Pulmonary Artery Stiffness in Chronic Obstructive Pulmonary Disease (COPD) and Emphysema: The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study

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Purpose: Chronic obstructive pulmonary disease (COPD) and particularly emphysema are characterized by stiffness of the aorta, due in part to accelerated elastin degradation in the lungs and aorta. Stiffness of the pulmonary arteries (PAs) may also be increased in COPD and emphysema, but data are lacking. We assessed PA stiffness using MRI in patients with COPD and related these measurements to COPD severity and percent emphysema.
Materials and Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study recruited 290 participants, age 50–79 years with 10 or more packyears and free of clinical cardiovascular disease. COPD severity were defined on post-bronchodilator spirometry by ATS/ERS criteria. Percent emphysema was defined as the percentage of regions of the lung $<$ -950 Hounsfield units on full-lung computed tomography (CT). PA stain was defined by the percent change in cross-sectional PA area between systole and diastole on MRI. Blood flow across the tricuspid and mitral valves was assessed by phase-contrast MRI for determination of the ventricular diastolic dysfunction (E/A ratio).
Results: PA strain was reduced in COPD compared with controls ($P = 0.002$) and was inversely correlated with COPD severity ($P = 0.004$). PA strain was inversely associated to percent emphysema ($P = 0.01$). PA strain was also markedly correlated with right ventricular diastolic dysfunction measured by E/A ratios in the fully adjusted mix models ($P = 0.02$).
Conclusion: PA strain is reduced in COPD, related in part to percent emphysema on CT scan, which may have implications for pulmonary small vessel flow and right ventricular function.
Level of Evidence: 2
Technical Efficacy: Stage 1

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States.[1] COPD prevalence and mortality are increasing, particularly among women and minorities.[2] COPD is defined by accelerated, age-related loss in lung function resulting in incompletely reversible airway obstruction. Emphysema partially

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overlaps with COPD and is defined by loss of lung architecture and parenchyma due, classically, to accelerated degradation of elastin in the lung. Cigarette smoking is the primary cause of COPD and emphysema and as reported from a cohort study, fifty percent of elderly smokers eventually developed COPD.[3]

Various studies have noted that aortic stiffness, mainly assessed by carotid-femoral (aortic) pulse wave velocity using micromanometer applanation tonometry,[4,5] is abnormal in COPD and particularly in emphysema. Using this method, arterial stiffness was increased in COPD independent of cigarette smoking exposure.[4] The likely mechanism of this relationship is aberrant elastin degradation in the aorta.[6]

Pulmonary artery (PA) strain is an important factor in smoothing the pulsatile flow from right ventricle (RV) to the steady flow in the smaller pulmonary vessels. Pulmonary vascular wall stiffness is a contributor to RV afterload[7] and increased PA stiffness has been documented in pulmonary hypertension using MRI.[8] The proximal PA and aorta have similar elastin content between 5th and 9th decades[9]; hence, it is likely that PA stiffness is increased in COPD as reported in aortic stiffness.

We, therefore, hypothesized that strain of the main, right, and left PA, measured by the strain (variations of the PA dimensions) using MRI phase-contrast velocity mapping techniques, would be reduced in COPD, inversely associated with percentage of emphysema-like lung (hereafter referred to as percent emphysema) and inversely associated with measures of RV diastolic dysfunction.

Materials and Methods

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study enrolled cases of COPD and controls predominantly from two prospective population-based cohort studies, MESA and the EMphysema and Cancer Action Project (EMCAP),[10] who were age 50–79 years old with a 10 or more pack-year smoking history and who did not have clinical cardiovascular disease, stage IIIb-V kidney disease, asthma before age 45 years, other lung disease, prior lung resection, cancer, allergy to gadolinium, claustrophobia, metal in the body, pregnancy or weight $>$ 300 lbs. We selected all eligible participants at four sites in the MESA Lung Study, oversampled participants with COPD or emphysema from the remainder of MESA and from EMCAP, and selected a small number from the general outpatient community.

Protocols were approved by the institutional review boards of the participating institutions and the National Heart, Lung, and Blood Institute (NHLBI). Written informed consent was obtained from all participants.

Spirometry

Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[11] on a dry-rolling-sealed spirometer (Occupational Marketing, Inc., Houston, TX) following the MESA Lung protocol.[12] COPD was defined as a postbronchodilator ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC) < 0.70 following the ATS/ERS and GOLD definitions.[13] COPD severity was classified as: mild, $FEV_1 \geq 80\%$ predicted; moderate, 50–80% predicted; and severe, $FEV_1 < 50\%$ predicted.[13] Predicted values were calculated using the Hankinson reference equations[14] with a 0.88 correction for Asians.[12]

Percent of Emphysema-Like Lung

All participants underwent full-lung computed tomography (CT) scans on 64-slice helical scanners following the MESA-Lung/SPIROMICS full-inspiration protocol (0.984 pitch, 0.5 s, 120 kVp).[15] The milliamperes (mA) for MESA participants was based on body mass index (BMI): 145 for $<$20 kg/m^2, 180 for 20–30 kg/m^2 and 270 for $>$30 kg/m^2, and was set at 200 for non-MESA participants. Images were reconstructed at 0.625 mm. Image attenuation was assessed using APOLLO software (VIDA Diagnostics, Coralville IA) at a single reading center by trained readers without knowledge of other participant information. Percent emphysema was defined as the percentage of total voxels within the lung field that fell below -950 Hounsfield units.[16]

JMRI

All participants were imaged using one of four 1.5 Tesla (T) whole-body MRI systems (Signa LX, GE Healthcare, Waukesha, WI; Avanto or Espree, Siemens Medical Systems, Erlangen, Germany) with a phased-array coil for signal reception placed around the thorax with anterior and posterior elements selected around the heart. To determine the planes needed for the short axis images, electrocardiogram-gated, cardiac four-chamber and two-chamber view cine steady state free precession sequences were performed. Participants were instructed to hold their breath in expiration during imaging. To measure ventricular function, the entire heart was imaged in short-axis orientation with 12 or more slices. All cine images had an acquired temporal resolution of 48 ms, retrospectively reconstructed as 40 cine frames at 20- to 35-ms intervals over the cardiac cycle. Left and right ventricular heart function including myocardial mass (left ventricle [LV] only), volume, stroke volume, and ejection fraction was measured through contouring of the LV and RV.

To determine the planes needed for main PA images, we used an oblique localizer prescribed from axial and coronal images to visualize the natural curvature of the main pulmonary artery. For the main PA strain measurement, an imaging plane above the pulmonary valve but below the pulmonary bifurcation was used. The right PA was imaged in cross-section between the trachea and the ascending aorta. The left PA was prescribed close to the pulmonary trunk to avoid left upper lobe artery. Phase-contrast images were obtained using a segmented fast gradient echo sequence (repetition time 7.5 ms, echo time 3.1 ms, slice thickness 8 mm, matrix 256 $\times$ 256, two segments, time per acquired cine frame 30 ms, reconstructed by the retrospective gating software as 30 cardiac phases over the cardiac cycle, two averages, velocity encoding 100 cm/s) without breath hold. Strain of the PA was measured from the largest systolic and the smallest diastolic areas derived from the magnitude images by the following formula, *100$\times$(maximum area*

– *minimum area)/minimum area*. Thirty studies were randomly selected for inter-reader variability. The coefficient of variation of main PA strain was 0.06.

The same phase-contrast protocol was used to measure blood flow across the tricuspid and mitral valves for determination of the right and left ventricular filling. The resulting biphasic diastolic inflow pattern consists of two peaks, representing the early filling phase and the atrial contraction. Analysis of the early filling phase and the atrial contraction was performed by calculating their peak filling rates and ratio of the peak filling rates (E/A). All phase-contrast images were analyzed quantitatively using a fully automated software for the PA area segmentation thought the cardiac cycle (QFLOW 7.2, Medis, Leiden, The Netherlands) by an experienced analyzer (C.-Y. Liu) with 15 years of cardiac MRI experience, and CIM (Cardiac Imaging Modeling, the University of Auckland, New Zealand) for the cardiac function. MRI readers were blinded from other participant information.

DLco and Plethysmography

Single-breath DLco was measured for a subset of participants with a Sensormedics Autobox 220 Series instrument (Viasys Healthcare, Yorba Linda, CA) following ATS/ERS guidelines.[17] The average of all acceptable tests (minimum of two tests) was reported. Breath-hold time was assessed by the method of Jones and Meade.[18]

Body plethysmography was performed for a subset of participants using a V6200 Series Autobox (Sensormedics, Yorba Linda, CA) following ATS/ERS recommendations.[19] Predicted lung volumes were calculated from Crapo questions for patients under 65 years and Garcia-Rio equations for patients 65 years and older. Residual lung volume (RLV) was defined as the volume of gas remaining in the lung after maximal exhalation, while total lung capacity (TLC) was defined as the volume of gas in the lungs after maximal inspiration.

Covariates

Age, gender, race/ethnicity, educational attainment, pack-years, and medical history were self-reported. Medication use was assessed by medication inventory.[20] Height, weight, and blood pressure were measured following standardized MESA protocols.[21] Participants with a blood cotinine level greater than 25 ng/mL, or a urine level greater than 500 ng/mL or a self-report of current smoking were classified as current smokers. Oxygen saturation was measured by pulse oximeter, off oxygen. Glucose, total cholesterol, and high-density lipoprotein (HDL) levels and complete blood counts were measured from blood samples after a 12-h fast. Low-density lipoprotein (LDL) level was calculated using the Friedewald equation.[22]

Diabetes was defined as a fasting plasma glucose $\geq$ 126 mg/dL or a self-report of physician diagnosis. Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg or physician diagnosis.[23]

Statistical Analysis

The cohort was stratified by the presence and severity of COPD. Initial analyses used multivariable regression to assess the association of cardiovascular risk factors with PA strain adjusted for age, sex, race/ethnicity, height, and weight.

For the main analyses, we first used mixed effects models with random slopes and intercepts to examine the relationships of the strain using measurements from all three PAs with COPD endpoints of interest to assess overall PA strain and to account for multiple comparisons. If the mixed effects model yielded a statistically significant result, we then examined each PA individually. The base model (model 1) was adjusted for age, gender, height, weight, race/ethnicity, and cohort of selection, and the full model (model 2) was additionally adjusted for smoking status, pack-years, diabetes mellitus, hypertension, oxygen saturation, LDL, HDL, and statin use.

Given that the study was recruited based upon COPD status rather than as a cohort study, continuous analyses (e.g., for percent emphysema) were weighted proportionate to the inverse ratio of the sample prevalence to the source study prevalence. COPD cases recruited from the outpatient community were assigned the same weights as cases from EMCAP. The Pearson correlation coefficient (r) and unadjusted linear regression analysis were used to examine the association between pulmonary strain and diastolic function. Sensitivity analyses were performed without weighting. Statistical significance was defined by a two-tailed P-value < 0.05. Analyses were performed in SAS 9.2 (Cary, NC and R version 2.14.1 Vienna, Austria).

Results

The study sample included 290 participants with complete spirometry, CT, and main PA MR strain measurements. The mean age was 68.4 $\pm$ 6.6 years and 47% had COPD (40% mild, 48% moderate, and 12% severe). Fifty-nine percent were men. Twenty-seven percent smoked currently and the median pack-years was 33. The race/ethnic distribution was 56% Non-Hispanic white, 25% African-American, 13% Hispanic, and 6% Chinese-American.

The characteristics of the study sample, stratified by COPD severity, are shown in Table 1. Participants with more severe COPD were more likely to be male, Non-Hispanic white and have greater pack-years.

Pulmonary Artery Strain and Cardiac Risk Factors

Table 2 displays the individual partial correlation coefficient and P value of each parameter in multivariable analysis adjusted for age, sex, race, height, and weight. Strain of all PA was significantly decreased in current smokers. Higher DBP was inversely correlated to main PA strain and diabetes was associated with left PA strain. Main PA strain was negatively related to right ventricular end systolic volume ($P = 0.001$) but positively associated with right ventricular mass ($P = 0.04$). Right ventricular ejection fraction was also positively associated with the main ($P < 0.001$) and right ($P = 0.017$) PA strain.

Pulmonary Artery Strain and COPD

PA strain was reduced in COPD of all categories compared with controls in the fully adjusted mixed model ($P = 0.002$). Strain of the main PA was reduced in COPD compared with controls in the fully adjusted model (mean difference, -1.59%; 95% confidence interval [CI]: -3.10–-0.08:

TABLE 1. Clinical Characteristics of Participants in the MESA COPD Study Stratified by COPD Severity[a]

		COPD		
	Controls (n = 155)	**Mild (n = 54)**	**Moderate (n = 65)**	**Severe/Very Severe (n = 16)**
Age, mean ± SD, years	67.95 ± 6.55	70.15 ± 6.25	67.80 ± 7.36	68.75 ± 5.90
Sex, male, no. (%)	83 (53.55)	41 (75.93)	38 (58.46)	10 (62.50)
Race/ethnicity				
White, no. (%)	74 (47.74)	37 (68.52)	39 (60.00)	12 (75.00)
African American, no. (%)	36 (23.23)	12 (22.22)	19 (29.23)	4 (25.00)
Other, no. (%)	45 (29.03)	5 (9.26)	7 (10.77)	0 (0.0)
Educational attainment				
≤ High school degree, no. (%)	39 (25.16)	11 (20.37)	15 (23.08)	3 (18.75)
Some college/assoc. degree/ vocational school, no. (%)	52 (33.55)	12 (22.22)	14 (21.54)	5 (31.25)
≥ College degree, no. (%)	64 (41.29)	31 (57.41)	36 (55.38)	8 (50.00)
Height (cm)	167.11 ± 9.52	172.18 ± 7.66	170.37 ± 9.64	169.61 ± 11.52
Weight (kg)	80.39 ± 16.97	79.33 ± 15.25	79.73 ± 18.38	80.70 ± 24.85
BMI (kg/m^2)	28.66 ± 4.96	26.63 ± 3.98	27.29 ± 5.09	27.56 ± 6.21
Cigarette smoking status				
Former, no. (%)	121 (78.06)	41 (75.93)	39 (60.00)	12 (75.00)
Current, no. (%)	34 (21.94)	13 (24.07)	26 (40.00)	4 (25.00)
Pack-years of smoking, median (IQR)	27.0 (17.7, 43.5)	34.3 (25.0, 60.0)	39.6 (25.5, 51.8)	46.3 (22.5, 62.3)
LDL (mg/dL)	109.93 ± 32.05	104.15 ± 30.84	96.71 ± 29.20	100.31 ± 41.82
HDL (mg/dL)	54.84 ± 17.15	58.57 ± 17.62	59.14 ± 19.64	54.56 ± 20.98
Statin, no. (%)	52 (33.55)	25 (46.30)	31 (47.69)	5 (31.25)
SBP (mmHg)	119.91 ± 18.73	120.49 ± 16.66	123.78 ± 16.30	128.59 ± 12.89
DBP (mmHg)	69.61 ± 9.36	70.30 ± 9.06	71.61 ± 8.99	74.84 ± 8.82
Hypertension, no. (%)	65 (41.94)	23 (42.59)	32 (49.69)	7 (43.75)
Fasting plasma glucose, median (IQR),mg/dL	96 (91.0, 105.0)	96 (88.0, 107.0)	100 (93.0, 105.0)	93 (83.5, 107.0)
Diabetes Mellitus, no. (%)	24 (15.48)	5 (9.26)	9 (13.85)	4 (25.00)
FEV_1 percent of predicted	101.26 ± 15.64	92.15 ± 9.61	68.58 ± 8.29	39.56 ± 7.54
FVC percent of predicted	98.11 ± 15.14	107.25 ± 12.62	90.70 ± 12.93	73.78 ± 14.86
FEV_1/FVC ratio (%)	0.78 ± 0.05	0.64 ± 0.05	0.58 ± 0.09	0.40 ± 0.08
DLco % predicted (%), n = 106	68.15 ± 10.62	62.77 ± 11.27	54.45 ± 14.50	40.90 ± 10.48
DLco VA % predicted (%), n = 106	79.42 ± 13.11	67.76 ± 10.63	68.79 ± 19.46	61.07 ± 15.40
RLV % predicted (%), n = 106	71.33 ± 18.05	81.47 ± 17.78	97.64 ± 29.57	138.01 ± 36
RLV/TLC ratio (%), n = 106	0.32 ± 0.07	0.30 ± 0.06	0.39 ± 0.08	0.52 ± 0.08
Percent $emphysema_{-950}$, median (IQR)	1.26 (0.59, 2.85)	3.36 (1.84, 8.18)	3.50 (1.33, 7.93)	16.56 (7.15, 24.80)
Oxygenation saturation (%)	99.94 ± 49.43	95.90 ± 4.70	96.16 ± 3.85	95.90 ± 2.03

TABLE 1: Continued

		COPD		
	Controls (n = 155)	**Mild (n = 54)**	**Moderate (n = 65)**	**Severe/Very Severe (n = 16)**
Sleep apnea, self-reported, No (%)	10 (6.45)	2 (3.70)	7 (10.77)	3 (18.75)
LV E/A ratio	0.93 ± 0.28	0.88 ± 0.29	0.92 ± 0.41	0.88 ± 0.26
RV E/A ratio	0.83 ± 0.39	0.81 ± 0.34	0.75 ± 0.29	0.73 ± 0.33
LV end-diastolic volume (mL)	120.38 ± 31.00	120.61 ± 28.47	114.84 ± 30.46	102.80 ± 42.94
LV end-systolic volume (mL)	47.09 ± 17.94	47.17 ± 15.73	47.23 ± 17.65	42.85 ± 21.11
LV mass (g)	125.66 ± 32.91	132.44 ± 32.58	130.17 ± 36.66	131.93 ± 40.47
LV stroke volume (mL)	73.29 ± 17.37	73.43 ± 18.01	67.61 ± 18.41	59.98 ± 23.84
LV ejection fraction (%)	61.50 ± 6.84	61.20 ± 7.55	59.17 ± 7.71	59.24 ± 7.05
RV end-diastolic volume (mL)	131.31 ± 33.42	137.59 ± 34.57	123.42 ± 33.12	111.06 ± 45.44
RV end-systolic volume (mL)	53.98 ± 21.56	57.01 ± 23.02	51.46 ± 22.04	50.30 ± 31.99
RV mass (g)	22.49 ± 9.50	21.79 ± 8.71	20.82 ± 8.67	22.23 ± 9.31
RV stroke volume (mL)	77.33 ± 18.70	80.57 ± 18.80	71.97 ± 17.38	60.76 ± 19.17
RV ejection fraction (%)	59.68 ± 8.45	59.36 ± 9.26	59.54 ± 9.84	57.09 ± 9.83
Main PA maximum area (cm^2)	6.94 ± 1.76	7.02 ± 1.84	7.45 ± 1.98	7.92 ± 1.91
Main PA minimum area (cm^2)	6.03 ± 1.56	6.22 ± 1.74	6.61 ± 1.88	7.06 ± 1.80
Right PA maximum area (cm^2)	4.51 ± 1.20	4.73 ± 1.07	4.72 ± 1.24	5.37 ± 1.37
Right PA minimum area (cm^2)	3.76 ± 1.08	3.94 ± 0.89	4.05 ± 1.18	4.6 ± 1.24
Left PA maximum area (cm^2)	4.26 ± 1.20	4.60 ± 1.21	4.53 ± 1.29	5.53 ± 1.33
Left PA minimum area (cm^2)	3.63 ± 1.10	4.03 ± 1.10	3.93 ± 1.18	4.8 ± 1.25

[a]Values express in mean ± SD unless specified otherwise.
IQR = interquartile range.

$P = 0.04$), as was strain of the right and left PA ($P = 0.01$ and $P < 0.001$), respectively.

PA strain was also reduced across categories of COPD severity in the fully adjusted mixed model ($P = 0.004$). The association of COPD severity and main PA strain was slightly attenuated in the full model but those for right and left PA strain were robust (Table 3).

Pulmonary Strain and Percent Emphysema

PA strain was inversely related to percent emphysema in the fully adjusted mixed model ($P = 0.01$). The significance of this association varied somewhat by vessel (Table 4). Figure 1 shows the relationship of the continuous measures of percent emphysema and right PA strain in the fully adjusted model. Right PA strain decreased quickly and plateaued as percent emphysema increased.

PA Strain and Measures of Diastolic Dysfunction

Diastolic function assessed by ventricular flow E/A ratio was performed in a subset of 194 subjects. PA strain was significantly related to measures of RV and LV diastolic function in the univariable analyses. Pearson correlations between main, right, and left PA strain and RV E/A ratio were 0.67, 0.45 and 0.36, respectively (all $P < 0.001$). Figure 2 demonstrates a significant positive correlation between main PA strain and RV E/A ratio. Similar correlations also existed between main, right and left PA strain and LV E/A ratio (Pearson correlation r = 0.37, 0.45, and 0.25, respectively; all $P < 0.001$). However, only RV E/A ratio was significantly related to PA strain in the fully adjusted mixed model ($P = 0.02$).

Both RV and LV E/A ratios in COPD were impaired compared with controls, but these differences did not attain statistical significance ($P = 0.3$ and 0.06 for RV and LV E/A, respectively).

Pulmonary Strain and Hyperinflation

In contrast to findings for COPD and percent emphysema, there was little evidence for an association between PA strain with diffusing capacity or measures of pulmonary hyperinflation in the subset with available measures (Table 5).

TABLE 2. Association of Cardiac Risk Factors and PA Strain in the MESA COPD Study[a]

	Strain (%)		
	Main PA	**Right PA**	**Left PA**
Smoking status	−0.182 (**0.002**)	−0.216 (**<0.001**)	−0.216 (**<0.001**)
Diabetes	−0.061 (0.30)	−0.087 (0.16)	−0.166 (**0.007**)
Fasting plasma glucose	−0.069 (0.25)	−0.084 (0.18)	−0.125 (**0.043**)
Hypertension	0.067 (0.26)	−0.062 (0.32)	−0.052 (0.40)
SBP	−0.053 (0.37)	−0.036 (0.56)	−0.009 (0.88)
DBP	−0.159 (**0.008**)	−0.139 (**0.02**)	0.068 (0.27)
Hypercholesterolemia	−0.030 (0.62)	−0.054 (0.38)	0.012 (0.84)
LDL	0.011 (0.86)	−0.059 (0.34)	0.015 (0.81)
HDL	0.055 (0.36)	0.074 (0.23)	0.76 (0.22)
RV end diastolic volume	−0.093 (0.12)	−0.024 (0.704)	−0.015 (0.817)
RV end systolic volume	−0.196 (**0.001**)	−0.098 (0.117)	−0.026 (0.681)
RV mass	0.123 (**0.04**)	0.105 (0.09)	0.007 (0.91)
RV stroke volume	0.079 (0.188)	0.080 (0.20)	0.007 (0.917)
RV ejection fraction	0.255 (**<0.001**)	0.150 (**0.017**)	0.033 (0.598)

[a]Partial coefficients (*P*-value, bold for $P < 0.05$) from correlation coefficients adjusted for age, sex, race, height, and weight.

TABLE 3. Predicted Mean Difference of Pulmonary Artery Strain in the MESA COPD Study by COPD Severity[a]

	Controls n = 155	**Mild n = 54**	**Moderate n = 65**	**Severe n = 16**	***P*−Trend**
Strain of main PA, %					
Model 1, mean difference	Reference	−1.49	−1.44	−2.78	0.04
Model 1, predicted mean	15.41	13.92	13.97	12.63	
Model 2, mean difference	Reference	−1.48	−1.44	−2.56	0.08
Model 2, predicted mean	15.40	13.92	13.96	12.84	
	n = 143	n = 50	n = 62	n = 14	
Strain of right PA, %					
Model 1, mean difference	Reference	−0.58	−3.30[b]	−3.83	0.005
Model 1, predicted mean	20.59	20.01	17.29	16.76	
Model 2, mean difference	Reference	−0.93	−3.62[b]	−3.85	0.01
Model 2, predicted mean	20.67	19.74	17.05	16.82	
Strain of left PA, %					
Model 1, mean difference	Reference	−4.17[b]	−3.34[b]	−4.08	0.002
Model 1, predicted mean	18.26	14.09	10.75	14.18	
Model 2, mean difference	Reference	−4.63[b]	−3.33[b]	−2.66	0.003
Model 2, predicted mean	18.25	13.62	14.92	15.59	

[a]Model 1 adjusted for age, race, gender, height, weight, and cohort. Model 2 adjusted for variables in model 2 in addition to smoking status, pack years, educational attainment, diabetes mellitus, hypertension, oxygen saturation, LDL, HDL, and statin use.
[b]$P < 0.05$.

TABLE 4. Predicted Mean Levels of PA Strain in the MESA COPD Study by Percent Emphysema[a]

	Percent emphysema					Difference per log increase in percent emphysema (95% CI)	*P*-Value
	Quintile 1 (n = 58)	Quintile 2 (n = 56)	Quintile 3 (n = 58)	Quintile 4 (n = 57)	Quintile 5 (n = 58)		
Strain of main PA							
Model 1, predicted value	15.40	14.92	14.63	14.34	13.86	-0.44 (-1.13, 0.25)	0.21
Model 2	16.03	15.29	14.86	14.41	13.68	-0.67 (-1.33, -0.01)	0.049
	(n = 53)	(n = 53)	(n = 53)	(n = 54)	(n = 53)		
Strain of right PA							
Model 1, predicted value	23.01	22.00	21.40	20.77	19.77	-0.92 (-1.92, 0.098)	0.07
Model 2	21.84	20.54	19.77	18.97	17.69	-1.18 (-2.50, -0.26)	0.01
Strain of left PA							
Model 1, predicted value	19.47	19.16	18.98	18.79	18.49	-0.28 (-1.18, 0.63)	0.55
Model 2	18.35	17.65	17.23	16.80	16.10	-0.64 (-1.51, 0.24)	0.15

[a]Model 1 adjusted for age, race, gender, height, weight, and cohort. Model 2 adjusted for variables in model 2 in addition to smoking status, pack years, educational attainment, diabetes mellitus, hypertension, oxygen saturation, LDL, HDL, statin use and mAs.

Sensitivity Analyses

Similar associations for strain and COPD were observed in analyses additionally adjusted for systolic and DBP, LV stroke volume, LV end diastolic volume, and mass, white blood cell (WBC) count, and cardiac output (Fig. 3). The results also did not change after restriction of the sample to MESA and EMCAP cohorts, former smokers, white participants, and those without diabetes or sleep apnea. The association between right PA strain and COPD was greater among participants with hypertension and attenuated among participants without hypertension (interaction *P*-value = 0.02), although additional adjustment SBP and DBP (in addition to hypertension) had no impact on the results (Fig. 3).

Discussion

In this relatively large MRI study of predominantly mild-moderate COPD, PA strain was independently reduced in COPD and was inversely associated with severity of COPD and percent emphysema on CT scan. These findings are important to cardiopulmonary function as PA stiffening affects pulmonary blood flow,[24] reduces functional

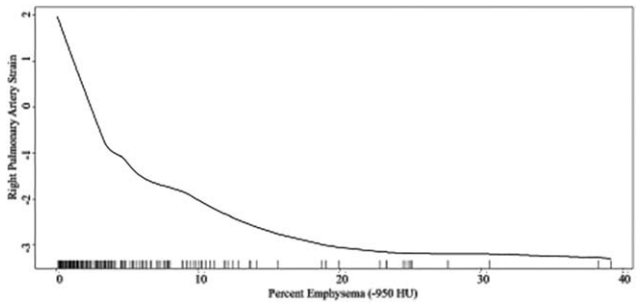

FIGURE 1: Multivariable relationship between right pulmonary artery strain and percent emphysema. Tick marks above the x-axis represent observed emphysema measures. The predicted change in PA strain is represented by the dark line and was obtained from a smoothed regression model adjusted for age, race, gender, height, weight, cohort, smoking status, pack years, educational attainment, diabetes mellitus, hypertension, oxygen saturation, LDL, HDL, statin use, and high mAs.

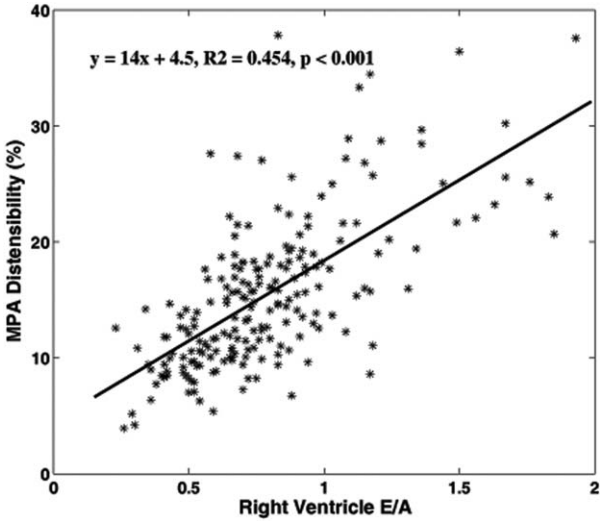

FIGURE 2: Main pulmonary artery strain and E/A ratio of the RV. Main PA strain was significantly correlated to RV E/A ratio.

TABLE 5. Association of Main PA Strain between Diffusing Capacity and Hyperinflation[a]

N = 87	DL_{CO} (per mL CO/min/mm Hg increase)	*P*-Value	DL_{CO}/VA (per unit increase)	*P*-Value	RLV (per mL increase)	*P*-Value	RLV/TLC ratio (per unit increase)	*P*-Value
Main PA strain								
Model 1 mean difference	−0.058 (−0.640, −0.527)	0.047	−0.011 (−0.023, 0.000)	0.06	0.003 (−0.006, 0.011)	0.54	0.000 (−0.001, 0.002)	0.51
Model 2 mean difference	−0.045 (−0.011, 0.010)	0.12	−0.010 (−0.001, 0.021)	0.08	0.003 (−0.005, 0.011)	0.46	0.001 (−0.001, 0.002)	0.44

[a]Model 1 adjusted for age, race, gender, height, weight, and cohort. Model 2 adjusted for variables in model 2 in addition to smoking status, pack years, educational attainment, diabetes mellitus, hypertension, oxygen saturation, LDL, HDL, statin use and mAs.

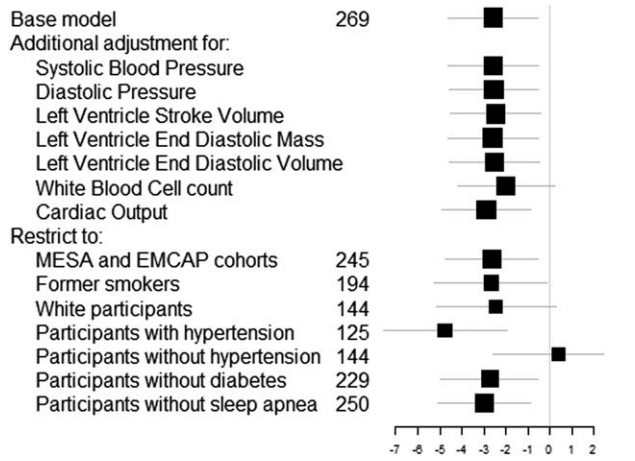

FIGURE 3: Sensitivity analysis of right pulmonary artery strain with COPD status. Predicted mean difference in base model adjusted for age, gender, race/ethnicity, cohort, smoking status, pack-years, height, weight, diabetes mellitus, hypertension, oxygen saturation, WBC count, sleep apnea, HDL, and statin use. Inclusion of co-variate, population subset, or dependent variable indicated.

capacity,[25] and is a significant contributor to increased right ventricular afterload.[7]

In a study by Vonk-Noordegraaf et al,[26] right PA strain was examined in 25 COPD patients with mild hypoxemia, and no difference was found compared with age-matched controls. However, our results are consistent with prior work in pulmonary arterial hypertension, which demonstrated similar findings.[8,27] Using MRI methods, Sanz et al[8] showed increased PA stiffness in patients with pulmonary hypertension at rest in comparison with those with exercise-induced or no pulmonary hypertension. Another study by Lau and co-workers[27] also reported increased stiffness in the proximal elastic PA in patients with pulmonary hypertension using intravascular ultrasound.

Our findings are also consistent with several prior studies of aortic stiffness in COPD. Mills et al[28] reported that patients with COPD had increased arterial stiffness compared with matched controls assessed as elevated augmentation pressures and a reduced time to wave reflection. McAllister et al[5] showed that arterial stiffness was increased with emphysema severity in patients with COPD. On the other hand, there was no association between proximal aortic strain measured by MRI phase contrast images and pulmonary function or percent emphysema in the larger MESA Lung Study.[29]

A likely mechanism underlying both PA and aortic stiffness in COPD and emphysema is loss of elastin in the lungs and the major vessels. Abnormal elastin degradation is clearly described in emphysema pathogenesis[30] and systematic elastin degradation outside of the lung in COPD was demonstrated by Maclay et al,[6] who showed enhanced skin elastin degradation in COPD patients compared with controls and was in association with emphysema severity and

carotid-femoral pulse wave velocity. Other COPD-related effects on the vasculature are also possible, including systematic inflammation, which is elevated in COPD[31] and correlates with aortic pulse wave velocity.[32]

PA strain was quite highly correlated with RV E/A ratio, which suggests that PA stiffness may contribute to RV diastolic dysfunction in COPD. Similar observations have been observed for aortic compliance and left ventricular diastolic dysfunction in a community-based cohort study,[33] in type 2 diabetes mellitus,[34] and in hypertensive hearts.[35] Vascular stiffness expresses opposition to steady flow. However, for the complete description of the RV-PA interaction, pulsatile properties, which are expressed by PA input impedance spectrum, must be taken into account. Characteristic PA input impedance was elevated in pulmonary hypertension and cor pulmonale patients.[36] Reduced pulmonary strain increases the impedance to outflow from the RV and contribute as much as 30% to 40% of the increase in load to which the RV is exposed.[37] It has been hypothesized that this increase in stiffness, which is associated with vascular remodeling in the proximal vessel, might be initiated by endothelial dysfunction in COPD[38] and leads to obstruction of the delivery of blood flow from RV and ultimately results in a loss of pulmonary flow during diastole. Previous study has revealed that greater residual lung volume was associated with larger PA area.[39] However, no relationship between residual lung volume and PA strain was found in the current study.

An unexpected finding was that the association of COPD with right PA strain was modified by hypertension. This was not explained by a possible treatment effect of antihypertensive drugs (data not shown) and may be a false positive finding. Possible explanations include hypertension being a marker for stiffness of the entire vascular system, with increased susceptibility to PA stiffness, endothelial dysfunction affecting both the systemic and pulmonary vasculature, or transmitted increased LV afterload. The last of these seems unlikely given the lack of change with adjustment for LV parameters.

The major limitation of this study is that cardiac catheterization was not performed in these patients. However, we did not expect participants with severe pulmonary hypertension in this study because patients who have clinical cardiovascular disease were excluded in the recruitment. Even though a large number of participants were examined in the study, the sample size of severe COPD was relatively small; hence, it is possible (although in our opinion unlikely) that the results may not apply to very severe COPD. The cross-sectional nature of the study does not allow casual relationships between pulmonary strain, diastolic function, COPD, and emphysema. Only a single reader for the MRI PA strain analysis may also be criticized; however, the software was robust which had been proven in the previous study.[40]

Results were generally consistent for main, right, and left PA but were weaker and more marginal for the main PA. This is likely due to greater variability in the assessment of the main PA, the tortuous course of which makes standardization of reading more challenging.

In conclusion, patients with COPD but without overt cardiovascular disease show increased PA stiffness, which is also related to percent emphysema on CT scan. The functional implications of this finding relate to RV load, and pulmonary strain was strongly related to the RV diastolic function.

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