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Analysis of ^{18}F-Fluorodeoxyglucose and ^{18}F-Fluoride Positron Emission Tomography in Korean Stroke Patients with Carotid Atherosclerosis

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ABSTRACT

Objective: The objective of this study was to analyze uptake patterns and intensity of ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-sodium fluoride (NaF) radioligands in carotid atheroma among stroke patients according to carotid atheroma characteristics.

Methods: Between September 2015 and January 2017, consecutive acute stroke or transient ischemic attack patients with 50% or more proximal internal carotid artery stenosis on brain computed tomography angiography were prospectively enrolled. All patients received FDG and NaF positron emission tomography (PET) evaluation when their neurological status was stabilized. Uptake values of FDG and NaF were compared by target to blood ratio (TBR) according to the calcification burden, atheroma volume and the presence of a necrotic core of carotid atheroma.

Results: A total of 18 patients with 36 carotid arteries were finally enrolled, with 10 patients diagnosed as acute cerebral infarction due to symptomatic carotid stenosis. FDG uptake at symptomatic carotid arteries was significantly more increased than that at asymptomatic arteries (TBR: 1.17±0.23 vs. 1.01±0.15, Mann-Whitney *U*-test, *p*=0.02), but NaF uptake was not different (TBR: 1.38±0.49 vs. 1.51±0.40, *p*=0.40). In terms of calcification degree, NaF uptake increased as calcification burden increased (none, 1.28±0.36; spotty, 1.29±0.29; linear, 1.74±0.44; analysis of variance, *p*=0.02).

Conclusion: Carotid evaluation by FDG is superior to NaF PET in the detection of symptomatic carotid atherosclerosis among stroke patients. NaF PET uptake reflects the overall calcification burden.

Keywords: Stroke; Aarotid artery; Atherosclerosis; Positron emission tomography; Glucose

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INTRODUCTION

Stroke is a leading cause of death and dependence, both in developing and developed countries.[1] Carotid atherosclerosis is one of the major causes of stroke due to atherosclerotic plaque rupture or interruption of cerebral blood flow and can be treated by medical treatment alone or in combination with surgical intervention.[2] Although conventional atherosclerosis evaluation modalities such as magnetic resonance (MR) and computed tomography angiography (CTA) are focused on the detection and measurement of luminal stenosis of arteries, recent studies have shown that symptomatic atherosclerotic vessels are not always the most stenotic ones. Instead, the composition of atheroma is a more important factor than absolute anatomical stenosis degree in dominating plaque vulnerability.[3]

Molecular functional study using various radioisotopes with positron emission tomography (PET) has been applied for patients with atherosclerosis to elucidate disease activity of atheroma.[4] The ^{18}F-fluorodeoxyglucose (FDG) ligand was the first radioisotope introduced in the field of atherosclerosis study to measure local inflammation activity.[5] Recently, ^{18}F-sodium fluoride (NaF) ligand representing calcification activity within atheroma has been applied to patients with coronary artery disease and aortic valve calcification. The NaF ligand has superior efficacy for detecting culprit coronary vessels compared with the FDG ligand.[6] However, research examining the use of the 2 different radioisotopes on carotid artery vasculature in cerebral infarction patients among the stroke population has been sparse.[7,8] We recently performed both FDG and NaF PET among stroke patients with 50% or more carotid stenosis and found that both radiotracer signals were prevalent in carotid atheroma, with a wide overlap of their uptake intensities between culprit and non-culprit segments.[8] In this study, we hypothesized that carotid evaluation by FDG would be superior to NaF PET in the detection of symptomatic carotid atherosclerosis among stroke patients. To test this hypothesis, we investigated the uptake patterns of both radiotracers in terms of atheroma characteristics, including atheroma volume, calcification burden and the presence of necrotic core, among stroke patients with carotid atherosclerosis.

MATERIALS AND METHODS

1. Patient inclusion

This is a post-hoc analysis of a recently published study comparing the ability of FDG and NaF to detect symptomatic carotid atherosclerosis among stroke patients.[8] Patients with acute ischemic stroke or transient ischemia attack who were admitted to Chung-Ang University Hospital between September 2015 and January 2017 were eligible for inclusion. Patients with carotid artery stenosis greater than 50% based on initial brain CTA who agreed to participate in this study were enrolled. We excluded patients with active cancer or other comorbid diseases such as active autoimmune disease, uncontrolled diabetes mellitus with blood glucose more than 11 mmol/L at admission, and renal dysfunction with an estimated glomerular filtration rate less than 45 mL/min/1.72 m². We also excluded patients with other etiologies or unknown etiology of stroke from Trial of Org 10172 in acute stroke treatment criteria after thorough evaluation.[9] Other exclusion criteria were as follows: age less than 50 years, previous history of carotid artery angioplasty or endarterectomy, and medically too unstable for 2 PET evaluations. All patients received standardized diagnostic evaluation and treatment according to recent stroke management guidelines. Stroke mechanism was evaluated and determined by 2 neurologists (Kim JM and Park KY) who are specialized

in stroke research and care after in-depth evaluation with brain MR imaging, including diffusion-weighted imaging, susceptibility weighted imaging, T1/T2 imaging and time of flight MR angiography, transcranial Doppler, Doppler echocardiogram, and routine electrocardiogram followed by 24-hour Holter monitoring for each patient. Transesophageal echocardiography was additionally performed when necessary. Based on imaging and cardiac evaluation results, symptomatic carotid atherosclerosis was diagnosed when a patient experienced a stroke confined within the internal carotid arterial (ICA) territory without any other potential etiologies. Asymptomatic carotid atherosclerosis was designated if a patient experienced a stroke that could not be explained by carotid atherosclerosis while other potential causes (such as a stroke due to intracranial atherosclerosis contralateral to the proximal internal carotid atherosclerosis or multiple cardioembolic ischemic lesions not attributable to unilateral carotid atherosclerosis) had been documented. High intensity statin (either 40–80 mg of atorvastatin or 20 mg of rosuvastatin) with dual antiplatelet agents was recommended for patients with symptomatic atherosclerosis. Moderate intensity statin and oral anticoagulant were prescribed for cardioembolic stroke patients with asymptomatic atherosclerosis. This study was reviewed and approved by the Institution Review Board of Chung-Ang University Hospital (approval No. C2015061), and it was registered in the Clinical Research Information Service (registration No. 170602-001), which is a part of the World Health Organization International Clinical Trials Registry Platform. Written informed consent was obtained from all participants or guardians of participants in the study.

2. Imaging analysis

Anatomical characteristics of the proximal ICA wall on brain CTA were evaluated. First, the degree of proximal carotid artery stenosis was measured as the percentage of stenosis at the most stenotic segment of ICA compared with the distally normal segment on brain CTA. The maximum percentage of atheroma was assessed as the percentage of the atheroma area over the total vessel area from the coronal section of the brain CTA source image and categorized into 3 groups (mild, <30%; moderate, 30%–70%; and severe, >70%) at the segment where the vessel area was maximized. Vessel wall remodeling index was derived from the maximum vessel area minus the lumen area divided by the minimum vessel area.[10] Calcification status was assessed from the level where calcification volume was the largest and then grouped into 3 categories: none, mild to moderate (calcification was spotty and did not fulfill the criterion of severe calcification), and severe (calcification was linear or continuous, longer than 10 mm). Other morphologic characteristics such as ulceration, necrotic core, and total occlusion were also recorded.

3. PET imaging protocol

When a patient was neurologically stabilized, FDG and NaF PET imaging was performed with the following protocol after obtaining informed consent. After the patient fasted for a minimum of 8 hours, 259–370 MBq (7–10 mCi) of FDG or NaF was injected intravenously. Approximately 60 minutes after the injection, PET images were acquired at 5 min/bed for the head and 1 min/bed from the skull base to the proximal thigh right after CT scan (120 kVp, 50mA). The maximum standardized uptake value (SUV) of the proximal carotid arterial wall where the atheroma volume was the greatest from brain CTA was selected and divided by SUV of aortic blood to derive the maximum target to blood ratio (TBR) of the carotid atheroma. The SUV value at carotid atherosclerosis with the greatest calcification burden was also measured and TBR was derived in a similar manner. Two specialists in nuclear medicine who were blinded to clinical information (Lee ES and Seok JW) performed all measurements. Inter-observer reliability was studied thereafter.

4. Statistical analysis

Categorical variables are illustrated as the number and percentages of patients while continuous variables are presented as mean with standard deviation. Since the primary outcome of this study was the difference of FDG and NaF PET uptake in terms of symptomatic carotid atheroma, maximal SUV and TBR values of FDG and NaF uptake between patients with symptomatic carotid atherosclerosis and those with asymptomatic carotid atherosclerosis were compared with Mann-Whitney *U*-test. Receiver operating characteristic curve analysis was performed to derive a cut-off value for diagnosing symptomatic carotid atherosclerosis. For sensitivity analysis, radiotracer uptake values in terms of 10 symptomatic and 26 asymptomatic carotid arteries were compared by generalized estimating equation after adjusting for age with a random effect model. Uptake values of both radiotracers were also compared in terms of atheroma volume status, calcification degree, and the presence of necrotic core by analysis of variance (ANOVA) followed with post-hoc comparison with Bonferroni method and generalized estimating equation. A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 22 patients were initially included in the PET study and patients were divided into symptomatic or asymptomatic carotid atherosclerosis groups. However, 2 patients with a concealed neoplasm (one patient with colon cancer, the other with adrenal adenoma) were excluded from the asymptomatic carotid atherosclerosis group and another 2 patients were excluded from the symptomatic carotid atherosclerosis group due to stroke mimic (one patient with brain tumor and the other with nonconvulsive seizure, **Fig. 1**). A total of 18 patients were finally assessed (mean age: 75±12 years, including 9 female patients). Ten patients had symptomatic carotid artery atherosclerosis. The other 8 patients had asymptomatic carotid atherosclerosis and included 3 stroke patients with intracranial atherosclerosis and 5 patients with cardioembolic stroke due to atrial fibrillation. Demographic characteristics and laboratory variables of all patients are summarized in **Table 1**. All patients underwent 2 PET evaluations without any adverse events. The quality of all imaging was acceptable for study analysis. The median time from stroke onset to PET imaging was 17 days (range, 3–37 days). PET evaluation was delayed for more than 30 days in 4 patients due to aspiration pneumonia or pulmonary embolism. Although mean age, sex, or vascular risk factor profile was not significantly different between the 2 groups, white blood cell count and initial stroke severity in terms of National Institute of Health Stroke Scale were increased in patients with asymptomatic carotid stenosis, which could be due to an initially large infarction burden among cardioembolic patients. The 2 groups showed no significant difference in considerable degree of stenosis (symptomatic group vs. asymptomatic group: 70.7±20.0% vs. 62.8±13.3%, *p*=0.57), although dual antiplatelet agent and high intensity statin were more commonly prescribed among patients with symptomatic carotid atherosclerosis. Representative cases of symptomatic and asymptomatic carotid atherosclerosis are shown in **Fig. 2**.

Carotid atheroma activity measured by 2 independent investigators (Lee ES and Seok JW) showed good inter-observer reliability with an intra-class coefficient more than 0.90 and without significant outlier or proportional bias by Bland Altman plot analysis. Comparison of the uptake levels of the 2 radiotracers between the 2 patient groups revealed that FDG
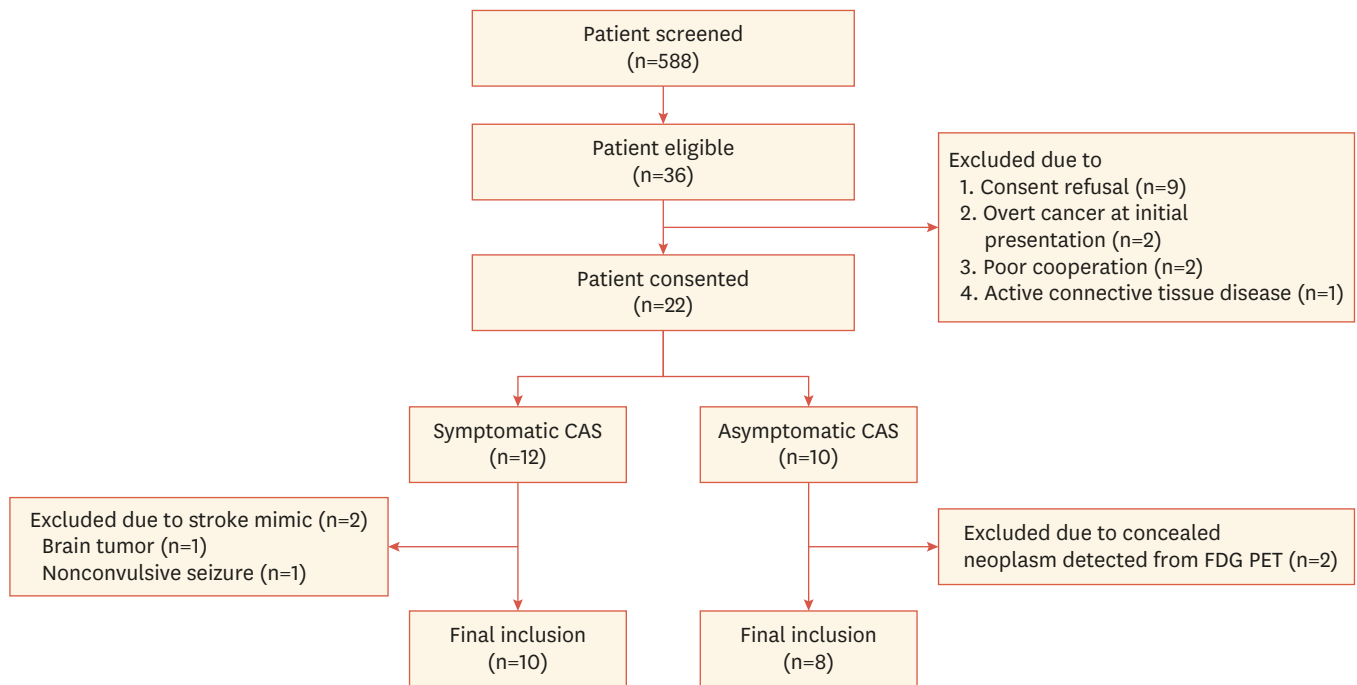
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                    │      (n=36)         │───────▶│ 1. Consent refusal (n=9)         │
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                              │                     │    presentation (n=2)            │
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                    │  Patient consented  │        │ 4. Active connective tissue      │
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│ Excluded due to stroke mimic (n=2)│◀─    ─▶│ Excluded due to concealed        │
│   Brain tumor (n=1)               │       │ neoplasm detected from FDG PET   │
│   Nonconvulsive seizure (n=1)     │       │ (n=2)                            │
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          │  Final inclusion    │  │  Final inclusion    │
          │      (n=10)         │  │      (n=8)          │
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Fig. 1. Study flow chart. A total of 22 patients were initially included in the study and classified in the symptomatic or asymptomatic carotid atherosclerosis groups. A total of 18 patients were finally assessed after PET study (mean age: 75±12 years, including 9 female patients). Two patients in the symptomatic carotid atherosclerosis group were excluded due to stroke mimic: one patient with sudden onset facial palsy and motor aphasia was found to have low grade glioma involving the left frontal cortex 2 months after the index event. The other patient with recurrent mental deterioration and dysarthria was found to have nonconvulsive seizure instead of transient ischemic attack. Another 2 patients were excluded from the asymptomatic carotid atherosclerosis group because concealed neoplasm was detected from FDG PET (one patient with colon cancer, the other with adrenal adenoma).
CAS, carotid atherosclerosis; FDG, fluorodeoxyglucose; PET, positron emission tomography.

Table 1. Comparison of demographic, clinical and laboratory variables of stroke patients with symptomatic carotid atherosclerosis or asymptomatic atherosclerosis

	Symptomatic carotid atherosclerosis (n=10)	Asymptomatic carotid atherosclerosis (n=8)	*p*-value
Age (yr)	72.9±8.2	77.1±10.9	0.12
Sex (female)	5	4	0.99
Hypertension	8	8	0.48
Diabetes mellitus	6	6	0.64
Atrial fibrillation	0	4	0.12
Coronary artery disease	1	1	0.99
Hemoglobin (g/L)	131.8±28.7	130.1±27.4	0.90
Platelet count (×10^9/L)	259±101	199±36	0.12
White blood cell count (×10^9/L)	6.5±1.2	8.2±1.6	0.03
HbA1c (%)	6.4±1.5	6.7±0.8	0.17
Total cholesterol (mmol/L)	4.92±1.76	3.94±1.01	0.27
Low density lipoprotein (mmol/L)	3.39±1.35	2.41±0.80	0.12
Admission NIHSS	5.7±7.1	11.0±6.1	0.07
Discharge NIHSS	3.7±6.8	6.6±5.7	0.08
Dual antiplatelet agent	8	3	0.15
High intensity statin	7	3	0.34
Stenosis degree (%)	70.7±20.0	62.8±13.3	0.57
FDG SUVmax at the largest atheroma segment	1.57±0.39	1.59±0.29	0.99
FDG TBRmax at the largest atheroma segment	1.24±0.30	1.04±0.11	0.02
NaF SUVmax at the largest atheroma segment	1.54±0.62	1.45±0.29	0.70
NaF TBRmax at the largest atheroma segment	1.53±0.54	1.34±0.20	0.46

Data are shown as mean±standard deviation or number (%).
NIHSS, National Institute of Health Stroke Scale; FDG, fluorodeoxyglucose; SUV, standardized uptake value; TBR, target to background ratio; NaF, sodium fluoride.
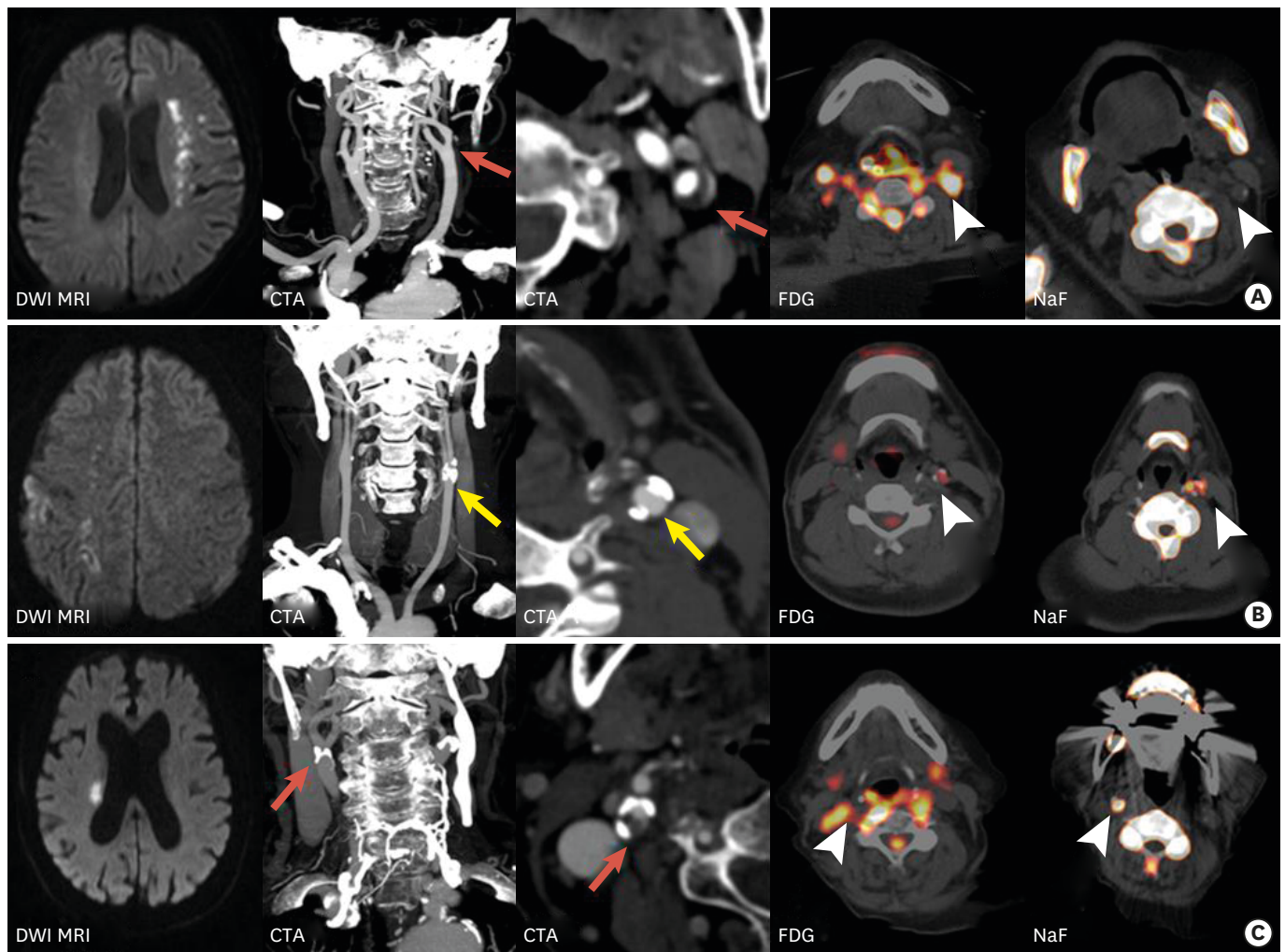
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Fig. 2. Representative radiotracer uptake patterns according to atheroma characteristics. (A) A 76-year-old female patient was diagnosed with left hemispheric border zone infarction from DWI MRI with a severe left carotid stenosis from CTA. Axial section of CTA revealed an atheroma with perivascular rim enhancement and minimal calcification (red arrows). PET images showed increased FDG uptake (arrowhead) and minimal NaF uptake (arrowhead). (B) A 55-year-old male patient had multiple infarctions involving the right middle cerebral artery territory from DWI and moderate stenosis at the left proximal carotid artery (asymptomatic atherosclerosis, yellow arrow). Axial CTA showed considerable atheroma burden with multiple spotty calcification and PET image revealed minimal FDG uptake and increased NaF uptake at atheroma (arrowhead). (C) An 85-year-old female patient was diagnosed with right corona radiata infarction due to proximal carotid atherosclerosis. Axial CTA showed large atheroma with heterogeneous signal intensity due to heavy calcification burden and necrotic core (red arrow). PET image showed increased uptake of both FDG and NaF radiotracers (arrowhead).

CTA, computed tomography angiography; FDG, fluorodeoxyglucose; PET, positron emission tomography; NaF, sodium fluoride; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.

uptake was significantly elevated at the most diseased segment (1.24±0.30 vs. 1.04±0.11, Mann-Whitney U-test, p=0.02) whereas NaF uptake was not significantly different (1.53±0.54 vs. 1.34±0.20, Mann-Whitney U-test, p=0.46, **Table 1**). The uptake value of NaF was heterogeneous among patients, but seemed to be pronounced in heavily calcified atherosclerotic lesions. The area under the receiver operating curve analysis showed that FDG uptake of more than 1.05 could detect symptomatic carotid atherosclerosis with a sensitivity of 0.90 and a specificity of 0.75 (area under the curve, 0.83; confidence interval, 0.62–1.00). The FDG cut-off value at 1.12 could detect symptomatic atheroma with a sensitivity of 0.70 and a specificity of 0.88. This difference remained significant when symptomatic arterial segment was compared to asymptomatic segment by a generalized estimating equation (1.24±0.30 vs. 1.08±0.13, p=0.04, **Table 2**). When measured on arterial walls at the most

Table 2. Comparison of anatomical and molecular characteristics between symptomatic and asymptomatic carotid arteries

	Symptomatic carotid artery (n=10)	Asymptomatic carotid artery (n=26)	*p*-value
Stenosis (%)	70.6±20.0	43.7±28.4	0.002
Vessel wall area at the most stenotic lesion (%)	75.1±21.3	45.0±28.1	0.004
Maximum lumen diameter (mm)	5.7±1.6	6.5±1.3	0.16
Minimum lumen diameter (mm)	2.8±2.2	4.8±2.0	0.04
Maximum vessel diameter (mm)	8.8±2.1	9.7±1.5	0.61
Remodeling index	2.7±1.4	1.9±1.0	0.07
Necrotic core	3	7	0.83
Ulceration	0	3	0.55
Occlusion	2	1	0.17
Severe calcification	3	5	0.38
FDG SUVmax at the largest atheroma segment	1.55±0.41	1.54±0.27	0.68
FDG TBRmax at the largest atheroma segment	1.24±0.30	1.08±0.13	0.04
FDG SUVmax at the most calcified segment	1.46±0.24	1.43±0.25	0.98
FDG TBRmax at the most calcified segment	1.17±0.23	1.01±0.15	0.06
NaF SUVmax at the largest atheroma segment	1.54±0.62	1.46±0.57	0.60
NaF TBRmax at the largest atheroma segment	1.53±0.54	1.39±0.45	0.37
NaF SUVmax at the most calcified segment	1.45±0.50	1.55±0.47	0.75
NaF TBRmax at the most calcified segment	1.47±0.49	1.48±0.41	0.90

Data are shown as mean±standard deviation or number (%). Generalized estimating equation was performed by independent correlation model with adjusting age.
FDG, fluorodeoxyglucose; SUV, standardized uptake value; TBR, target to background ratio; NaF, sodium fluoride.

calcified segment, FDG uptake tended to be elevated at the symptomatic side (1.17±0.23 vs. 1.01±0.15, *p*=0.06, **Table 2**). However, the difference in NaF uptake was insignificant between the 2 sides (1.53±0.54 vs. 1.39±0.45, *p*=0.45).

Radiotracer uptake levels were next compared according to radiological and morphological characteristics of carotid atheroma. In the comparison of radiotracer uptake according to calcification status, NaF uptake showed the maximum uptake level in advanced calcified carotid atheroma (none, 1.28±0.36; spotty, 1.29±0.29; linear, 1.74±0.44; ANOVA, *p*=0.02), but FDG uptake was not altered (none, 1.12±0.15; spotty, 1.00±0.14; linear, 1.08±0.23; ANOVA, *p*=0.38, **Fig. 3A**). The presence of a necrotic core did not significantly alter FDG uptake levels (1.15±0.24 vs. 1.09±0.14, Mann Whitney *U*-test, *p*=0.67), although NaF uptake levels showed a tendency to be increased in atherosclerotic walls with a necrotic core (1.51±0.38 vs. 1.34±0.55, Mann Whitney *U*-test, *p*=0.09, **Fig. 3B**). In the comparison of radiotracer uptake levels according to atheroma volume status, neither of the 2 radiotracers showed significant differences (**Fig. 4**).

DISCUSSION

This study examined the clinical usefulness of FDG and NaF radiotracers for the diagnosis of symptomatic carotid atherosclerosis in stroke patients and found that increment of FDG uptake seemed to be more robust than NaF on symptomatic carotid atherosclerosis. NaF uptake showed a tendency for increase as calcification burden was increased and also at the carotid atheroma with a necrotic core.

The application of PET with different radioisotopes in atherosclerosis evaluation is a promising imaging technology because it can detect various pathologic cascades and their intensities within atheroma related to plaque vulnerability.[5] FDG indicates inflammation
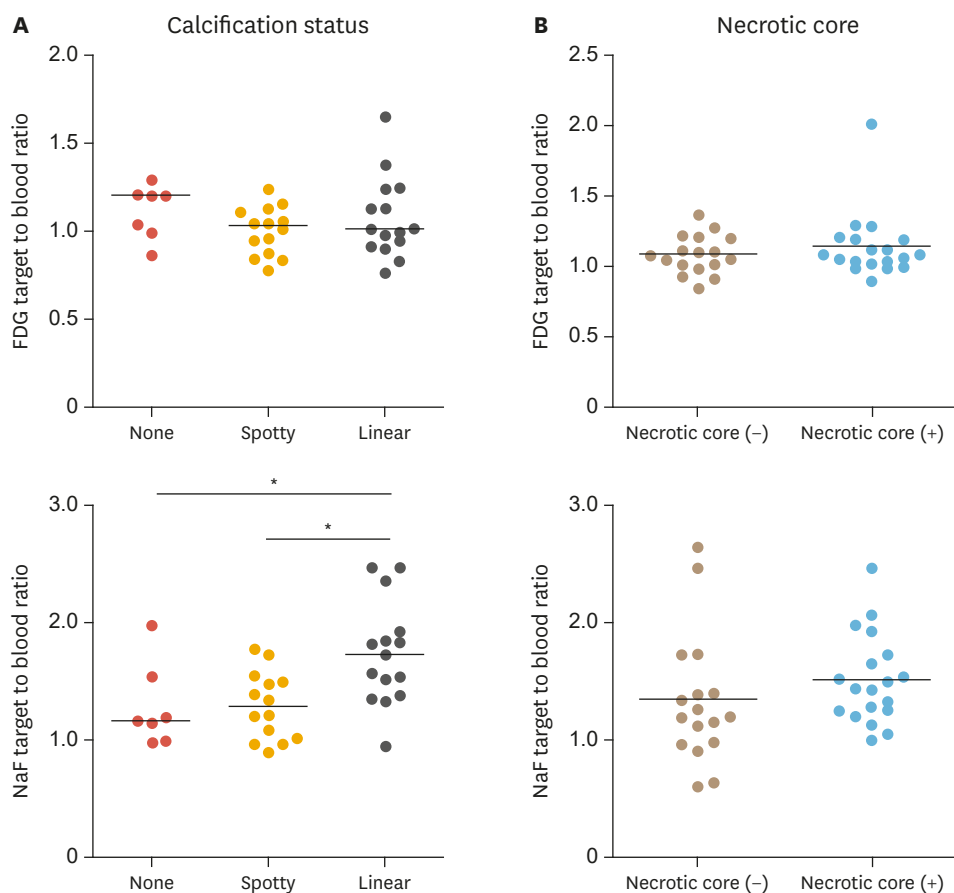
Fig. 3. Comparison of FDG and NaF uptake in terms of atheroma characteristics. (A) Although FDG uptake was not significantly different according to calcification status of internal carotid arteries (none, 1.12±0.15; spotty, 1.00±0.14; linear, 1.08±0.23; ANOVA, p=0.38), uptake values of NaF showed the maximum intensity on the severe calcified atheroma group (none, 1.28±0.36; spotty, 1.29±0.29; linear, 1.74±0.44; ANOVA, p=0.02). (B) Uptake values of FDG radiotracers were not significantly different according to the presence of necrotic core (1.09±0.14 vs. 1.15±0.24, Mann Whitney U-test, p=0.67), although levels of NaF tended to be increased in atherosclerotic walls with necrotic core (1.34±0.55 vs. 1.51±0.38, Mann Whitney U-test, p=0.09).
FDG, fluorodeoxyglucose; NaF, sodium fluoride; ANOVA, analysis of variance.
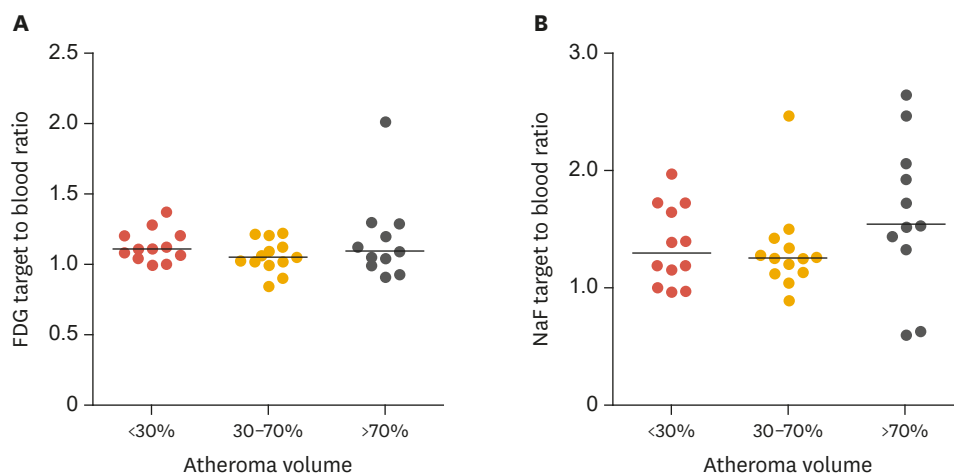

Fig. 4. Comparison of FDG and NaF uptake values in terms of atheroma volume. The uptake levels of FDG or NaF radiotracer were not significantly different according to atheroma volume status (FDG: mild, 1.13±0.11; moderate, 1.06±0.12; severe, 1.18±0.31; ANOVA, p=0.34; NaF: mild, 1.36±0.34; moderate, 1.32±0.38; severe, 1.63±0.65; ANOVA, p=0.25).
ANOVA, analysis of variance; FDG, fluorodeoxyglucose; NaF, sodium fluoride.

intensity within atheroma because it reflects metabolically active macrophages.[5] NaF uptake can detect microcalcification activity within atheroma by the exchange of fluoride ions with hydroxyl groups in hydroxyapatite.[5,11] Our study suggests that the application of molecular imaging using the FDG radiotracer could be helpful to detect symptomatic atherosclerotic lesions among stroke patients by reflecting the inflammation status at the tissue level. The application of the cut-off value of TBR FDG 1.12 at the most stenotic segment detected symptomatic carotid lesions with a specificity of 88%. The level of NaF uptake was not significantly different between symptomatic and asymptomatic sides, although it was localized in atheroma with severe calcification and a necrotic core.

A comparison study of the 2 radiolabeled ligands among myocardial infarction patients has illustrated that the uptake of NaF is significantly increased in the culprit lesion of the coronary artery and the detection of culprit lesions by NaF PET is superior to FDG imaging.[6] Recently, the same group compared the 2 radioisotopes in stroke patients with carotid atherosclerosis in which the other side of carotid arterial wall served as control.[7] The authors found significant NaF uptake at the vulnerable segment from both *in vivo* and *ex vivo* specimen studies.[7] Although our results showed that NaF uptake was proportional to calcification status of a proximal carotid atheroma from CTA, NaF was not superior to FDG in the detection of symptomatic carotid atherosclerosis. The reason for the discrepancy in the results from our study and previous studies could be due to differences in demographic characteristics such as ethnicity and older age, medical treatment status of high intensity statin, and atheroma characteristics. The patients included in this study were older and the calcification status of atheroma might be more advanced compared with patients in the previous study. These differences might have attenuated the differential potential of the NaF tracer.

This study has several limitations. First, the number of included patients was relatively small. Although PET imaging was performed after patients had been stabilized, it was not easy for older stroke patients to undergo 2 PET imaging procedures 24 hours apart. Moreover, 2 out of 20 patients were excluded because concealed neoplasm was detected by FDG PET. The risk of concealed cancer among patients with advanced atherosclerosis is another important issue that needs to be validated in future studies. Second, the level of FDG uptake in our study was lower than that reported in recent studies.[12] This might be due to statin treatment status and timing of imaging. Third, histological data were not derived from carotid endarterectomy specimens to reinforce our clinical data in the diagnosis of culprit lesions. However, our study participants were chosen after extensive stroke etiology work up to detect cardioembolic source or other symptomatic atherosclerotic lesions such as intracranial atherosclerosis.

In summary, comparison of the FDG and NaF radiotracers in the diagnosis of symptomatic carotid atherosclerosis revealed that FDG TBR at the most stenotic segment of carotid artery can be used as an indicator for the detection of a culprit lesion among stroke patients with a moderate degree of carotid atherosclerosis. Further studies are warranted to investigate whether this modality can be used to predict future stroke recurrence.

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