CHEST

CT Emphysema Subtypes and Cardiac Hemodynamics Estimated on MRI

The Multi-Ethnic Study of Atherosclerosis COPD Study

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BACKGROUND: COPD is traditionally associated with pulmonary hypertension, but treatments targeting elevated pulmonary artery pressure in COPD have largely failed, possibly due to an incomplete understanding of subphenotypes of the disease.

RESEARCH QUESTION: Are novel machine-learned CT emphysema subtypes associated with specific cardiac hemodynamic profiles?

STUDY DESIGN AND METHODS: The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited participants with and without COPD aged 50 to 79 years with ≥ 10 pack-years of smoking and without clinical cardiovascular disease, predominantly from MESA and a lung cancer screening cohort. COPD and COPD severity were defined by standard spirometric criteria. CT emphysema subtypes were defined by unsupervised machine learning in an independent study and labeled on chest CT scans. Hemodynamics were estimated on cardiac MRI using validated equations. Linear regression models were weighted by the inverse probability of sampling and adjusted for potential confounders.

RESULTS: The mean age of the 300 participants was 68 ± 7 years, 60% were male, 28% currently smoked, and 47% had COPD (45% of mild and 41% of moderate severity). More severe COPD was associated with lower estimated pulmonary arterial wedge pressure (ePAWP; P trend = .02) and greater estimated pulmonary vascular resistance (ePVR; P trend = .03) but not estimated pulmonary artery pressure (ePAP; P trend = 0.83). Only the combined bronchitic-apical emphysema subtype was associated with greater ePAP (1.08 mm Hg/10%; 95% CI, 0.40-1.75). The diffuse emphysema subtype was associated with lower ePAWP (–0.49 mm Hg/10%; 95% CI, –0.75 to –0.24) and greater ePVR (0.36 Wood units/10%; 95% CI, 0.10-0.61).

INTERPRETATION: In this case-control study of predominantly mild-moderate COPD, greater ePAP was specific to the combined bronchitic-apical emphysema subtype whereas the diffuse emphysema subtype and COPD severity were associated with lower ePAWP and greater ePVR. The CT emphysema subtype findings suggest more precise avenues to therapeutic interventions in cardiopulmonary dysfunction. CHEST 2025; 168(2):364-378

KEY WORDS: COPD; emphysema; pulmonary hypertension; pulmonary vascular resistance

Take-Home Points

Study Question: Do novel, machine-learned CT emphysema subtypes provide insights into cardiopulmonary dysfunction in COPD, particularly in light of findings suggesting that left ventricular underfilling is more common than pulmonary hypertension in contemporary COPD?

Results: COPD severity was associated with lower estimated pulmonary arterial wedge pressure (ePAWP) and greater estimated pulmonary vascular resistance (ePVR), while combined bronchitic-apical emphysema was associated with greater estimated pulmonary artery pressure (ePAP) and diffuse emphysema was associated with lower ePAWP and greater ePVR.

Interpretation: The predominant hemodynamic alterations in mild-moderate COPD seen in this study were a reduction in ePAWP and an increase in ePVR without an increase in ePAP, suggesting that novel CT emphysema subtypes may provide precise avenues for potential therapeutic interventions targeting cardiopulmonary dysfunction in COPD.

COPD was the third leading cause of death worldwide in 2019 and is associated with significant morbidity.[1] COPD is defined as airflow limitation on spirometry that does not fully reverse with a bronchodilator.[2] More than 10% of adults over the age of 40 years meet spirometric criteria for COPD, approximately 90% with mild-moderate COPD.[3]

The classic cardiac complication of COPD is cor pulmonale, or right ventricular (RV) hypertrophy, due to elevated pulmonary artery pressure (PAP).[4] Elevated PAP in COPD of any severity is associated with mortality, but contemporary studies suggest the predominant cardiac complication in COPD is underfilling of the left ventricle (LV) with a small RV.[5-7] Moreover, elevated pulmonary vascular resistance (PVR) is associated with greater mortality risk than cor pulmonale in COPD.[8] A classic study suggested that "bronchial" COPD was associated with elevated PAP, and that "emphysematous" COPD was associated with elevated PVR without change in PAP[9]; however, these subtypes have largely been discarded; inferences based on cardiac hemodynamics in contemporary COPD are limited by the invasive nature of right heart catheterization, leaving uncertainty about hemodynamic changes in patients with COPD in the community, particularly those with mild-moderate disease.

COPD overlaps partially with emphysema, which is defined anatomically as destruction of pulmonary parenchyma.[2,10] Emphysema is common in the general population and predicts morbidity and mortality in individuals with and without COPD.[11,12] Historically categorized as centrilobular, panlobular, or paraseptal, more recent large-scale unsupervised machine learning identified 6 highly reproducible emphysema subtypes on CT scanning.[2,13-16] The 2 most common subtypes, combined bronchitic-apical emphysema (CBaE) and diffuse emphysema, bore clinical resemblance to classic descriptions of "bronchial" and "emphysematous" COPD.[16,17] The CBaE subtype was associated with a variant near a gene implicated in exaggerated hypoxic pulmonary vasoconstriction[16]; the diffuse emphysema subtype was associated with loss of pulmonary microvascular volume.[16,18] These observations suggest distinct cardiac hemodynamic profiles.

ABBREVIATIONS: CBaE = combined bronchitic-apical emphysema; CPFE = combined pulmonary fibrosis and emphysema; EMCAP = Emphysema and Cancer Action Project; ePAP = estimated pulmonary artery pressure; ePAWP = estimated pulmonary arterial wedge pressure; ePVR = estimated pulmonary vascular resistance; fSAD = functional small-airway disease; LA = left atrial; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; PA = pulmonary artery; PAP = pulmonary artery pressure; PH = pulmonary hypertension; PMBF = pulmonary microvascular blood flow; PMBV = pulmonary microvascular blood volume; PVR = pulmonary vascular resistance; RCT = randomized control trial; RV = right ventricle; RV/TLC = residual volume/total lung capacity; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study

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We therefore estimated cardiac hemodynamics on MRI using validated formulas in a community-based, case-control study of mild-to-moderate COPD to test hypotheses that the CBaE subtype is associated with greater estimated PAP (ePAP), whereas the diffuse emphysema subtype is associated with greater estimated PVR (ePVR).

Study Design and Methods

Study Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited participants with COPD and unmatched control participants from 4 of 6 sites of MESA, a population-based prospective cohort study of subclinical atherosclerosis; the Emphysema and Cancer Action Project (EMCAP), a lung cancer screening study; and the local community at 1 MESA site.[19,20] Participants with COPD from MESA and EMCAP were oversampled based on airflow limitation on earlier spirometry or emphysema on prior CT scan; control participants were sampled randomly. Inclusion criteria were age 50 to 79 years with ≥ 10 pack-years of smoking. Exclusion criteria were a clinical diagnosis of cardiovascular disease (coronary artery disease, congenital heart disease, valvular disease, and heart failure), asthma before age 45 years, other lung disease, cancer, weight > 300 lb, stage IIIb-V chronic kidney disease, and contraindications to MRI, gadolinium, or albuterol. Participants with spirometry, chest CT scan, and at least 1 estimated cardiac hemodynamic measure were included in this report.

COPD

Postbronchodilator spirometry was performed in accordance with American Thoracic Society/European Respiratory Society recommendations.[21] COPD was defined as a postbronchodilator FEV_1/FVC ratio < 0.70.[2] COPD severity was defined as mild (≥ 80% predicted FEV_1), moderate (50% ≤ predicted FEV_1 < 80%), and severe (FEV_1 < 50% predicted).[2] Control participants had a postbronchodilator FEV_1/FVC ratio ≥ 0.70. Global Lung Initiative race-neutral equations were used to calculate predicted values.[22]

CT Emphysema Subtypes and Percent Emphysema

Chest CT scans were acquired at full inspiration on multidetector scanners, in accordance with the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) protocol, with reconstructions at 0.75-mm slice thickness and, for non-MESA participants, fixed mAs (milliampere-seconds) of 200.[23] Lung segmentation was performed by anonymized readers at a single reading center using Apollo software (VIDA Diagnostics).

CT emphysema subtypes were defined previously using an unsupervised machine-learning algorithm that clustered emphysematous regions of lung based on their texture and anatomic location among more than 1.8 million emphysematous lung regions on 2,853 CT scans in SPIROMICS, an independent COPD case-control study.[16,24] Six CT emphysema subtypes were identified: CBaE, diffuse emphysema, senile emphysema, restrictive combined pulmonary fibrosis and emphysema (CPFE), obstructive CPFE, and vanishing lung.[16] Relevant voxels in the segmented lung of CT scans in the current study were labeled as a given subtype and are expressed as the percentage of lung with a given subtype. CT emphysema subtypes are continuous measures and may co-occur in individuals. The intraclass correlation coefficients of labeling on repeat CT scans acquired 6 weeks apart in SPIROMICS were 0.99, 0.94, 0.84, 0.97, 0.74, and 0.99, respectively.[25]

Percent emphysema was defined as the percentage of voxels within the lung with density < –950 Hounsfield units.[10] The scan-rescan intraclass correlation coefficient of percent emphysema, following this protocol, was 0.99.[25]

Cardiac MRI

Participants underwent MRI on one of four 1.5-T scanners (Signa LX [GE Healthcare]; Avanto or Espree [Siemens Medical Systems]). ECG-gated 2- and 4-chamber cine images of the heart with time resolution < 50 ms were acquired during breath-holding at functional residual capacity. The protocol included assessment of the pulmonary microvasculature following a bolus of 0.05 mmol/kg body weight Gd-DTPA (Magnevist; Berlex).[26]

MRI Analysis

MRI analysis was performed by independent anonymized analysts at a central reading center using CIM software for the LV and Qmass software (version 4.2; Medis) for the RV.[7,27] End-diastolic and end-systolic volumes were calculated using the Simpson rule by summation of areas on each slice multiplied by the sum of

slice thickness and image gap. Stroke volumes and ejection fractions were calculated from the end-diastolic and end-systolic volumes. Cardiac output (CO) was calculated by multiplying LV stroke volume by heart rate. Ventricular masses were determined at end diastole as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05 g/cm^3). Ventricular mass index (VMI) was defined as RV mass divided by LV mass. The interventricular septal angle was measured on mid-chamber short-axis cine images at the phase of maximal septal displacement on a DICOM viewer (OsiriX).[28] Maximal and minimal pulmonary artery (PA) areas were measured from PA flow images; PA area change was defined as maximal – minimal/minimal PA area. Left atrial (LA) area was estimated using the biplane area length method. LA volume index was calculated using the equation: (0.85 × LA area 2-chamber view × LA area 4-chamber view)/([LA length 2-chamber + LA length 4-chamber]/2) and normalized to body surface area.

Estimation of Cardiac Hemodynamics

Cardiac hemodynamics were estimated using the following formulas previously derived and validated by right heart catheterization.[29]

ePAP = interventricular septal angle × 0.31 + VMI × 11.5 + minimal PA area × 0.1 – PA relative area change × 0.22 – 21.806

Estimated pulmonary arterial wedge pressure (ePAWP) = 6.43 + LA index × 0.22

ePVR = (ePAP – ePAWP)/CO

ePAP estimated as above and dichotomized at a 25-mm Hg threshold for PH demonstrated a sensitivity of 92% and specificity of 80% for PH when compared with right heart catheterization.[29]

Other Measures

Age, sex, educational attainment, and race/ethnicity were self-reported, the latter by US Census 2000 definitions. Height, weight, blood pressure, and resting pulse oximetry were measured in accordance with the MESA protocol. Smoking history was self-reported; smoking status was confirmed by determination of plasma and urine cotinine (Immulite 2000 nicotine metabolite assay; Diagnostic Products). Seated blood pressure was measured with an automated oscillometric sphygmomanometer (Critikon; GE Healthcare) and hypertension defined according to the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[30] Diabetes was defined as a hemoglobin A1c level ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or use of diabetes medication. Fasting total and high-density lipoprotein levels were measured; low-density lipoprotein levels were calculated using the Friedewald equation. Medication inventory was performed. Sleep apnea was self-reported.

Airways were labeled from the trachea to subsegmental bronchi. Wall and lumen area were measured perpendicular to and averaged along the middle third of each airway, using a subvoxel resolution algorithm; within-participant averages across the segmental airways were used for analyses.[31]

Expiratory CT scans were acquired for a subset of participants and were coregistered to inspiratory scans using Apollo software, yielding a continuous metric of functional small-airway disease (fSAD).[25]

Pulmonary microvascular blood volume (PMBV) and flow (PMBF) were measured on gadolinium-enhanced MRI in the peripheral 2 cm of lung on a coronal slice at the level of the trachea.[26]

A subset of participants underwent determination of diffusing capacity and plethysmography, using an Autobox 220 (Sensormedics) and V6200 series (Viasys Healthcare), respectively.[32]

Statistical Methods

Data were summarized as mean ± SD or as median (interquartile range). Linear regression models included categories of COPD severity or continuous measures of CT emphysema subtypes as independent variables and continuous cardiac hemodynamic parameters as dependent variables. A test of trend across categories of COPD severity was performed using the Wald test. Models were weighted according to the inverse probability of enrollment into the MESA COPD Study.[27] Plots were generated and nonlinearity of associations was tested with generalized additive models using smoothing splines, robust errors, and the same sample weighting. Details are provided in the online Supplemental Material.

Minimally adjusted models included age, sex, race/ethnicity, height, weight, smoking status, pack-years of smoking, and recruitment cohort. Fully adjusted models also included educational attainment, systolic BP, diabetes, sleep apnea, oxygen saturation, and, for

CT emphysema subtype analyses, other CT emphysema subtypes. Missing data were minimal except for measures collected on a subset of participants, in which case analyses were restricted to that subset. All analyses were performed as complete-case analyses.

Sensitivity analyses included unweighted analyses, analyses restricted to participants sampled from MESA and EMCAP, tests of effect modification on a multiplicative scale, and analyses of Box-Cox-transformed CT emphysema subtypes to address unbalanced data distribution.

P values were 2-tailed with statistical significance defined as $P < .05$. Analyses were performed in SAS 9.3 (SAS Institute) and R version 2.24.1 (R Foundation).

Study Oversight

The institutional review boards of participating institutions (Columbia University, AAAA6484 and AAAA7791; Johns Hopkins University, STU00021057; Northwestern University, A34968; University of California, Los Angeles, 99-11-057-23B) and the National Heart, Lung, and Blood Institute approved the study procedures. Written informed consent was obtained from all participants.

Results

Of 338 MESA COPD participants, 320 completed cardiac MRI, 300 of whom had a CT scan and at least 1 estimated hemodynamic measure (Fig 1). The mean age of the 300 participants was 68 ± 7 years; 60% were male; the race/ethnic distribution was 54% White, 26% Black, 14% Hispanic, and 6% Asian; and 28% currently smoked cigarettes. Most participants were recruited from MESA (59%). Forty-seven percent had COPD (45% mild, 41% moderate, and 14% severe). The mean ePAP was 24 ± 3 mm Hg, mean ePAWP was 9 ± 2 mm Hg, and mean ePVR was 3.4 ± 1.5 Wood units.

Table 1 shows the characteristics of study participants stratified by COPD severity. Participants with severe COPD were more likely to be male and White and have a heavy smoking history compared with control participants without COPD. Participants with severe COPD also had greater percent emphysema, greater LV mass, lower LV stroke volume, and lower RV mass than control participants. Among those with plethysmography (n = 115), severely reduced diffusing capacity of the lungs for carbon monoxide and pulmonary hyperinflation were more prevalent among those with severe COPD. Participants with plethysmography were more likely to be White and currently smoke but were otherwise demographically similar to those without plethysmography (e-Table 1).

There was more CBaE and vanishing lung emphysema in severe COPD, whereas the diffuse emphysema subtype was reasonably evenly distributed. Distribution of participants with subtype-predominant disease across COPD severity is shown in e-Table 2 and co-occurrence of CT emphysema subtypes is shown in e-Table 3.

Missing data were minimal; the distribution of missing data is outlined in e-Table 4.

COPD Severity and Estimated Hemodynamics

There was no evidence that COPD severity was associated with greater ePAP (Table 2). Greater COPD severity was associated with lower ePAWP in crude and fully adjusted analyses (both *P* trend = .02) and with higher ePVR in crude and fully adjusted analyses (*P* trend = .02 and .03, respectively). Unweighted models demonstrated similar associations (e-Table 5), as did analyses restricted to participants recruited from MESA or EMCAP (ePAWP adjusted *P* trend = .04; ePVR adjusted *P* trend = .02).

CT Emphysema Subtypes and Estimated Hemodynamics

Greater CBaE was associated with greater ePAP, including after adjustment for co-occurrence of other CT emphysema subtypes (1.1 mm Hg/10%; 95% CI, 0.4-1.8; $P = .002$) (Table 3). This relationship was approximately linear over the range of CBaE in this study (Fig 2A). In contrast, CBaE was not associated with ePAWP or ePVR (Table 3; Figs 2C, 2E).

There was no effect modification of the association of CBaE with ePAP by sex, age, race/ethnicity, height, weight, smoking status, pack-years of smoking, educational attainment, hypertension, diabetes, sleep apnea, hypoxemia, β-blocker use, or recruitment cohort (e-Fig 1).

Diffuse emphysema was not associated with ePAP (Table 3) but was associated with lower ePAWP (–0.5 mm Hg/10%; 95% CI, –0.8 to –0.2; $P < .001$) and greater ePVR (0.4 Wood units/10%; 95% CI, 0.1-0.6; $P = .006$) in fully adjusted models adjusted for co-occurrence of other CT emphysema subtypes. These relationships were approximately linear (Figs 2D, 2F).

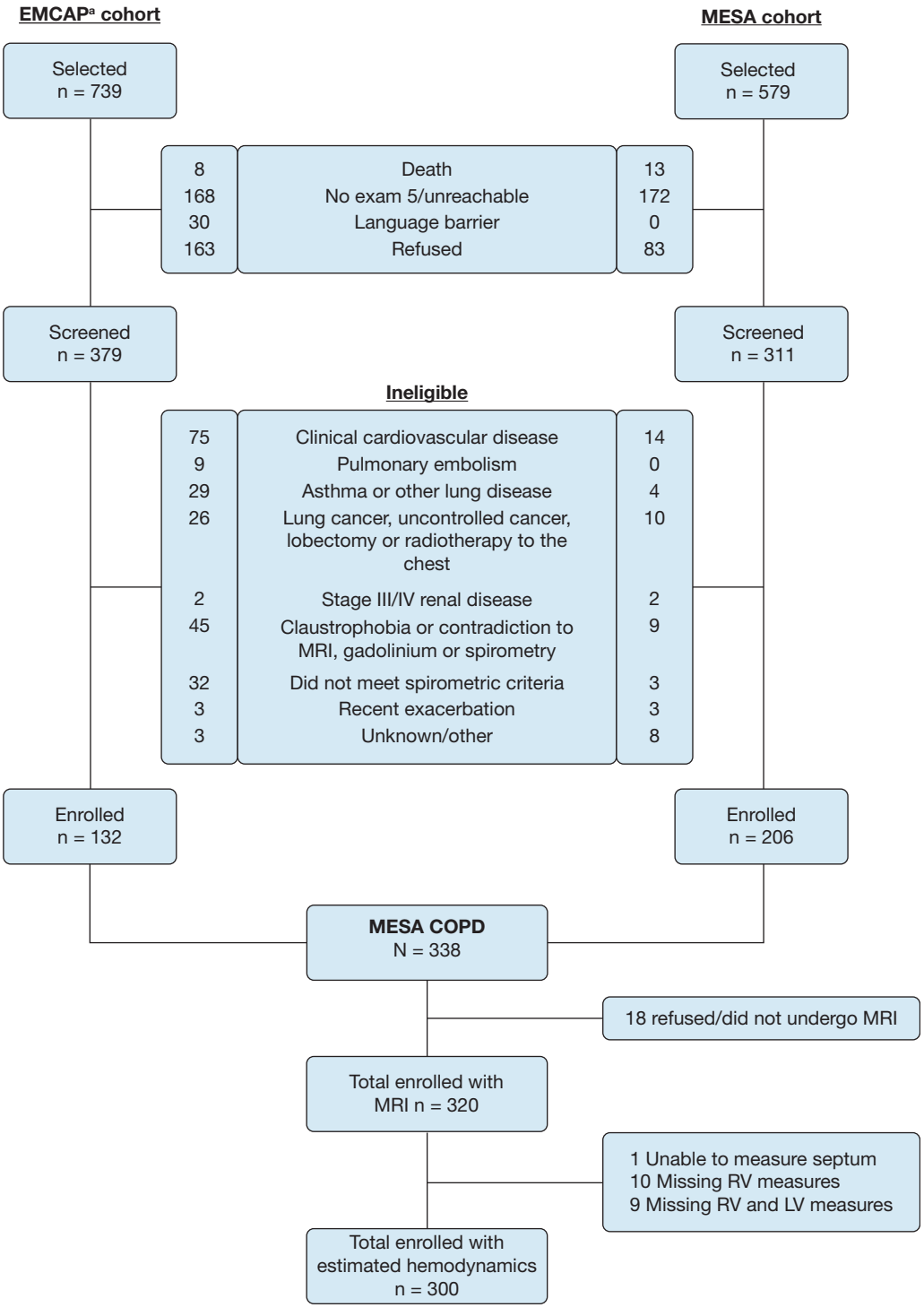

Figure 1 – *CONSORT diagram of participants in the MESA COPD Study. [a]The numbers for the EMCAP cohort include 40 participants recruited from the local community, 33 of whom underwent cardiac MRI and had estimated hemodynamics. CONSORT = Consolidated Standards of Reporting Trials; EMCAP = Emphysema and Cancer Action Project; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricle.*

Of other CT emphysema subtypes, vanishing lung emphysema was associated with lower ePAP (–2.1 mm Hg/10%; 95% CI, –3.7 to –0.8; $P = .002$), whereas senile and restrictive CPFE subtypes had a borderline association with lower ePAWP (Table 3).

TABLE 1] Characteristics of Participants (n = 300) in the MESA COPD Study, Stratified by COPD Severity

Characteristic	No COPD (n = 158)	COPD		
		Mild (n = 64)	Moderate (n = 58)	Severe (n = 20)
Age (mean ± SD), y	67 ± 7	69 ± 6	67 ± 8	69 ± 6
Sex (male)	86 (54)	46 (72)	35 (60)	14 (70)
Race/ethnicity				
White	70 (44)	52 (81)	27 (46)	14 (70)
Black	40 (25)	6 (9)	26 (44)	6 (30)
Hispanic	35 (22)	3 (5)	3 (5)	0 (0)
Asian	13 (8)	3 (5)	2 (3)	0 (0)
Educational attainment				
≤ High school degree	43 (27)	11 (17)	15 (26)	5 (25)
Some college	52 (33)	14 (22)	16 (28)	6 (30)
≥ College degree	63 (40)	39 (61)	27 (47)	9 (45)
Height (mean ± SD), cm	167 ± 10	172 ± 8	171 ± 10	169 ± 11
Weight (mean ± SD), kg	80 ± 17	79 ± 15	79 ± 18	81 ± 24
BMI (mean ± SD), kg/m^2	29 ± 5	27 ± 4	28 ± 4	30 ± 8
Pack-years of smoking, median (IQR)	27 (17, 43)	34 (24, 59)	39 (25, 52)	43 (25, 55)
Current smoking	34 (22)	12 (20)	26 (45)	2 (10)
Other cardiac risk factors				
LDL (n = 299) (mean ± SD), mg/L	111 ± 32	101 ± 28	99 ± 31	97 ± 40
Hypertension	72 (46)	26 (41)	32 (54)	10 (50)
Systolic BP (mean ± SD), mm Hg	121 ± 19	120 ± 16	125 ± 16	127 ± 14
Diastolic BP (mean ± SD), mm Hg	69 ± 10	70 ± 9	72 ± 10	75 ± 9
Diabetes mellitus	23 (15)	5 (8)	13 (22)	5 (25)
Sleep apnea	12 (8)	5 (8)	5 (9)	4 (20)
Medication use				
Statin	53 (34)	26 (44)	26 (45)	6 (30)
ACE inhibitors or angiotensin antagonists	27 (17)	11 (17)	16 (28)	5 (25)
Calcium channel blockers	19 (12)	7 (12)	10 (16)	8 (44)
β-blockers	13 (8)	9 (14)	10 (17)	1 (5)
Cardiac parameters, mean ± SD				
LV mass, mg	127 ± 33	129 ± 32	134 ± 40	135 ± 39
LV end-diastolic volume, mL	120 ± 31	122 ± 29	112 ± 30	107 ± 41
LV stroke volume, mL	73 ± 18	73 ± 17	67 ± 20	61 ± 22
Cardiac output, L/min	5.0 ± 1.3	4.9 ± 1.2	4.7 ± 1.3	4.6 ± 1.4
LV ejection fraction, %	62 ± 7	61 ± 8	60 ± 8	58 ± 7
RV mass, mg	23 ± 10	22 ± 8	21 ± 9	22 ± 9
Spirometry (mean ± SD), % predicted				
FVC	98 ± 15	107 ± 12	91 ± 13	75 ± 14
FEV_1	100 ± 16	92 ± 21	69 ± 8	41 ± 7
Other pulmonary function tests (n = 115), mean ± SD				
D_{LCO} (% predicted)	68 ± 11	63 ± 10	57 ± 16	38 ± 11
Residual volume (% predicted)	71 ± 18	84 ± 19	99 ± 29	138 ± 32
Residual volume-to-total lung capacity ratio (% predicted)	79 ± 17	84 ± 17	104 ± 23	139 ± 28

(Continued)

TABLE 1] *(Continued)*

Characteristic	No COPD (n = 158)	COPD		
		Mild (n = 64)	Moderate (n = 58)	Severe (n = 20)
Residual volume-to-total lung capacity ratio > 120%	0 (0)	0 (0)	8 (31)	10 (71)
Oxygenation saturation [median (IQR)], %	97 (96, 99)	97 (95, 98)	97 (96, 98)	96 (94, 97)
Percent emphysema (mean ± SD), %	1.8 ± 1.9	5.4 ± 4.8	5.1 ± 6.1	16.6 ± 12.3
CT emphysema subtypes (n = 289) (mean ± SD), %				
Combined bronchitic-apical emphysema	0.2 ± 0.5	2.4 ± 5.2	4.0 ± 7.9	24.7 ± 23.8
Diffuse emphysema	2.7 ± 6.8	10.8 ± 13.1	5.9 ± 9.5	11.0 ± 12.5
Senile emphysema	4.2 ± 6.7	5.1 ± 6.5	7.0 ± 7.9	7.6 ± 6.7
Restrictive CPFE	1.2 ± 2.9	1.2 ± 2.6	4.7 ± 8.9	6.5 ± 7.1
Obstructive CPFE	2.2 ± 4.7	1.5 ± 3.1	3.6 ± 4.8	2.9 ± 6.0
Vanishing lung	0.0 ± 0.0	0.1 ± 0.5	0.7 ± 3.3	4.8 ± 7.1

Data are presented as No. (%) unless otherwise indicated. ACE = angiotensin-converting enzyme; CPFE = combined pulmonary fibrosis and emphysema; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; IQR = interquartile range; LDL = low-density lipoprotein; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricle.

Unweighted analyses demonstrated similar associations for the CBaE and diffuse emphysema subtypes (e-Table 6), as did analyses restricted to participants recruited from the MESA and EMCAP studies (e-Table 7). Box-Cox transformation of CT emphysema subtypes yielded similar trends (e-Figs 2-4) as did generalized additive models with different levels of smoothing (e-Figs 5-7).

Other Emphysema Measures and Estimated Hemodynamics

Percent emphysema had a borderline association with greater ePAP (e-Table 8) (0.7 mm Hg/10%; 95% CI, 0.0, 1.5; $P = .045$) and was associated with lower ePAWP (–0.8 mm Hg ePAWP/10%; 95% CI, –1.4, –0.3; $P = .003$) and greater ePVR (0.7 Wood units ePVR/10%; 95% CI, 0.3, 1.1; $P < .001$).

TABLE 2] Associations of COPD Severity With Estimated Cardiac Hemodynamics

	No COPD	COPD			*P* Value
		Mild	Moderate	Severe	
ePAP, mm Hg					
n = 276	n = 147	n = 58	n = 54	n = 17	
Unadjusted	24.0	23.4	23.8	24.4	.95
Model 1, predicted mean	23.6	22.9	23.3	24.2	.84
Model 2, predicted mean	23.6	22.8	23.7	24.4	.83
ePAWP, mm Hg					
n = 296	n = 157	n = 63	n = 58	n = 18	
Unadjusted	9.0	8.6	8.4	7.8	.02
Model 1, predicted mean	9.3	9.0	8.8	7.7	.01
Model 2, predicted mean	9.2	8.9	8.5	7.4	.02
ePVR, Wood units					
n = 272	n = 146	n = 57	n = 53	n = 16	
Unadjusted	3.3	3.3	3.7	4.6	.02
Model 1, predicted mean	2.7	2.6	3.2	4.1	.04
Model 2, predicted mean	2.8	2.7	3.4	4.3	.03

Model 1 adjusted for age, sex, race/ethnicity, height, weight, smoking status, pack-years of smoking, and cohort. Model 2 adjusted for variables in model 1 in addition to education level, systolic BP, diabetes mellitus, low-density lipoprotein, sleep apnea, and oxygen saturation. ePAP = estimated pulmonary artery pressure; ePAWP = estimated pulmonary arterial wedge pressure; ePVR = estimated pulmonary vascular resistance.

TABLE 3] Associations of CT Emphysema Subtypes With Estimated Cardiac Hemodynamics

	Mean Difference per 10% CT Emphysema Subtype											
	Combined Bronchitic-Apical Emphysema β (95% CI)	*P* Value	Diffuse Emphysema β (95% CI)	*P* Value	Senile Emphysema β (95% CI)	*P* Value	Restrictive CPFE β (95% CI)	*P* Value	Obstructive CPFE β (95% CI)	*P* Value	Vanishing Lung Emphysema β (95% CI)	*P* Value
ePAP, mm Hg												
(n = 265)												
Unadjusted	0.4 (0.0, 0.9)	.04	0.4 (−0.0, 0.8)	.06	−0.1 (−0.7, 0.5)	.74	−0.4 (−1.0, 0.3)	.25	−0.8 (−1.7, 0.2)	.13	−0.3 (−2.1, 1.5)	.76
Model 1	0.9 (0.2, 1.5)	.01	0.3 (−0.1, 0.7)	.18	−0.1 (−0.7, 0.5)	.71	−0.2 (−0.9, 0.5)	.51	−0.8 (−1.8, 0.3)	.14	−0.3 (−1.9, 1.4)	.73
Model 2	1.1 (0.4, 1.8)	.002	0.1 (−0.3, 0.6)	.58	−0.3 (−1.1, 0.5)	.53	−0.4 (−1.1, 0.3)	.29	−0.5 (−1.8, 0.8)	.44	−2.1 (−3.7, −0.8)	.002
ePAWP, mm Hg												
(n = 284)												
Unadjusted	−0.1 (−0.5, 0.3)	.52	−0.6 (−0.8, −0.3)	< .001	−0.5 (−0.9, −0.2)	.003	−0.4 (−1.0, 0.1)	.14	−0.2 (−0.9, 0.5)	.58	−0.1 (−1.3, 1.2)	.94
Model 1	−0.2 (−0.6, 0.2)	.42	−0.6 (−0.9, −0.4)	< .001	−0.7 (−1.0, −0.4)	< .001	−0.7 (−1.3, −0.0)	.04	−0.5 (−1.2, 0.1)	.11	−0.0 (−1.2, 1.2)	.99
Model 2	0.2 (−0.2, 0.7)	.27	−0.5 (−0.8, −0.2)	< .001	−0.4 (−0.8, −0.0)	.049	−0.7 (−1.3, −0.0)	.04	0.1 (−0.7, 0.9)	.81	−0.5 (−1.9, 1.0)	.51
ePVR, Wood units												
(n = 261)												
Unadjusted	0.3 (−0.0, 0.7)	.07	0.5 (0.3, 0.7)	< .001	0.2 (−0.1, 0.4)	.13	0.1 (−0.4, 0.5)	.75	−0.2 (−0.5, 0.2)	.33	0.0 (−0.9, 0.9)	.95
Model 1	0.3 (−0.0, 0.7)	.08	0.4 (0.2, 0.7)	< .001	0.2 (−0.0, 0.4)	.06	0.1 (−0.5, 0.6)	.79	−0.2 (−0.5, 0.2)	.42	0.1 (−0.8, 1.0)	.86
Model 2	0.3 (−0.1, 0.7)	.10	0.4 (0.1, 0.6)	.006	−0.0 (−0.4, 0.3)	.81	0.0 (−0.6, 0.6)	.93	−0.2 (−0.7, 0.3)	.44	−0.6 (−1.5, 0.4)	.23

Model 1 adjusted for age, sex, race/ethnicity, height, weight, smoking status, pack-years, and cohort. Model 2 adjusted for variables in model 1 in addition to education level, systolic BP, diabetes mellitus, low-density lipoprotein, sleep apnea, oxygen saturation, and other CT emphysema subtypes. CPFE = combined pulmonary fibrosis and emphysema; ePAP = estimated pulmonary artery pressure; ePAWP = estimated pulmonary arterial wedge pressure; ePVR = estimated pulmonary vascular resistance.

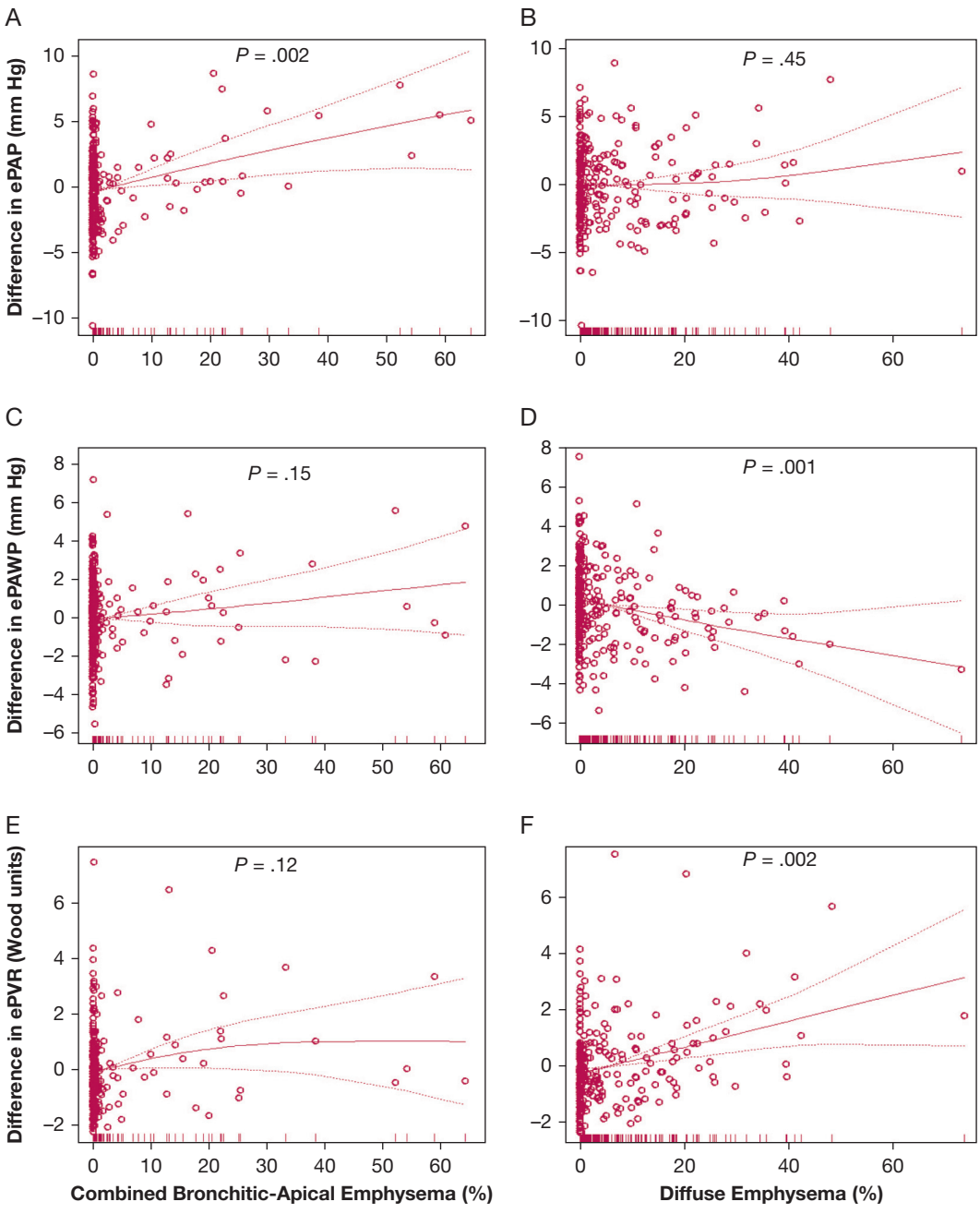

Figure 2 – *A-F, Associations of the combined bronchitic-apical emphysema subtype and the diffuse emphysema subtype with estimated cardiac hemodynamics. Solid lines show smoothed regression lines from multivariable generalized additive models including age, sex, race/ethnicity, height, weight, cohort, smoking status, pack-years of smoking, educational attainment, systolic BP, diabetes, low-density lipoprotein, sleep apnea, resting oxygen saturation, and other CT emphysema subtypes. Dashed lines show 95% CIs. Dots represent predicted residual values. The* P *value for nonlinearity was* > *.20 for models 2A, 2D, and 2F. ePAP = estimated pulmonary artery pressure; ePAWP = estimated pulmonary arterial wedge pressure; ePVR = estimated pulmonary vascular resistance.*

Other Risk Factors and Estimated Hemodynamics

Figure 3 shows multivariable associations of CT emphysema subtypes and other possible risk factors for elevated ePAP, including FEV_1, fSAD, airway wall and lumen area, residual volume, residual volume/total lung capacity (RV/TLC), diffusing capacity, PMBV, PMBF, oxygen saturation, and LV ejection fraction; none were associated with ePAP. Hyperinflation (RV/TLC > 120%) was not associated with ePAP (adjusted $P = .84$; not shown). PMBV and fSAD were associated with

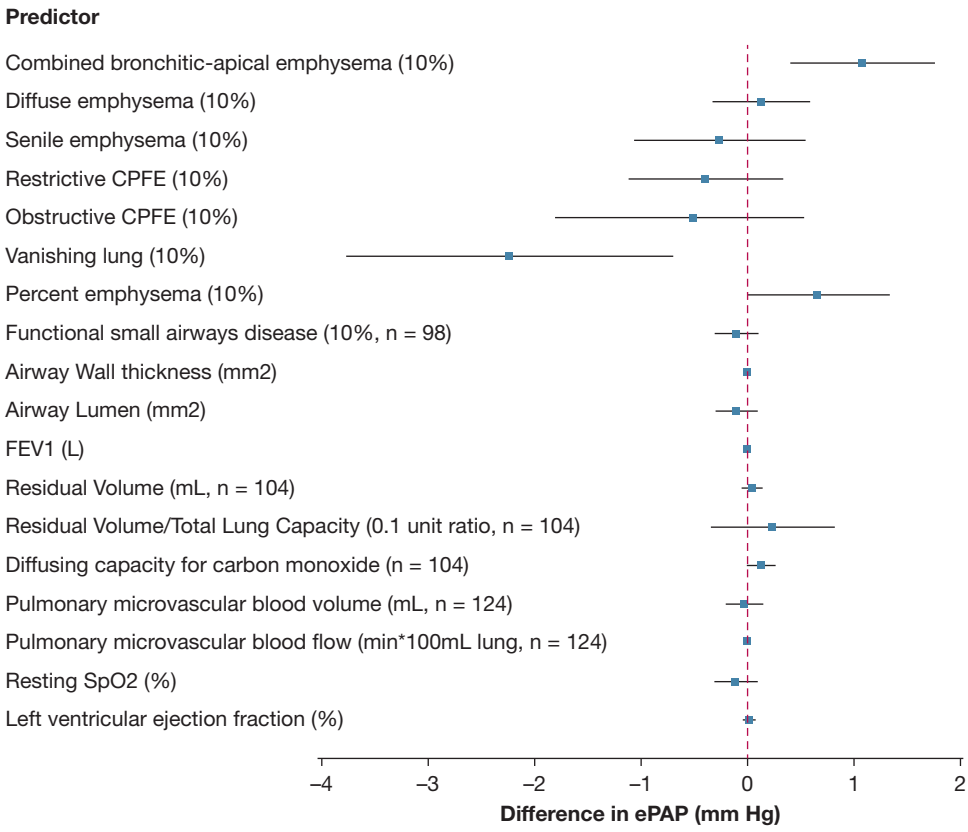

Figure 3 – *Associations of risk factors with estimated pulmonary artery pressure. Models adjusted for age, sex, race/ethnicity, height, weight, cohort, smoking status, pack-years of smoking, educational attainment, systolic BP, diabetes, low-density lipoprotein, sleep apnea, and resting oxygen saturation. CT emphysema subtype models were additionally adjusted for other CT emphysema subtypes. ePAP = estimated pulmonary artery pressure; CPFE = combined pulmonary fibrosis and emphysema; Spo_2 = oxygen saturation.*

ePAWP (0.14 mm Hg/mL; 95% CI, 0.01-0.26; $P = .03$; and –0.03 mm Hg/10%; 95% CI, –0.05 to –0.01; $P = .002$, respectively) (Fig 4). No risk factor was associated with ePVR (Fig 5).

Discussion

In this community-based sample with mostly mild-to-moderate COPD, greater severity of COPD was associated with lower ePAWP and greater ePVR estimated by MRI. Investigation of machine-learned CT emphysema subtypes demonstrated that these hemodynamic changes were specific to the diffuse emphysema subtype, whereas elevations in ePAP were unique to the CBaE subtype.

Although COPD is traditionally associated with cor pulmonale due to elevated PAP,[4] our findings suggest that the predominant hemodynamic change in COPD is greater PVR, consistent with work suggesting that LV underfilling is common in contemporary COPD.[5,7,33,34] A potential mechanism for our observations is pulmonary vascular compression due to greater intrathoracic pressures caused by pulmonary hyperinflation from gas trapping and small-airway obstruction.[16] Indeed, randomized controlled trials (RCTs) of long-acting bronchodilators and lung volume reduction in individuals with pulmonary hyperinflation have demonstrated improved LV filling and CO.[35-37] In this cohort, however, we found no association between measures of hyperinflation and greater PVR. Another potential mechanism for greater PVR is pulmonary microvascular damage, which is observed in emphysematous lung on histology.[15,38] Because the pulmonary circulation is a low-pressure, high-flow system, microvascular destruction may increase PVR and lower LV preload.[34,39] No work to our knowledge has investigated the impact of microvascular therapies on cardiac hemodynamics in this population. Finally, precapillary pulmonary arterial remodeling may play a role in raising PVR in COPD.[40] In support of this, pulmonary vasodilators have been shown to increase CO in some patients with COPD[41-43]; however, they also exacerbate ventilation-perfusion mismatch, leading to poor outcomes in some RCTs.[44]

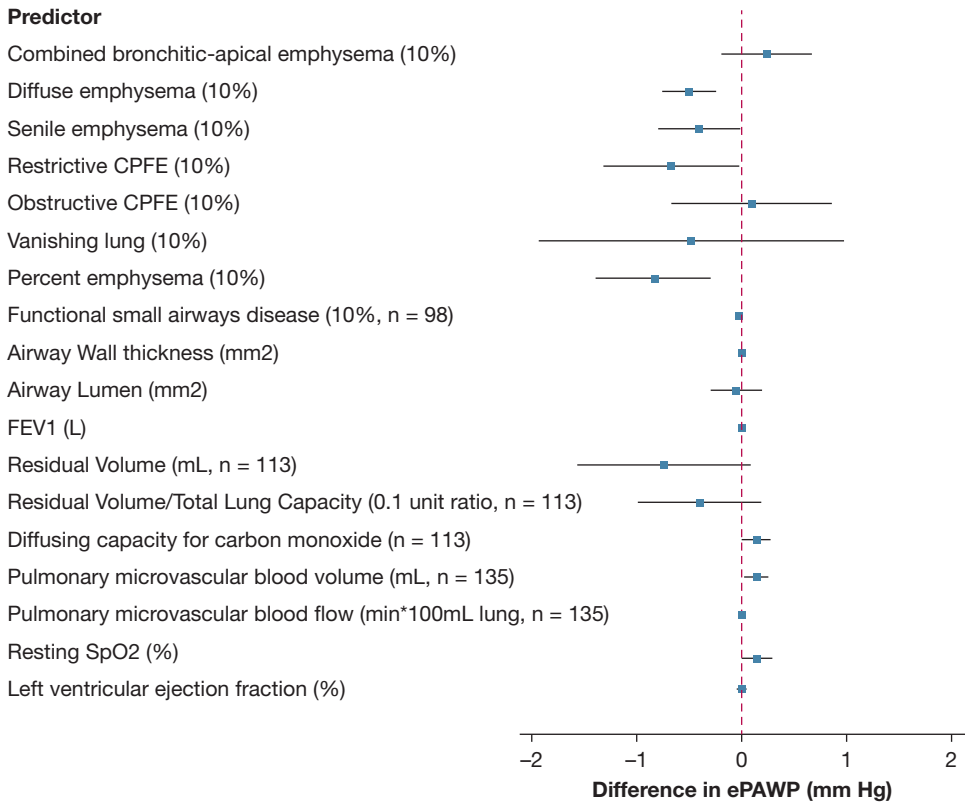

Figure 4 – *Associations of other risk factors with estimated pulmonary arterial wedge pressure. Models adjusted for age, sex, race/ethnicity, height, weight, cohort, smoking status, pack-years of smoking, educational attainment, systolic BP, diabetes, low-density lipoprotein, sleep apnea, and resting oxygen saturation. CT emphysema subtype models were additionally adjusted for other CT emphysema subtypes. ePAWP = estimated pulmonary arterial wedge pressure; CPFE = combined pulmonary fibrosis and emphysema; Spo_2 = oxygen saturation.*

The CBaE subtype was associated with elevated ePAP in this cohort, reminiscent of the report by Burrows and colleagues[9] describing a pattern of increased PAP and cor pulmonale in "bronchial" COPD. The CBaE subtype primarily occurs in severe COPD and is linked to smoking, small airways disease, greater risk of hospitalization, and mortality.[16] It is also associated with a variant near the dopamine D1 receptor gene, which is implicated in exaggerated hypoxic pulmonary vasoconstriction.[42,43] Given the dopaminergic effects of nicotine, this suggests a potential direct mechanism whereby tobacco inhalation leads to precapillary elevations of PAP in the CBaE subtype.[45]

Lower PAWP and greater PVR were specific to the diffuse emphysema subtype, which is not related to smoking and is characterized by increased total lung volume, lung function decline, and increased risk of hospitalizations and mortality.[16] The diffuse emphysema subtype is also associated with lower pulmonary microvascular volume.[18] Diffuse pulmonary capillary loss is a potential mechanism for both the observed increase in ePVR and reduction in ePAWP and suggests a microvascular therapeutic target for the diffuse emphysema subtype.

CT emphysema subtypes may help phenotype cardiopulmonary physiology in early COPD, offering an opportunity to target therapies and conduct RCTs in at-risk subpopulations. For example, although pulmonary vasodilators and endothelin receptor antagonists have improved cardiac hemodynamics in some patients with COPD, they have had neutral or deleterious impact on exercise capacity and oxygenation in others and are not recommended for use.[41-44,46] Recognition of individuals with CBaE-prominent emphysema may improve RCT recruitment and direct use of therapies targeting PAP. Conversely, the diffuse emphysema subtype offers a promising, precision biomarker to identify a COPD subpopulation characterized by vascular damage and capillary PH at risk for elevated PVR.[47] Although CT emphysema subtypes may co-occur, we suggest that CT emphysema subtypes represent distinct, targetable mechanistic pathways.

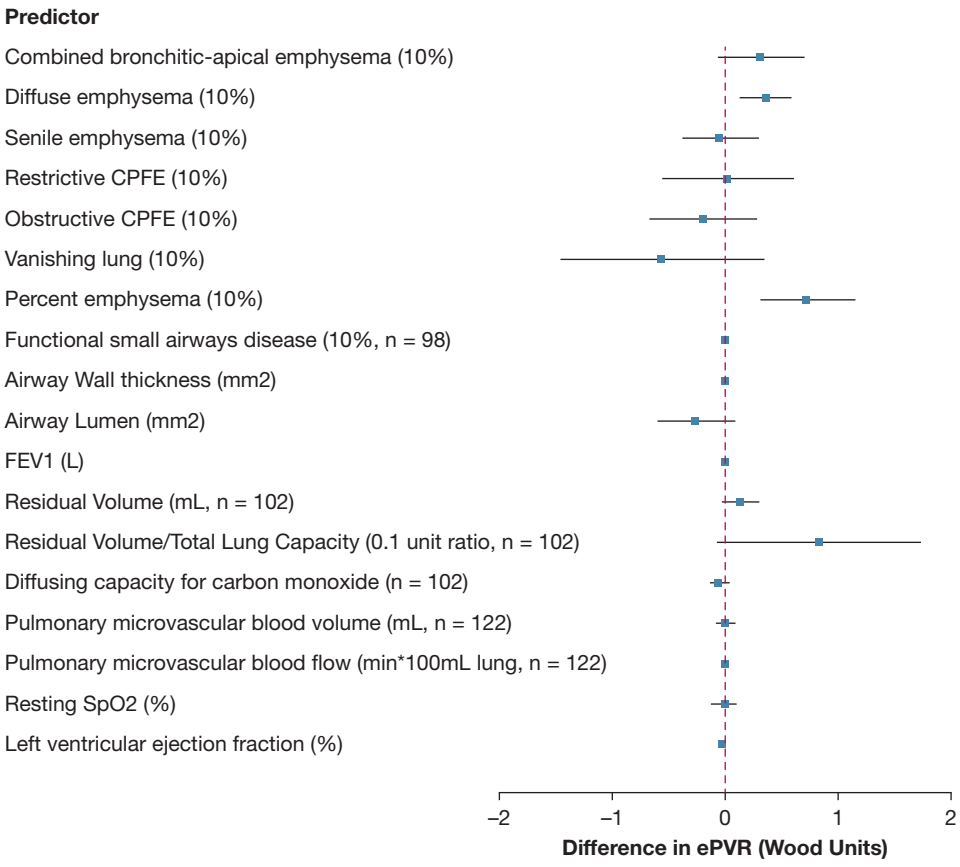

Figure 5 – *Associations of other risk factors with estimated pulmonary vascular resistance. Models adjusted for age, sex, race/ethnicity, height, weight, cohort, smoking status, pack-years of smoking, educational attainment, systolic BP, diabetes, low-density lipoprotein, sleep apnea, and resting oxygen saturation. CT emphysema subtype models were additionally adjusted for other CT emphysema subtypes. ePVR = estimated pulmonary vascular resistance; CPFE = combined pulmonary fibrosis and emphysema; Spo_2 = oxygen saturation.*

This is the largest study of estimated cardiac hemodynamics in a community-based cohort of mild-moderate COPD of which we are aware, and the first to our knowledge to include contemporary CT-based phenotypes; however, it has several limitations. The formulas used to estimate hemodynamics were validated in patients with suspected or confirmed PH and may overestimate PAP in individuals without PH.[28,29] Hemodynamics were estimated at rest, so exercise-induced PH, which is prevalent in mild-to-moderate COPD, was not investigated.[48] We excluded participants with clinically apparent heart failure and thromboembolic disease, which may limit generalizability, although the community-based design meant that few individuals were excluded on this basis. The overall study sample was not entirely nested, but results were unchanged when the sample was restricted to fully nested participants. CT emphysema subtypes may co-occur, but models adjusted for all subtypes showed similar or stronger associations. CT emphysema data were right-skewed, but sensitivity analyses with transformed data yielded similar trends, suggesting that associations are robust. Finally, histologic validation of CT emphysema subtypes is ongoing.[10,49]

Interpretation

Greater COPD severity was associated with lower ePAWP and greater ePVR in this multiethnic, community-based sample with mild-moderate COPD, suggesting that the predominant hemodynamic change in mild-moderate COPD is underfilling of the LV due to low preload. Further, machine-learned CT emphysema subtypes demonstrated that these alterations were specific to the diffuse emphysema subtype, whereas the CBaE subtype alone was associated with greater ePAP, suggesting that CT emphysema subtypes might provide

precision subphenotypes for more targeted therapies for cardiopulmonary dysfunction in COPD.

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Data availability: The data sets supporting the conclusions of this article can be accessed by reasonable request to MESA Publication and Presentations (https://www.mesa-nhlbi.org).

Additional information: The e-Figures and e-Tables are available online under "Supplementary Data."

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