Effects of age and cardiovascular risk factors on 
$^{18}$F-FDG PET/CT quantification of atherosclerosis 
in the aorta and peripheral arteries

**Abstract**

**Objective:** To quantify fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) uptake in the aorta and peripheral arteries and assess the variation of $^{18}$F-FDG uptake with age and cardiovascular risk factors. **Methods:** The subject population of this retrospective study comprises melanoma patients who underwent whole-body $^{18}$F-FDG PET/CT scans. The patients' medical records were examined for cardiovascular risk factors and for a history of coronary artery disease or peripheral artery disease. Fluorine-18-FDG uptake in the peripheral arteries (iliac and femoral) and aorta was semi-quantified as a weighted-average mean standardized uptake value (wA-SUVmean), while background noise was accounted for by measuring mean venous blood pool SUV (V-SUVmean) in the superior vena cava. Atherosclerosis was semi-quantified by the tissue-to-background ratio (TBR) (wA-SUVmean divided by V-SUVmean). A regression model and t-test were used to evaluate the effect of age and location on the degree of atherosclerosis. To assess the effect of cardiovascular risk factors on atherosclerotic burden, the wA-SUVmean of patients with at least one of these risk factors was compared to that of patients without any risk factors. **Results:** A total of 76 patients (46 men, 30 women; 22-91 years old) were included in this study. The average TBR of the aorta and peripheral arteries were 2.68 and 1.43, respectively, and increased with age in both locations. In regression analysis, the beta coefficients of age for TBR in the aorta and peripheral arteries were 0.55 (P<0.001) and 0.03 (P<0.001), respectively. In all age groups, the TBR of the aorta was significantly greater than that of the peripheral arteries. The Pearson correlation coefficients between the four age groups and the TBR of the aorta and peripheral arteries were 0.83 (P<0.001) and 0.75 (P<0.001), respectively. The wA-SUVmean of patients with cardiovascular risk factors was only significant (P<0.05) in the aorta. **Conclusion:** An increase in $^{18}$F-FDG uptake was observed in the peripheral arteries and aorta with increasing age. Cardiovascular risk factors were significantly correlated with $^{18}$F-FDG uptake in aorta. The early detection of atherosclerosis with $^{18}$F-FDG PET may allow for the initiation of preventative interventions prior to the manifestation of significant structural abnormalities or symptoms of disease.

**Introduction**

Atherosclerosis, the leading cause of cardiovascular mortality [1], often remains clinically silent for long periods of time and may even start as early as childhood [2-4]. It is a chronic and progressive disease with a range of clinical manifestations [5]. The nascent atherosclerotic lesion begins with a diapedesis of monocytes and T-lymphocytes into the intimal space at sites rich in lipids and lipoprotein particles, particularly at vessel bifurcations. The activation of these monocytes leads to the release of proteolytic enzymes, cytokines, chemokines, and growth factors that not only induce the proliferation of smooth muscle cells, but also the accumulation of fat-laden macrophages [6, 7]. The cycle of monocyte accumulation, smooth muscle proliferation, and fibrous tissue formation stimulates further enlargement of the atherosclerotic plaque, as well as its restructuring through cell death and degeneration [6]. Hydroxyapatite mineralization, and in some instances ossification, occurs as hallmarks of advanced lesions [7, 8]. The extent of inflammation in the atheroma is a marker of its vulnerability to rupture [9]. Thus, atherosclerosis is a dynamic inflammatory process where the molecular composition and inflammatory state of the plaque are more important than its degree of stenosis or size [10, 11].

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) measures the presence and degree of inflammation in atherosclerotic plaques and detects plaque formation at the molecular and cellular levels.
before structural changes are detectable. Early detection of atherosclerosis before any significant structural changes are visualized may allow for preventative interventions to be utilized to potentially stop or reverse the progression of atherosclerosis. The ideal modality to diagnose and quantify the disease should be safe, non-invasive, accurate, and reproducible. Positron emission tomography/CT is a very promising tool with all of these qualities that can be used to detect and quantify the inflammatory atherosclerotic process based on the sites and degree of $^{18}$F-FDG uptake. The extent of $^{18}$F-FDG uptake correlates with the amount of inflammation present in the atherosclerotic plaque, and is a semi-quantitative measure of metabolic activity.

In this study we aimed to quantify $^{18}$F-FDG uptake in the aorta and peripheral arteries in order to correlate $^{18}$F-FDG uptake with age and cardiovascular risk factors.

**Subjects and methods**

This was a retrospective study approved by our university institutional review board. The study was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

**Study population**

Seventy-six patients (46 men, 30 women) were retrospectively selected through the dedicated radio-pathology search engine at our university. The study population consisted of melanoma patients who had undergone whole body $^{18}$F-FDG PET/CT scans between 2009 and 2011. Patients with malignant tumors in the vicinity of vessels such as the femoral vessels were excluded to prevent counts from metabolically active lesions spilling over into the arteries. Patient medical records were then screened for the presence or absence of several cardiovascular risk factors, namely hypertension, hyperlipidemia, diabetes mellitus, tobacco use, coronary artery disease, and peripheral artery disease. Tobacco use was not considered as a risk factor for those patients who had quit smoking 10 or more years before the date of their PET/CT scan. Patients with technically limited studies that precluded interpretation were not included in the study.

**Image acquisition**

PET/CT imaging was performed on a dedicated whole body PET/CT scanner (Gemini TF; Philips Medical System, Bothell, WA, USA). Patients fasted for at least 4h before $^{18}$F-FDG intravenous (i.v.) injection and serum glucose levels were confirmed to be below 200mg/dL. Image acquisition began about 1 hour after i.v. administration of 5.18MBq/kg of $^{18}$F-FDG, and was performed from the vertex of the skull to the toes. Five millimeters axial, coronal, and sagittal PET image reconstructions (Figure 1) were created using non-contrast CT images for attenuation correction.

**Image analysis**

PET/CT image analysis was performed using the Extended Brilliance Workstation (EBW; Philips Medical System, Bothell, WA, USA). $^{18}$F-FDG uptake in the peripheral arteries (iliac and femoral) and aorta was semi-quantified via the weighted average mean standardized uptake value (wA-SUV mean), which was calculated as: $\sum$ (vessel SUVmean per slice $\times$ vessel surface area per slice $\times$ slice thickness) / $\sum$ (vessel volume), by placing regions of interest (ROI) around the arterial wall on every slice of the fused images. Background $^{18}$F-FDG uptake in the superior vena cava was determined by placing ROI in the center of the vein on every transverse slice in order to measure mean venous blood pool SUV (V-SUVmean). Atherosclerosis was semi-quantified by the tissue to background ratio (TBR), which was in turn calculated as wA-SUVmean divided by V-SUVmean. A regression model was then used to assess the effect of age and location on the degree of atherosclerosis while considering other risk factors.

**Statistical analysis**

After all measurements were recorded and entered into a spreadsheet (Microsoft Excel 2007; Microsoft Corporation, Redmond, Washington, USA), regression analysis was used to evaluate the predictive value of age for the semi-quantitative degree of $^{18}$F-FDG uptake in the aorta and peripheral arteries.

To compare vascular $^{18}$F-FDG uptake between the four age groups (20-40, 41-60, 61-80, >80 years), post-hoc analysis of variance, followed by Fisher’s least significant difference test with multiple comparisons, and Pearson correlation analysis were performed. These statistical tests assessed the correlations of the TBR of the peripheral arteries and aorta with age. The difference between $^{18}$F-FDG uptake in the peripheral arteries and aorta was assessed with paired t-testing. On the other hand, the difference between the mean SUV of patients with and without a history of cardiovascular risk factors were compared in different vessels using an unpaired t-test. A chi squared test was also performed to compare the prevalence of the various risk factors across genders.

Statistical software packages (SPSS, SPSS Inc., Chicago, IL, USA; Version 19) and STATA software (STATA, Statacorp, College Station, TX, USA; Version 10) were used for data analysis. P values <0.05 were considered to be statistically significant.

**Figure 1.** Relationship between age and mean TBR in the aorta and peripheral arteries. The beta coefficients for these comparisons were 0.55 (P < 0.001) for the aorta and 0.03 (P < 0.001) for the peripheral arteries. The Pearson correlation coefficients between the four age groups and the TBR of the aorta and peripheral arteries were 0.83 (P < 0.001) and 0.75 (P < 0.001), respectively.
Results

A total of 76 patients diagnosed with melanoma were included in the study population. The subject group had a mean age of 59.7 years, with a range of 22-91 years. None of the patients suffered from diabetes mellitus, obesity, or peripheral vascular disease (Table 1). More than half of the patients (43/76, 56.6%) had at least one cardiovascular risk factor. The average TBR of the aorta and peripheral arteries were 2.68 and 1.43, respectively. As shown in Figure 1, the TBR increases with age in both the aorta and peripheral arteries.

Using regression analysis, the beta coefficients of age for TBR in the aorta and peripheral arteries were found to be 0.55 (P<0.001) and 0.03 (P<0.001), respectively. In Table 2, we categorized the patients into different age groups. With increasing age, the TBR goes up significantly in both the peripheral arteries and aorta (Figure 2). Furthermore, the Pearson correlation coefficients between the TBR of the peripheral arteries and the four age groups was 0.75 (P<0.001), while the corresponding coefficient between the TBR of the aorta and the four age groups was 0.83 (P<0.00).

To compare the degree of 18F-FDG uptake in the aorta and peripheral arteries, we compared the TBR of the aorta and peripheral arteries in various age groups. In all age groups, the TBR of the aorta was significantly higher than that of the peripheral arteries (Table 2 and Figure 2).

The effect of a host of cardiovascular risk factors—namely hypertension, hyperlipidemia, diabetes mellitus, tobacco use, coronary artery disease, and peripheral artery disease—on 18 F-FDG uptake was measured in the aorta as well as the femoral and iliac arteries (Table 3). In all three locations, subjects with a history of at least one of these risk factors demonstrated higher 18 F-FDG uptake than those without such a history. However, the difference in SUVmean between these groups was only significant in the aorta (P<0.05).

Discussion

Atherosclerosis is a chronic progressive inflammatory disease process affecting the arteries [12]. Atherosclerotic plaques begin to form as early as childhood, and become vulnerable to rupture as they mature and grow [13]. Atherosclerotic plaque instability followed by rupture is considered to be the single most frequent cause of sudden cardiovascular events. Inflammation is a feature of atherosclerosis that has been hypothesized to play a significant role in enhancing the vulnerability of plaques to rupture [14–18].

Calcification, on the other hand, stabilizes plaques and reduces their risk of rupturing.

An optimal strategy to reduce cardiovascular morbidity and mortality would be to detect asymptomatic patients with atherosclerotic lesions that are prone to rupture [19, 20]. These patients would, theoretically, benefit most from intensive preventative intervention. Currently, structural imaging modalities such as conventional angiography, ultra-
by Yun et al. (2001) [28]. Retrospective analysis observed that identifying and quantifying arterial luminal stenosis, but provide minimal information about plaque composition. Since a significant number of cardiovascular events occur in subjects with less than 50% stenosis of the coronary arteries [21], quantifying the degree of arterial luminal stenosis is an unreliable measurement of CVD risk [22].

Until recently, atherosclerotic plaque imaging focused on defining the anatomical features of vessels. However, 18F-FDG PET/CT imaging can not only detect but also quantify the inflammatory component of atherosclerotic lesions prior to their appearance on any structural imaging scans [23]. Since 18F-FDG PET can detect atherosclerosis years before the structural imaging modalities, 18F-FDG PET provides critical opportunities to prevent and treat atherosclerosis before it becomes irreversible.

An understanding of the pathophysiological mechanisms of atherosclerosis at a molecular level is critical for the development of improved prevention and treatment methods for atherosclerosis. Fluorine-18-FDG uptake is a marker of inflammation and potential plaque instability, whereas CT-based detection of calcification signifies past inflammation and hence, relative stability. Serial 18F-FDG PET/CT imaging can track changes in the degree of plaque inflammation, and therefore can be used to provide objective evidence of the efficacy of lipid-lowering drugs. Positron emission tomography has been validated as an accurate, noninvasive, and reproducible imaging modality for the identification and quantification inflammatory processes [24-27]. This makes 18F-FDG PET/CT a promising imaging technique to identify patients with atherosclerosis and those who are at risk for plaque rupture.

Additional research is necessary to persuade cardiovascular specialists to use PET imaging for assessing and monitoring atherosclerosis, as well as to demonstrate the cost-effectiveness of PET for this application. Several investigators have studied the feasibility of 18F-FDG PET/CT imaging for detecting and quantifying atherosclerotic plaque burden in humans. The first systematic study linking 18F-FDG uptake in the large arteries to atherosclerosis was performed by Yun et al. (2001) [28]. Retrospective analysis observed that 50% of patients studied by 18F-FDG-PET imaging for other purposes had uptake of 18F-FDG in the large vessels (abdominal aorta, iliac, and proximal femoral arteries) 1 hour after injection of 18F-FDG [28]. Subsequent studies have shown that: a) 18F-FDG uptake in carotid plaques correlated consistently to macrophage staining from corresponding histological sections of post-endarterectomy specimens [29, 30], b) 18F-FDG-PET detected 18F-FDG accumulation in both stenotic and non-stenotic atherosclerotic lesions as evaluated by carotid artery ultrasonography [31], c) a positive correlation existed between arterial 18F-FDG uptake and various cardiovascular risk factors (i.e., aging [28, 32], hypercholesterolemia [32], hypertension [27], metabolic syndrome [33], and type 2 diabetes mellitus [34]), d) assessment of athero-oburden by 18F-FDG PET is highly reproducible with low inter- and intraobserver variability [26, 30, 35], and e) 18F-FDG uptake in patients treated with lipid-lowering medications, anti-diabetic drugs, and life-style interventions was significantly reduced after a period of 3-6 months [36-39].

A study was performed exploring the association between 18F-FDG accumulation and the biological characteristics of atherosclerotic lesions in a rabbit model. Fluorine-18-FDG accumulation was noted to be higher in the aortas of heritable hyperlipidemic rabbits than in those of controls. Also, the degree of 18F-FDG uptake and the number of macrophages present in plaques were strongly related [40]. There have been studies reinforcing the role of 18F-FDG PET in monitoring plaque inflammation and hence, for evaluating the therapeutic effects of drugs which can stabilize or reverse vulnerable plaques [36, 41].

Encouraged by these important observations, Rudd et al. (2002) investigated the relationship between 18F-FDG uptake and cardiovascular events [42]. Fluorine-18-FDG uptake was significantly higher (27% more) in symptomatic lesions (angiographically designated as "culprit" lesions) compared to contralateral asymptomatic lesions. Davies et al. (2005) confirmed these data, despite the presence of relatively high 18F-FDG uptake in angiographically non-stenotic lesions located in the vascular territory responsible for the presenting symptoms [43]. Further evidence of the relationship between increased 18F-FDG uptake and cardiovascular risk were observed in a pilot study investigating 13 patients with previously symptomatic carotid atherosclerosis [44]. Restenosis, recurrence of cardiovascular events, or death occurred in subjects who had high amounts of 18F-FDG accumulation (maximum SUV ≥2.7) during the 6 months of follow-up. More recently, Paulmier et al. (2008) showed a higher rate of recent cardiovascular events in subjects with high vascular 18F-FDG accumulation than in subjects with low vascular 18F-FDG accumulation [45]. This effect was only observed in patients who had experienced cardiovascular events less than 6 months before undergoing PET imaging, suggesting a correlation between plaque inflammation and plaque instability. Two subsequent studies confirmed these results by reporting increased cardiovascular risk in asymptomatic patients with increased 18F-FDG accumulation in the arterial vasculature [46, 47].

In this study, an increase in 18F-FDG uptake was observed in the peripheral arteries and aorta with increasing age. These findings are a manifestation of cumulative plaque in-

### Table 3. Average SUVmean values (and standard deviations) measured in the aorta, femoral arteries, and iliac arteries of subjects with and without cardiovascular risk factors. Sample sizes differed among these groups for the aorta (n=32, 43), femoral (n=20, 28), and iliac arteries (n=32, 40).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Average SUVmean in aorta (o)</th>
<th>Average SUVmean in femoral arteries (o)</th>
<th>Average SUVmean in iliac arteries (o)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cardiovascular risk factors</td>
<td>1.53 (0.30)</td>
<td>0.98 (0.25)</td>
<td>1.34 (0.31)</td>
</tr>
<tr>
<td>≥1 cardiovascular risk factor</td>
<td>1.70 (0.41)</td>
<td>1.03 (0.33)</td>
<td>1.42 (0.35)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.046</td>
<td>0.559</td>
<td>0.365</td>
</tr>
</tbody>
</table>

encouraging by these important observations, Rudd et al. (2002) investigated the relationship between 18F-FDG uptake and cardiovascular events [42]. Fluorine-18-FDG uptake was significantly higher (27% more) in symptomatic lesions (angiographically designated as "culprit" lesions) compared to contralateral asymptomatic lesions. Davies et al. (2005) confirmed these data, despite the presence of relatively high 18F-FDG uptake in angiographically non-stenotic lesions located in the vascular territory responsible for the presenting symptoms [43]. Further evidence of the relationship between increased 18F-FDG uptake and cardiovascular risk were observed in a pilot study investigating 13 patients with previously symptomatic carotid atherosclerosis [44]. Restenosis, recurrence of cardiovascular events, or death occurred in subjects who had high amounts of 18F-FDG accumulation (maximum SUV ≥2.7) during the 6 months of follow-up. More recently, Paulmier et al. (2008) showed a higher rate of recent cardiovascular events in subjects with high vascular 18F-FDG accumulation than in subjects with low vascular 18F-FDG accumulation [45]. This effect was only observed in patients who had experienced cardiovascular events less than 6 months before undergoing PET imaging, suggesting a correlation between plaque inflammation and plaque instability. Two subsequent studies confirmed these results by reporting increased cardiovascular risk in asymptomatic patients with increased 18F-FDG accumulation in the arterial vasculature [46, 47].
flammation over time, which is consistent with the designation of age as a non-modifiable risk factor for atherosclerosis. The finding of a dramatic increase in the degree of atherosclerosis with age is consistent with invasive studies that have utilized complex molecular techniques [48]. This study also suggests that $^{18}$F-FDG PET may be used to tailor the management of atherosclerosis in individual patients. The finding that cardiovascular risk factors are significantly correlated with increases in $^{18}$F-FDG uptake adds more evidence that cardiovascular risk factors are significantly correlated with progression of atherosclerosis in individual patients. The finding of age as a non-modifiable risk factor for atherosclerosis.

This study is limited in its retrospective design and sample size of 76 patients. These factors make it difficult to rule out the effect of confounding variables on the results, despite the efforts made to account for risk factors. The retrospective nature of this study also means that imaging and follow-up protocols could not be standardized. However, these preliminary results justify further prospective research on this novel approach for detecting atherosclerosis.

In conclusion, we observed increases in $^{18}$F-FDG uptake in the peripheral arteries and aorta that accompanied advancing age. This reflects the cumulative escalation of a continuous inflammatory processes occurring over time in the arteries with increasing age. In our study, we also observed that cardiovascular risk factors are significantly correlated with increases in $^{18}$F-FDG uptake, a relationship that was particularly pronounced in the abdominal aorta. Early detection and quantification of atherosclerosis by $^{18}$F-FDG PET/CT may allow for the use of preventative treatments which are tailored for individual patients who are potentially at risk.

The authors declare that they have no conflicts of interest.

Bibliography


