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ORIGINAL RESEARCH

Pulmonary Abnormalities and Carotid Atherosclerosis in Ex-Smokers without Airflow Limitation

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Abstract

It is well-established that COPD patients have a burden of vascular disease that cannot be fully-explained by smoking history but the mechanistic links between atherosclerosis and pulmonary disease in COPD patients are not well-understood. Moreover, in ex-smokers without symptoms or other evidence of COPD, subclinical pulmonary and vascular disease, although potentially present, has not been described or evaluated. Hence our aim was to use sensitive three-dimensional (3D) pulmonary and carotid imaging to quantify pulmonary airway/parenchyma abnormalities and atherosclerosis in ex-smokers without airflow limitation or symptoms consistent with COPD. We evaluated 61 subjects without airflow limitation including 34 never- (72 ± 6 years) and 27 ex-smokers (73 ± 9 years), who provided written informed consent to spirometry, plethysmography, ³He magnetic resonance imaging (MRI) and carotid ultrasound (US) and, for ex-smokers alone, thoracic X-ray computed tomography (CT). Ex-smokers had significantly greater ³He ventilation defect percent (VDP = 7%, *p* = 0.001) and carotid total plaque volume (TPV = 250 mm³, *p* = 0.002) than never-smokers, although there were no significant differences for spirometry or plethysmography, and CT airway and emphysema measurements were normal. There were univariate relationships for ³He VDP with carotid intima media thickness (IMT, *r* = 0.42, *p* = 0.004), TPV (*r* = 0.41, *p* = 0.006) and vessel wall volume (VWV, *r* = 0.40, *p* = 0.007). Multivariate models that included age, BMI, FEV₁, DL_{CO} and VDP showed that only VDP significantly predicted IMT (β = 0.41, *p* = 0.001), VWV (β = 0.45, *p* = 0.003) and TPV (β = 0.38, *p* = 0.005). In summary, there was imaging evidence of mild airways disease and carotid plaque burden that were related and significantly greater in ex-smokers without airflow limitation than in never-smokers.

Introduction

Cardiovascular disease is the single largest cause of hospitalization in patients with mild and moderate chronic obstructive pulmonary disease (COPD), and after lung cancer, the leading cause of death (1, 2). In addition, in COPD patients, there is a dose-response relationship for pulmonary structure-function abnormalities with carotid atherosclerosis (3–8), coronary artery calcification (9–12) and vascular dysfunction (13–16). Although these studies have shown the presence of cardiovascular disease in patients with COPD that cannot be explained by smoking history alone (3, 4, 6–8, 17), the mechanisms by which cardiovascular disease may be accelerated in COPD are not clear, nor is our understanding of these relationships in early or milder subclinical stages.

Keywords: atherosclerosis, COPD, magnetic resonance imaging, tobacco, ultrasound

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Although the diagnosis and monitoring of COPD is mainly based on spirometry measurements of airflow obstruction (18, 19), such measurements cannot fully characterize the pathophysiological changes that occur in obstructive lung disease (20). These include regional small-airways disease and microstructural changes in the terminal bronchi and parenchyma. In this regard, regional imaging measurements provided by hyper-polarized ^3He magnetic resonance imaging (MRI) are highly sensitive to pulmonary abnormalities in asymptomatic ex-smokers (21, 22) and never-smokers with second-hand smoke exposure (23). Similarly, airway morphology and parenchyma density X-ray computed tomography (CT) measurements from the ECLIPSE (24) and COPDGene (25) studies showed the utility of CT phenotypes (26) for stratifying COPD patients (27–29).

Cardiovascular disease, predominated by large vessel atherosclerosis, is associated with obstructive lung disease (30, 31) that can be regionally and quantitatively evaluated using carotid ultrasound (US). The burden of atherosclerosis can be quantified (32) using carotid intima-media thickness (IMT) measurements and this is believed to reflect medial hypertrophy and intima abnormalities, and importantly, IMT correlates with cardiovascular outcomes (32, 33). In a similar manner, three-dimensional ultrasound (3DUS) carotid atherosclerosis measurements (34) of carotid wall and plaque abnormalities are sensitive predictors of cardiovascular risk (35–37) and in some patients, these provide a better estimate of plaque burden and risk than IMT alone (37).

There is a paucity of direct evidence relating subclinical lung disease and atherosclerosis in otherwise healthy ex-smokers. To provide a better understanding of the relationship between carotid atherosclerosis and pulmonary abnormalities common to ex-smokers with obstructive lung disease, our objective was to acquire highly sensitive pulmonary and carotid 3D imaging measurements in never- and ex-smokers with normal pulmonary function. We hypothesized that quantitative 3D imaging phenotypes would provide a way to tease out potential relationships for early or mild sub-clinical emphysema or airways disease with atherosclerosis in subjects at risk.

Methods

Study subjects

Ex-smokers (≥ 10 pack-year smoking history) without symptoms or a physician-diagnosis of COPD and normal spirometry ($\text{FEV}_1/\text{FVC} \geq 70\%$) as well as never-smokers (< 1 pack-year smoking history) with no history of chronic respiratory or significant or uncontrolled cardiovascular disease between 50–90 years of age were recruited. These subjects enrolled in response to advertisements placed within the community and at local healthy ageing exercise and atherosclerosis prevention clinics. All subjects provided written informed consent to a protocol approved by a local research ethics board and Health Canada.

Spirometry and plethysmography

Spirometry, plethysmography and diffusing capacity of carbon monoxide (DL_{CO}) measurements were performed according to the American Thoracic Society guidelines (19). An ndd EasyOne spirometer (nnd Medizintechnik AG, Zurich, Switzerland) was used to measure FEV_1 and FVC. Whole body plethysmography was performed for lung volumes and DL_{CO} measurements were recorded using a gas analyzer (MedGraphics Corporation, St. Paul, Minnesota, USA).

Image acquisition

High-resolution B-mode ultrasound (US) images were acquired (ATL HDI 5000; Philips, Bothel, Washington, USA) as previously described (38) using a 50 mm L12-5 MHz transducer (frequency = 8.5 MHz, Philips). Gain, focal points and time-depth compensation were optimized by the sonographer taking into consideration neck size, carotid anatomy and tissue depth. Two dimensional images were reconstructed into a 3D volume as previously described (39, 40). MRI was performed on a whole body 3.0 Tesla Discovery 750MR (General Electric Health Care, Milwaukee, Wisconsin, USA) MRI system. ^1H and ^3He MRI were performed as previously described (41) with the subject in an inspiration breath-hold (FRC+1L). For ex-smokers only, computed tomography (CT) was acquired within 10 minutes of MRI and at the same lung volume (FRC+1L) to ensure similar parenchymal distension in a method previously described (41).

Image analysis

Carotid IMT was measured from the longitudinal plane of the 3DUS volume using Prowin 24.0 software (Medical Technologies International Inc., Palm Desert, California, USA) as previously described (42). Carotid total plaque volume (TPV) and vessel wall volume (VWV) were measured as previously described (43).

^3He MRI ventilation defect percent (VDP) and apparent diffusion coefficients (ADC) were measured using semi-automated segmentation generated using custom-built software in MATLAB R2007b (The Math-works Inc., Natick, Massachusetts, USA) as previously described (44, 45). CT volumes were analyzed using Pulmonary Workstation 2.0 (PW2, VIDA Diagnostics Inc., Coralville, Iowa, USA). Pulmonary CT images were analyzed for airway dimensions including wall area percent (WA%), lumen area (LA) and standardized wall thickness of airways with an inner perimeter of 10 mm (Pi_{10}) (46). In addition, the relative area of the lung with CT attenuation values less than -950HU (RA_{950}) and total airway count were also measured using PW2.

Statistics

Normality of data was tested using the Shapiro–Wilk test and when significant, the Mann-Whitney U-test for nonparametric data was performed using SPSS Statistics V20.0 (SPSS Inc, Chicago, Illinois, USA). Unpaired two

tailed *t*-test comparisons were performed using GraphPad Prism V4.0 (GraphPad Software Inc, California, USA) and Welch's correction used when the *F*-test for equal variances was significant. The Holm-Bonferroni correction (47) was performed for multiple unpaired *t*-test comparisons. Multiple regression analyses were performed in SPSS to determine the relationship between carotid US measurements with ³He MRI VDP and pulmonary function parameters. Partial correlations were computed using SPSS. Multiple regression and correlation models were adjusted for age, BMI and DL_{CO} since these parameters are established risk factors for cardiovascular and pulmonary diseases (8, 48). Results were considered significant when the probability of two-tailed type I error was less than 5% (*p* < 0.05) and summary data are presented as mean ± SD unless otherwise indicated.

Results

As shown in Table 1, 61 subjects including 27 ex-smokers (73 ± 9 years, 18 male) and 34 never-smokers (72 ± 6 years, 18 male) were evaluated. Except for BMI, (*p* = 0.001) there were no significant differences between subject groups for demographic characteristics.

Figure 1 shows ³He MRI center coronal slices and 3DUS axial and longitudinal images for representative ex- and never-smokers. ³He MRI ventilation images show homogeneous ventilation in never-smokers, whereas there is heterogeneous signal intensity with visually obvious ventilation defects in ex-smokers. 3DUS axial images show carotid plaque that is qualitatively greater in the two ex-smokers.

Quantitative results are provided in Figure 2 and Table 1 that show that the ex-smokers subgroup had significantly greater TPV, (250 ± 200 mm³, *p* = 0.002) and ³He MRI VDP, (7 ± 3%, *p* = 0.001) than never-smokers. No significant differences were observed for VWV (*p* = 1.0), IMT (*p* = 0.11), ADC (*p* = 0.20) or FEV₁ (*p* = 0.89). For ex-smokers, CT mean RA₉₅₀ (1.5 ± 1.4%), airway wall thickness at an internal perimeter of 10 mm (Pi10, 4.1 ± 0.17 mm), WA% (61 ± 2%), and LA (17 ± 11 mm²) were within normal range as previously published (49, 50).

Using previously established age-normalized values for IMT (51), 28 subjects (15 ex-smokers and 13 never-smokers, 28/61 = 46%) exceeded the upper limit of normal for IMT and 33 subjects (12 ex-smokers and 21 never-smokers, 33/61 = 54%) had normal IMT. As shown in Figure 3, subjects with abnormally elevated IMT had significantly greater VDP (*p* = 0.04) than subjects with normal IMT, but the two subgroups were not significantly different with respect to ADC (*p* = 0.06), FEV₁%_{pred} (*p* = 1.0) or DL_{CO}%_{pred} (*p* = 0.85). CT measurements for the 15 ex-smokers with abnormal IMT were not significantly different than ex-smokers with normal IMT for RA₉₅₀ (*p* = 0.96), WA% (*p* = 0.66) or LA (*p* = 0.63).

As shown in Figure 4, univariate Pearson correlations between ³He MRI VDP and carotid ultrasound mea-

Table 1. Demographic, pulmonary function, thoracic CT and carotid ultrasound data for all study subjects

	Ex-smokers n = 27	Never-smokers n = 34	Significance of Difference <i>p</i> *
Age yrs (±SD)	73 (9)	72 (6)	1.0
Male n	18	18	–
BMI kg·m ⁻² (±SD)	30 (3)	27 (3)	0.001
Pack years (±SD)	27 (18)	–	–
Years quit (±SD)	26 (6)	–	–
FEV ₁ % _{pred} (±SD)	106 (16)	106 (18)	0.89
FVC % _{pred} (±SD)	97 (13)	101 (17)	1.0
FEV ₁ /FVC (±SD)	81 (7)	77 (5)	0.36
TLC % _{pred} (±SD)	102 (14)	106 (15)	1.0
IC % _{pred} (±SD)	107 (14)	107 (22)	1.0
RV % _{pred} (±SD)	110 (26)	109 (29)	1.0
RV/TLC (±SD)	42 (7)	39 (13)	0.96
Raw% _{pred} (±SD)	115 (72)	76 (34)	0.11
DL _{CO} % _{pred} (±SD)	83 (17)	87 (20)	1.0
ADC cm ² /s (±SD)	0.29 (0.04) ¹	0.26 (0.03) ²	0.20
VDP % (±SD)	7 (3) ¹	3 (2) ²	0.001
IMT mm (±SD)	0.84 (0.10)	0.77 (0.09)	0.11
TPV mm ³ (±SD)	250 (200)	60 (90)	0.002
VWV mm ³ (±SD)	910 (190) ³	890 (170) ⁴	1.0
5th gen. WA% (±SD)	61 (2)	–	–
5th gen. LA mm ² (±SD)	17 (11)	–	–
Pi10 mm (±SD)	4.1 (0.17)	–	–
RA ₉₅₀ % (±SD)	1.5 (1.4)	–	–
Airway Count n (±SD)	127 (35)	–	–

BMI: Body mass index, FEV₁: Forced expiratory volume in one second, FVC: Forced vital capacity, TLC: Total lung capacity, IC: Inspiratory capacity, RV: Residual volume, Raw: Airways resistance, DL_{CO}: Diffusing capacity for carbon monoxide, ADC: Apparent diffusion coefficient, VDP: Ventilation defect percentage, IMT: Intima-media thickness, TPV: Total plaque volume, VWV: Vessel wall volume, 5th gen.: Fifth generation airway, WA%: Airway wall area percentage, LA: Airway lumen area, Pi10: Standardized wall thickness of airways with an inner perimeter of 10 mm, RA₉₅₀: Relative area of the lung with attenuation values below -950HU, SD: Standard deviation, %pred: Percent of predicted value.

*Data are Holm-Bonferroni corrected *p*-values for unpaired *t*-test comparisons ¹n = 26, ²n = 29, ³n = 22, ⁴n = 30.

surements revealed a moderate significant relationship for VDP with carotid IMT (*r* = 0.42, *p* = 0.004), TPV (*r* = 0.41, *p* = 0.006) and VWV (*r* = 0.40, *p* = 0.007). Multivariate regression models for IMT, VWV and TPV are provided in Table 2. VDP was a significant determinant of IMT (β = 0.41, *p* = 0.001), VWV (β = 0.45, *p* = 0.003) and TPV (β = 0.38, *p* = 0.005). For the ex-smokers alone, CT-derived measurements including RA₉₅₀ and airway count, WA%, LA and Pi10 did not correlate with carotid US measurements of IMT, TPV and VWV.

Discussion

We tested the hypothesis that atherosclerosis and pulmonary structure-function measurements were significantly different in ex-smokers without airflow

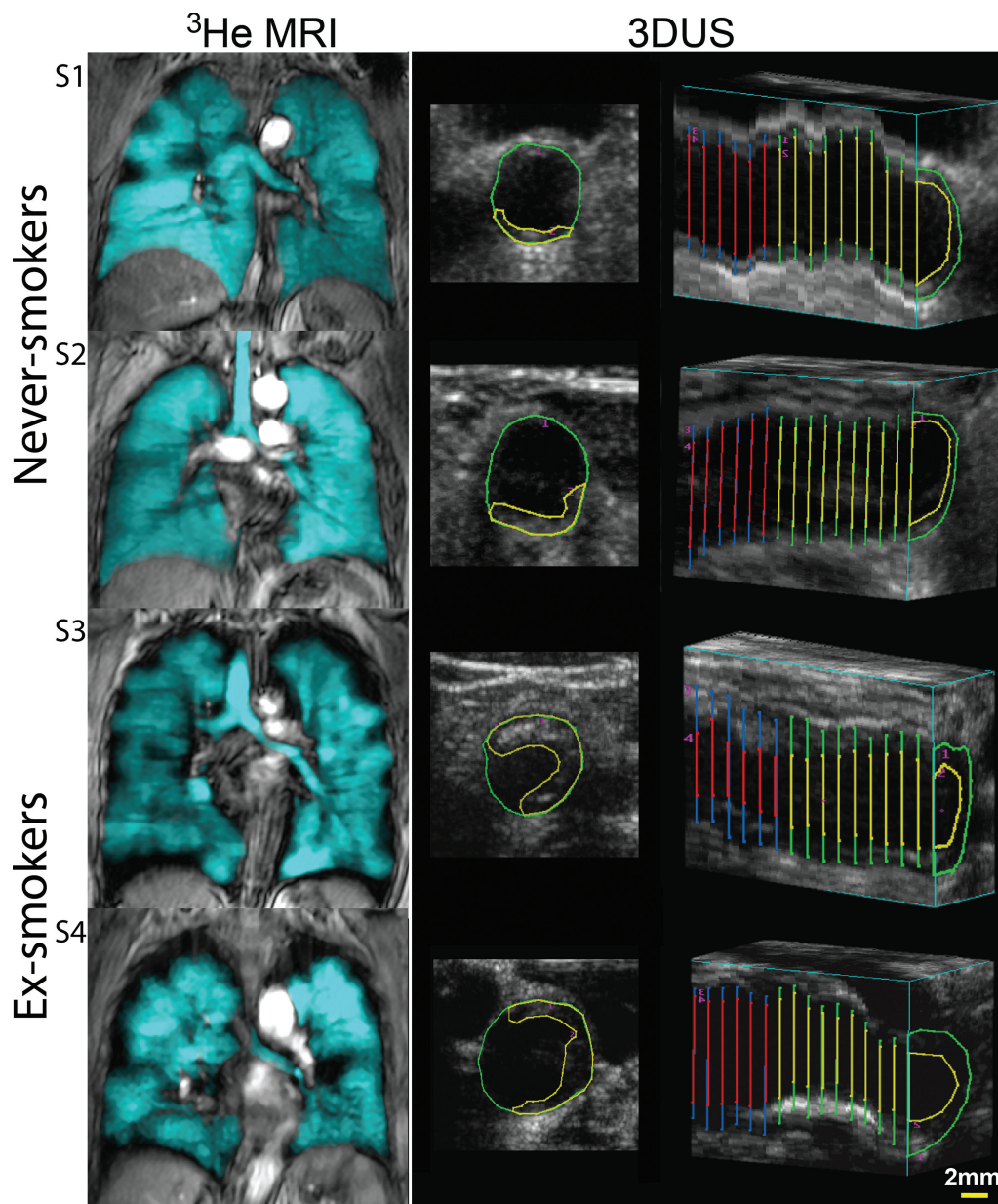


Figure 1. Representative ^3He MRI and 3DUS images for two never-smokers (S1 and S2) and two ex-smokers (S3 and S4). Never-smoker S1 is a 67-year-old female with $\text{FEV}_1 = 120\%$, $\text{FEV}_1/\text{FVC} = 0.77$, ^3He MRI VDP = 3%, TPV = 20 mm^3 and IMT = 0.79 mm. Never-smoker S2 is a 68-year-old male with $\text{FEV}_1 = 93\%$, $\text{FEV}_1/\text{FVC} = 0.79$, ^3He MRI VDP = 2%, TPV = 30 mm^3 and IMT = 0.73 mm. Ex-smoker S3 is a 79-year-old female with $\text{FEV}_1 = 88\%$, $\text{FEV}_1/\text{FVC} = 0.71$, VDP = 8%, TPV = 500 mm^3 and IMT = 0.94 mm. Ex-smoker S4 is a 85-year-old male with $\text{FEV}_1 = 139\%$, $\text{FEV}_1/\text{FVC} = 0.79$, VDP = 8%, TPV = 340 mm^3 and IMT = 0.96 mm. The axial 3DUS image of the common carotid artery shows the intima-lumen boundary in green and carotid plaque-lumen boundary in yellow. The longitudinal 3DUS carotid image shows IMT segmentation of the common carotid artery.

limitation or symptoms consistent with COPD than in never-smokers. We observed: 1) ex-smokers had significantly greater carotid TPV and worse ^3He VDP than never-smokers, but were not significantly different with respect to pulmonary function test measurements, 2) 28 subjects including 15 ex- and 13 never-smokers with abnormally elevated IMT had significantly worse VDP but ADC, FEV_1 , DL_{CO} and CT measurements were not different compared to subjects with normal IMT, 3) ^3He VDP was significantly related to carotid atherosclerosis measurements (IMT, VWV and TPV) but pulmonary function tests were not, and 4), multivariate regression models showed that VDP, a measurement of small air-

way function, was the only significant determinant of carotid artery IMT, VWV and TPV.

In these older subjects without COPD, we observed, as expected, that spirometry and plethysmography measurements were not different in ex- and never-smokers, but importantly ^3He VDP was significantly worse for ex-smokers. This finding is concordant with previous findings in asymptomatic ex-smokers that showed significant differences in ^3He MRI ventilation defects compared to never-smokers (22). Although we did not observe differences between subgroups for ^3He MRI ADC, abnormally elevated ^3He ADC has been previously reported in asymptomatic smokers

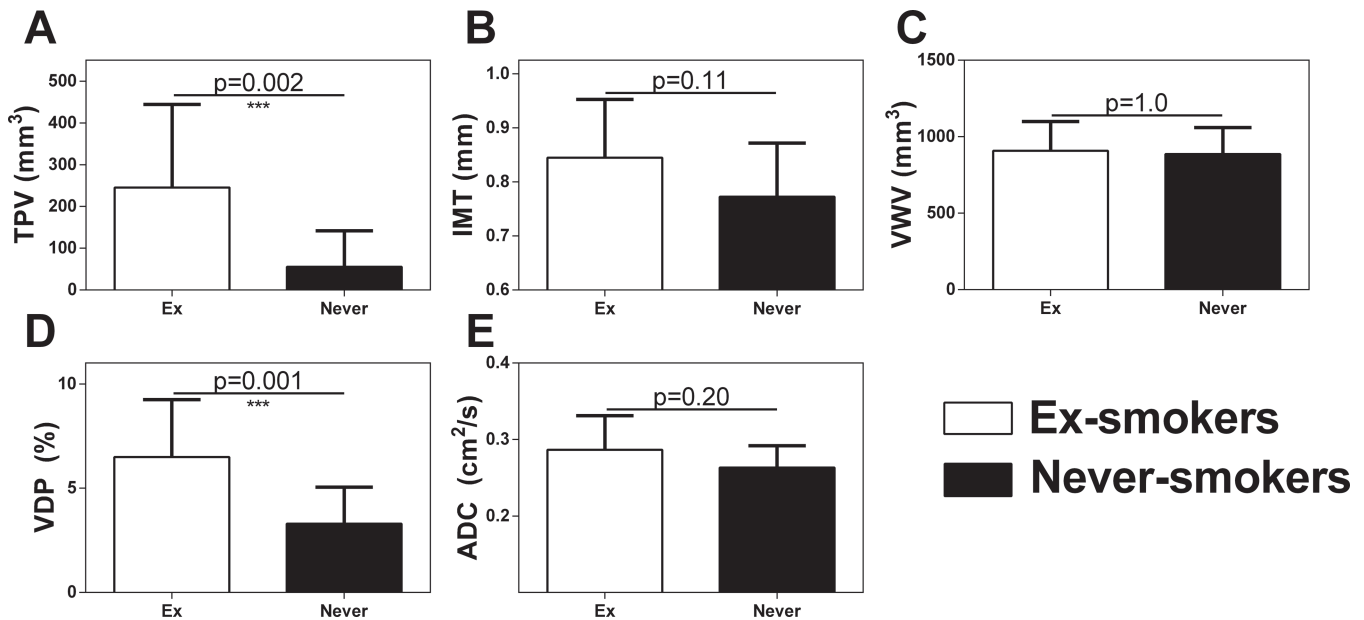


Figure 2. Imaging phenotypes in asymptomatic ex-smokers and never-smokers. Ex-smokers have significantly greater: A) TPV ($p = 0.002$) and D) VDP ($p = 0.001$) than never-smokers. No significant differences were observed for: B) IMT ($p = 0.11$), C) VVW ($p = 1.0$), or E) ADC ($p = 0.20$). Holm-Bonferroni corrected p values are shown.

(21) and never-smokers with second-hand smoke exposure (23). Our finding of abnormal ^3He ventilation in the absence of abnormal DL_{CO} , ADC or CT RA_{950} in ex-smokers is in agreement with the notion that “silent” airway disease (20) and small airway remodeling (52) may be the source of ventilation defects in these subjects.

We think that the significant differences observed for VDP in the absence of differences in DL_{CO} , ADC or RA_{950} suggests mild, sub-clinical airway abnormalities, although we must point out that a definitive structure-function etiology for ^3He ventilation defects (46, 53, 54) is yet to be determined. It is also worth noting that for the healthy ex-smokers evaluated here, there was no CT

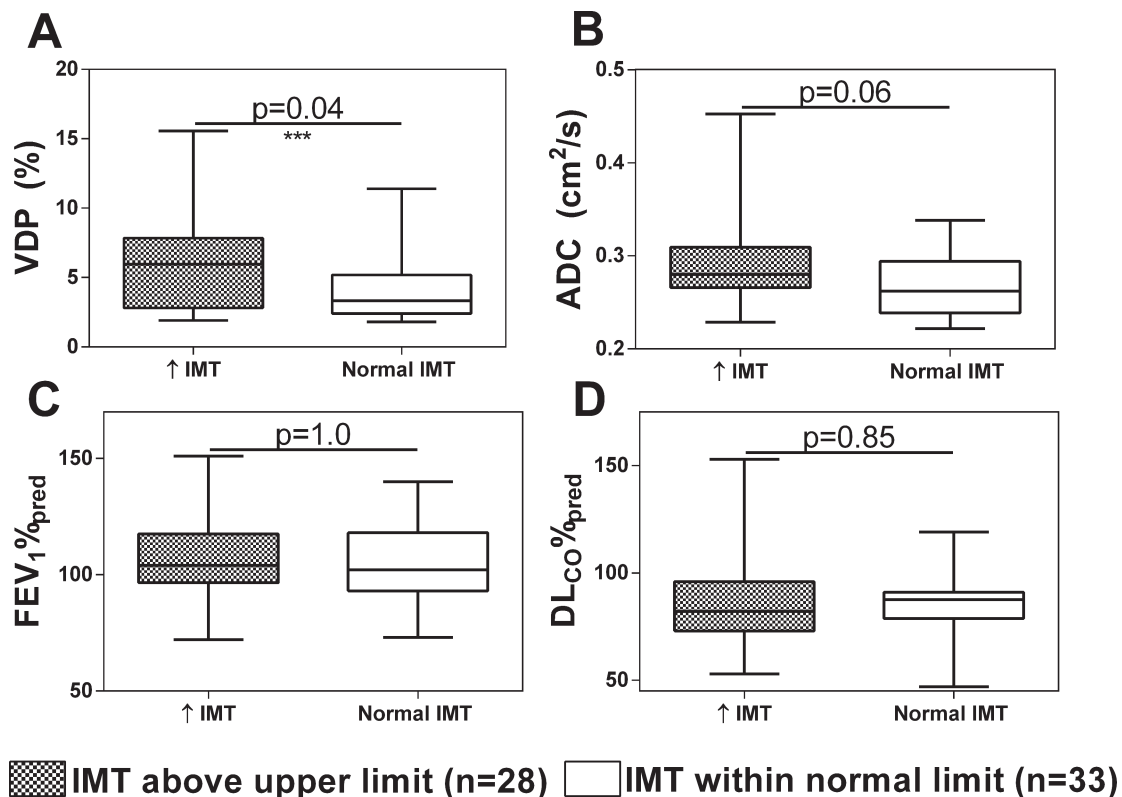


Figure 3. Comparisons between never- and ex-smokers with $\text{IMT} \geq$ age-related upper limit of normal ($\text{IMT} > 97.5\%$ confidence interval (CI)) and subjects with $\text{IMT} \leq$ age-related normal limit ($\text{IMT} \leq 97.5\%$ CI). A) Subjects with abnormally elevated IMT have statistically significantly different VDP ($p = 0.04$) than subjects with normal IMT . No significant differences were observed for: B) ADC ($p = 0.06$), C) FEV_1 ($p = 1.0$) or D) DL_{CO} ($p = 0.85$). Comparisons displayed are Holm-Bonferroni corrected p values.

Table 2. Multiple regression models for IMT, VWV and TPV

	IMT		VWV		TPV	
	β coefficient	p value	β coefficient	p value	β coefficient	p value
Age	0.32	0.02	-0.08	0.63	0.18	0.20
BMI	0.20	0.11	-0.11	0.44	0.09	0.47
FEV ₁	-0.03	0.81	0.21	0.18	0.10	0.48
DLCO	0.15	0.22	-0.08	0.59	-0.10	0.46
VDP	0.41	0.001	0.45	0.003	0.38	0.005

Dependent Variables: IMT, $r^2 = 0.27$, $p = 0.001$; VWV, $r^2 = 0.21$, $p = 0.08$; TPV, $r^2 = 0.16$, $p = 0.02$.

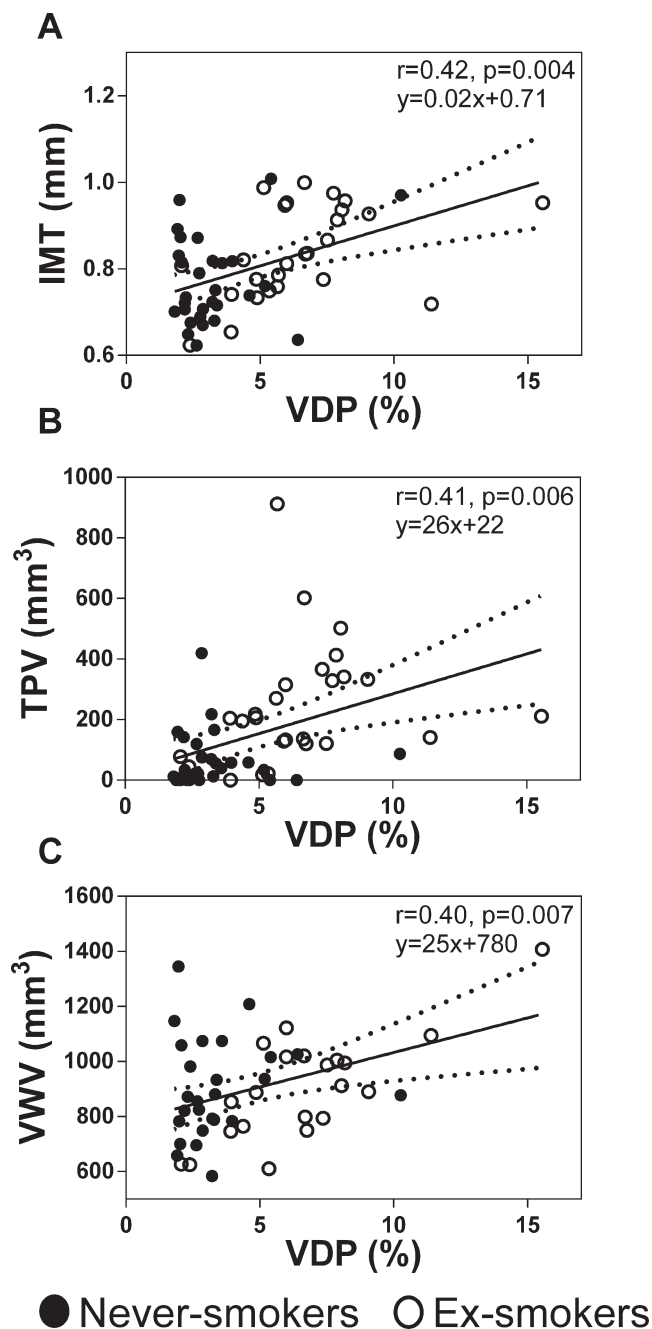


Figure 4. Relationships for carotid atherosclerosis and pulmonary VDP. Significant relationships between ^3He MRI VDP and: A) carotid IMT ($r = 0.42$, $p = 0.004$), B) TPV ($r = 0.41$, $p = 0.006$), and, C) VWV ($r = 0.40$, $p = 0.007$).

evidence of emphysema or airways disease and such values were in agreement with those reported in healthy non-smokers in the COPDGene study (49, 50). This finding underscores the sensitivity of ^3He MRI ventilation measurements for detecting functional abnormalities that may not be apparent using CT or spirometry.

Previous work in COPD patients (3, 4, 6, 7, 17, 55, 56) reported a relationship for IMT with FEV₁ and emphysema measurements, but this was not observed here in ex-smokers without COPD. We were likely underpowered to detect differences in IMT between subgroups as these previous studies investigating IMT in COPD and healthy older subjects used sample sizes ranging from 305 to 14,480 subjects. On the other hand, significantly elevated 3DUS TPV in the ex-smoker subgroup was consistent with previous work (35, 36) that showed smaller sample sizes can be used when employing 3D measurements of plaque as compared to IMT. Although no difference was observed for IMT between ex- and never-smokers, when age-normalized IMT values were used to stratify subjects (51), subjects with abnormal IMT had significantly worse VDP. This finding suggests that in both never- and ex-smokers with elevated IMT, there is evidence of mild, subclinical airways disease that may be related to factors other than cigarette smoking.

We also observed significant univariate relationships for ^3He VDP with carotid artery IMT, TPV and VWV, consistent with previous studies that showed relationships between spirometry measurements and carotid IMT (3, 4, 6, 17, 55, 56), although this is the first report of such relationships in subjects with normal pulmonary function. Similarly, multivariate regression models that controlled for cardiovascular and pulmonary disease risk factors showed that VDP is a significant predictor of carotid artery IMT, VWV and TPV. It is also important to note that carotid TPV and VWV provide measurements of intima echogenic (TPV and VWV) and echolucent (VWV) plaque (38, 57, 58). Hence, these relationships between VDP and IMT, VWV and TPV suggest that in this relatively small group of never- and ex-smokers, mild, subclinical airways disease may be related to carotid plaque burden and wall thickening.

Although it was recently shown that COPD patients may have atherosclerotic plaque characteristics that make them more vulnerable to rupture (6), we did not evaluate carotid plaque composition here. The significant carotid plaque burden quantified in some of the ex-smokers investigated here may be amenable to more complex image methods (59) to develop a better understanding of plaque composition/texture and outcomes. We acknowledge that the main limitation of this study was the relatively small sample size of never- and ex-smokers, and that this may have limited our power to detect any potential differences in IMT and FEV₁ between subgroups.

Certainly, one of the strengths of 3D imaging is that significantly different measurements can be detected in

small groups of subjects, because of the high dynamic range and sensitivity of 3D measurements to structure-function abnormalities. This is an important consideration when powering studies to detect differences in small groups of subjects. Finally, we cannot infer the temporal or causal nature of carotid and pulmonary abnormalities in this cross-sectional evaluation. Questions related to “which came first” still need to be answered in longitudinal natural disease and intervention studies (60).

In conclusion, we acquired sensitive 3D imaging measurements of atherosclerosis and pulmonary structure-function in order to illuminate potential relationships between early or mild sub-clinical pulmonary disease with atherosclerosis in otherwise healthy ex-smokers. Although a number of studies have provided evidence that pulmonary and carotid abnormalities are both present and related in COPD patients, here, this important relationship was shown in never- and ex-smokers with normal pulmonary function. Although the clinical relevance of these observations is not yet clear, these data suggest that lung abnormalities and carotid atherosclerosis in never- and ex-smokers without airflow limitation may be directly related. As our knowledge of co-morbid lung and vascular disease increases, such findings may potentially have implications for patient management decision strategies in preclinical stages.

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Declaration of Interest Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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