilation was not an explanation for our findings. Although results for emphysema and vascular pruning were similar when restricted to a specific lobe, further studies are needed to understand whether arterial pruning predicts localized progression of emphysema.

Second, the clinical implications of change in percent $emphysema_{-950}$ on CT scan is uncertain, and the magnitude of change in FEV_1 to FVC ratio and FEV_1 related to arterial pruning were small. However, the reported average difference in emphysema progression resulting from arterial pruning was 0.55 percentage points over the 5-year study, representing a 40% faster rate of emphysema progression. Because percent emphysema has been linked to increased mortality,[7,50] even this magnitude change may be important. The changes in lung function were more modest, with an approximately 15% faster decline in FEV_1 to FVC ratio.

Third, selection bias is possible because of loss to follow-up that impacted inclusion in the longitudinal study sample. Those not included in the study were more likely to have COPD, emphysema, and pulmonary arterial pruning; however, those with COPD at baseline constituted 41% of the current sample, and results were of greater magnitude among that group. Although we cannot exclude the possibility of bias, it is unlikely to have led to significant bias in our findings.

Fourth, although the longitudinal study design allows us to make some inference as to causality, pulmonary vascular pruning has been associated with more severe emphysema and airflow obstruction in cross-sectional studies,[16] making baseline lung disease a possible confounder. Because we used a random intercept, we did not adjust for baseline values of the dependent variable in the main models, but did explore this in sensitivity analyses. In the emphysema analysis, results were of greater magnitude with adjustment for baseline percent $emphysema_{-950}$ and were attenuated, but still significant, with adjustment for baseline FEV_1. Further, the emphysema findings remained significant when considering only those with percent $emphysema_{-950}$ of $< 5\%$ and those without COPD. After adjustment for baseline values, both FEV_1 results were null, whereas results for decline in FEV_1 to FVC ratio were of greater magnitude.

Finally, measures of emphysema used a threshold-based technique, and differences in protocol among the different sites and scanner changes may have impacted the results. The coefficient of variation for repeat CT scans in the COPDGene Study was 16%, in part because of differences in inhalation. We showed similar results in analyses restricted to those whose CT scans were obtained with the same scanner and without a large change in lung volume. We also showed similar results for measures of lung density at the lower 15th percentile (PD15) with lung volume correction.

In conclusion, greater pulmonary arterial pruning was associated with a faster progression of percent $emphysema_{-950}$ and decline in FEV_1 to FVC ratio over 5 years among ever smokers with and without COPD in the COPDGene Study. This study adds to prior data suggesting that the pulmonary vasculature may be important in emphysema and COPD, and further study of small pulmonary arteries and vascular pruning may yield insights into disease progression.

Acknowledgments

Author contributions: C. L. P. is the guarantor of the manuscript, responsible for the content of this manuscript, including the data and analysis. C. L. P., G. R. W., and R. S. J. E. conceived and designed the study. S. Y. A., C. E. C., A. A. D., J. E. H., G. L. K., P. N., F. N. R., R. G. B., J. P. S., K. A. Y., R. C. W., and J. M. W. collected the data. C. L. P., G. R. W., and R. S. J. E. analyzed and interpreted the data and guarantee the data. C. L. P. drafted the manuscript. All authors critically revised and approved the final manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: C. L. P. received research grants from the Alpha1 Foundation and Boehringer Ingelheim and personal fees from Lancet Respiratory Medicine and Horizon CME. S. Y. A. received a research grant from the Pulmonary Fibrosis Foundation and an ownership distribution from Quantitative Imaging Solutions. R. G. B. received research grants from the Foundation for the NIH and COPD Foundation. J. M. W. received research grants from Vertex Pharmaceuticals, Inc., Bayer AG, ARCUS-MED, LLC, and Mereo BioPharma and personal fees from GlaxoSmithKline, Boehringer Ingelheim, and Takeda. G. R. W. received research grants from Boehringer Ingelheim, BTG Interventional Medicine, and Janssen Pharmaceuticals and personal fees from Boehringer Ingelheim, PulmonX, Janssen Pharmaceuticals, and GlaxoSmithKline. R. S. J. E. received personal fees from Toshiba, Boehringer Ingelheim, Eolo Medical, and Leuko Labs. R. S. J. E. and G. R. W. are founders and co-owners of Quantitative Imaging Solutions, a company that provides image-based consulting and develops software to enable data sharing. None declared (P. N., C. E. C., A. A. D., F. N. R., K. A. Y., G. L. K., J. P. S., R. C. W., and J. E. H.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

* **COPDGene Investigators: Core Units**–*Administrative Center*: James D. Crapo, MD (PI); Edwin K. Silverman, MD, PhD (PI); Barry J. Make, MD; Elizabeth A. Regan, MD, PhD; *Genetic Analysis Center*: Terri H. Beaty, PhD; Peter J. Castaldi, MD, MSc; Michael H. Cho, MD, MPH; Dawn L. DeMeo, MD, MPH; Adel El Boueiz, MD, MMSc; Marilyn G. Foreman, MD, MS; Auyon Ghosh, MD; Lystra P. Hayden, MD, MMSc; Craig P. Hersh, MD, MPH; Jacqueline Hetmanski, MS; Brian D. Hobbs, MD, MMSc; John E. Hokanson, MPH, PhD; Wonji Kim, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD; Merry-Lynn McDonald, PhD; Dmitry Prokopenko, PhD; Matthew Moll, MD, MPH; Jarrett Morrow, PhD; Dandi Qiao, PhD; Elizabeth A. Regan, MD, PhD; Aabida Saferali, PhD; Phuwanat Sakornsakolpat, MD; Edwin K. Silverman, MD, PhD; Emily S. Wan, MD; Jeong Yun, MD, MPH; *Imaging Center*: Juan Pablo Centeno; Jean-Paul Charbonnier, PhD; Harvey O. Coxson, PhD; Craig J. Galban, PhD; MeiLan K. Han, MD, MS; Eric A. Hoffman, Stephen Humphries, PhD; Francine L. Jacobson, MD, MPH; Philip F. Judy, PhD; Ella A. Kazerooni, MD; Alex Kluiber; David A. Lynch, MB; Pietro Nardelli, PhD; John D. Newell, Jr, MD; Aleena Notary; Andrea Oh, MD; Elizabeth A. Regan, MD, PhD; James C. Ross, PhD; Raul San Jose Estepar, PhD; Joyce Schroeder, MD; Jered Sieren; Berend C. Stoel, PhD; Juerg Tschirren, PhD; Edwin Van Beek, MD, PhD; Bram van Ginneken, PhD; Eva van Rikxoort, PhD; Gonzalo Vegas Sanchez- Ferrero, PhD; Lucas Veitel; George R. Washko, MD; Carla G. Wilson, MS; *PFT QA Center, Salt Lake City, UT*: Robert Jensen, PhD; *Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO*: Douglas Everett, PhD; Jim Crooks, PhD; Katherine Pratte, PhD; Matt Strand, PhD; Carla G. Wilson, MS; *Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO*: John E. Hokanson, MPH, PhD; Erin Austin, PhD; Gregory Kinney, MPH, PhD; Sharon M. Lutz, PhD; Kendra A. Young, PhD; *Mortality Adjudication Core:* Surya P. Bhatt, MD; Jessica Bon, MD; Alejandro A. Diaz, MD, MPH; MeiLan K. Han, MD, MS; Barry Make, MD; Susan Murray, ScD; Elizabeth Regan, MD; Xavier Soler, MD; Carla G. Wilson, MS; *Biomarker Core*: Russell P. Bowler, MD, PhD; Katerina Kechris, PhD; Farnoush Banaei-Kashani, PhD; **Clinical Centers**–*Ann Arbor VA:* Jeffrey L. Curtis, MD; Perry G. Pernicano, MD; *Baylor College of Medicine, Houston, TX*: Nicola Hanania, MD, MS; Mustafa Atik, MD; Aladin Boriek, PhD; Kalpatha Guntupalli, MD; Elizabeth Guy, MD; Amit Parulekar, MD; *Brigham and Women's Hospital, Boston, MA*: Dawn L. DeMeo, MD, MPH; Craig Hersh, MD, MPH; Francine L. Jacobson, MD, MPH; George Washko, MD; *Columbia University, New York, NY*: R. Graham Barr, MD, DrPH; John Austin, MD; Belinda D'Souza, MD; Byron Thomashow, MD; *Duke University Medical Center, Durham, NC*: Neil MacIntyre, Jr., MD; H. Page McAdams, MD; Lacey Washington, MD; *HealthPartners Research Institute, Minneapolis, MN*; Charlene McEvoy, MD, MPH; Joseph Tashjian, MD; *Johns Hopkins University, Baltimore, MD*: Robert Wise, MD; Robert Brown, MD; Nadia N. Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS; *Lundquist Institute for Biomedical Innovation at Harbor UCLA Medical Center, Torrance, CA*: Richard Casaburi, PhD, MD; Alessandra Adami, PhD; Matthew Budoff, MD; Hans Fischer, MD; Janos Porszasz, MD, PhD; Harry Rossiter, PhD; William Stringer, MD; *Michael E. DeBakey VAMC, Houston, TX*: Amir Sharafkhaneh, MD, PhD; Charlie Lan, DO; *Minneapolis VA:* Christine Wendt, MD; Brian Bell, MD; Ken M. Kunisaki, MD, MS; *Morehouse School of Medicine, Atlanta, GA*: Eric L. Flenaugh, MD; Hirut Gebrekristos, PhD; Mario Ponce, MD; Silanath Terpenning, MD; Gloria Westney, MD, MS; *National Jewish Health, Denver, CO*: Russell Bowler, MD, PhD; David A. Lynch, MB; *Reliant Medical Group, Worcester, MA*: Richard Rosiello, MD; David Pace, MD; *Temple University, Philadelphia, PA:* Gerard Criner, MD; David Ciccolella, MD; Francis Cordova, MD; Chandra Dass, MD; Gilbert D'Alonzo, DO; Parag Desai, MD; Michael Jacobs, PharmD; Steven Kelsen, MD, PhD; Victor Kim, MD; A. James Mamary, MD; Nathaniel Marchetti, DO; Aditi Satti, MD; Kartik Shenoy, MD; Robert M. Steiner, MD; Alex Swift, MD; Irene Swift, MD; Maria Elena Vega-Sanchez, MD; *University of Alabama, Birmingham, AL:* Mark Dransfield, MD; William Bailey, MD; Surya P. Bhatt, MD; Anand Iyer, MD; Hrudaya Nath, MD; J. Michael Wells, MD; *University of California, San Diego, CA*: Douglas Conrad, MD; Xavier Soler, MD, PhD; Andrew Yen, MD; *University of Iowa, Iowa City, IA*: Alejandro P. Comellas, MD; Karin F. Hoth, PhD; John Newell, Jr., MD; Brad Thompson, MD; *University of Michigan, Ann Arbor, MI:* MeiLan K. Han, MD MS; Ella Kazerooni, MD MS; Wassim Labaki, MD MS; Craig Galban, PhD; Dharshan Vummidi, MD; *University of Minnesota, Minneapolis, MN*: Joanne Billings, MD; Abbie Begnaud, MD; Tadashi Allen, MD; *University of Pittsburgh, Pittsburgh, PA*: Frank Sciurba, MD; Jessica Bon, MD; Divay Chandra, MD, MSc; Joel Weissfeld, MD, MPH; University of Texas Health.

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

References

1. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788.
2. Xu J, Murphy SL, Kochanek KD, Arias E. *Mortality in the United States, 2018*. NCHS Data Brief; 2020 Jan(355):1-8.
3. Castaldi PJ, Benet M, Petersen H, et al. Do COPD subtypes really exist? COPD heterogeneity and clustering in 10 independent cohorts. *Thorax*. 2017;72(11):998-1006.
4. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*. 2001;163(5):1256-1276.
5. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med*. 2011;365(13):1184-1192.
6. McAllister DA, Ahmed FS, Austin JH, et al. Emphysema predicts hospitalisation and incident airflow obstruction among older smokers: a prospective cohort study. *PLoS One*. 2014;9(4):e93221.

7. Johannessen A, Skorge TD, Bottai M, et al. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med*. 2013;187(6):602-608.
8. Voelkel NF, Cool CD. Pulmonary vascular involvement in chronic obstructive pulmonary disease. *Eur Resp J Suppl*. 2003;46:28s-32s.
9. Peinado VI, Pizarro S, Barbera JA. Pulmonary vascular involvement in COPD. *Chest*. 2008;134(4):808-814.
10. Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am J Physiol*. 1998;274(6 pt 1):L908-L913.
11. Peinado VI, Ramirez J, Roca J, Rodriguez-Roisin R, Barbera JA. Identification of vascular progenitor cells in pulmonary arteries of patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2006;34(3):257-263.
12. Kasahara Y, Tuder RM, Taraseviciene-Stewart L, et al. Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. *J Clin Invest*. 2000;106(11):1311-1319.
13. Reid JA, Heard BE. The capillary network of normal and emphysematous human lungs studied by injections of indian ink. *Thorax*. 1963;18:201-212.
14. Liebow AA. Pulmonary emphysema with special reference to vascular changes. *Am Rev Respir Dis*. 1959;80(1 part 2):67-93.
15. Hueper K, Vogel-Claussen J, Parikh MA, et al. Pulmonary microvascular blood flow in mild chronic obstructive pulmonary disease and emphysema. The MESA COPD Study. *Am J Respir Crit Care Med*. 2015;192(5):570-580.
16. Estepar RS, Kinney GL, Black-Shinn JL, et al. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. *Am J Respir Crit Care Med*. 2013;188(2):231-239.
17. Nardelli P, Jimenez-Carretero D, Bermejo-Pelaez D, et al. Pulmonary artery-vein classification in CT images using deep learning. *IEEE Trans Med Imaging*. 2018;37(11):2428-2440.
18. Regan EA, Hokanson JE, Murphy JR, et al. Genetic Epidemiology of COPD (COPDGene) study design. *COPD*. 2010;7(1):32-43.
19. Stoel BC, Putter H, Bakker ME, et al. Volume correction in computed tomography densitometry for follow-up studies on pulmonary emphysema. *Proc Am Thorac Soc*. 2008;5(9):919-924.
20. Hoffman EA, Ahmed FS, Baumhauer H, et al. Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample. The MESA Lung Study. *Ann Am Thorac Soc*. 2014;11(6):898-907.
21. Ross JC, Kindlmann GL, Okajima Y, et al. Pulmonary lobe segmentation based on ridge surface sampling and shape model fitting. *Med Phys*. 2013;40(12):121903.
22. Kindlmann GL, San Jose Estepar R, Smith SM, Westin CF. Sampling and visualizing creases with scale-space particles. *IEEE Trans Vis Comput Graph*. 2009;15(6):1415-1424.
23. Estepar RS, Ross JC, Krissian K, Schultz T, Washko GR, Kindlmann GL. Computational vascular morphometry for the assessment of pulmonary vascular disease based on scale-space particles. *Proc IEEE Int Symp Biomed Imaging*. 2012:1479-1482.
24. Rahaghi FN, Argemí G, Nardelli P, et al. Pulmonary vascular density: comparison of findings on computed tomography imaging with histology. *Eur Resp J*. 2019;54(2):1900370.
25. Matsuoka S, Yamashiro T, Matsushita S, et al. Relationship between quantitative CT of pulmonary small vessels and pulmonary perfusion. *AJR Am J Roentgenol*. 2014;202(4):719-724.
26. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med*. 2012;367(10):913-921.
27. Wells JM, Iyer AS, Rahaghi FN, et al. Pulmonary artery enlargement is associated with right ventricular dysfunction and loss of blood volume in small pulmonary vessels in chronic obstructive pulmonary disease. *Circ Cardiovasc Imaging*. 2015;8(4):e002546.
28. LaFon DC, Bhatt SP, Labaki WW, et al. Pulmonary artery enlargement and mortality risk in moderate to severe COPD: results from COPDGene. *Eur Resp J*. 2020;55(2):1901812.
29. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152(3):1107-1136.
30. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555.
31. Scarrow GD. The pulmonary angiogram in chronic bronchitis and emphysema. *Proc R Soc Med*. 1965;58(9):684-687.
32. Iyer KS, Newell JD Jr, Jin D, et al. Quantitative dual-energy computed tomography supports a vascular etiology of smoking-induced inflammatory lung disease. *Am J Respir Crit Care Med*. 2016;193(6):652-661.
33. Saruya S, Matsuoka S, Yamashiro T, et al. Quantitative CT measurements of small pulmonary vessels in chronic obstructive pulmonary disease: do they change on follow-up scans? *Clin Physiol Funct Imaging*. 2016;36(3):211-217.
34. Takayanagi S, Kawata N, Tada Y, et al. Longitudinal changes in structural abnormalities using MDCT in COPD: do the CT measurements of airway wall thickness and small pulmonary vessels change in parallel with emphysematous progression? *Int J Chron Obstr Pulmon Dis*. 2017;12:551-560.
35. Hoffman EA, Simon BA, McLennan G. State of the Art. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006;3(6):519-532.
36. Liao JK. Linking endothelial dysfunction with endothelial cell activation. *J Clin Invest*. 2013;123(2):540-541.
37. Selby C, Drost E, Lannan S, Wraith PK, MacNee W. Neutrophil retention in the lungs of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1991;143(6):1359-1364.
38. Doerschuk CM. Mechanisms of leukocyte sequestration in inflamed lungs. *Microcirculation*. 2001;8(2):71-88.
39. Ekpenyong AE, Toepfner N, Fiddler C, et al. Mechanical deformation induces depolarization of neutrophils. *Sci Adv*. 2017;3(6):e1602536.
40. Eichhorn ME, Ney L, Massberg S, Goetz AE. Platelet kinetics in the pulmonary microcirculation in vivo assessed by intravital microscopy. *J Vasc Res*. 2002;39(4):330-339.
41. Remy-Jardin M, Remy J, Gosselin B, Becette V, Edme JL. Lung parenchymal changes secondary to cigarette smoking: pathologic-CT correlations. *Radiology*. 1993;186(3):643-651.
42. Karimi R, Tornling G, Forsslund H, et al. Lung density on high resolution computer tomography (HRCT) reflects degree of inflammation in smokers. *Respir Res*. 2014;15(1):23.
43. Aaron CP, Hoffman EA, Lima JAC, et al. Pulmonary vascular volume, impaired left ventricular filling and dyspnea: the MESA Lung Study. *PLoS One*. 2017;12(4):e0176180.
44. Aaron CP, Hoffman EA, Kawut SM, et al. Ambient air pollution and pulmonary vascular volume on computed tomography: the MESA Air Pollution and Lung cohort studies. *Eur Resp J*. 2019;53(6):1802116.
45. Frank RC, Min J, Abdelghany M, et al. Obesity is associated with pulmonary hypertension and modifies outcomes. *J Am Heart Assoc*. 2020;9(5):e014195.
46. Docherty CK, Harvey KY, Mair KM, Griffin S, Denver N, MacLean MR. The role of sex in the pathophysiology of pulmonary hypertension. *Adv Exp Med Biol*. 2018;1065:511-528.
47. Coxson HO, Dirksen A, Edwards LD, et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE Study. *Lancet Respir Med*. 2013;1(2):129-136.
48. Al-Naamani N, Paulus JK, Roberts KE, et al. Racial and ethnic differences in pulmonary arterial hypertension. *Pulm Circ*. 2017;7(4):793-796.
49. Thomsen LH, Dirksen A, Shaker SB, Skovgaard LT, Dahlbäck M, Pedersen JH. Analysis of FEV1 decline in relatively healthy heavy smokers: implications of expressing changes in FEV1 in relative terms. *COPD*. 2014;11(1):96-104.
50. Oelsner EC, Hoffman EA, Folsom AR, et al. Association of emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Ann Intern Med*. 2014;161(12):863-873.