Arterial Stiffness Is Independently Associated with Emphysema Severity in Patients with Chronic Obstructive Pulmonary Disease

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Rationale: More patients with chronic obstructive pulmonary disease (COPD) die of cardiovascular causes than of respiratory causes, and patients with COPD have increased morbidity and mortality from stroke and coronary heart disease. Arterial stiffness independently predicts cardiovascular risk, is associated with atheromatous plaque burden, and is increased in patients with COPD compared with control subjects matched for cardiovascular risk factors. Elastin fragmentation and changes in collagen are found in the connective tissue of both emphysematous lungs and stiff arteries, but it is not known whether the severity of arterial stiffness in patients with COPD is associated with the severity of emphysema.

Objectives: To identify whether the extent of arterial stiffness is associated with emphysema severity.

Methods: We performed a cross-sectional study in 157 patients with COPD.

Measurements and Main Results: We measured pulse wave velocity (a validated measure of arterial stiffness), blood pressure, smoking pack-years, glucose, cholesterol, and C-reactive protein in 157 patients with COPD. We assessed emphysema using quantitative computed tomography scanning in a subgroup of 73 patients. We found that emphysema severity was associated with arterial stiffness ($r = 0.471$, $P < 0.001$). The association was independent of smoking, age, sex, FEV₁% predicted, highly sensitive C-reactive protein and glucose concentrations, cholesterol-high-density lipoprotein ratio, and pulse oximetry oxygen saturations.

Conclusions: Emphysema severity is associated with arterial stiffness in patients with COPD. Similar pathophysiological processes may be involved in both lung and arterial tissue and further studies are now required to identify the mechanism underlying this newly described association.

Keywords: humans; elasticity; cardiovascular diseases; pulmonary emphysema

More patients with chronic obstructive pulmonary disease (COPD) die of cardiovascular causes and lung cancer than die of respiratory causes, and patients with COPD have high morbidity and mortality from stroke and coronary heart disease (1–3). Moreover, airflow limitation, as measured by FEV₁% predicted, is associated with cardiovascular risk, even after adjusting for

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Arterial stiffness, a marker of cardiovascular risk, is increased in patients with chronic obstructive pulmonary disease compared with matched control subjects and is associated with FEV₁% predicted in healthy men. The mechanism is unknown but systemic inflammation in chronic obstructive pulmonary disease has been implicated.

What This Study Adds to the Field

Emphysema severity is associated with arterial stiffness in patients with COPD. This association is independent of airflow limitation and systemic inflammation.

established cardiovascular risk factors, including age, sex, smoking, cholesterol, and socioeconomic deprivation (4, 5).

The biological mechanisms responsible for the association between COPD and cardiovascular disease are poorly understood, but early studies suggest that systemic inflammation in COPD may promote atherosclerosis (6). Arterial stiffness is a useful noninvasive measure of vascular function, is associated with atheromatous plaque burden (7), and is an independent predictor of cardiovascular events in subjects with diabetes (8), renal disease (9), hypertension (10), and in the general population (11). Arterial stiffness is not simply a measure of cardiovascular risk, because reduced vascular compliance itself increases cardiac afterload and reduces coronary blood flow, and promotes myocardial ischemia (12).

Arterial stiffness is associated with airflow limitation in healthy men (13), and Sabit and colleagues recently reported increased arterial stiffness in patients with COPD compared with control subjects matched for age, sex, blood pressure, and other cardiovascular risk factors (14). Together, these studies are important because they suggest a link between pulmonary and vascular disease that may explain a proportion of the excess cardiovascular mortality in patients with COPD.

The mechanism by which arterial stiffness is increased in patients with COPD is unknown. We suspect that impaired lung function and increased arterial stiffness in COPD may both be due to increased susceptibility to degradation of connective tissue in this group of patients. In the lung, elastin degradation leads to loss of alveolar attachments, decreased compliance, and emphysema (15). While in the arteries, age-related elastin degradation is associated with increased collagen, larger, thicker arteries, and increased arterial stiffness (12). Elastin is also involved in the regulation of vascular smooth muscle cells, changes in which may also contribute to arterial stiffness (16). Elastolytic activity (matrix metalloproteinase [MMP]-9 and MMP-12) is increased in both emphysema and arteriosclerosis, and both emphysema and

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arterial stiffness appear to be at least partly genetically determined (15, 17). Despite smoking being by far the largest risk factor for emphysema, the severity of emphysema is highly variable among smokers (18), and mouse models also demonstrate variation in their susceptibility to emphysema (19). In the Klotho mouse (a mouse model of accelerated aging), arteriosclerosis, emphysema, and loss of skin elasticity coexist (20), whereas in Marfan's syndrome (the human autosomal dominant condition characterized by defective fibrillin synthesis), aortic root arterial stiffness is characteristic, and emphysema has been described in never-smokers (21). Loss of skin elasticity is also associated with emphysema independent of age and smoking history, providing intriguing clinical evidence for the presence of loss of elasticity systemically in patients with COPD (22).

Therefore, we hypothesize that the extent of arterial stiffness is associated with the severity of emphysema in patients with COPD.

METHODS

Patients Studied

Blood pressure and arterial stiffness were measured in 177 subjects with COPD who participated in a cohort study designed to identify prognostic markers in COPD. During recruitment, ethical approval was obtained to perform high-resolution computed tomography (HRCT) of the chest. All subsequently enrolled subjects ($n = 73$) had HRCT scans. All studies were approved by the Lothian Regional Ethics Committee, and all subjects gave written, informed consent.

All subjects had a clinical history compatible with COPD, a history of risk factors (history of at least 10 pack-years of smoking) and evidence of chronic airflow limitation on spirometry (post-bronchodilator $FEV_1/FVC < 70\%$) (23). Subjects were not taking oral anti-inflammatory drugs, including corticosteroids. Subjects with systemic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) were excluded. Cardiovascular comorbidity was not an exclusion criterion but was carefully recorded. Visits were performed when subjects were clinically stable (≥ 4 wk since last exacerbation as defined by a worsening of symptoms requiring intervention with antibiotic therapy or oral corticosteroids).

Height, weight, and post-bronchodilator spirometry were measured (Alpha Spirometer; Vitalograph, Buckingham, UK) according to American Thoracic Society/European Respiratory Society standards in all subjects (24). Venous blood was sampled and stored at -80°C for subsequent analysis. Serum C-reactive protein (CRP) concentrations were measured using a highly sensitive immunonephelometric assay (Behring BN II nephelometer; Dade Behring, Marburg, Germany). Glucose and cholesterol were measured in the locally accredited clinical biochemistry laboratory (Olympus Analyzers, Center Valley, PA). Oxygen saturations were measured at rest breathing air by pulse oximetry (Nellcor Puritan Bennett Sensor; Nellcor, Pleasanton, CA). Individuals who underwent HRCT also had six-minute-walk tests in accordance with American Thoracic Society guidelines (25).

Hemodynamic Studies

Arterial stiffness and peripheral blood pressure measurements were obtained before spirometry and venipuncture in a quiet, temperature-controlled room, with subjects resting supine at 15° . Patients had abstained from smoking, caffeine, and all medications on the day of the test. Systolic and diastolic blood pressures were measured in duplicate using an automated noninvasive oscillometric sphygmomanometer (Omron 705IT; Milton Keynes, UK) after a 10-minute rest period.

After 30 minutes of rest, arterial stiffness was measured using pulse wave velocity (PWV) by specifically trained staff. PWV measures the rate at which the systolic pressure wave travels to the peripheral vasculature. Faster wave transit times reflect stiffer arteries. We used the Q-wave of a simultaneously recorded ECG to identify the onset of the pressure wave, and used applanation tonometry (Millar Instruments, Houston, TX) at the carotid and radial arteries to record the pressure waveform at the peripheral site. The SphygmoCor system

(AtCor Medical, Sydney, Australia) software applied an intersecting tangent algorithm to identify the onset of the wave. The difference in wave transit time between the carotid and radial sites was used to calculate the PWV.

Quality-control checks were made for all measurements according to manufacturer's guidelines (26). Results with a standard deviation of 15% or greater were not included in the analysis, nor were measurements with a standard deviation of 10 to 15% in which the onset of the waveform was not clearly identified.

CT Imaging

HRCT scanning of the lungs was performed at full inspiration using a 16-slice multidetector-row CT scanner (135 kV, 20 mAs; Toshiba Aquilion, Toshiba, Japan). Patients were coached to perform full inspiration. Contrast media was not administered. Images were reconstructed with a slice thickness of 5 mm and 2.5-mm increment using an FC-03 filter (Toshiba). The calibration of air CT density measurements was made using a background air region above the sternum. Emphysema was quantified by in-house software using the 15th percentile point of the frequency distribution of lung density and pixel index for -950 and -910 Hounsfield units (27–29).

Data Analysis

Analysis was performed using SPSS version 14 (SPSS, Inc., Chicago, IL). A univariate analysis of PWV on all variables of interest was performed in the subgroup who underwent HRCT of the chest (Pearson's correlation and independent sample t tests as appropriate). Backward multiple linear regression of PWV on the variables found to be significant (at the $P < 0.1$ level) in the univariate analysis was performed. Significance was taken at the $P < 0.05$ level. This analysis was repeated in the full cohort, including those with and without measures of emphysema (Table E2 in the online supplement).

RESULTS

PWV was performed in 177 patients with COPD, with satisfactory measurements obtained in 157 patients. The full cohort ($n = 157$) and HRCT subgroup ($n = 73$) were similar for all clinical, laboratory, hemodynamic, and spirometric characteristics (Table 1).

In the full cohort, PWV was higher in men, and there were statistically significant associations (at $P < 0.05$) between PWV and height, oxygen saturations, $FEV_1\%$ predicted, FEV_1/FVC , heart rate, and blood pressure. There was no association between CRP and PWV, or between smoking pack-years and PWV (Tables 2 and 3).

In the subgroup of patients who underwent HRCT, height, body mass index (BMI), heart rate, diastolic pressure, $FEV_1\%$ predicted (Figure 1), and FEV_1/FVC , were associated with PWV on univariate analysis (Table 2). PWV was higher in patients with severe and very severe COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stage 3 and 4) than in those with mild and moderate disease (GOLD stage 1 and 2; 9.05 vs. 8.37 m/s, $P = 0.004$), and was greater in men than women (0.99 m/s, $P = 0.006$), but there was no difference in PWV between subjects with or without a history of ischemic heart disease or between current and ex-smokers (Table 3). Pack-years of smoking history was not associated with PWV ($r = -0.180$, $P = 0.132$), or with emphysema severity ($r = -0.96$, $P = 0.428$, Figure E1). No relationship was found between high-sensitivity CRP (hsCRP) and PWV, or between leukocytes and PWV (Table 2). There was a robust and highly significant correlation between PWV and severity of emphysema regardless of which measure was used ($P < 0.001$; Table 2, Figure 1).

After multiple linear regression modeling, severity of emphysema ($r^2 = 0.13$, $P = 0.002$) and mean arterial pressure ($r^2 = 0.08$, $P = 0.043$) were the factors most closely associated with

TABLE 1. PATIENT CHARACTERISTICS

	All Subjects	Non-HRCT	HRCT Subjects
No. subjects	157	84	73
Age, yr	67.9 (7.6)	67.9 (8.0)	67.9 (7.2)
Male, n (%)	92 (59%)	46 (55%)	46 (63%)
Height, cm	166.5 (10.0)	165.4 (9.5)	167.9 (10.4)
Weight, kg	71.3 (18.1)	68.32 (17.4)	74.6 (18.4)
BMI, kg/m ²	25.6 (5.6)	24.9 (5.5)	26.4 (5.8)
Clinical			
Oxygen saturations*	96 (94–97)	96 (95–98)	96 (94–97)
SGRQ total score*	50 (33–63)	50 (35–67)	49 (32–61)
Pack-years smoking*	40 (30–56)	43 (25–50)	40 (30–52)
Current smoker	62 (39%)	38 (45%)	24 (33%)
Chronic bronchitis	74 (50%)	37 (44.6%)	37 (58%)
Ankle edema	37 (24%)	21 (25%)	16 (22%)
Inhaled corticosteroid	103 (66%)	54 (64%)	49 (67%)
Long-acting β -agonist	83 (53%)	47 (56%)	36 (49%)
History of ischemic heart disease	32 (20%)	19 (23%)	13 (18%)
History of hypercholesterolemia	21 (13%)	11 (13%)	10 (14%)
History of diabetes	3 (2%)	1 (1%)	2 (3%)
Spirometry			
FEV ₁ , L	1.29 (0.58)	1.21 (0.56)	1.37 (0.59)
FEV ₁ /FVC	49 (14)	49 (15)	50 (13)
FEV ₁ % predicted	51 (20)	50 (20)	53 (20)
Hemodynamic			
Heart rate	69 (11)	69 (10)	69 (11)
Systolic pressure, mm Hg	144 (23)	144 (24)	144 (21)
Diastolic pressure, mm Hg	81 (11)	80 (11)	81 (12)
Pulse pressure, mm Hg	64 (19)	64 (20)	63 (17)
Mean arterial pressure, mm Hg	102 (13)	101 (12)	102 (13)
Pulse wave velocity, m/s	8.69 (1.51)	8.55 (1.52)	8.85 (1.50)
Laboratory			
Glucose, mmol/L	6.12 (1.28)	6.03 (1.23)	6.13 (1.33)
Cholesterol:HDL ratio	3.74 (1.09)	3.71 (1.14)	3.77 (1.04)
White cell count, $\times 10^9$ /L	7.48 (2.10)	7.43 (2.28)	7.55 (1.87)
Neutrophil count, $\times 10^9$ /L	4.79 (1.67)	4.91 (1.88)	4.65 (1.40)
Platelet count, $\times 10^9$ /L	262 (66)	260 (67)	263 (65)
CRP, mg/L*	3.66 (1.87–7.25)	3.76 (1.98–8.32)	3.48 (1.67–6.72)

Definition of abbreviations: BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; HRCT = high-resolution computed tomography; SGRQ = St. George's Respiratory Questionnaire.

Values represent mean (SD) or number (%), except where indicated otherwise.

* Median (interquartile range).

PWV, with BMI and gender almost reaching statistical significance (Table 4). The full model, prior to the removal of any variables, has been included on the online supplement (Table E1). In the full cohort of 157 patients including those with and without emphysema measures, height, BMI, diastolic blood pressure, and heart rate were found to be independently associated with PWV on backward multiple linear regression (Table E2).

DISCUSSION

We have shown that emphysema severity is associated with arterial stiffness independent of cigarette smoking. The association is also independent of age, sex, blood pressure, hsCRP, dyslipidemia, inflammation, hypoxemia, and airflow obstruction. Arterial stiffness increases cardiac afterload, impairs coronary blood flow (12), and is associated with increased cardiovascular risk in a number of conditions as well as in the general population (7–11). As such, the association between emphysema and arterial stiffness is likely to be clinically significant, as well as highly statistically significant.

The association that we found between arterial stiffness and emphysema severity was independent of low BMI, airflow limitation, and the subject's six-minute-walk distance, all of which are markers of COPD severity (30). No marker of cardiovascular risk has been validated in a COPD population. However, because arterial stiffness has previously been shown to be higher in patients

with COPD than in control subjects (14), and because we have shown that that severity of emphysema is associated with arterial stiffness independent of COPD severity, longitudinal studies are now required to identify whether patients with COPD with an emphysematous phenotype are at increased cardiovascular risk compared with patients with a nonemphysematous phenotype.

In a previous study, by Sabit and colleagues, PWV was associated with IL-6, and the authors postulated that the increased systemic inflammation seen in COPD may be responsible for the observed increase in arterial stiffness (14). In a larger cohort, we did not find any association between PWV and hsCRP, whose release is stimulated by IL-6. Nor did we find a relationship between emphysema severity and hsCRP. As such, our results do not support the hypothesis that systemic inflammation is an important cause of arterial stiffness in patients with COPD. Nonetheless, we used a different measure of PWV than Sabit and colleagues (14), and there may be other circulating inflammatory factors, oxidized lipids or proteins that, through their effect on endothelium and smooth muscle, link the lung inflammation and oxidative stress that are found in patients with emphysema to the development of arterial stiffness.

Another possible mechanism to explain the association between emphysema severity and arterial stiffness is hypoxia. We did not find an association between pulse oximetry oxygen saturations and arterial stiffness after controlling for other variables. Although pulse oximetry does not directly measure tissue hypoxia,

TABLE 2. ASSOCIATIONS BETWEEN CONTINUOUS VARIABLES AND PULSE WAVE VELOCITY IN THE FULL COHORT AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY SUBGROUP (PEARSON'S CORRELATIONS)

	All Subjects (n = 157)		HRCT Subjects (n = 73)	
	r Value	P value	r Value	P value
Age	-0.013	0.868	-0.137	0.246
Clinical				
Height, cm	0.266	0.001*	0.279	0.017*
Weight, kg	-0.020	0.806	-0.332	0.332
BMI, kg/m ²	-0.155	0.052†	-0.280	0.016*
Oxygen saturations	-0.167	0.039‡	-0.114	0.336
SGRQ total score	0.073	0.366	-0.072	0.547
Pack-years smoking	-0.023	0.780	-0.180	0.132
Six-minute-walk distance, m	N/A	N/A	0.074	0.576
Spirometry				
FEV ₁ , L	-0.012	0.881	0.029	0.805
FEV ₁ /FVC	-0.295	<0.001†	-0.419	0.001*
FEV ₁ % predicted	-0.208	0.009†	-0.243	0.038‡
Laboratory				
Glucose, mmol/L	0.138	0.085†	-0.024	0.843
Cholesterol:HDL ratio	-0.048	0.562	-0.082	0.496
Log CRP	-0.63	0.435	-0.199	0.093†
White cell count	0.023	0.772	0.023	0.846
Neutrophil count	0.039	0.634	-0.026	0.828
Platelet count	-0.042	0.615	<0.001	>0.999
Hemodynamic				
Heart rate	0.246	0.002*	0.231	0.049‡
Systolic pressure, mm Hg	0.180	0.024†	0.125	0.293
Diastolic pressure, mm Hg	0.403	<0.001*	0.367	0.001*
Mean arterial pressure, mm Hg	0.332	<0.001*	0.282†	0.016‡
Pulse pressure, mm Hg	-0.027	0.740	-0.095	0.423
Emphysema indices				
-950 HU pixel index	N/A	N/A	0.471	<0.001*
-910 HU pixel index	N/A	N/A	0.476	<0.001*
15th Percentile density, HU	N/A	N/A	-0.409	<0.001*

Definition of abbreviations: BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; HRCT = high-resolution computed tomography; HU = Hounsfield units; SGRQ = St. George's Respiratory Questionnaire.

* $P < 0.01$.

† $P < 0.1$.

‡ $P < 0.05$.

it seems unlikely, given the relatively large regression coefficient we found, that tissue hypoxia could completely account for the observed association between emphysema and PWV, even with a measure such as mixed venous oxygenation.

TABLE 3. MEAN DIFFERENCE IN PULSE WAVE VELOCITY BETWEEN DICHOTOMOUS GROUPS IN THE FULL COHORT AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY SUBGROUP*

	Full Cohort (n = 157)		HRCT Subgroup (n = 73)	
	m/s	P Value	m/s	P Value
Gender	0.783	0.001†	0.99	0.006‡
Current smoking	0.181	0.464	0.30	0.418
Chronic bronchitis	0.338	0.173	0.25	0.509
Ankle edema	0.369	0.195	0.05	0.906
Inhaled corticosteroid	0.023	0.929	0.42	0.322
Long-acting β -agonist	0.156	0.521	0.47	0.182
Ischemic heart disease	0.351	0.242	0.34	0.480
Hypercholesterolemia	0.591	0.095§	0.80	0.124

Definition of abbreviation: HRCT = high-resolution computed tomography.

* t Tests.

† $P < 0.05$.

‡ $P < 0.01$.

§ $P < 0.1$.

There are a number of pathologic features common to arterial stiffness and emphysema, which suggest that, in some individuals with COPD, there may be an acquired or inherited tendency to develop emphysema and arterial stiffness. Elastin loss (15) and increased alveolar septal thickening (31) occur in emphysema, whereas in stiff arteries, elastin fragmentation is found, together with increased numbers of collagen fibers, and increased vessel lumen size and thickness (12). In humans, a polymorphism in gelatinase B (MMP-9) is associated with increased risk of arterial stiffness (32, 33) as well as upper zone emphysema (34). In Marfan's syndrome, increased aortic root stiffness is well described and has important clinical consequences, but these patients may also develop emphysema even in the absence of cigarette smoke exposure (21).

Increased levels of MMP-9 are found both in bronchoalveolar lavage (35) and sputum (36) in subjects with emphysema, and levels of MMP-9 are increased in the serum of subjects with arterial stiffness (37). MMP-12 (macrophage elastase) knockout mice are protected against cigarette smoke-induced emphysema compared with wild-type mice (38), and MMP-12/apoE-deficient mice are protected against elastin degradation in atherosclerosis compared with single-deficiency apoE mice (39). Finally, the Klotho mouse (a model of accelerated aging) develops early emphysema, loss of skin elasticity, and increased arterial stiffness (20). Subjects with an emphysematous phenotype of COPD may therefore have a systemic susceptibility to lung, skin, and arterial connective tissue damage.

Lung and artery susceptibility to connective tissue damage could be due to congenital variation in the synthesis, destruction, and/or repair of extracellular matrix. Factors we were unable to measure, such as low birth weight, poor diet, recurrent infection, and environmental pollution, might plausibly increase the susceptibility of both the lung and vasculature to connective tissue destruction, particularly in early life (40–43). Furthermore, recent evidence that COPD may have an autoimmune component characterized by an abnormal immune response to elastin (44) is of interest, as an autoimmune mechanism linking arterial stiffness to emphysema might be amenable to therapeutic intervention. Further work is needed to elucidate these potential mechanisms, and to identify whether there are similar associations between loss of lung tissue and arterial stiffness in individuals without COPD.

Limitations of this Study

In this study, we performed PWV measurement using the carotid–radial method, which is associated with coronary artery plaque burden, and increases linearly with age (45, 46). Using this technique allowed us to perform PWV with subjects lying supine at 15°, which meant we could include patients with severe dyspnea. However, carotid–femoral PWV (in which the tonometer is placed over the femoral artery), rather than carotid–radial PWV, is now the recognized “gold standard” measure of arterial stiffness (47). Carotid–femoral PWV has been shown to predict cardiovascular risk in longitudinal studies, and because it measures stiffness in the central arteries, which have comparatively little smooth muscle, carotid–femoral PWV is largely unaffected by changes in smooth muscle remodeling and vascular tone (47). No measure of arterial stiffness has been validated as a marker of cardiovascular risk in a COPD population. However, if we had shown an association between emphysema severity and arterial stiffness using carotid–femoral rather than carotid–radial PWV, a stronger case could have been made for emphysematous patients being at increased cardiovascular risk.

Nevertheless, in this cohort, using carotid–radial PWV we replicated the findings reported previously that arterial stiffness is higher in patients with severe COPD than in patients with

Figure 1. Associations between emphysema severity, FEV₁% predicted and arterial stiffness in the high-resolution computed tomography subgroup. Scatter plots of pulse wave velocity on emphysema severity (A), and airflow limitation (B). Scatter plot of emphysema severity on airflow limitation (C). Bar chart of percentage change between first quartile of pulse wave velocity and higher quartiles in terms of airflow limitation (1 – FEV₁% predicted) and emphysema severity (pixel index 910) (D).

mild and moderate COPD (14), and that FEV₁ is associated with arterial stiffness after adjusting for age and height (13). The mean difference we found was smaller, and the association with FEV₁ we demonstrated was weaker, than was previously described using carotid–femoral PWV (13, 14). Despite this, we found a strong association between emphysema severity and arterial stiffness ($r = 0.47$, $P < 0.001$). Consequently, had we used carotid–femoral PWV rather than carotid–radial PWV, it seems likely that we would have found an even stronger association between arterial stiffness and emphysema severity.

Other noninvasive measurements that we could have used without subjects lying completely flat include time to wave reflection and augmentation index. However, these measures of arterial stiffness are more vulnerable to the effects of heart rate, and are less useful in elderly populations (45, 48).

Ideally, we would have performed HRCT in all patients. Nevertheless, there was no evidence of selection bias in the patients undergoing CT (Table 1), and the association between PWV and emphysema severity was highly statistically significant even in this smaller sample.

In previous studies, increased BMI has been associated with increased arterial stiffness (49), presumably as a result of the effects of obesity and the metabolic syndrome. We instead found that low BMI was associated with increased PWV on univariate testing, and approached significance on multivariable testing (Table 4). However, low BMI is a marker of more severe COPD (30) and is likely to reflect a more catabolic state, which may explain this apparently contradictory finding, as well as

explain why other metabolic factors such as hyperglycemia and hypercholesterolemia were not significantly associated with PWV in our cohort.

Cigarette smoke exposure has a causal relationship with both emphysema and cardiovascular disease. It was therefore important to control for smoking in our analysis. Pack-years is the most widely used measure for assessing smoke exposure retrospectively and is vulnerable to inaccuracy, but not bias (50). In 157 patients with COPD, we found no relationship between PWV and smoking pack-year history, nor did we find any relationship between smoking pack-years and emphysema severity

TABLE 4. MULTIPLE LINEAR REGRESSION OF PULSE WAVE VELOCITY ON EMPHYSEMA, HEIGHT, GENDER, HEART RATE, BODY MASS INDEX, MEAN ARTERIAL BLOOD PRESSURE, LOG C-REACTIVE PROTEIN, AND FEV₁% PREDICTED

HRCT Subjects (n = 73)*	Regression Coefficient	Standard Error	Partial r ²	t Statistic	P Value
Constant	6.730	1.311			
Male gender	0.610	0.339	0.05	1.78	0.077
Body mass index, kg/m ²	−0.053	0.028	0.08	−1.90	0.061
Mean arterial pressure, mm Hg	0.026	0.013	0.08	2.06	0.043
Emphysema pixel index −950	4.648	1.331	0.15	3.49	0.001

* Global significance test (analysis of variance); $P < 0.001$, $r^2 = 0.360$

in the HRCT subgroup. In previous work, there was no association between smoking pack-years and PWV (14), and in a recently published study on 274 subjects with COPD who underwent HRCT, there was no relationship between severity of emphysema (scored visually) and smoking pack-year history (18). We did not find a difference in PWV between current and ex-smokers, which is consistent with previous findings in a COPD population (14). Therefore, it seems reasonable to conclude that total cigarette smoke exposure is not an important determinant of emphysema or arterial stiffness severity within a group of patients with COPD, who have in effect been selected as a result of their relative susceptibility to cigarette smoke. As such, we can be reasonably confident that the association between emphysema and PWV is not due to confounding from cigarette smoke exposure.

Conclusions

We have shown for the first time that, in patients with COPD, severity of emphysema correlates with a measure of arterial stiffness. This association may be due to the systemic effects of COPD (inflammation, oxidative stress, and hypoxia), to environmental factors such as pollution, or to a shared susceptibility to degradation of elastin and other components of the extracellular matrix in both systemic arteries and the lung. Studies that explore a mechanism for the shared susceptibility hypothesis are now required, and may provide insights into the search for distinct phenotypes in patients with COPD as well as future therapeutic strategies to reduce cardiovascular risk in COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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