Imaging Atherosclerosis in the Carotid Arteries with F-18-Fluoro-2-deoxy-D-glucose Positron Emission Tomography: Effect of Imaging Time after Injection on Quantitative Measurement

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Abstract

Purpose To compare F-18-fluoro-2-deoxy-D-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) imaging at two different circulation times after injection of F-18 FDG in order to measure atherosclerosis in carotid arteries.

Methods We assessed 12 patients with recent symptomatic plaques in the carotid arteries. F-18 FDG PET/CT carotid plaque imaging was performed for 20 min at 2 h after F-18 FDG injection in five patients and at 3 h in seven patients. We measured vessel wall uptake using the maximal standardized uptake value (SUV), and the mean and maximal blood target-to-background ratios (TBR) of the symptomatic carotid arteries. Blood pool activity (BPA) was measured as the mean SUV of the superior vena cava (SVC) and jugular vein of these 12 patients, and in 14 age- and gender-matched patients who underwent whole-body F-18 FDG PET/CT examinations 1 h after injection.

Results F-18 FDG PET/CT revealed visible F-18 FDG uptake in all patients with symptomatic carotid plaques. Maximal SUV did not differ between groups evaluated at 2 h and 3 h (2.62 ± 0.45 vs 3.00 ± 0.85 , $p=0.335$). However,

mean (2.04 ± 0.22 vs 3.54 ± 0.62 , $p<0.05$) and maximal (1.65 ± 0.15 vs 2.70 ± 0.42 , $p<0.05$) TBR values that were normalized to BPA in the SVC differ significantly.

Conclusions Symptomatic carotid plaques are visualized for a relatively short period of imaging time on ≥ 1 -h PET/CT images. Quantitative parameters of atherosclerotic carotid arteries are preserved or even increased over time, whereas those of blood pools are decreased.

Keywords F-18 FDG PET/CT · Atherosclerosis · Carotid arteries · Imaging time

Introduction

Cardiovascular events are the leading causes of death in developed countries worldwide, with plaque rupture being the primary cause of most such events. Inflammatory processes, caused primarily by macrophages, within the plaques have been reported to increase the risk of rupture and subsequent thromboembolic events such as stroke and myocardial infarction [1]. As conventional anatomic imaging technologies can only quantify the extent of disease in terms of luminal stenosis and visualization of some plaque elements [2], imaging of vulnerable plaques is critical. F-18-fluoro-2-deoxy-D-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is a unique, noninvasive measure of plaque inflammation [3], because F-18 FDG is retained within plaque macrophages more avidly than within other plaque elements [4]. F-18 FDG PET/CT has been utilized to image macrophage-rich areas of plaque in carotid arteries [5].

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As F-18 FDG uptake occurs over a longer time course in atherosclerotic arteries than in tumors [6], a longer F-18 FDG circulation time may provide a better target-to-background ratio (TBR) [7]. However, the longer acquisition time required to circumvent image noise may be problematic [6]. For example, a recent study showed that imaging over 1 h after F-18 FDG injection was not useful because the data were statistically noisy [8]. Presently, no standardized F-18 FDG PET/CT protocol for imaging of atherosclerosis has been established.

In this study, we measured F-18 FDG uptake values of symptomatic atherosclerosis in carotid arteries and compared them with venous F-18 FDG uptake values 2 h and 3 h after administration of F-18 FDG to patients with symptomatic carotid artery stenosis. To better assess the symptomatic carotid plaque, we used a highly sensitive PET/CT scanner enabling three-dimensional F-18 FDG PET [9]. We also compared blood pool activity in our oncology patients who underwent whole-body F-18 FDG PET/CT examinations 1 h after F-18 FDG injection.

Materials and Methods

Study Population

We enrolled 12 patients (age range, 58–78 years) who had experienced recent (<6 months) strokes, or transient ischemic attacks (TIAs), and who had been diagnosed by neurologists as having ipsilateral carotid plaque causing lumen diameter stenosis $\geq 30\%$ as shown by duplex ultrasonography.

All patients underwent F-18 FDG PET/CT examinations between January and October 2009 at the Asan Medical Center, Seoul, Korea. All female patients were post-menopausal and were not using effective contraceptive measures. Patients with active inflammatory disease, vasculitis, or uncontrolled or insulin-treated diabetes mellitus were excluded. From January to April 2009, five patients underwent F-18 FDG PET/CT examinations 2 h after F-18 FDG injection, whereas between May and October seven patients underwent F-18 FDG PET/CT examinations 3 h after F-18 FDG injection. All patients provided written informed consent, and the study was approved by the Institutional Review Board of the Asan Medical Center.

To compare blood pool activity, we selected as a control group 14 age- and gender-matched patients with stable colorectal or gynecologic cancer, who underwent whole-body F-18 FDG PET/CT examinations 1 h after F-18 FDG injection as part of routine follow-up between May and October 2009 (the clinical characteristics of the 1-h group are also shown in Table 1). None of these patients had been previously diagnosed with carotid stenosis.

PET/CT Protocol

All examinations were performed using a Biograph 40 TruePoint PET/CT scanner (Siemens/CTI, Knoxville, Tenn.). All patients with symptomatic carotid stenosis were instructed to fast for at least 8 h prior to the test. Diabetic patients were instructed to adhere to their regular schedules of drugs controlling glucose level. Serum glucose levels were routinely

Table 1 Demographic data and patient characteristics. Data are presented as mean $\pm$ standard deviation; *LBM* lean body mass, *FBG* fasting blood glucose, *NS* not significant

Characteristic	Control	Symptomatic carotid stenosis		<i>p</i> value
		2h (<i>n</i> =5)	3h (<i>n</i> =7)	
Imaging time after FDG injection	1h (<i>n</i> =14)			
Age	67 $\pm$ 5	69 $\pm$ 8	67 $\pm$ 5	NS
Sex (M/F)	10/4	5/0	5/2	NS
LBM	55.6 $\pm$ 5.2	49.1 $\pm$ 7.6	48.0 $\pm$ 6.8	NS
Diabetes mellitus	1	0	3	NS
FBG	106.3 $\pm$ 11.0	99.8 $\pm$ 4.5	104.1 $\pm$ 15.0	NS
Hypertension	8	4	7	NS
Hyperlipidemia	0	2	4	$p<0.05^b$, $p>0.017^c$
Smoking	4	5	2	$p<0.05^b$, $p>0.017^c$
Statin therapy	0	4	7	$p<0.05^b$, $p>0.017^c$
Numbers of cardiovascular risk factors ^a	1.7 $\pm$ 1.2	3.8 $\pm$ 1.3	4.1 $\pm$ 0.9	$p<0.05^b$, $p>0.017^c$

^a Cardiovascular risk factors: hypertension, diabetes mellitus, hyperlipidemia, alcohol, smoking, history of previous stroke, previously diagnosed cardiac disease, family history of previous stroke

^b *p* value among the three groups

^c *p* value between the 2-h and 3-h groups with symptomatic carotid stenosis

measured and were under 130 mg/dl in all patients. Two or three hours after injection of 7.4 MBq/kg body weight (330–630 MBq) F-18 FDG, a three-dimensional PET/CT scan was initiated. CT was performed first, without administration of contrast medium to correct photon attenuation and scattering, using a continuous spiral 40-slice technique with a voltage of 120 kV, a pitch of 0.7, a slice thickness of 2.0 mm, a current of 200 mA, and a rotation speed of 0.5 s/revolution. PET was performed immediately afterwards, using a full-ring dedicated scanner with an axial field of view (FOV) of 21.6 cm and an image reconstruction matrix of 336×336 . Patients were imaged in the supine position using a head fixation device, which holds the patient's neck firm with respect to the shoulders, and features an extension [10]. Images were acquired for 10 min in each bed position during normal tidal breathing, with an overlapping scans from the skull base to the upper chest obtained using two bed positions. Images were reconstructed after CT-based attenuation and scattering corrections using the three-dimensional ordered subsets expectation maximization reconstruction algorithm (three iterations, 21 subsets) with the point spread function [11]. The PET data were routinely recalculated to display images of standardized uptake values (SUVs) based on lean body mass.

Control patients with malignancies underwent routine whole-body PET/CT examinations without neck extension 1 h after FDG administration, using the same PET/CT scanner. CT was performed with a slice thickness of 5.0 mm and a current was 100 mA, and PET was performed as described above, except that the reconstruction matrix was 168×168 .

Image Analysis

Image analysis was performed on a dedicated workstation (Singo; Siemens). Carotid artery PET was quantified after

identification of the artery using non-contrast-enhanced CT images. Approximately 50 PET slices were read for each carotid study, starting from the origin at the aortic arch or right subclavian artery to a position 2 cm above the carotid bulb, where the artery is recognizable on non-enhanced CT images. PET images were subsequently visually evaluated for the presence of focal F-18 FDG uptake by the carotid arteries, by measurement of maximal SUVs.

Arterial F-18 FDG uptake in the neck, (as a measure of arterial inflammation) was determined by drawing a simple circular region-of-interest (ROI) around the artery on every slice of the co-registered transaxial PET/CT images (Fig. 1). On each image slice, the mean and maximal SUVs of FDG in the ROI (containing the arterial wall and the lumen) were calculated as the mean and maximal pixel activity, respectively [12]. The SUV is the decay-corrected tissue concentration of FDG (in kBq/g), adjusted for injected F-18 FDG dose and lean body mass. By averaging the SUVs of all artery slices within an arterial territory, we derived mean and maximal SUVs for each region. These SUVs were normalized to blood FDG activity by dividing the SUVs by the average blood ROI (calculated from at least six venous ROI measurements), estimated from either the superior vena cava (SVC) or the jugular vein [12]. This calculation yielded an arterial TBR.

Using similar methods, we measured the mean SUVs of the SVC and jugular vein of the group scanned 1 h post injection, to compare blood pool activity at different F-18 FDG circulation times.

Statistical Analysis

Continuous variables are shown as means $\pm$ SDs. Categorical variables are expressed as numbers only. Continuous variables were compared within groups and between groups using one-

Fig. 1 An example of image analysis on transverse CT (a), fused PET/CT (b), and PET (c) images of the right carotid artery. A circular ROI was drawn around right carotid artery on the CT image. Data from this same ROI on PET image provides mean and maximal SUV

values within defined ROI. For each carotid artery, this analysis is repeated on all transverse slices, averaged, and divided by venous SUV to obtain mean and maximal TBR, respectively

way ANOVA and the independent *T*-test. Categorical variables were compared using the chi-squared test or when the observed cell numbers were less than five by Fisher's exact test. Bonferroni's multiple comparison post hoc analysis was performed among controls and different patient groups with symptomatic stenosis in carotid arteries. A *p* value <0.05 was considered statistically significant. In multiple comparisons, a *p* value <0.017 was considered significant. All statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences for Windows, version 17.0, SPSS, Chicago, Ill.).

Results

Patient Characteristics

The clinical characteristics of each group are presented in Table 1. There were no significant differences in between patients analyzed 2 h and 3 h after F-18 FDG injection in terms of the number of cardiovascular risk factors per individual, including hypertension, diabetes mellitus, hyperlipidemia, alcohol use, smoking status, history of previous stroke, previously diagnosed cardiac disease, or family history of prior stroke (*p*>0.016 for all comparisons). Of the 12 patients, 11(82%) were taking statins.

All patients with diabetes mellitus were well controlled by oral hyperglycemic agents. Prescan glucose levels did not differ significantly between the 1-, 2-, and 3-h groups (106.3±11.0 mg/dl, vs 99.8±4.5 mg/dl, vs 104.1±15.0 mg/dl, respectively; *p*>0.05).

F-18 FDG PET/CT

In the 1-, 2-, and 3-h groups, F-18 FDG PET/CT commenced on average 58.1±8.2 min, 124.4±6.8 min, and 183.6±6.7 min, respectively, after injection of F-18 FDG. All patients, except for one in each of the 2-h and 3-h groups, were fasted for at least 8 h before F-18 FDG PET/CT.

All patients with symptomatic stenosis of the carotid arteries showed visible F-18 FDG uptake. The mean and

maximal SUVs and the mean and maximal TBR uptake values for the carotid arteries in each group are shown in Table 2. Although maximal SUV did not differ between the 2-h and 3-h groups (2.62±0.45 vs 3.00±0.85, *p*=0.335), mean SUV was significantly lower in the 2-h than in the 3-h group (1.26±0.02 vs 1.47±0.12, *p*<0.05). Moreover, the two groups differed significantly in the mean and maximal TBR values normalized to blood pool activity in the SVC (2.04±0.22 vs 3.54±0.62, *p*<0.05 and 1.65±0.15 vs 2.70±0.42, *p*<0.05, respectively, and jugular vein (2.16±0.20 vs 2.95±0.29, *p*<0.05 and 11.75±0.13 vs 2.25±0.20, *p*<0.05, respectively).

Blood pool activities in the SVC and jugular vein of all three groups are shown in Table 3 and Fig. 2. We observed time-dependent decreases in SUV values in the SVC (1.18±0.15, 0.85±0.05, and 0.56±0.10 at 1 h, 2 h, and 3 h, respectively; *p*<0.05) and jugular vein (1.04±0.16, 0.79±0.03, and 0.66±0.04 at 1 h, 2 h, and 3 h, respectively; *p*<0.05). Mean SUV values in the SVC differed significantly between each group and between any one group and a combination of the two other groups (*p*<0.01). Mean SUV values in the jugular vein were significantly lower for the 2-h and 3-h groups than the 1-h group (*p*<0.01), but the mean SUVs of the 2 h and 3 h groups were similar (*p*=0.183).

Discussion

In this study, we compared two F-18 FDG PET/CT time protocols in 12 patients with symptomatic carotid stenosis, which was strongly associated with a cerebral vascular accident such as stroke or TIA. The presence of inflammation in atherosclerotic carotid arteries was clearly identified in the 2-h and 3-h groups. Blood pool activity, as measured by mean SUV of the SVC, was significantly lower in the 3-h than in the 1-h and 2-h groups. This affected TBR values by maximizing the contrast between inflammation of the vessel wall and the background.

Although a recent study found no significant difference in SUV and TBR values when 1-h and >1-h evaluation protocols were employed [8]. The cited work was

Table 2 Quantitative F-18 FDG uptake of carotid arteries in patients with symptomatic carotid stenosis (NS not significant)

Quantitative parameters	Imaging time after F-18 FDG injection		<i>p</i> value
	2h (<i>n</i> =5)	3h (<i>n</i> =7)	
Maximal SUV	2.62±0.45	3.00±0.85	NS
Mean SUV	1.26±0.02	1.47±0.12	<i>p</i> <0.05
Mean TBR (SVC)	1.65±0.15	2.70±0.42	<i>p</i> <0.05
Mean TBR (jugular vein)	1.75±0.13	2.25±0.20	<i>p</i> <0.05
Maximal TBR (SVC)	2.04±0.22	3.55±0.62	<i>p</i> <0.05
Maximal TBR (jugular vein)	2.16±0.20	2.95±0.29	<i>p</i> <0.05

Table 3 F-18 FDG blood pool activity in SVC and jugular vein at different circulation times after F-18 FDG injection

Quantitative parameters	Imaging time after F-18 FDG injection			<i>p</i> value
	1h (<i>n</i> =14)	2h (<i>n</i> =5)	3h (<i>n</i> =7)	
Mean SUV of SVC	1.10±0.15	0.85±0.05	0.56±0.10	<i>p</i> <0.05 ^a , <i>p</i> <0.01 ^b
Mean SUV of jugular vein	1.04±0.16	0.79±0.03	0.66±0.04	<i>p</i> <0.05 ^a , <i>p</i> <0.01 ^c

^a *p* value among groups^b *p* value between groups^c *p* value between 1 h and 2 h groups, and 1 h and 3 h groups (not significant between the 2-h and 3-h groups, *p*=0.183)

performed on patients with abdominal aortic aneurysms and background blood signals were derived from the lumen of the aorta rather than from an adjacent vein such as the inferior vena cava [13]. Moreover, data from imaging at 3 h were statistically noisy. In contrast, our 3-h imaging results differed significantly from those obtained at relatively shorter acquisition times. As the maximal SUV did not increase significantly, the increase in TBR we observed was likely attributable to a fall in blood pool activity. This may have arisen because we chose patients with symptomatic carotid arteries and conducted blood pool measurements using the SVC or jugular vein. In addition, we employed a highly sensitive PET/CT scanner [9] with 21.6 cm of axial FOV, and used two bed positions with overlapping axial FOV, for 10 min per position, which may have contributed to the significant differences between the 2-h and 3-h results.

We also observed a significant time-dependent decrease in the mean SUV at jugular vein. When a single bed position is chosen for the imaging of carotid arteries from the skull base to the supraclavicular area, the jugular vein may be an acceptable site for the sampling of blood pool activity, even if imaging is performed 3 h after F-18 FDG injection. Furthermore, use of the SUV of the SVC is likely

to be affected by intense cardiac F-18 FDG uptake, use of the mean SUV of the jugular vein as a measure of blood pool activity may be an acceptable alternative. The relatively long acquisition times used in previous studies, being up to 30 min for each bed position [7, 14–16], may have limited the wide spread of F-18 FDG PET/CT for the purpose for which we employed the technique in the present report. Using a shorter acquisition time (10 min), and a highly sensitive PET/CT scanner, we observed increased F-18 FDG uptake in all carotid stenosis [9]. Because of the increasing demand for vascular imaging with this emerging technique to identify vulnerable atheromatous plaques and arterial inflammation and to monitor the effects of pharmacological or surgical interventions [3, 14, 17–20], F-18 FDG PET/CT is becoming more popular in clinical practice. To compensate for the low counts obtained from delayed dual-time F-18 FDG PET/CT scans in oncology patients, which are the main cause of noisy results, it has been recommended that scans should be delayed, using approximately three- to fourfold longer acquisition times per bed position [21]. The main advantage of delayed PET scanning, the increase in TBR, may be offset by reduced counts, thus limiting the sensitivity of PET/CT. Our findings suggest that carotid PET/CT imaging

Fig. 2 Blood pool activity in SVC (*left*) and jugular vein (*right*) at different circulation time after FDG injection. Blood pool activities in SUV values showed a significant decrease with time after F-18 FDG injection

is feasible 3 h after F-18 FDG injection with an acquisition time of 10 min per bed position.

Our study had several limitations. First, 11 of our 12 patients were on statin therapy. As such drugs attenuate plaque inflammation [17], the SUV may have been underestimated in these patients. Second, we utilized, as a control group for blood pool activity, stable oncologic patients without known stenosis in their carotid arteries, as patients with known stenosis who underwent PET/CT examination 1 h after F-18 FDG injection were not available for comparison. Lastly, the TBR quantifies atherosclerotic inflammation. Several recent studies have considered TBR to be representative of the atherosclerotic burden of specific vascular walls. By definition, the TBR includes not only the metabolic activity of the vascular wall but also that of the blood pool activity. Although we corrected TBR by blood pool activity in an adjacent vein (i.e., the SVC or jugular vein), this approach has limitations when used to measure genuine atherosclerotic inflammation. New parameters that quantify arterial inflammation more accurately may be required in future studies.

In conclusion, symptomatic carotid plaques are visualized for a relatively short period of imaging time on 2-h or 3-h delayed PET/CT images. Methodologically, it is possible to shorten acquisition time, thus possibly making PET/CT convenient in the imaging of atherosclerosis, without a decline in image quality. Quantitative parameters of atherosclerotic carotid arteries are preserved or even increased over time, whereas those of blood pools were decreased. Additional studies seeking to define an optimal imaging protocol, and considering all aspects of imaging and quantitation, are crucial.

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