Atherosclerotic inflammatory activity in the aorta and its correlation with aging and gender as assessed by ^{18}F-FDG-PET

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Abstract

Recent literature demonstrates the potential of fluorine-18 fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) to detect, localize, and quantify the degree of inflammatory changes in the arterial wall due to early atherosclerosis. *Our aim was* to assess the correlation between the age and ^{18}F-FDG uptake of aortic segments and determine its correlation with respect to in both age and genders. *Fluorine-18-FDG uptake in aortic segments in 143 subjects* (58 men, 85 women; ages 5-82 years) was evaluated in this study. Subjects were initially grouped according to the gender, and then by age (below or above 50) with at least 26 subjects per group. Mean standardized uptake value (SUV) of ascending aorta, arch, descending thoracic aorta, and abdominal aortic segments were calculated in each subject. Correlative analyses between age and mean SUV of aortic segments in all subjects were undertaken. Mean SUV between genders for all groups were also compared. *There was a positive correlation* between age and mean SUV of all aortic segments. The correlation values in all aortic segments were higher in subjects below 50 years old compared to those above 50 years in the entire group of patients as well as when they were subdivided and analyzed according to both genders ($P<0.001$). Descending thoracic and ascending aortic segments in men below 50 years of age had the highest correlation of ^{18}F-FDG uptake and age (0.85 and 0.80, respectively) whereas abdominal aortic segments in men the above 50 years age group had the lowest correlation value (0.20). Comparison between mean SUV in four visible arterial segments between the two genders did not reveal any statistically significant difference. *In conclusion*, ^{18}F-FDG uptake in aortic segments increases with age irrespective of genders. The increase with age is more significant in younger subjects compared to older subjects for both men and women. This finding may indicate a deceleration in the inflammatory component of atherosclerosis with aging in older subjects.

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Introduction

Aortic fluorine-18 fluorodeoxyglucose (^{18}F-FDG) accumulation was initially interpreted as physiologic, representing blood pool activity [1]. Work by investigators at the Hospital of the University of Pennsylvania then correctly linked ^{18}F-FDG uptake in the large arteries to atherosclerosis [2]. Atherosclerosis is a slowly progressive disease that may start in childhood [3]. Cardiovascular diseases including atherosclerosis increases with aging, which is considered to be a major factor associated with the process. Atherosclerosis, thus, can also be described as a universal form of vascular aging in humans. It has been reported that the severity of ^{18}F-FDG uptake (as measured by SUV in ^{18}F-FDG-PET studies) in large arteries increases with aging [4]. Prominent ^{18}F-FDG uptake in any segment of large arteries is a sign of atherosclerosis, unless there is any other underlying vascular pathology responsible for ^{18}F-FDG uptake. The aim of this research study was to assess the correlation between age and ^{18}F-FDG uptake in the four segments of the aorta in subjects of either gender.

Materials and methods

Institutional Review Board (IRB) approval for the retrospective data collection and image analysis along with a Health Information Portability Accountability (HIPA) Act waiver were obtained at the Hospital of the University of Pennsylvania prior to the study initiation.

Study population

The presence of vascular ^{18}F-FDG uptake was retrospectively evaluated in 143 subjects (58 males, 85 females; age 5-82 years) who underwent whole body ^{18}F-FDG-PET imaging for the assessment of non-cardiovascular disorders. In these subjects, no abnormal sites of disease activity that could interfere with arterial wall ^{18}F-FDG uptake measurement were noted on the whole body PET scans. Subjects were initially grouped by age (below and above 50 years) and then by gender, with at least 26 subjects per group. Mean standardized uptake values (SUV) of the ascending aorta, aortic arch, descending thoracic aorta, and abdominal aorta segments were recorded (Fig. 1). Correlation between age and mean SUV of aortic segments in various age groups, and in men and women in the two major age-related sub-groups (as mentioned above) were analyzed. Mean SUV in visible arterial segments between the genders were also compared.

^{18}F-FDG-PET study

Imaging by ^{18}F-FDG-PET was performed on a dedicated whole body PET scanner (Allegro; Philips Medical Systems, Bothell WA, USA). At the time of ^{18}F-FDG injection, all subjects had fasted for at least 6 hours and had blood sugar levels of <150mg/dL. Image acquisition for the whole body scan started at a mean time point of 60min after injection of 2.52MBq/kg of body weight. Scanning included the neck, thorax, abdomen, pelvis, and upper thighs. Images consisted of 4 or 5 emission frames of 25.6cm length with an overlap of 12.8cm covering an axial length of 64-76.8cm. Image reconstruction was performed with an iterative ordered-subsets expectation maximization algorithm with 4 iterations and 8 subsets. Attenuation-corrected images were obtained by applying transmission maps with a cesium-137 source interleaved with the emission scans.

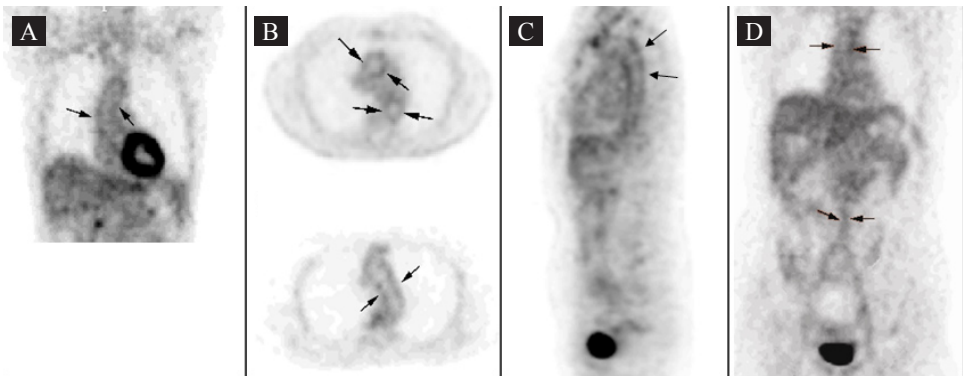

Figure 1. ^{18}F-FDG uptake in the ascending aorta, arch of aorta, descending thoracic and abdominal segments of the aorta (arrows) on coronal (A, E), axial (B, C), and sagital (D) slices. Mean SUV were calculated using axial slices (B, C).

Table 1. *Correlation between aortic segmental ^{18}F-FDG uptake (mean SUV) and age in all subjects (n=143)*

Correlation coefficients (r)	Ascending thoracic Aorta	Arch of aorta	Descending thoracic aorta	Abdominal aorta
Subjects below 50 years old (n=71)	0.76	0.75	0.81	0.50
Subjects above 50-year old (n=72)	0.46	0.36	0.34	0.36
P values	<0.001	<0.001	<0.001	<0.001

Table 2. *Correlation between aortic segmental ^{18}F-FDG uptake (mean SUV) and age men (n=58)*

Correlation coefficients (r)	Ascending thoracic aorta	Arch of aorta	Descending thoracic aorta	Abdominal aorta
Subjects below 50 years old (n=32)	0.80	0.78	0.85	0.37
Subjects above 50 years old (n=26)	0.45	0.35	0.27	0.20
P values	<0.001	<0.001	<0.001	<0.001

Table 3. *Correlation between aortic segmental ^{18}F-FDG uptake (mean SUV) and age in women (n=85)*

Correlation coefficients (r)	Ascending thoracic aorta	Arch of aorta	Descending thoracic aorta	Abdominal aorta
Subjects below 50 years old (n=39)	0.75	0.74	0.72	0.62
Subjects above 50 years old (n=46)	0.52	0.40	0.43	0.43
P values	<0.001	<0.001	<0.001	<0.001

Table 4. *Comparison of mean SUV for genders in four segments of the aorta*

	Ascending thoracic aorta	Arch of aorta	Descending thoracic aorta	Abdominal aorta
Men Mean SUV	1.74	1.81	1.9	1.96
Women Mean SUV	1.87	1.96	2.0	1.98
P values ns=P>0.05	ns	ns	ns	ns

Table 5. *Correlation between aortic segmental ^{18}F-FDG uptake (mean SUV) and age in men and women (n=143)*

Correlation coefficients (r)	Ascending thoracic aorta	Arch of aorta	Descending thoracic aorta	Abdominal aorta
Men (n=58)	0.78	0.76	0.75	0.53
Women (n=85)	0.79	0.73	0.72	0.32
P values	ns	ns	ns	ns

Results

A positive correlation was observed between age and mean SUV of four aortic segments (ascending aorta, aortic arch, descending thoracic aorta, and abdominal aorta) in both age subgroups i.e. subjects below 50 years and subjects above 50 years (Table 1). A positive correlation was determined between age and mean SUV for all four aortic segments in men (Table 2) and in women (Table 3) in both subgroups. In other words, ^{18}F-FDG uptake increased with age in the four major segments of the aorta in men and women less than 50 years old and men and women 50 years old and older. Correlation values in all aortic segments were higher in subjects below 50 years of age compared to those at or above 50 years of age in the entire group (P<0.001) (Table 1). Correlation values in all aortic segments were higher in men below 50 years of age compared to those 50 and above in males (P<0.001) (Table 2) as well as in females (P<0.001) (Table 3). Descending thoracic and ascending aortic segments in men below 50 years of age had the highest correlation between ^{18}F-FDG uptake and age (0.85 and 0.80, respectively). Abdominal aortic segment in men 50 years of age and above had the lowest correlation value (0.20).

Mean SUV in visible arterial segments between genders did not reveal any statistically significant difference (Table 4). Correlation values of ^{18}F-FDG uptake in all aortic segments in the two gender subgroups did not reveal any statistically significant differences (Table 5).

Discussion

Atherosclerosis is a dynamic ongoing inflammatory process that has been the major cause of myocardial infarctions, cerebrovascular accidents, and acute coronary syndromes. Despite the widespread use of drug therapies, it continues to be a global health concern [5]. Vascular aging is an independent risk factor for the cardiovascular disease starting from atherosclerosis to target organ damage [6, 7]. Understanding the mechanisms underlying the age related vascular pathophysiological changes holds great promise for reducing the cardiovascular mortality in an aging population

[8]. Vascular atherosclerotic disease evolves over decades with progressive accumulation of cellular and extracellular materials and many inflammatory processes [7]. The uptake of ^{18}F-FDG in inflammatory cells related, to enhanced anaerobic glycolysis in the region of leukocytic infiltration and to over expression of GLUT receptors on the surface of activated inflammatory cells, enhanced glucose transport under the stimulation of inflammatory mediators such as multiple cytokines and growth factors [9, 10] and allowed for imaging of inflammation by PET in various disease processes [11-14].

Animal studies have shown that there is no measurable ^{18}F-FDG uptake in the normal vessel wall, and that ^{18}F-FDG is taken up by the inflammatory cells, predominantly macrophages, in the atherosclerotic plaque. The concept that inflammation plays a major role in atherogenesis has now been well recognized [15, 16]. As a functional imaging modality, ^{18}F-FDG-PET detects and localizes inflammatory changes in the arterial wall, representing early stages of atherosclerosis [4, 17, 18]. It has been already reported that the magnitude of atherosclerosis increases with aging [4]. The present study is the first to assess changes in the early inflammatory component of atherosclerosis in younger and older subjects (with 50 years as the cut-off point) and between men and women.

We observed a positive correlation of vascular ^{18}F-FDG uptake with age in four different segments of the aorta in both genders in both subjects below 50 years old (young subjects) and 50 years old and above (old subjects). The ^{18}F-FDG uptake within the walls of all segments increased with increasing age, which is evidence that atherosclerosis is a systemic disease involving all vascular beds. The correlation values in younger subjects were higher than those in older subjects in both genders, indicating that the rate of the increase of the inflammatory component of atherosclerosis is greater in younger subjects than in older subjects.

The lowest correlation value was noted in the abdominal aortic segment in men 50 years old and above. A necropsy study by Mitchell et al (1977) showed that aortic calcification occurs earlier and more severely in men in the abdominal aorta [19], which is compatible with our observation of an associated decreased rate of increase of atherosclerotic inflammation in older men in the later stages of the atherosclerotic process.

No differences were seen for the ^{18}F-FDG uptake values among the both genders in the entire age group. Also, correlation values were not significantly different between younger and older subjects amongst the men and women i.e. although the severity declined with age in men and women, no difference was seen for correlation values between younger women and men or for older women and men. This suggests that the rate of increase of the inflammatory component of atherosclerosis is similar in men and women within similar age groups.

One limitation of this study was that other risk factors for atherosclerosis, such as diabetes mellitus, hypertension, smoking or serum lipid levels were not evaluated. These risk factors accelerate the atherosclerotic process [20-23], and were more likely to occur in the older than younger subjects. However, we had effectively excluded from the patients' clinical records any patient with a history of cardiovascular disorders. As such, these risk factors could possibly increase the severity of the entire atherosclerotic process leading to faster replacement of vascular beds with areas of calcification in the older subjects. As a result, it may be expected that in older subjects with more areas of calcification, the severity of inflammatory component would decrease, leading to lower correlation values, as we observed in our data.

One other limitation is that no partial volume correction was applied to the data. The size of the aortic wall was documented to be 2-3mm [24, 25], which is under the resolution of the PET scanner, likely resulting in underestimation of the true ^{18}F-FDG uptake values in the aortic segments. However, this factor will be applicable for the entire study population and in a comparison like this will be effectively nullified. Future prospective research studies could be directed towards addressing these limitations.

In conclusion, although there is a positive correlation with age in four different segments of aorta in both genders in subjects below 50 years old and 50 years old and above, the rate of increase of the inflammatory component of atherosclerosis is higher in the younger subjects than in older subjects in both genders. This is consistent with a deceleration of the inflammatory component of atherosclerosis with aging in both genders. The rate of change of the inflammatory component of atherosclerosis appears to be similar in men and women within the same age range.

The authors declare that they have no conflicts of interest.

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