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Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA Lung Study

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ABSTRACT: Airflow obstruction is an independent risk factor for cardiovascular events in the general population. The affected vascular bed and contribution of emphysema to cardiovascular risk are unclear. We examined whether an obstructive pattern of spirometry and quantitatively defined emphysema were associated with subclinical atherosclerosis in the carotid, peripheral and coronary circulations.

The Multi-Ethnic Study of Atherosclerosis recruited participants aged 45–84 yrs without clinical cardiovascular disease. Spirometry, carotid intima-media thickness (IMT), ankle-brachial index (ABI) and coronary artery calcium (CAC) were measured using standard protocols. Percentage of emphysema-like lung was measured in the lung windows of cardiac computed tomography scans among 3,642 participants. Multiple linear regression was used to adjust for cardiac risk factors, including C-reactive protein.

Decrements in forced expiratory volume in 1 s (FEV_1) and FEV_1/forced vital capacity ratio were associated with greater internal carotid IMT, particularly among smokers ($p=0.03$ and $p<0.001$, respectively) whereas percentage emphysema was associated with reduced ABI regardless of smoking history ($p=0.004$). CAC was associated with neither lung function (prevalence ratio for the presence of CAC in severe airflow obstruction 0.99, 95% CI 0.91–1.07) nor percentage emphysema.

An obstructive pattern of spirometry and emphysema were associated distinctly and independently with subclinical atherosclerosis in the carotid arteries and peripheral circulation, respectively, and were not independently related to CAC.

KEYWORDS: Cardiopulmonary interactions, cardiovascular epidemiology, chronic, emphysema, obstructive pulmonary disease

Coronary heart disease, chronic lower respiratory disease and stroke are the first, third and fourth leading causes of death, and jointly accounted for almost 1 million (40%) of deaths in the USA in 2005 [1, 2].

An obstructive pattern of spirometry is an independent risk factor for myocardial infarction, cardiovascular mortality [3–10] and stroke [11–14] in general population samples regardless of smoking history. However, the specific systemic vascular beds underlying this strong and consistent relationship are not well defined. Precise and valid measures of subclinical atherosclerosis are available for the carotid, peripheral and epicardial circulations; however, there are few studies of lung function and subclinical atherosclerosis [15–20] and no one study, to date, has compared lung function to measures of subclinical atherosclerosis in all three circulations.

Emphysema is defined as a permanent enlargement of airspaces distal to the terminal bronchioles with destruction of walls [21] and can be measured quantitatively on a computed tomography (CT) scan. Percentage of emphysema-like lung (hereafter referred to as percentage emphysema) is associated with impaired left ventricular filling [22]; however, its association with subclinical atherosclerosis has not been reported.

We therefore examined whether lung function and percentage emphysema were associated with subclinical atherosclerosis in the carotid, peripheral and coronary circulations in a general population sample. We hypothesised that an

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obstructive pattern of spirometry, percentage emphysema and upper-lobe emphysema would be associated with greater carotid intima-media thickness (IMT), reduced ankle-brachial index (ABI) and increased coronary artery calcium (CAC) on cardiac CT.

METHODS

Study sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicentre, prospective cohort study designed to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in individuals without clinical cardiovascular disease [23]. MESA recruited 6,814 males and females aged 45–84 yrs in 2000–2002 from six US communities. MESA participants are white, African-American, Hispanic or Asian (mostly of Chinese origin). Exclusion criteria included clinical cardiovascular disease, weight >300 lb (~136 kg), pregnancy and impediment to long-term participation. The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD, USA). All patients provided appropriate informed consent.

The MESA Lung Study enrolled 3,965 MESA participants out of 4,484 selected who were sampled randomly among those who consented to genetic analyses, underwent baseline measures of endothelial function, and attended an examination during the MESA Lung Study recruitment period in 2004–2006 (99%, 89% and 91% of the MESA cohort, respectively). Chinese-Americans were over-sampled to improve the precision of estimates in this group.

For comparability with other spirometry studies, the main analyses for spirometry included all participants except for 129 participants lacking valid spirometry measures (due to no technician (n=13), contraindication (n=20), declined (n=29) and no acceptable manoeuvres (n=67)). Secondary analyses for obstructive spirometric pattern and the main analyses for emphysema excluded 322 participants with a restrictive pattern of spirometry, defined as a forced vital capacity (FVC) less than the lower limit of normal (LLN) [24] with a forced expiratory volume in 1 s (FEV_1)/FVC ratio >LLN, since the primary hypotheses related to obstructive lung disease and emphysema. Participants missing measurements of percentage emphysema (n=1) and upper-lobe emphysema (n=8) were also excluded from the respective analyses.

Measurements

All measurements were obtained at the MESA baseline examination, except for spirometry, which was performed during the MESA Lung Study recruitment period. All imaging measures were obtained at central reading centres without access to participant information. Random 10% or 100% replicate measures were performed for quality control purposes; results of reproducibility testing are in the online supplementary material.

Subclinical atherosclerosis

Carotid intima-media thickness

Trained technicians performed B-mode ultrasonography of the right and left near and far walls of the internal carotid and common carotid arteries [25] using the Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, WI, USA). Maximal IMT of the internal and common carotid was measured as the mean of the maximum IMT of the near and far walls of the right and left sides.

Ankle-brachial index

Measurements for calculation of ABI were obtained using a hand-held Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, CO, USA). Systolic blood pressure measurements were obtained from bilateral brachial, dorsalis pedis and posterior tibial arteries [26].

Coronary artery calcium

Cardiac CT scans were performed on multidetector and electron-beam CT scanners following a standardised protocol [27, 28]. Certified technologists scanned all participants twice on separate breath-holds at full inspiration. A phantom of known physical calcium concentration was included in the field of view; the average phantom-adjusted Agatston score of the two scans was used for analyses [29, 30].

Spirometry

Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society guidelines [31] on a dry rolling seal spirometer with automated quality checks (Occupational Marketing, Inc., Houston, TX, USA) and over-reading by one investigator [32].

For secondary analyses, airflow obstruction was defined as pre-bronchodilator FEV_1/FVC ratio <LLN and severity was graded as FEV_1 >70% predicted (mild), 50–70% pred (moderate) or <50% pred (severe) [33]. Predicted values were calculated using reference equations from the National Health and Nutrition Examination Survey III [24, 31] with a 0.88 correction for Asians [32].

Percentage of emphysema-like lung

Quantitative measures of emphysema were performed on the lung fields of the cardiac CT scans, which imaged ~70% of the lung volume from the carina to the lung bases. Image attenuation was assessed using the modified Pulmonary Analysis Software Suite [34]. Percentage emphysema was defined as the percentage of the voxels in the lung below -910 HU. This threshold was chosen based upon pathological comparisons [35] and the generally mild degree of emphysema in the sample. Upper-lobe emphysema was computed as the percentage emphysema in the cranial eighth divided by that in the caudal third of the imaged lung.

The scan with the higher air volume was used for analyses except in cases of discordant scan quality, in which case the higher quality scan was used [36]. Attenuation of air outside the body was measured for each scan and emphysema measures were recalculated after the attenuation of each pixel was corrected to have the value (-1,000 × measured pixel attenuation)/mean air attenuation.

Percentage emphysema measurements from the carina to the lung base are highly correlated (r=0.99) with full-lung measures on the same full-lung scans in smokers, and emphysema measures from cardiac scans correlate with those

from full-lung scans from the same MESA participants (*e.g.* r=0.93 for percentage emphysema and r=0.76 for upper-lobe emphysema on multidetector scanners) [36].

Clinical covariates

Age, sex, race/ethnicity, educational attainment, medical history, medication use and alcohol intake were self-reported. Smoking history was assessed using standard questionnaire items [37] and urinary cotinine levels (Immulite 2000 Nicotine Metabolite Assay; Diagnostic Products Corp., Los Angeles, CA, USA) from the day of CT examination. Hypertension, diabetes, C-reactive protein and cholesterol were assessed using standardised methods (see online supplementary material).

Statistical analysis

The cohort was stratified by quintiles of percentage emphysema for descriptive purposes. Tests of trend across categories of emphysema and airflow obstruction were performed with Spearman and Cochran-Armitage tests, as appropriate. Generalised additive models with Loess smoothing functions were used to test the linearity of relationships of independent variables and covariates with the -2 log likelihood test and to generate multivariate plots. Relationships were generally linear; hence, generalised linear models were used, except as described. A Gaussian distribution with identity link was used for all analyses except for the analysis of the presence of CAC, for which a binomial distribution with log link and robust standard errors was used in order to estimate prevalence ratios [38]. Initial multivariate analyses regressed subclinical atherosclerosis measures on lung function or quintiles of emphysema after adjustment for age and sex. Full multivariate models also included the variables listed in the footnotes to the tables.

The primary hypothesis tests and 95% confidence intervals for continuous measures were estimated from linear or smoothed functions [39]. Statistical significance was defined as two-tailed p-value <0.05. No adjustment was made for multiple comparisons but all major comparisons are reported, as recommended [40]. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and *R* 2.6 (*R* Foundation, Vienna, Austria).

RESULTS

The study sample had a mean age of 61 yrs, 49% were male, and the race/ethnic distribution was 35% white, 26% African-American, 22% Hispanic and 16% Chinese-American. 13% were current cigarette smokers, 39% had smoked in the past and 47% had never smoked.

Cardiac risk factors

Table 1 shows the characteristics of the 3,642 participants by quintiles of percentage emphysema. Participants with greater percentage emphysema were more likely to be older, male, white, less obese and former smokers compared to those with lower values of percentage emphysema. Participants with greater percentage emphysema had a lower FEV1/FVC ratio.

Lung function and subclinical atherosclerosis

Associations of FEV1 with IMT and ABI were modified by pack-yrs of smoking (interaction $p<0.05$); therefore, analyses for lung function were stratified by smoking.

Table 2 shows associations of lung function and measures of subclinical atherosclerosis stratified by smoking history. Among participants with a history of smoking, a lower FEV1 and FEV1/FVC ratio was associated with increased IMT of the internal carotid artery and increased IMT of the common carotid artery. In contrast, there was no evidence for an association of FVC with either IMT measurement. Both the FEV1 and FVC were associated with ABI, as was the FEV1/FVC ratio. Findings for IMT and ABI were generally similar among never-smokers although the associations were of smaller magnitude and of more borderline statistical significance (table 2).

In contrast, there was no evidence for an association of any measurement of lung function with the presence or extent of CAC in smokers or never-smokers (table 2) or in the whole cohort (*e.g.* prevalence ratio for the presence of CAC in severe airflow obstruction 0.99, 95% CI 0.91–1.07).

Findings were similar for categories of airflow obstruction. Severity of airflow obstruction was associated with internal carotid IMT, common carotid IMT and, of borderline statistical significance, ABI among smokers but not among never-smokers (online supplementary table 1).

Percentage emphysema and subclinical atherosclerosis

In contrast to our findings for lung function, there was no evidence for a consistent relationship of percentage emphysema with IMT in fully adjusted models (table 3). Percentage emphysema was associated inversely with ABI and the magnitude of this association was not modified by smoking history (interaction p=0.56). Indeed, percentage emphysema was significantly related with reduced ABI among participants with <10 pack-yrs of smoking (p=0.004).

There was no evidence for an association between percentage emphysema and either the presence or the extent of CAC (table 3).

Upper-lobe emphysema and subclinical atherosclerosis

Figure 1 shows the associations of upper-lobe emphysema with internal carotid IMT, ABI and prevalence of CAC. There was evidence for nonlinearity in the association of upper-lobe emphysema with internal carotid IMT (p=0.003) but not to ABI (p=0.12) or CAC (p=0.11).

Upper-lobe emphysema was significantly related to IMT of the internal carotid artery (p=0.003; fig. 1); however, the significance of the association was highly dependent on a few extreme values and no consistent relationship was observed across quintiles of upper-lobe emphysema (table 4).

Upper-lobe emphysema was significantly and inversely associated with the ABI (fig. 1 and table 4), and this association was not modified by pack-yrs (interaction p=0.58). There was no evidence for an association of upper-lobe emphysema with either the presence or the extent of CAC.

Lung phenotypes and subclinical atherosclerosis

In multivariate models that simultaneously adjusted for the FEV1/FVC ratio, percentage emphysema and upper-lobe emphysema, the significance of the association of obstructive spirometric pattern and upper-lobe emphysema with IMT of the internal carotid artery increased (*e.g.* mean difference

TABLE 1 Baseline characteristics of participants stratified by severity of percentage emphysema

	Percentage emphysema				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Participants n	728	729	728	729	728
Age yrs	60±10	61±10	61±10	62±10	63±10
Males	164 (23)	263 (36)	350 (48)	454 (62)	554 (76)
Race/ethnicity					
White	132 (18)	213 (29)	242 (33)	301 (41)	391 (54)
African-American	217 (30)	181 (25)	189 (26)	193 (26)	185 (25)
Hispanic	234 (32)	199 (27)	154 (21)	136 (19)	84 (12)
Asian	145 (20)	136 (19)	143 (20)	99 (14)	68 (9)
Educational attainment					
No high school degree	200 (27)	141 (19)	122 (17)	81 (11)	62 (9)
High school degree	162 (22)	146 (20)	123 (17)	118 (16)	109 (15)
Some college	206 (28)	210 (29)	206 (28)	207 (28)	184 (25)
College degree	88 (12)	119 (16)	129 (18)	164 (22)	167 (23)
Bachelor degree or more	71 (10)	113 (15)	148 (20)	159 (22)	203 (28)
Body mass index kg·m^{-2}	29.3 (5.8)	28.5 (5.7)	27.8 (5.0)	27.5 (4.7)	26.4 (4.1)
Cigarette smoking status					
Never-smokers	405 (56)	363 (50)	351 (48)	335 (46)	263 (36)
Former smokers	191 (26)	242 (33)	282 (39)	308 (42)	389 (53)
Current smokers	132 (18)	124 (17)	95 (13)	86 (12)	76 (10)
Smoking history$^{\#}$ pack-yrs	17 (5–33)	19 (7–38)	15 (6–33)	20 (7–38)	17 (6–35)
Hypertension	324 (45)	323 (44)	320 (44)	282 (39)	287 (39)
Systolic blood pressure mmHg	125±21	125±20	125±20	124±19	123±18
Diastolic blood pressure mmHg	70±10	71±10	72±10	72±10	73±10
Diabetes mellitus	108 (15)	85 (12)	74 (10)	69 (9)	46 (6)
Fasting plasma glucose mg·dL^{-1}	98 (90–108)	96 (89–105)	96 (90–105)	96 (90–105)	95 (90–102)
LDL mg·dL^{-1}	118±30	116±31	117±30	119±32	117±30
HDL mg·dL^{-1}	51±14	52±15	51±15	51±15	50±14
Use of statin	89 (12)	111 (15)	96 (13)	104 (14)	116 (16)
C-reactive protein mg·L^{-1}	2.3 (1.1–5.7)	1.9 (0.8–4.3)	1.7 (0.9–3.7)	1.7 (0.8–3.6)	1.2 (0.6–2.8)
Self-reported asthma					
<45 yrs	50 (7)	54 (7)	51 (7)	64 (8)	67 (9)
⩾45 yrs	11 (1)	8 (1)	12 (2)	12 (2)	19 (3)
FEV_1 % pred	96±15	96±16	96±17	96±18	95±20
FVC % pred	94±14	96±14	97±15	99±15	102±16
FEV_1/FVC ratio %	78±7	76±7	75±8	73±9	70±10
Percentage emphysema	3.4 (1.8–4.8)	8.9 (7.6–10.3)	14.7 (13.2–16.5)	22.1 (20.0–24.8)	34.3 (30.3–40.8)
Upper-lobe emphysema ratio	1.08 (0.57–1.93)	1.09 (0.76–1.67)	1.11 (0.85–1.46)	1.04 (0.81–1.33)	1.02 (0.88–1.18)

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. LDL: low-density lipoprotein; HDL: high-density lipoprotein; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. $^{\#}$: among ever-smokers.

-0.35 mm per 1% increase in the FEV_1/FVC ratio, 95% CI -0.59– -0.12 mm; p=0.003) whereas the association for CT percentage emphysema was further attenuated (p=0.87).

For ABI, the associations with CT percentage emphysema and upper-lobe emphysema remained significant (*e.g.* -0.005 per 10% increase in percentage emphysema, 95% CI -0.09– -0.0001; p=0.011) and that of lung function was attenuated (p=0.97).

Additional analyses

There was no evidence that self-reported physician-diagnosed asthma (at any age) was associated with increased IMT of the internal carotid artery (0.012 mm, 95% CI -0.032– -0.057 mm), reduced ABI (-0.002, 95% CI -0.011–0.008) or presence of CAC (rate ratio 1.00, 95% CI 0.97–1.04). Results for self-reported asthma before age 45 yrs and for symptoms of chronic bronchitis were similarly negative. The main results were generally similar with the inclusion or exclusion of participants with a restrictive pattern of spirometry and were not modified by sex or race/ethnicity.

DISCUSSION

An obstructive pattern of spirometry and upper-lobe emphysema were independently associated with increased IMT of the internal carotid artery in this population-based study, whereas

TABLE 2 Differences in measures of subclinical atherosclerosis in the carotid, peripheral and coronary vascular beds per unit change in lung function among smokers and never-smokers

	FEV_1		FVC		FEV_1/FVC	
	Difference per 1-L increase (95% CI)	p-value	Difference per 1-L increase (95% CI)	p-value	Difference per 1% increase (95% CI)	p-value
Smokers[#]						
IMT mm						
Internal carotid[¶]	-0.060 (-0.115– -0.005)	0.03	-0.000 (-0.051– -0.050)	0.99	-0.006 (-0.009– -0.003)	<0.001
Common carotid[¶]	-0.028 (-0.045– -0.012)	<0.001	-0.013 (-0.028–0.022)	0.09	-0.001 (-0.002– -0.000)	0.007
ABI[¶]	0.012 (0.002–0.023)	0.02	0.004 (-0.005–0.014)	0.39	0.0008 (0.0002–0.0014)	0.006
Presence of CAC[+]	1.01 (0.97–1.04)	0.76	1.00 (0.97–1.03)	0.96	1.001 (0.997–1.002)	0.58
Log Agatston score[¶,§]	0.099 (-0.137–0.334)	0.41	0.14 (-0.074–0.360)	0.20	-0.004 (-0.016–0.008)	0.55
Never-smokers[ƒ]						
IMT mm						
Internal carotid[¶]	-0.053 (-0.105– -0.001)	0.047	-0.008 (-0.053–0.036)	0.71	-0.004 (-0.007– -0.002)	0.002
Common carotid[¶]	-0.028 (-0.044– -0.013)	<0.001	-0.014 (-0.027–0.000)	0.04	-0.001 (-0.002– -0.000)	0.01
ABI[¶]	0.013 (0.003–0.023)	0.01	0.0066 (-0.002–0.015)	0.13	0.0006 (0.0000–0.0011)	0.045
Presence of CAC[+]	1.00 (0.97–1.03)	0.92	0.99 (0.97–1.02)	0.65	1.001 (0.999–1.003)	0.40
Log Agatston score[¶,§]	0.020 (-0.197–0.237)	0.86	0.020 (-0.163–0.203)	0.82	-0.001 (-0.012–0.010)	0.83

Multivariate models were adjusted for age, sex, race/ethnicity, smoking status, pack-yrs, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, height, body mass index, hypertension, systolic and diastolic blood pressure, low- and high-density lipoprotein, statin medication, alcohol use, and C-reactive protein. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IMT: intima-media thickness; ABI: ankle-brachial index; CAC: coronary artery calcium. [#]: n=2,024; [¶]: multivariate mean difference; [+]: multivariate prevalence ratio; [§]: among participants with detectable CAC; [ƒ]: n=1,812.

TABLE 3 Differences in measures of subclinical atherosclerosis in the carotid, peripheral and coronary vascular beds according to quintiles of percentage emphysema on computed tomography (CT)

	CT percentage emphysema					Difference per 10% increase in percentage emphysema (95% CI)	p-value
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Participants n	728	729	728	729	728		
IMT mm							
Internal carotid							
Median value	0.778	0.807	0.844	0.840	0.897		<0.001
Age- and sex-adjusted mean difference	0	0.0132	0.0270	-0.0045	-0.0385	-0.009 (-0.025–0.007)	0.29
Multivariate mean difference	0	0.0182	0.0417	0.0252	0.0068	0.005 (-0.012–0.022)	0.59
Common carotid							
Median value	0.815	0.829	0.835	0.848	0.843		0.002
Age- and sex-adjusted mean difference	0	-0.0035	-0.0073	-0.0051	-0.0362	-0.010 (-0.014– -0.005)	<0.001
Multivariate mean difference	0	0.0025	0.0014	0.0089	-0.0128	-0.003 (-0.008–0.002)	0.30
ABI							
Median value	1.11	1.12	1.13	1.13	1.13		0.03
Age- and sex-adjusted mean difference	0	0.0061	0.0080	0.0070	-0.0048	-0.002 (-0.006–0.001)	0.13
Multivariate mean difference	0	0.0021	0.0026	-0.0005	-0.0133	-0.005 (-0.008– -0.002)	0.004
Presence of CAC							
Prevalence %	39	43	46	48	56		<0.001
Age- and sex-adjusted prevalence ratio	1	1.01	0.984	0.938	0.976	0.987 (0.963–1.01)	0.33
Multivariate prevalence ratio	1	1.01	0.992	0.952	0.976	0.986 (0.960–1.01)	0.29
Mean Agatston score[#]							
Median value	48.9	60.0	82.6	83.4	108		<0.001
Age- and sex-adjusted mean difference	0	2.07	6.27	8.80	5.49	1.035 (-0.999–3.068)	0.36
Multivariate mean difference	0	0.57	5.35	6.26	7.21	1.045 (-0.995–3.085)	0.27

Multivariate models were adjusted for age, sex, race/ethnicity, smoking status, pack-yrs, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, height, body mass index, hypertension, systolic and diastolic blood pressure, low- and high-density lipoprotein, statin medication, alcohol use, C-reactive protein, scanner type, and milliamp seconds. IMT: intima-media thickness; ABI: ankle-brachial index; CAC: coronary artery calcium. [#]: among participants with detectable CAC.

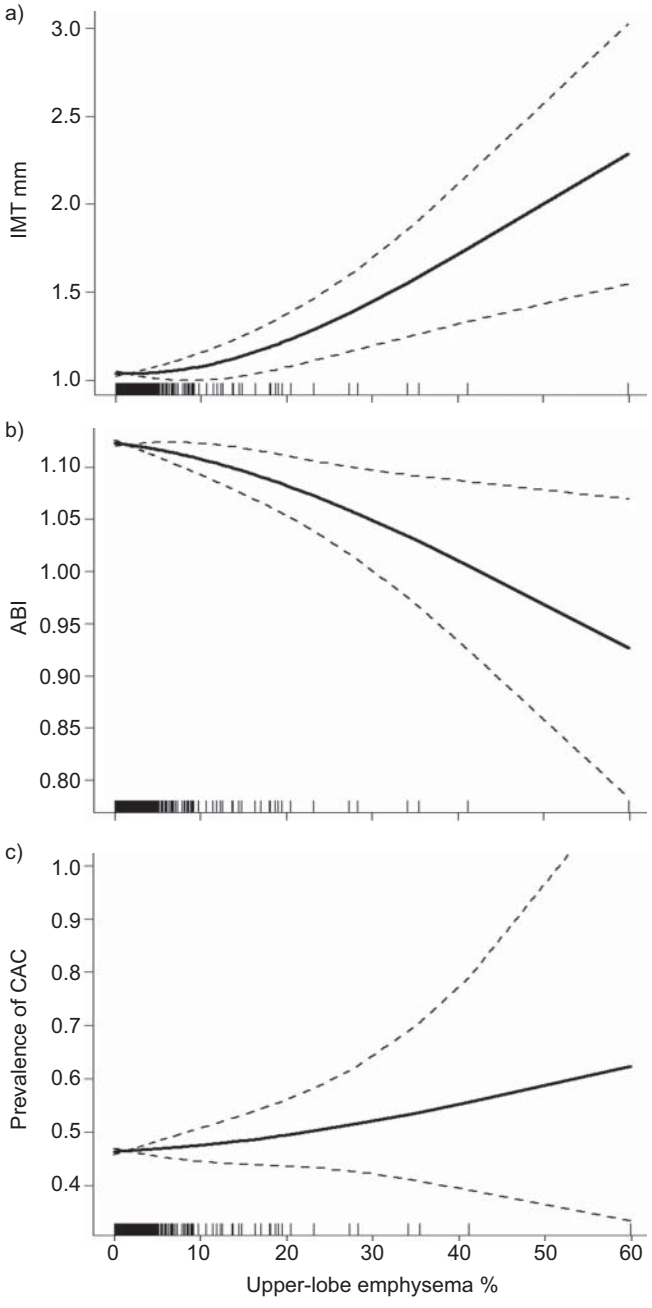

FIGURE 1. Multivariate relationships of upper-lobe emphysema to measures of subclinical atherosclerosis in the carotid, peripheral and coronary vascular beds. Multivariate relationships of upper-lobe emphysema to the a) intima-media thickness (IMT) of the internal carotid artery (p=0.003), b) ankle-brachial index (ABI) (p=0.004) and c) prevalence of coronary artery calcium (CAC) (p=0.29). Multivariate models adjusted for age, sex, race/ethnicity, smoking status, pack-yrs, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, height, body mass index, alcohol use, hypertension, systolic and diastolic blood pressure, C-reactive protein, low- and high-density lipoprotein, statin medication, alcohol use, scanner type, and milliamp seconds. The relationship of upper-lobe emphysema with the IMT of the internal carotid artery was nonlinear (p=0.002), although those of ABI and prevalence of CAC were not (p=0.12 and p=0.45, respectively). ——: smoothed regression lines, which allow for nonlinear relationships; -------: 95% confidence intervals.

percentage emphysema and upper-lobe emphysema were associated with decrements in ABI. In contrast, neither lung function nor emphysema measures were associated with CAC. These findings suggest that cardiovascular risk from smoking-related obstructive ventilatory defects is preferentially related to atherosclerosis of the internal carotid artery whereas emphysema is related to atherosclerosis of the peripheral arteries among smokers and non-smokers alike.

Our results for lung function and IMT are consistent with and expand upon those from the Atherosclerosis Risk in Communities (ARIC) Study. In ARIC, lower lung function was associated with increased mean (average of the common and internal carotid arteries and their bifurcation) IMT among smokers but not among never-smokers [16]. The British Regional Heart Study found IMT of the carotid bifurcation to be inversely associated with FEV_1 [15] and a small study of Japanese smokers found increased IMT among participants with an obstructive pattern of spirometry compared with controls [18]. None of these studies reported IMT of the internal carotid artery, for which we observed the strongest associations, or ascertained percentage emphysema.

Low lung function was also associated with reduced ABI in ARIC and the Males Born in the 1914 cohort [16, 17]. Ascertainment of percentage emphysema in the current study, however, revealed that the association of lung function with ABI was entirely explained by percentage emphysema. This finding, along with the lack of association of asthma with subclinical measures of atherosclerosis, might suggest that cardiovascular risk due to low lung function among never-smokers may result not from airflow obstruction itself but from subclinical emphysema, panlobular emphysema being not uncommon in never-smokers [41].

A retrospective study of 4,905 Korean males undergoing clinical screening for CAC found that CAC was increased in the lowest quartiles of FEV_1 and FVC but not the FEV_1/FVC ratio [20]. In contrast, we found no association of CAC with lung function in MESA. The Korean study may have had better power to detect an association since it was larger, was restricted to one race and sex, and excluded only ''severe'' cardiac disease (whereas MESA excluded clinical cardiovascular disease). However, the results of the Korean study were adjusted only for age, smoking status and BMI. Given the apparent lack of adjustment for other important determinants of lung function and CAC (*e.g.* pack-yrs), it is unclear if a fully adjusted model in that study would have yielded results similar to those in MESA. In either case, both studies show a consistent and null association of CAC with the FEV_1/FVC ratio.

We speculate that the subclinical atherosclerosis occurring in early obstructive lung disease and emphysema may be due to endothelial dysfunction, microvascular disease and oxidative stress rather than the traditional lipid-driven atherosclerosis of the coronary epicardial arteries. Endothelial dysfunction and microvascular disease are prominent features of peripheral vascular disease [42], and flow-mediated dilation of the brachial artery, a measurement of nitric oxide-dependent endothelial function, is significantly impaired in peripheral vascular disease [43]. Endothelial dysfunction has also been implicated in the pathogenesis of emphysema [44, 45] and

TABLE 4 Differences in measures of subclinical atherosclerosis in the carotid, peripheral and coronary vascular beds according to quintiles of upper-lobe emphysema

	Upper to lower lobe ratio of percentage emphysema					Difference per 10-unit increase in upper-lobe emphysema (95% CI)	p-value
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Participants n	727	727	727	727	727		
IMT mm							
Internal carotid							
Median value	0.860	0.863	0.826	0.829	0.786		0.056
Age- and sex-adjusted mean difference	0	-0.0533	-0.0909	-0.0750	-0.1067	¶	0.048
Multivariate mean difference	0	-0.0199	-0.0377	-0.0076	-0.0371	¶	0.002
Common carotid							
Median value	0.838	0.856	0.843	0.823	0.820		0.07
Age- and sex-adjusted mean difference	0	-0.0168	-0.0251	-0.0337	-0.0384	¶	0.20
Multivariate mean difference	0	-0.0003	-0.0038	-0.0060	-0.0131	¶	0.84
ABI							
Median value	1.13	1.14	1.13	1.12	1.12		<0.001
Age- and sex-adjusted mean difference	0	-0.0012	-0.0075	-0.0074	-0.0103	-0.027 (-0.043– -0.011)	0.001
Multivariate mean difference	0	-0.0047	-0.0083	-0.0075	-0.0056	-0.023 (-0.039– -0.007)	0.004
Presence of CAC							
Prevalence %	44	48	46	46	48		0.46
Age- and sex-adjusted prevalence ratio	1	0.942	0.915	0.916	0.972	1.034 (0.905–1.18)	0.63
Multivariate prevalence ratio	1	0.937	0.925	0.951	1.01	1.062 (0.934–1.21)	0.40
Mean Agatston score#							
Median value	63.1	75.7	88.3	80.6	70.3		0.84
Age- and sex-adjusted mean difference	0	-12.2	-4.6	-2.79	-13.8	0.858 (-1.47–3.19)	0.37
Multivariate mean difference	0	-9.19	1.17	4.17	-8.07	0.992 (-1.00–2.99)	0.96

Multivariate models were adjusted for age, sex, race/ethnicity, smoking status, pack-yrs, urine cotinine, educational attainment, diabetes mellitus, fasting plasma glucose, height, body mass index, alcohol use, hypertension, systolic and diastolic blood pressure, low- and high-density lipoprotein, statin medication, alcohol use, C-reactive protein, scanner type, and milliamp seconds. IMT: intima-media thickness; ABI: ankle-brachial index; CAC: coronary artery calcium. #: among participants with detectable CAC; ¶: relationship was nonlinear therefore linear term not reported (see figure 1 for graph of association).

flow-mediated dilation of the brachial artery is reduced with an obstructive pattern of spirometry and percentage emphysema, the association with the former explained by the latter [46], similarly to the current findings for ABI. Oxidative stress is implicated in atherosclerosis and particularly atherosclerosis of the internal carotid artery [47, 48], for which we found the strongest associations. In contrast, IMT of the common carotid artery is related more to hypertension and shear stress [48, 49]. Of note, IMT of the internal carotid artery is a better predictor of myocardial infarction than IMT of the common carotid artery [50].

A novel component of this study was the measurement of percentage emphysema, which allowed, for the first time, the assessment of subclinical atherosclerosis and objectively defined emphysema in a population-based study. Percentage emphysema was measured on partial-lung scans, which has been previously validated against full-lung scans in this cohort [36]. Nonetheless, the correlation between partial- and full-lung scans was lower for upper-lobe emphysema than for percentage emphysema. Reassuringly, visual inspection of CT scans with high values for upper-lobe emphysema demonstrated clinical emphysema.

Lung function was assessed ~4 yrs after the other measures; however, the expected mean change in the FEV_1/FVC ratio over 4 yrs in an epidemiologic cohort such as MESA is small (~1% [51]) relative to the standard deviation of the FEV_1/FVC ratio (9%).

Post-bronchodilator measurements of spirometry were not performed in this large cardiovascular cohort. All published epidemiological studies on lung function and cardiovascular risk are, however, based on pre-bronchodilator measurements.

The lack of post-bronchodilator measurements limited our ability to distinguish the cause of the obstructive pattern of spirometry. However, associations for lung function were of significantly greater magnitude in smokers than nonsmokers, there were consistent associations for upper-lobe emphysema, and there was no evidence for an association of self-reported asthma with subclinical atherosclerosis. Hence, our findings probably apply to smoking-related obstructive lung disease.

Participants with clinical cardiovascular disease were excluded and only 52 participants had severe airflow obstruction. On the one hand, this is a limitation, since these results may not fully

generalise to patients with severe lung disease. On the other hand, it is a strength, since analyses were not confounded appreciably by medication use. Confounding by unmeasured or imprecisely measured confounders is of concern in any observational study. However, standard and novel cardiac risk factors were measured precisely and current smoking status was confirmed with cotinine levels.

Finally, an alternative explanation for circulation-specific findings for lung function and lung density might be differential measurement error. However, of the measurements of subclinical atherosclerosis, CAC was the most precise and the best predictor of cardiovascular events in this cohort [28, 52]. Of the measurements of lung disease, lung function was more accurate and precise than percentage emphysema; however, measurement error in percentage emphysema was small and was not differentially related to IMT, ABI and CAC. We therefore doubt that the negative findings for CAC or the circulation-specific findings are due to measurement error.

In conclusion, an obstructive pattern of spirometry was independently associated with atherosclerosis in the carotid arteries predominantly among smokers whereas quantitatively defined emphysema was associated with reduced ABI regardless of smoking history, and neither measurement was associated with CAC. Cardiovascular risk related to chronic lower respiratory disease differs by phenotype and appears unrelated to CAC, a measurement of epicardial atherosclerosis.

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STATEMENT OF INTEREST

Statements of interest for R.G. Barr, E.A. Hoffman and S.M. Kawut can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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