Original research

Associations of pulmonary microvascular blood volume with per cent emphysema and CT emphysema subtypes in the community: the MESA Lung study

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ABSTRACT

Background Pulmonary microvasculature alterations are implicated in emphysema pathogenesis, but the association between pulmonary microvascular blood volume (PMBV) and emphysema has not been directly assessed at scale, and prior studies have used non-specific measures of emphysema.

Methods The Multi-Ethnic Study of Atherosclerosis Lung Study invited participants recruited from the community without renal impairment to undergo contrast-enhanced dual-energy CT. Pulmonary blood volume was calculated by material decomposition; PMBV was defined as blood volume in the peripheral 2 cm of the lung. Non-contrast CT was acquired to assess per cent emphysema and novel CT emphysema subtypes, which include the diffuse emphysema subtype and small-airways-related combined bronchitic-apical emphysema subtype. Generalised linear regression models included age, sex, race/ethnicity, body size, smoking, total lung volume and small airway count.

Results Among 495 participants, 53% were never-smokers and the race/ethnic distribution was 35% white, 31% black, 15% Hispanic and 18% Asian. Mean PMBV was 352±120 mL; mean per cent emphysema was 4.95±4.75%. Lower PMBV was associated with greater per cent emphysema (−0.90% per 100 mL PMBV, 95% CI: −1.29 to −0.51). The association was of larger magnitude in participants with 10 or more pack-years smoking and airflow obstruction, but present among participants with no smoking history or airflow limitation, and was specific to the diffuse CT emphysema subtype (−1.48% per 100 mL PMBV, 95% CI: −2.31 to −0.55).

Conclusion In this community-based study, lower PMBV was associated with greater per cent emphysema, including in participants without a smoking history or airflow limitation, and was specific to the diffuse CT emphysema subtype.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies from the autopsy era and those employing non-contrast CT and contrast-enhanced MRI imaging suggest peripheral pulmonary vascular changes in pulmonary emphysema. However, non-contrast scans are unable to measure the pulmonary microvasculature directly and contrast-enhanced MRI studies have been small. Further, these studies used non-specific measures of emphysema whereas recent large-scale work has identified six new quantitative CT emphysema subtypes, including the diffuse subtype, which is the most common subtype in the general population and also common in smoking-related chronic obstructive pulmonary disease, and the combined bronchitic-apical subtype, which is characterised by small airways disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by incompletely reversible airflow limitation and was the third leading cause of death worldwide in 2019.[1 2] Approximately one-half of individuals with COPD have emphysema, as do up to 10% of the older general population, including those without a smoking history.[3] Emphysema is defined morphologically as the enlargement of airspaces with alveolar destruction,[4] and emphysema assessed quantitatively on CT is associated with respiratory symptoms, hospitalisations and death, including among individuals without COPD.[5]

Early emphysema pathogenesis is linked to pulmonary microvascular destruction on histology,[6 7] but direct assessment in vivo is limited. Non-contrast CT studies have provided evidence of peripheral vascular changes in emphysema using semi-automated measures of the volume of vessels 1.5–5 mm^2 diameter and total pulmonary vascular volume.[8–10] Without intravenous contrast, however, CT cannot quantify the microvasculature or distinguish pre-capillary from capillary changes, which has implications for diffusion, pulmonary vascular resistance and potential therapies.[8–12] Several contrast-enhanced MRI studies have demonstrated decrements in pulmonary microvascular blood flow with greater emphysema, but these investigations were small and limited to heavy smokers, mostly with COPD.[13 14] Direct investigation of pulmonary

WHAT THIS STUDY ADDS

⇒ This study performed contrast-enhanced dual-energy CT to measure pulmonary microvascular blood volume in a population-based, multicentre sample in the USA. Among 495 participants, lower pulmonary microvascular blood volume was associated with greater per cent emphysema. The association was of greater magnitude among those with airflow limitation and a heavy smoking history but was also significant among participants with no airflow limitation or smoking history and was specific to the diffuse CT emphysema subtype.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This large study demonstrated that decrements in pulmonary microvascular blood volume were associated with per cent emphysema in vivo, supporting prior work hypothesising pulmonary microvascular damage in emphysema pathogenesis. Further, the finding was specific to the diffuse CT emphysema subtype, which might suggest a subpopulation in which to test treatments targeting the pulmonary microvasculature.

microvasculature blood volume in emphysema is therefore lacking, particularly among nonsmokers and in a community-based sample, which is less subject to selection and collider biases.

Further, while emphysema is traditionally divided into centrilobular, panlobular and paraseptal patterns,[4] recent large-scale unsupervised machine learning identified six new CT emphysema subtypes with distinct risk factors, clinical characteristics and prognosis.[15] The most common subtype in the general population (and second-most common in COPD), diffuse emphysema, was associated with reduced total pulmonary vascular volume on non-contrast CT, dyspnoea, desaturation with exertion and increased mortality.[15] The most common subtype in participants with COPD, the combined bronchitic-apical emphysema (CBaE), was associated with small airways disease and increased mortality, as well as a variant near a gene implicated in aberrant hypoxic pulmonary vasoconstriction (HPV).[15] These observations suggest two distinct subphenotypes in COPD: one characterised by generalised emphysema and microvascular disease; the second characterised by small airways disease and precapillary pulmonary hypertension without microvascular alterations.

We, therefore, measured pulmonary microvascular blood volume (PMBV) using contrast-enhanced dual-energy CT (DECT) in a large multicentre, community-based cohort of older adults to test the hypotheses that lower PMBV was associated with per cent emphysema and the diffuse emphysema subtype. We studied a multi-ethnic sample to maximise the generalisability of the results.

METHODS

Study sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that recruited self-reported white, black, Hispanic and Asian participants ages 45–84 years from six US communities using random digit dialling in 2000–2002.[16] Individuals with clinical cardiovascular disease, cancer, weight over 300 lbs and impediments to follow-up were excluded; participants from two or more race/ethnic groups were recruited at each site to minimise race-by-site confounding.

The MESA Lung Study invited participants attending the sixth MESA examination in 2017–2018 with an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m^2 to undergo contrast-enhanced DECT of the lungs. Exclusion criteria included allergy to iodinated contrast and cardiac defibrillator or pacemaker. The current report was limited to participants at four MESA sites with CT scanners that permitted dose reduction, allowing the acquisition of both DECT and non-contrast CT at the same visit.

CT scanning

Participants underwent contrast-enhanced DECT scanning at functional residual capacity on Siemens SOMATOM Force scanners (CareDose on, pitch 0.55, 0.25 s exposure time, 0.5 mm slice thickness, iterative reconstruction with ADMIRE-5 using Qr40).[17] Iopamidol contrast 370 mg/mL at 50% concentration was delivered at 4 mL/s via peripheral intravenous catheter starting 17 s prior to scanning and continuing for the full scan.

Immediately prior to the DECT, a non-contrast CT scan was acquired at total lung capacity following the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) protocol (CareDose on, pitch 1.0, 0.25 s exposure time, 0.75 mm slice thickness and iterative reconstruction with advanced modeled iterative reconstruction (ADMIRE)5 using Qr40).[18]

The average doses of the scans were 3 mSv and 1 mSv, respectively.

Pulmonary blood volume and pulmonary microvascular blood volume

Perfused pulmonary blood volume (PBV) was calculated from DECT as previously described.[17 19] Material decomposition yielded anatomical maps of iodine attenuation from high-energy and low-energy images obtained during DECT which were normalised to iodine concentration in the main pulmonary artery to generate perfusion maps.[19] This method employs less contrast and lower radiation doses than conventional CT angiography and quantifies perfused blood at the voxel level (approximately 0.6 mm^3).[19] PMBV was defined as the volume of blood within the peripheral 2 cm of the lung, a region shown on autopsy to contain vessels smaller than 500 µm in diameter (most less than 20 µm in diameter),[20] consistent with prior assessments of the pulmonary microvasculature.[13] The 2 cm peel was selected automatically by an algorithm developed by the MESA Lung CT Reading Centre and excluded the region adjacent to the mediastinum. For secondary analyses, PMBV was normalised as the percentage of blood in the peripheral 2 cm of lung (hereafter referred to as per cent PMBV).

The scan–rescan reproducibility of PMBV was an intraclass correlation coefficient (ICC) of 0.86 among 21 healthy, actively smoking participants who underwent the same DECT protocol in a separate study (NCT02682147).

DECT scans with a mistimed contrast bolus, defined as the mean iodine attenuation in the left atrium minus that in the pulmonary artery greater than the 95th percentile of the distribution in the study sample,[17] were excluded. This quality control step was applied prior to statistical analyses.

Per cent emphysema

Lung segmentation and standard quantitative CT measures were assessed on non-contrast scans using Apollo software (VIDA Diagnostics, Coralville, Iowa, USA). Per cent emphysema$_{-950HU}$ was defined as the percentage of voxels within the lung below −950 HU, which had a scan−rescan ICC in SPIROMICS of

0.99.[21] Given the known bias in per cent emphysema$_{-950HU}$ at low doses on the contemporary scanners used in this study, per cent emphysema was corrected using a Hidden Markov Measure Field model,[22] as previously performed in this cohort.[23]

Quantitative CT emphysema subtypes

Six quantitative CT emphysema subtypes were previously identified using an unsupervised machine-learning algorithm applied to over 1.8 million 25×25×25 mm emphysematous regions of the lung on CT scans from 2853 SPIROMICS participants. Emphysematous regions were defined by per cent emphysema$_{-950HU}$ above the upper limit of normal (ULN), which accounted for body size, demographics, current smoking and scanner, and were clustered based on their texture and anatomical location.[24] The CT emphysema subtypes are diffuse emphysema, CBaE, senile emphysema, obstructive combined pulmonary fibrosis emphysema (CPFE), restrictive CPFE and vanishing lung emphysema. CT emphysema subtypes are continuous measures and may co-occur in individuals. They have distinct molecular and environmental risks, symptom profiles, physiology and prognoses.[15] Their scan−rescan ICC was 0.94, 0.99, 0.84, 0.74, 0.97 and 0.99, respectively.[21] Preliminary histological validation suggests that the diffuse emphysema is characterised by homogeneous emphysema without loss of the terminal bronchioles, whereas CBaE is associated with loss of the terminal bronchioles and heterogeneous emphysema.[25]

CT scans from the fifth MESA examination were previously labelled with CT emphysema subtypes.[15] Scans in the present study were labelled in the same way after updating the ULN at the fifth MESA examination by the ratio of per cent emphysema$_{-950HU}$ / per cent emphysema to account for scanner differences.

Other standard quantitative CT measures

Total lung volume (TLV) was defined as the volume of voxels in the lung fields. Tissue volume and air volume were measured as previously described, with scan−rescan ICCs of 0.99.[21] Per cent air volume was calculated as air volume divided by TLV.

Airways were labelled from the trachea (generation 0) to subsegmental bronchi along five prespecified paths at a single reading centre blinded to participant information. The small airway count is the sum of airway counts for generation 6 or greater.

Qualitative emphysema subtypes

The percentages of the lung with centrilobular, panlobular and paraseptal emphysema were qualitatively assessed on full-lung CT scans at the fifth MESA examination by chest radiologists following a standardised protocol.[26]

Covariates

Age, sex, educational attainment and race/ethnicity were self-reported, the latter defined by the 2000 US Census criteria. Smoking history was assessed using a standard MESA questionnaire. Height and weight were measured using standardised protocols.[16] eGFR was estimated using the chronic kidney disease epidemiology collaboration (CKD-epi) equation. Clinical cardiovascular disease included adjudicated cardiovascular events prior to MESA examination 6 and self-reported diagnosis of heart failure. Scans were read for interstitial lung disease (ILD) following a standardised protocol and checked for pulmonary emboli.

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines following the MESA Lung protocol.[27] Predicted values for spirometry were calculated with the Global Lung Initiative race-neutral equations.[28] Airflow limitation was defined as a pre-bronchodilator ratio of forced expiratory volume in one second to forced vital capacity of<0.7.[1]

Exposure to vapours, gas, dust and fumes (VDGF) was self-reported. Average participant-specific exposure to air pollutant concentrations in the year prior to MESA examination 6 including particulate matter with aerodynamic diameter<2.5 microns ($PM_{2.5}$) and ozone (O_3) were estimated at residential address using validated spatio-temporal prediction models.[29]

Statistical analysis

PMBV was divided into quintiles for descriptive purposes. Dichotomous variables were presented as proportions and continuous variables as means with SD, unless otherwise indicated. Missing data were minimal (see table 1); all analyses were performed as complete-case analyses.

The association between PMBV and per cent emphysema was described at the individual level using linear regression. Unadjusted, TLV-adjusted and multivariate models are presented, the latter additionally including age, sex, height, weight, smoking status, pack-years, study site, small airway count and proxy measures of socioeconomic stressors, educational attainment and self-reported race/ethnicity. Estimated marginal means in each quintile of PMBV were reported for descriptive purposes. Analyses were also stratified by sex and smoking status.

A generalised additive model investigated potential non-linear relationships. Effect modification was evaluated using multiplicative interaction terms between PMBV and covariates of interest.

Additional analyses were performed after the exclusion of participants with clinical cardiovascular disease, ILD and pulmonary embolism, with further adjustment for air pollution and VDGF exposures, and with inverse probability weighting to estimate the relationship in the population of MESA participants eligible for DECT. The weight for the last analysis was calculated as one divided by the predicted probability of being in the analysis sample, calculated using a logistic regression model and covariates in the multivariate model. An additional analysis was performed of the association between PMBV and per cent air volume with covariates as in the multivariate model.

Associations between PMBV and CT emphysema subtypes and qualitative emphysema subtypes were investigated using the same analytical approach as the main analyses.

Statistical significance was defined by a two-tailed p value<0.05. Analyses were performed using SAS V.9.4 (SAS Institute) and R package 4.0.2 (The R Project).

RESULTS

Of 3303 participants in the sixth MESA examination, 1617 (49%) were seen at the four sites with requisite scanners and 1269 met eligibility criteria for contrast-enhanced DECT based on renal function. Of these, 528 (42%) completed the DECT, yielding valid PMBV measures for 495 (39%) (online supplemental figure 1). There were small or modest differences between the included participants and eligible but not included participants (online supplemental table 1).

The mean age of included participants was 71 years, 56% were men and the race/ethnic distribution was 35% white, 31% black, 15% Hispanic and 18% Asian. 72% did not have airflow

Table 1 Characteristics of the study participants by quintiles of pulmonary microvascular blood volume (n=495)

	Pulmonary microvascular blood volume (mL)				
	Q1 145–253	Q2 254–302	Q3 303–355	Q4 356–438	Q5 439–1318
N	99	99	98	98	101
Age, years—mean±SD	74±8	72±7	70±7	71±8	68±6
Sex, male—%	22	43	51	71	94
Race/ethnicity—%					
White	43	33	31	31	39
Black	25	28	38	42	26
Hispanic	9	15	13	15	23
Asian	23	24	19	12	13
Height, cm—mean±SD	159±7	164±8	167±9	169±7	175±8
BMI, kg/m^2—mean±SD	25±4	26±4	27±4	28±4	29±3
Cigarette smoking status—%					
Never	66	48	54	42	52
Former	33	45	43	53	42
Current	1	7	3	5	6
Pack-years (ever-smokers)—median (IQR), n=334	11 (0–22)	6 (2–19)	6 (2–18)	6 (1–19)	5 (0–22)
Educational attainment—%					
<High school	13	5	13	11	6
High school graduate	12	14	20	12	12
Some college	26	26	26	25	23
College graduate	19	18	16	28	31
>Bachelor's degree	29	36	26	24	29
Hypertension—%	54	60	52	62	56
Diabetes—%	12	19	18	20	19
Clinical cardiovascular disease—%	1	11	4	5	3
eGFR, mL/min/1.73 m^2—mean±SD	81±11	82±10	85±12	83±13	84±11
FEV1, L—mean±SD	1.8±0.5	2.2±0.5	2.3±0.5	2.5±0.6	3.0±0.6
Per cent predicted FEV1, %—mean±SD	91±18	94±17	96±17	97±18	96±16
FVC, L—mean±SD	2.5±0.5	2.9±0.7	3.2±0.7	3.4±0.8	3.9±0.8
Per cent predicted FVC, %—mean±SD	99±19	100±17	102±24	100±17	99±17
FEV1/FVC—mean±SD	0.7±0.1	0.7±0.1	0.7±0.1	0.7±0.1	0.7±0.1
Airflow limitation, FEV1/FVC<0.7—%	31	25	24	26	28
Small airway count—median (IQR)	15 (12–17)	16 (13–17)	14 (12–17)	15 (12–17)	16 (13–17)
Per cent emphysema, % – mean±SD	4.67±3.96	5.25±4.24	5.18±6.91	4.88±4.65	4.74±3.25
Per cent emphysema above the upper limit of normal—%	14	26	17	14	14
Combined bronchitic-apical emphysema, %—mean±SD	0.07±0.26	0.35±1.53	0.49±3.76	0.08±0.35	0.04±0.16
Diffuse emphysema, %—mean±SD	4.91±9.71	5.65±10.93	6.83±10.59	4.98±10.62	4.74±9.27
Senile emphysema, %—mean±SD	6.37±7.72	8.57±9.42	7.43±7.87	6.43±7.78	7.95±7.50
Restrictive CPFE, %—mean±SD	0.36±0.75	0.91±1.78	0.90±2.80	0.41±0.97	0.14±0.38
Obstructive CPFE, %—mean±SD	7.28±8.11	8.71±9.74	4.96±7.85	6.49±8.28	4.33±6.70
Vanishing emphysema, %—mean±SD	0.00±0.00	0.03±0.08	0.19±1.57	0.01±0.5	0.00±0.01
Total lung volume, L—mean±SD	4.0±1.0	4.6±1.0	4.8±1.1	5.1±1.1	5.7±1.1

Small airway count was defined as the number of generation 6 airways (where the trachea is generation 0). The upper limit of normal for per cent emphysema accounts for body size, demographics, current smoking and scanner, adjusted by the ratio of per cent emphysema$_{-950HU}$ / per cent emphysema to account for scanner differences.[24]
Data were missing for educational attainment (two participants) and left ventricular ejection fraction (seven participants). 36 participants are missing spirometry (FEV1, FVC and airflow limitation). Nine former/current smokers were missing pack-years smoking history. Two participants were missing per cent emphysema.
BMI, body mass index; cm, centimetre; CPFE, combined pulmonary fibrosis emphysema; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; kg, kilogram; L, litre; m, metre; mL, millilitre.

limitation on spirometry. 53% had never smoked cigarettes, 4% smoked cigarettes at the time of the examination and 43% had previously smoked. Among those with a smoking history, 19% had 10 or more pack-years.

Mean PMBV was 352±120 mL and mean per cent emphysema was 4.9±4.7%. Participants had a mean diffuse emphysema of 5.4±10.2%, CBaE of 0.2±1.8%, senile emphysema of 7.3±8.0%, restrictive CPFE of 0.5±1.6%, obstructive CPFE of

Table 2 Associations of pulmonary microvascular blood volume as assessed on DECT and per cent emphysema on CT in the full sample (n=493), among female (n=217) and male (n=276) participants and among participants with no history of smoking cigarettes (n=260) and those with former smoking history (n=211)

	Pulmonary microvascular blood volume (mL)					Estimate per 100 mL PMBV β (95% CI)	P value
Per cent emphysema (%)							
Total sample	Q1 145–253	Q2 254–302	Q3 303–355	Q4 356–438	Q5 439–1318		
N	98	99	98	98	100		
Unadjusted	4.69±3.96	5.25±4.24	5.18±6.91	4.88±4.65	4.74±3.25	−0.08 (−0.43, 0.27)	0.661
Lung volume adjusted	6.70	5.99	5.38	4.22	2.50	−1.21 (−1.54, −0.88)	<0.001
Multivariate adjusted	5.51	5.05	4.66	3.45	2.36	−0.90 (−1.29, −0.51)	<0.001
Female	Q1 145–234	Q2 235–260	Q3 261–300	Q4 301–345	Q5 346–561		
N	43	43	44	44	43		
Unadjusted	4.31±3.81	4.14±3.18	4.13±3.27	3.36±2.65	3.04±2.30	−0.67 (−1.25, −0.08)	0.025
Lung volume adjusted	4.85	4.30	4.11	3.23	2.50	−1.19 (−1.73, −0.65)	<0.001
Multivariate adjusted	4.15	3.87	3.78	2.80	2.16	−0.96 (−1.58, −0.34)	0.003
Male	Q1 169–296	Q2 297–355	Q3 356–415	Q4 416–481	Q5 482–1318		
N	56	53	56	55	56		
Unadjusted	6.85±5.11	6.91±8.77	4.99±4.05	5.51±4.94	4.97±3.41	−0.57 (−1.08, −0.06)	0.028
Lung volume adjusted	8.13	7.09	5.84	4.39	3.87	−1.12 (−1.68, −0.76)	<0.001
Multivariate adjusted	6.29	5.58	4.27	3.77	3.22	−0.85 (−1.39, −0.32)	0.002
Never-smokers	Q1 145–246	Q2 247–297	Q3 298–345	Q4 346–439	Q5 440–1318		
N	52	53	51	52	52		
Unadjusted	4.22±3.25	4.97±3.59	4.36±3.84	4.08±3.98	5.32±3.62	0.13 (−0.21, 0.48)	0.439
Lung volume adjusted	5.66	5.69	4.68	3.60	3.32	−0.70 (−1.03, −0.37)	<0.001
Multivariate adjusted	5.29	4.72	4.64	4.05	3.71	−0.41 (−0.75, −0.02)	0.042
Former smokers	Q1 148–269	Q2 270–317	Q3 318–367	Q4 368–436	Q5 437–726		
N	42	41	43	42	43		
Unadjusted	6.51±5.76	4.55±3.60	6.57±9.54	5.38±5.21	4.23±2.84	−0.49 (−1.26, 0.27)	0.201
Lung volume adjusted	8.38	5.75	6.65	4.66	1.87	−1.98 (−2.66, −1.30)	<0.001
Multivariate adjusted	7.93	5.11	6.44	4.15	1.72	−1.85 (−2.71, −1.10)	<0.001

Multivariate model adjusts for age, sex, height, race/ethnicity, weight, smoking status, pack-years, educational attainment, study site, total lung volume and small airway count.
Sex-stratified models do not include sex in the multivariate model.
Models for never-smokers do not include smoking covariates in the multivariate model.
DECT, dual-energy CT; PMBV, pulmonary microvascular blood volume.

6.3±8.2% and vanishing emphysema of 0.0±0.7%. 27 participants had cardiovascular disease, two had ILD and one had a pulmonary embolism on DECT.

Table 1 shows participant characteristics by quintile of PMBV. PMBV differed by age, sex, race/ethnicity, height and weight but not smoking status or educational attainment. Per cent PMBV normalised to peel volume was lower with greater age (online supplemental table 2).

Pulmonary microvascular blood volume and per cent emphysema

There was no association between PMBV and per cent emphysema in unadjusted analyses but after TLV adjustment, per cent emphysema was 6.70% in the highest quintile of PMBV and 2.50% in the lowest, with an average decrement of 1.21% per cent emphysema per 100 mL PMBV (95% CI: −1.54 to −0.88; p<0.001) (table 2). The inverse association of PMBV and per cent emphysema was little changed in fully adjusted models (−0.90%; 95% CI: −1.29 to −0.51; p<0.001). per cent PMBV was significantly associated with per cent emphysema in both unadjusted and adjusted analyses (online supplemental table 3).

PMBV was significantly associated with per cent emphysema in unadjusted and adjusted analyses stratified by sex, and the unadjusted association was monotonic among women (table 2). The adjusted associations persisted among participants with no, and prior, history of smoking cigarettes (table 2). Figure 1 shows representative DECT scans for non-smoking female participants in the first-quintile and fifth-quintile of per cent emphysema, demonstrating decrements in PMBV.

Generalised additive models showed a significant, linear relationship between PMBV and per cent emphysema (figure 2A)

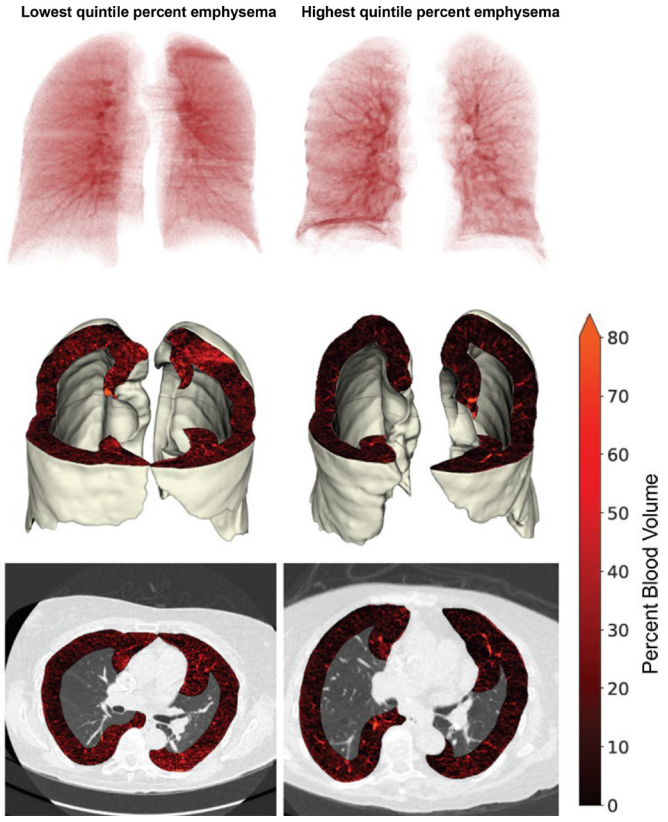

Figure 1 Contrast-enhanced, dual-energy CT (DECT) scans showing pulmonary blood masks and three-dimensional and two-dimensional reconstructions of pulmonary microvascular blood volume in representative participants with low and high per cent emphysema. Participants from the lowest and highest quintile per cent emphysema are shown. Pulmonary microvascular blood volume, or volume of blood in the peripheral 2 cm peel of lung parenchyma, is demonstrated in red on pulmonary blood volume maps (top) and on three-dimensional reconstructions of the lungs (middle), and axial two-dimensional sections (bottom) of DECT images. Participants are female non-smokers with age and body mass index within 1 SD of the population mean.

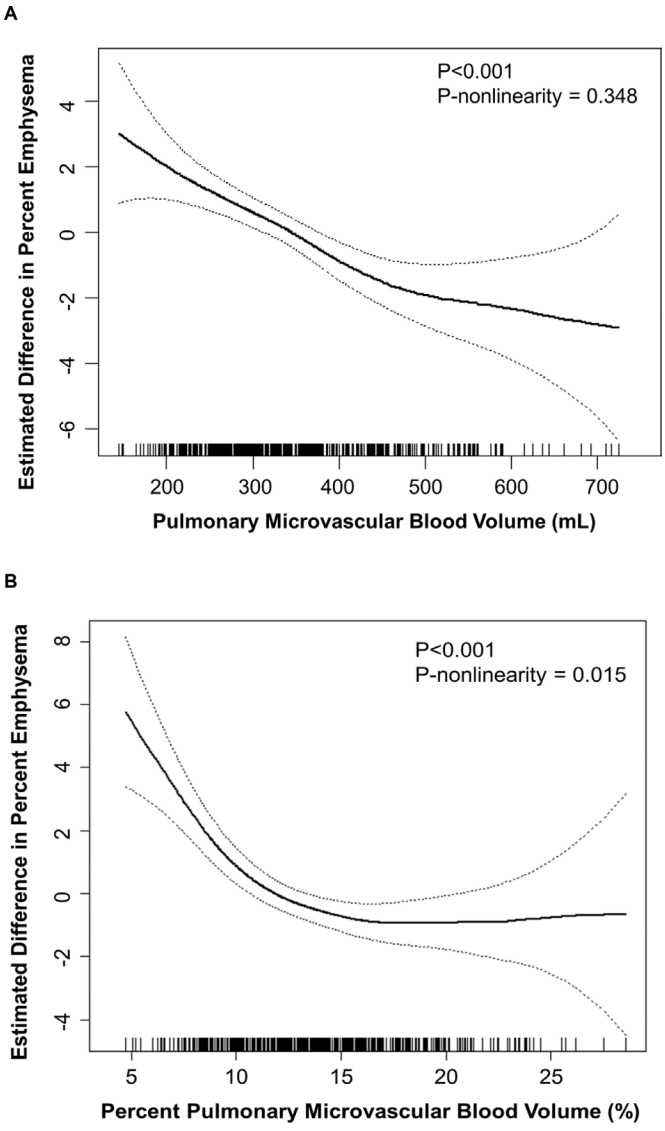

Figure 2 Generalised additive models of the associations between pulmonary microvascular blood volume and per cent pulmonary microvascular blood volume on dual-energy CT and per cent emphysema on CT. Top panel (A) shows the association between pulmonary microvascular blood volume and per cent emphysema adjusted for age, sex, height, race/ethnicity, weight, smoking status, pack-years, educational attainment, study site, total lung volume and small airway count. p<0.001, p-non-linearity=0.348. Bottom panel (B) shows the association between per cent pulmonary microvascular blood volume and per cent emphysema adjusted for age, sex, height, race/ethnicity, weight, smoking status, pack-years, educational attainment, study site and small airway count. p<0.001, p-non-linearity=0.015. Note: Dashed lines represent 95% CIs.

and a significant, non-linear association between per cent PMBV and per cent emphysema (figure 2B).

The association of PMBV and per cent emphysema was similar across the four major US race/ethnic groups but was of greater magnitude among participants with 10 or more pack-years of smoking (p-interaction=0.036; online supplemental figure 2) and airflow limitation (p-interaction=0.022), although it persisted among participants without airflow limitation (online supplemental table 4).

Exclusion of participants with cardiovascular disease, ILD and pulmonary embolism did not meaningfully alter the associations (online supplemental table 5), nor did adjustment for exposure to $PM_{2.5}$, O_3 and VDGF (online supplemental table 6), or back-weighting to the eligible MESA examination sample (online supplemental table 7).

Because quantitative lung density measures such as per cent emphysema are affected by vascular volume, we also assessed the relationship of PMBV to per cent air volume, which demonstrated the expected inverse association in the multivariate models (−0.74% air volume per 100 mL PMBV; 95% CI: −0.91 to −0.48; p<0.001).

Pulmonary microvascular blood volume and CT emphysema subtypes

The association between PMBV and the diffuse emphysema and CBaE subtypes is shown in table 3. PMBV was negatively associated with diffuse emphysema in adjusted models, including after adjustment for other CT emphysema subtypes (−1.48% diffuse emphysema per 100 mL PMBV; 95% CI: −2.31 to −0.55; p=0.002). Associations of PMBV and diffuse emphysema were significant among women and men in sex-stratified unadjusted and adjusted analyses (online supplemental table 8). In contrast,

Table 3 Adjusted associations of pulmonary microvascular blood volume as assessed on DECT and predicted mean combined bronchitic-apical and diffuse CT emphysema subtypes in the full sample (n=365)

	Pulmonary microvascular blood volume (mL)					Estimate per 100 mL increment in PMBV β (95% CI)	P value
Total sample	Q1 145–253	Q2 254–302	Q3 303–355	Q4 356–438	Q5 439–1318		
Diffuse emphysema (%)							
N	79	67	70	68	81		
Unadjusted	4.91±9.71	5.65±10.93	6.83±10.58	4.98±10.62	4.74±9.27	−0.12 (−0.94, 0.71)	0.780
Lung volume adjusted	9.61	8.10	6.89	3.37	−0.39	−2.66 (−3.44, −1.89)	<0.001
Multivariate adjusted	5.17	5.01	4.09	1.27	−0.65	−1.57 (−2.46, −0.69)	<0.001
Multivariate adjusted including other subtypes	5.34	5.03	3.83	2.00	−0.10	−1.48 (−2.31, −0.55)	0.002
Combined bronchitic-apical emphysema (%)							
N	79	67	70	68	81		
Unadjusted	0.07±0.26	0.35±1.53	0.50±3.76	0.08±0.35	0.04±0.16	−0.05 (−0.19, 0.09)	0.494
Lung volume adjusted	0.35	0.50	0.48	−0.02	−0.26	−0.20 (−0.37, −0.04)	0.014
Multivariate adjusted	0.21	0.26	0.27	−0.30	−0.47	−0.18 (−0.34, 0.02)	0.064
Multivariate adjusted including other subtypes	0.07	0.29	0.05	0.08	0.14	−0.01 (−0.08, 0.07)	0.876

Multivariate model adjusts for age, sex, height, race/ethnicity, weight, smoking status, pack-years, educational attainment, study site, total lung volume and small airway count.
Multivariate model including other subtypes adjusts for variables in the multivariate model as well as other CT emphysema subtypes.
DECT, dual-energy CT; PMBV, pulmonary microvascular blood volume.

findings for PMBV and CBaE were generally null, with the exception of after minimal adjustment for TLV. Similar associations were observed with per cent PMBV (online supplemental table 9).

There were no associations between PMBV and other CT emphysema subtypes, including the senile emphysema and obstructive CPFE subtypes which have a generalised anatomical distribution and were as common as diffuse emphysema in this sample (online supplemental table 10).

PMBV was not associated with radiologist-read traditional emphysema subtypes (centrilobular p=0.202, panlobular p=0.791, paraseptal p=0.934).

DISCUSSION

In this community-based, multiethnic study of older adults, lower PMBV on contrast-enhanced DECT was associated with greater per cent emphysema. This association was of greater magnitude among participants with a heavy smoking history and airflow limitation but was also present in participants without a smoking history or airflow limitation. Moreover, the association was specific to the diffuse CT emphysema subtype.

Destruction of the pulmonary microvasculature has long been associated with emphysema based on observations initially made on autopsy[6 30] and, more recently, on non-contrast CT of larger pulmonary blood vessels[8–10] and contrast-enhanced MRI studies of pulmonary microvascular blood flow.[13 14] The present findings are consistent with and extend these studies by employing a direct measure of the pulmonary microvasculature in a larger, community-based sample, including a majority of participants without a smoking history or COPD, and by assessing novel CT emphysema subtypes.

While severe emphysema includes the destruction of the microvasculature, there has been a longstanding debate on whether some subtypes of emphysema may reflect end-organ damage that is a consequence rather than a cause of microvascular destruction.[6 30] Prior and current cross-sectional studies were not optimally designed to assess directionality; however, the linear association between PMBV and per cent emphysema in the current sample with subclinical and mild disease, and the specificity of the association for the diffuse emphysema subtype, supports the hypothesis that microvascular abnormalities precede the development of the diffuse emphysema subtype. Longitudinal and interventional studies are needed to further assess directionality.

The underlying mechanisms driving pulmonary microvascular loss in emphysema progression are not fully elucidated in these observational studies; however, both smoking and non-smoking-related airborne exposures have been associated with endothelial cell and vascular damage via direct injury and maladaptive repair.[31 32] Oxidative stress induces endothelial cell apoptosis and inhibition of vascular endothelial growth factor, resulting in loss of alveolar capillary networks and destruction of adjacent lung structure.[31 32] We observed a stronger association between decrements in PMBV and per cent emphysema among former smokers, but the persistent association among never-smokers and with adjustment for air-pollution exposures suggests additional, unmeasured precipitants of microvascular damage.

In the present study, we found that PMBV was inversely associated with diffuse emphysema, but not with CBaE or other subtypes with a generalised anatomical distribution, suggesting distinct pathophysiology.[15] The diffuse emphysema subtype overlaps with panlobular emphysema and is correlated with per cent emphysema in mild disease.[15] It is also associated with older age, lower body mass index and greater TLV,[15] mirroring the original description of Type A 'emphysematous' COPD ('pink puffers').[33] Early investigations of the cardiac consequences of Type A 'emphysematous' COPD found increased pulmonary vascular resistance and reduced cardiac output without an increase in pulmonary arterial pressure, findings consistent with damage of the pulmonary capillaries and the current findings for PMBV.[34] Indeed, prior investigations have reported an inverse association of per cent emphysema with left ventricular filling,[35] which has been associated with greater mortality.[36]

The lack of association with CBaE, despite its association with smoking and a gene implicated in aberrant HPV, may reflect the apical distribution of this subtype such that assessment of PMBV

of the whole lung periphery, as reported here, may be insensitive to potential regional changes. CBaE was also less common in this community-based sample than diffuse emphysema, limiting statistical power for the former. The current findings are, however, consistent with prior work[15] and pathological results[25] that suggest CBaE is characterised by early small airways loss, such that microvascular destruction would not be expected early in CBaE pathomorphology.

Although this study did not investigate diffusion capacity or the pulmonary vasculature during exercise, our observations might clarify the underlying physiology for wasted ventilation and hypoxaemia observed in functional testing of patients with mild COPD and emphysema.[37] We also suggest that the current findings may explain, in part, the failure of vasodilators for the treatment of pulmonary hypertension in COPD, as prior work has generally targeted individuals with severe COPD.[38 39] Therapies targeting the microvasculature may be efficacious in patients with predominantly diffuse emphysema who may not have airflow obstruction or traditional COPD risk factors such as smoking.[15] Indeed, DECT assessment of PMBV may assist in subphenotyping individuals at risk for COPD-related cardiopulmonary disease, particularly as DECT technology is relatively more available than contrast-enhanced MRI.

This study has multiple strengths, including the use of quantitative measures of PMBV and emphysema in a large, multi-ethnic, community-based, multicentre cohort; however, it has several limitations. There is no gold standard for assessing PMBV. DECT measures of PBV have been validated against pulmonary blood flow[19] but have not been directly compared with contrast-enhanced MRI or histology. While we employed a definition of PMBV based on prior literature,[13 20] PMBV excluded the more central pulmonary microvasculature and was associated with lung size. Nevertheless, TLV-adjusted and per cent PMBV analyses yielded similar results. Noise reduction of modern Siemens Force scanners permitted lower radiation dosages but altered density-based measures relative to earlier scanners,[40] therefore we modified per cent emphysema measures to make them comparable to prior work using a robust algorithm.[22] Per cent emphysema may be affected by subvoxel phenomenon including a reduction in blood volume; the negative association between PMBV and per cent air volume in the lung suggests this did not explain the main findings. Potential methodological confounders included site-specific differences in protocol adherence and breath-hold variability; however, rigorous quality control procedures and TLV adjustment ameliorate this concern. Pulmonary hypertension was not assessed in this sample, but is likely to be rare in this community-based sample with low prevalence of clinical cardiovascular disease, and subgroup analyses excluding those with cardiovascular disease and ILD yielded similar results. Although our findings may be especially pertinent for individuals with clinically significant emphysema, the mild nature of our cohort limits extrapolation. Finally, a minority of MESA participants underwent DECT, which may introduce selection bias; however, back-weighting to the eligible population yielded consistent results.

CONCLUSION

In conclusion, lower PMBV was associated with greater per cent emphysema in a large, multi-ethnic, community-based cohort, a finding that was present in participants without a smoking history or airflow limitation on spirometry, and which was specific to the diffuse CT emphysema subtype. These findings contribute to a growing understanding of precision emphysema subtypes and suggest pathways to targeted treatment strategies for subtypes of COPD and emphysema.

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