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Original Article

Detection of pulmonary artery atherosclerosis by FDG-PET/CT: a new observation

Abdullah Al-Zaghal[1], Mustafa Aras[2], Austin J Borja[1], Mateen Moghbel[3], Yusuf Demir[4], Sina Houshmand[5], Esra Ciftci[6], Thomas J Werner[1], Poul F Høilund-Carlsen[7], Drew A Torigian[1], Yuchi Han[8], Abass Alavi[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [2]Department of Nuclear Medicine, Etimed Hospital, Ankara, Turkey; [3]Department of Radiology, Massachusetts General Hospital, Boston, MA, USA; [4]Department of Nuclear Medicine, School of Medicine, Yüzüncü Yıl University, Van, Turkey; [5]Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [6]Department of Nuclear Medicine Cumhuriyet Universitesi, Sivas, Turkey; [7]Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark; [8]Cardiovascular Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

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Abstract: The aim of this study was to investigate the feasibility of FDG-PET/CT imaging to detect pulmonary artery atherosclerosis and to assess the correlation between pulmonary function testing (PFT) results and the overall pulmonary artery metabolic activity. Twenty-nine subjects between the ages of 57-75, with a history of clinical suspicion of lung cancer, underwent PET/CT imaging at 3 hours following the administration of FDG. Global FDG uptake in the central pulmonary artery branches was determined. Average SUVmax, SUVmean, and tissue-to-background (TBR) mean and maximum were calculated within each vessel. The degree of FDG uptake in non-COPD and COPD patients and its correlation with PFT were examined in this population. Furthermore, the results from patients were compared with those of 10 age-matched controls. Based on these data, the number of lesions with varying degrees of FDG uptake among patients was higher than that in the normal control group. However, there was no statistically significant difference in average SUVmax, average SUVmean, average TBRmax, or average TBRmean between non-COPD and COPD patients. This indicates that the atherosclerotic process is focal and is not diffuse in nature. Although the global quantitative data generated did not reveal evidence for diffuse artery inflammation in patients with COPD, qualitative examination showed clear-cut evidence for focally increased FDG uptake in the pulmonary arteries. This observation indicates the presence of atherosclerotic plaques which are prevalent in patients with COPD. Future prospective studies with larger numbers of subjects are needed to confirm this important observation.

Keywords: Pulmonary artery, atherosclerosis, inflammation, FDG-PET

Introduction

Atherosclerosis, a leading cause of morbidity and mortality worldwide, has been studied extensively in the coronary, cerebral, carotid, and femoral arteries. However, this disease process remains less understood in the pulmonary arteries [1]. Atherosclerosis in these vessels may emerge secondary to increased pulmonary flow or pressure, and this pathology is more common with increasing age [2, 3]. Autopsy studies have demonstrated that thrombotic lesions are frequently present in the pulmonary arteries of older patients with pulmonary hypertension [4]. Furthermore, in a study that compared patients with chronic obstructive pulmonary disease (COPD) to control subjects without COPD, there was a tenfold higher prevalence of central pulmonary atherosclerotic lesions in the patient group (36% vs. 3.7%) [5].

Atherosclerotic plaques can be detected by a variety of imaging modalities. A popular method is intra-vascular ultrasonography (IVUS), which provides visualization of different types of plaque (calcific versus non-calcific) of different ages at the stenotic wall segment. Alternatively, three-dimensional (3D) ultrasonography (US) can be used to visualize carotid artery

plaques and to quantify plaque and vessel volume. Other modalities include computed tomography (CT) angiography, which depicts calcification and plaque density features, and magnetic resonance imaging (MRI), which provides information about plaque composition by assessment of a lipid core, fibrous cap thickness, and intraplaque hemorrhage [6]. In contrast to these structural imaging modalities, ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) provides functional/molecular information by demonstrating increased metabolism as a marker of inflammation, which can be an early sign of atherosclerotic disease. FDG-PET/CT can also be used for follow-up assessment after treatment in different vascular structures such as the aorta, femoral arteries, and carotid arteries [7-9].

The aim of this study was to investigate the feasibility of FDG-PET/CT to detect pulmonary artery atherosclerosis and its correlation with abnormal pulmonary function tests. A handful of previous studies have investigated the utility of FDG-PET/CT to assess the pulmonary vasculature in the setting of pulmonary hypertension [10-13]. However, to our knowledge, no prior PET studies have been employed for evaluating pulmonary arterial atherosclerosis using regional and global metabolic activity in the vascular structures.

Methods

Patient population

The subjects included in this study were drawn from a cohort of 67 patients who were previously scanned as part of a prospective study for the evaluation of suspected lung cancer by FDG-PET/CT imaging. The Human Studies Subcommittee (IRB II) of the Department of Veteran Affairs Medical Center Research and Development Service approved the protocol (ID# 01199) and all participants gave informed consent. In the 29 patients who were selected for this analysis, there were no abnormal sites of disease activity, such as metastatic lymph nodes, which could interfere with pulmonary arterial wall FDG uptake assessment. As part of routine clinical practice, these patients also underwent spirometric pulmonary function tests (PFT). Patients were included in the analysis if the following criteria were met: (1) past medical history of smoking, and (2) availability of FDG-PET/CT scans and PFT results. Spirometry values were used to determine disease severity/stage of patients with COPD in accordance with the guidelines established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (1). As such, COPD stage 0 was defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) > 0.7. COPD stages 1-4 were defined as FEV_1/FVC < 0.7 and $FEV_1 \geq 80\%$ predicted (stage 1), 50% predicted $\leq FEV_1 < 80\%$ predicted (stage 2), 30% predicted $\leq FEV_1 < 50\%$ predicted (stage 3), or $FEV_1 < 30\%$ predicted (stage 4), respectively. The correlations between PFT results and pulmonary artery metabolic activity and diameter were determined.

Healthy controls

Healthy controls used in this study are part of the Cardiovascular Molecular Calcification Assessed by 18F-NaF PET/ CT (CAMONA) protocol. CAMONA is a prospective trial and was approved by the Danish national committee on biomedical research ethics, registered at ClinicalTrials.gov (NCT01724749), and conducted from 2012 to 2016 in accordance with the Declaration of Helsinki. Volunteers were recruited from the general population by local advertisement or from the blood bank of Odense University Hospital, Denmark. Negative history of cardiovascular disease, oncologic disease, chronic inflammatory disease, autoimmune disease, immunodeficiency syndromes, alcohol abuse, illicit drug use, or any prescription medication were inclusion criteria for healthy volunteers [14]. The data from 10 age- and sex-matched control subjects were selected for comparison with those of the patient population included in this study.

Imaging method

All patients had fasted for at least 4 hours and had serum glucose levels below 150 mg/dl. All patients underwent PET/CT imaging at 3 hours after intravenous administration of 2.52 MBq of FDG per kilogram of body weight. Images were acquired by employing an integrated PET/CT system (Biograph 64 hybrid PET/CT imaging systems; Siemens Medical Solutions, Inc. USA, Inc. Malvern, PA). A low-dose CT scan was performed for attenuation correction and anatomic orientation. The acquisition time was 4 min-

utes per bed position on the 3-hour images. PET images were acquired from mid-skull to mid-thigh in 3D-mode and reconstructed in transverse, coronal, and sagittal planes.

For healthy control subjects, FDG-PET/CT images were acquired on hybrid PET/CT systems (GE Discovery STE, VCT, RX, and 690/710 systems (General Electric, Chicago, Illinois, USA)). PET/CT imaging was performed 3 hours after intravenous administration of 4.0 MBq/kg, after an overnight fast of at least 8 hours and a confirmed blood glucose concentration of below 8 mmol/L. PET images were corrected for scatter, attenuation, random coincidences, and scanner dead time. Low-dose CT imaging (140 kV, 30-110 mA, noise index 25, 0.8 sec/rotation, slice thickness 3.75 mm) was performed for attenuation correction and anatomical orientation.

Image analysis

A dedicated workstation (Extended Brilliance™ Workspace, Philips Healthcare, Bothell, WA) was used for image analysis. Global assessment of FDG uptake in the central pulmonary arterial branches was performed only in the patient population. As described previously, this entailed the measurement of metabolic activity in the main pulmonary artery (MPA) (superior to the right ventricular outflow tract and proximal to the bifurcation into right and left pulmonary arteries), right pulmonary artery (RPA) (distal to MPA bifurcation and proximal to subsequent branching), and left pulmonary artery (LPA) (distal to MPA bifurcation and proximal to subsequent branching) by manually drawing regions of interest (ROIs) around the outer boundary of the arteries on every slice starting inferiorly from the right ventricular outflow tract to the superior limit of the pulmonary arterial trunk on attenuation corrected transverse PET/CT images [10].

To perform a global quantification of arterial metabolic activity, the mean, maximum, and sum of the FDG activity (Bq/mL) of each ROI, along with the ROI area (mm^2) at each transverse slice, were measured and recorded. The standardized uptake value (SUV) of each transverse slice was multiplied by the area and thickness of that particular slice, then summed and averaged over all transverse slices for each pulmonary artery segment of interest. We also calculated the tissue to background ratio (TBR), a common method to quantify vascular inflammation, by dividing the average pulmonary artery SUV by the average inferior vena cava blood pool FDG activity [15].

For qualitative analysis, the activity of visually identified FDG-avid lesions presumed to be atherosclerotic plaques in the pulmonary arteries was assessed by an experienced nuclear physician. Each individual's overall plaque activity was given a subjective score (Negative = 0, Mild = 1, Moderate = 2, Severe = 3) based on visual assessment of plaque presence and the intensity of FDG uptake in the plaque.

Statistical analysis

The means and standard deviations of PET/CT based measurements were calculated for each patient. Calculations were similarly performed for 1-hour, 2-hour, and 3-hour time point PET/CT images. Correlations were performed using Spearman correlation coefficients. All statistical analyses were performed with the Stata software (Stata/IC Version 10.1, StataCorp, College Station, TX). P values < 0.05 were regarded as statistically significant.

Results

Of the 29 patients included in the study, 10 with stage 0 COPD served as a patient-control group and the remaining 19 constituted the patient group with the following classifications: 4 patients as stage 1, 11 patients as stage 2, 3 patients as stage 3, and 1 patient as stage 4. The characteristics of the patient and control groups are listed in full in **Table 1**.

Table 2 shows the average SUVmean and average SUVmax of the MPA, RPA, and LPA along with their corresponding standard deviations at multiple time points.

The SUVmax and SUVmean of the MPA were greater in COPD patients than in non-COPD patients ($P > 0.05$). For the LPA, SUVmax was non-significantly greater in non-COPD patients, although SUVmean was greater in COPD patients. Overall, there was no statistically significant difference in average SUVmax, average SUVmean, average TBRmax, or average TBRmean between non-COPD and COPD patients.

Table 1. Patient characteristics for non-COPD (stage 0) and COPD groups

Patient characteristic	non-COPD Stage 0	COPD Stages 1-4	*P* value
Total	10	19	NS
Age	65.3 ± 7.6	69 ± 6.2	NS
Gender (M/F)	10/0	16/0	NS
BMI (kg/m^2)	24.4 ± 5.7	24.5 ± 5.1	NS
Smoking (current/ex)	8/3	13/2	NS
Smoking (Pack Yrs)	43.1 ± 24	62.5 ± 30.2	0.009
FEV_1/FVC	0.75 ± 0.04	0.60 ± 0.07	< .001
Lung Cancer % (n)	85% (11)	75% (12)	NS
Hypertension % (n)	77% (10)	75% (12)	NS
CVD % (n)	15% (2)	56% (9)	0.029

BMI = body mass index; CVD = cardiovascular disease including cerebral vascular disease, transient ischemic attack, mitral valve insufficiency, congestive heart failure, coronary artery disease, arrhythmia, myocardial infarction, ischemic cardiomyopathy, peripheral vascular disease, and abdominal aortic aneurysm.

Table 2. Average pulmonary artery SUV measurements in non-COPD and COPD patients

Vessel	Non-COPD				COPD				*P* value
	Average SUVmax	Average SUVmean	TBRmax	TBRmean	Average SUVmax	Average SUVmean	TBRmax	TBRmean	
MPA	1.88 ± 0.45	1.13 ± 0.23	1.68 ± 0.41	1.72 ± 0.33	1.92 ± 0.45	1.15 ± 0.22	1.71 ± 0.33	1.25 ± 0.17	NS
RPA	2.16 ± 0.74	1.27 ± 0.31	1.91 ± 0.55	1.36 ± 0.33	1.86 ± 0.48	1.21 ± 0.28	1.67 ± 0.39	1.31 ± 0.27	NS
LPA	1.97 ± 0.57	1.19 ± 0.28	1.76 ± 0.56	1.27 ± 0.28	1.81 ± 0.43	1.19 ± 0.25	1.62 ± 0.29	1.28 ± 0.22	NS

COPD = chronic obstructive pulmonary disease; MPA = main pulmonary artery; RPA = right pulmonary artery; LPA = left pulmonary artery; SUV = standardized uptake value; TBR = tissue to background ratio.

Table 3. Correlations of average SUVmax and SUVmean of MPA with pulmonary function test results

Correlation	r value	*P* value
MPA SUVmax vs. FVC	-0.2711	0.1548
MPA SUVmax vs. FEV_1	-0.1651	0.3921
MPA SUVmean vs. FVC	-0.3193	0.0913
MPA SUVmean vs. FEV_1	-0.2662	0.1628

MPA = main pulmonary artery; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; SUV = standardized uptake value.

Although PFT results were significantly different between COPD patients and non-COPD patients, no statistically significant correlation was observed between PFT results and either pulmonary arterial FDG uptake parameters (SUVmax and SUVmean) (**Table 3**).

In the qualitative analysis, 8 healthy controls were given a score of 0 (negative), and only 2 were scored as 1 (mild). For non-COPD patients, 4 were given a score of 0 (negative), another 4 scored as 1 (mild), and the remaining 2 were given a score of 2 (moderate). Finally, within the COPD patients, 8 subjects were given a score of 0 (negative), 3 were given a score of 1 (mild), 6 were scored as 2 (moderate), and the final 2 subjects were given a score of 3 (severe) (**Figures 1**-**3**).

Discussion

In this research study, FDG uptake in the main pulmonary artery was observed to be greater in COPD patients compared to controls, although without statistical significance. There were no statistically significant differences in SUV or TBR measurements of the main, right, and left pulmonary arterial segments between non-COPD and COPD patients. No correlation was found between pulmonary arterial FDG uptake measurements and PFT results. Visual qualitative assessment of the pulmonary artery showed that COPD patients had more FDG activity in the pulmonary artery.

Our study utilized a visual approach to assess delayed time point FDG-PET images. Kothekar *et al*. previously demonstrated a visual grading analysis to assess respiratory muscle activity in a cohort of 33 patients with COPD [16]. On the

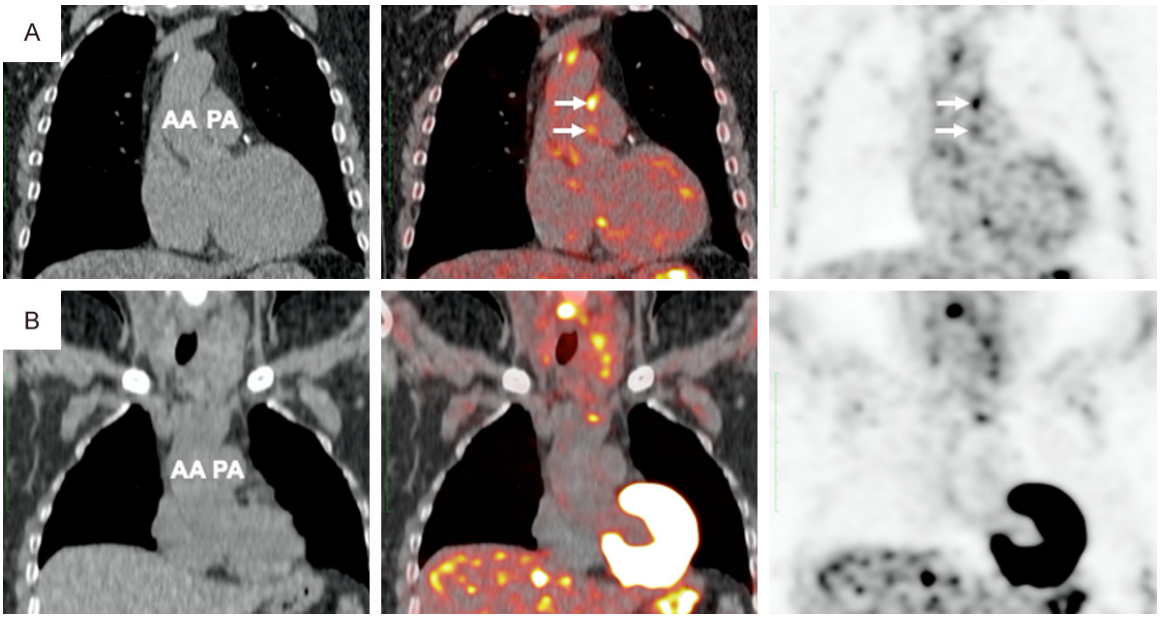

Figure 1. CT, fused PET/CT, and PET images of the main pulmonary artery (PA) and the ascending aorta (AA) in (A) a COPD patient and (B) a healthy control. In the COPD patient, there was focal FDG uptake (arrowheads) in the wall of PA. In contrast, no FDG uptake was visualized within the PA of the healthy control (the series of hot spots above the aorticopulmonary trunk is likely incidental from cervical lymph nodes).

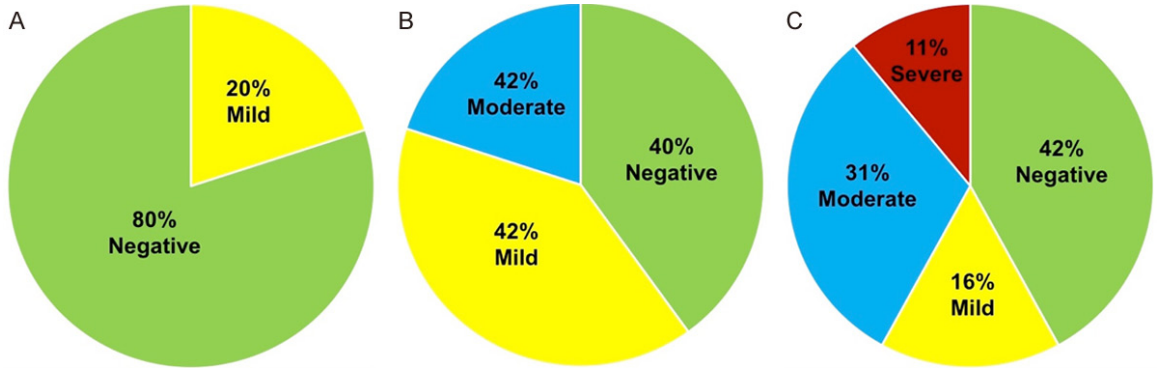

Figure 2. Scores of the activity of visually identified FDG-avid lesions presumed to be atherosclerotic plaques in the pulmonary arteries in the (A) healthy controls, (B) non-COPD patients, and (C) COPD patients.

other hand, Blomberg *et al*. demonstrated that delayed time point imaging was able to produce significant improvement in the visualization of atherosclerotic plaque inflammation as a result of increasing SUVmax-calculated TBRs and decreasing blood pool activity over time [17]. The authors stated that the TBR significantly increased for the aorta and carotid arteries whereas the SUVmax and SUVmean values decreased over a three-hour time period.

Significant correlations of pulmonary artery atherosclerosis with age, right ventricular diameter and hypertrophy, pulmonary emphysema, and aortic atherosclerosis have been reported previously [1]. In an FDG-PET study, Coulson *et al.* prospectively demonstrated increased aortic inflammation in 7 ex-smokers with COPD (mean $FEV_1/FVC = 0.43$) as compared to 7 ex-smokers without COPD (mean $FEV_1/FVC = 0.78$) [18]. Moreover, the mean TBR in the aorta was significantly greater in COPD patients than in ex-smoking patients without COPD (1.60 vs. 1.34, $P = 0.001$). With these findings in mind, we hypothesized that FDG-PET/CT can serve as a marker for the detection of pulmonary arterial atherosclerosis just as it has for aortic athero-

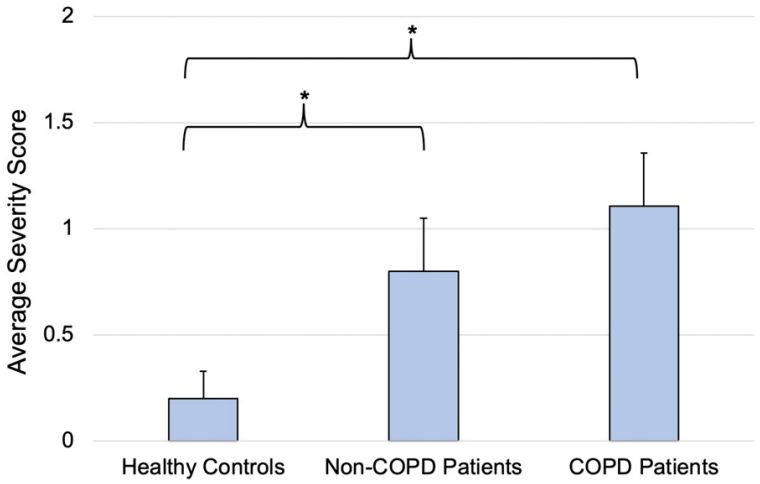

Figure 3. FDG uptake was visually assessed in the pulmonary artery of the 3 groups. A severity score was given for each subject (Negative = 0, Mild = 1, Moderate = 2, Severe = 3). This graph shows the average scores among the different groups: healthy controls had a score of 0.20, while non-COPD patients had a score of 0.80 and COPD patients had an average score of 1.11 (*$P < 0.05$).

sclerosis in COPD patients. To this end, we compared the average SUVmax and SUVmean of the main pulmonary artery in patients with COPD and to values from a non-COPD control group. Our results showed that these measurements were greater in COPD patients, although there was no statistical significance based on the values generated. This discrepancy could be due to the subtle differences between our COPD cases and those of the control group regarding FEV_1/FVC (0.60 vs. 0.75). It is also worth noting that the study population for Coulson *et al*. consisted of patients with more advanced disease.

Increased lung and right ventricular FDG uptake were previously reported in studies of patients with idiopathic pulmonary arterial hypertension (IPAH) and patients with severe pulmonary disease [10, 19]. Hagan *et al*. also measured the FDG uptake of large pulmonary arteries and did not find a significant difference between IPAH and control patients, in contrast to earlier reports [1]. The authors attributed this finding to an inadequate difference in inflammatory markers between their case and control groups. Our results regarding differences in FDG uptake in COPD and non-COPD groups had a similar trend as in this study.

The average main pulmonary artery diameter can be affected by clinical conditions such as obesity, hypertension, history of COPD or pulmonary embolism, adult-onset diabetes mellitus, dyslipidemia, and prevalent cardiovascular disease [20]. In measurements based on contrast-enhanced CT, the upper limit of normal for main pulmonary artery diameter has been reported to be 29-32.6 mm in healthy subjects and 25.3 ± 3.2 mm in patients with COPD [20, 21]. Our results are comparable with these findings.

The results of our study should be interpreted within the context of its limitations. First, we retrospectively evaluated a relatively small sample of patients and most of our subjects were male. Second, some potentially confounding variables that were not accounted for, such as lung cancer, heart disease, hypertension, hyperlipidemia, and peripheral vascular diseases, may have affected FDG uptake in the pulmonary arteries. In particular, there was a higher incidence of a history of cardiovascular disease in COPD patients compared to non-COPD patients [22]. Third, contrast-enhanced CT for improved visualization of the vascular structures was not utilized.

By now, it is well established that plaques in major arteries such as the aorta and the coronaries have incidence for molecular calcification as noted on 18F-sodium fluoride (NaF)-PET imaging [23, 24]. Plans are underway to employ this approach in assessing pulmonary calcification in patients with COPD and other pulmonary disorders.

Conclusion

This study was conducted to compare FDG uptake in the central pulmonary arteries of COPD patients and non-COPD controls to evaluate it as a marker of atherosclerosis and inflammation. Our quantitative assessments did not show pulmonary artery inflammation to be significantly different between these groups. Yet, based on qualitative assessment, we observed findings suggestive of focally increased FDG uptake in the pulmonary arteries, which may

imply the presence of accelerated pulmonary artery atherosclerosis. Future prospective studies with larger numbers of subjects will be necessary to confirm this very interesting observation which may prove to be of value in the management of patients with COPD.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Abass Alavi, Department of Radiology, University of Pennsylvania, 3400 Spruce St, Philadelphia 19104, Pennsylvania, USA. Tel: 215-662-3069; Fax: 215-573-4107; E-mail: abass.alavi@uphs.upenn.edu

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