Special Issue: Carotid Artery Plaque Diagnosis

Diagnosis of Carotid Plaque Using FDG-PET

Eiichi Kobayashi

Positron emission tomography (PET) with ^{18}F -2-deoxy-2-fluoro-D-glucose (FDG) provides valuable metabolic information regarding arteriosclerotic lesions and may be applied for the detection of vulnerable plaque. When FDG, as a glucose analog, is phosphorylated in the intracytoplasmic area, its metabolism stops and remains, so-called intracellular metabolic trapping, and images are made utilizing this characteristic. Pathological examination of extirpated plaque confirmed that FDG accumulation was strongly correlated with the distribution and density of inflammatory cells, especially macrophages. Images suggestive of plaque inflammation and therefore its vulnerability were obtained. Even in patients with relatively slight stenosis, FDG accumulation was often observed; it was not always correlated with the percent stenosis, but quantitative values of FDG uptake or its changes may reflect the progression of arteriosclerosis. FDG is also utilized as a surrogate marker of drug efficacy, such as statin. Some studies indicated its association with vascular events, but no long-term, large-scale, prospective study excluding cancer-bearing patients has been conducted. In the future, data must be further accumulated. Concerning carotid artery lesions, there are no data on the onset of asymptomatic lesions or prediction of treatment-related risks, and future studies may provide promising information.

Keywords ► positron emission tomography with ^{18}F -2-deoxy-2-fluoro-D-glucose, carotid artery, plaque imaging, inflammation, atherosclerosis

Introduction

Carotid artery stenosis is an important etiological factor for ischemic stroke. The incidence of this disorder can be reduced through therapeutic intervention at an appropriate timing. In particular, the recurrence rate of carotid artery stenosis within 6 months after onset is high, and carotid endarterectomy (CEA) or percutaneous carotid artery stenting

(CAS) is considered. In the context, it is important to evaluate the vulnerability of arteriosclerotic plaque for treatment-related risk/prognosis assessment. On the other hand, asymptomatic, moderately or slightly stenotic lesions are stable, with a low incidence of stroke. Medical treatment is generally effective, and therefore, surgical intervention may not be necessary. However, all symptomatic stenotic lesions are initially asymptomatic. If not severe conditions, such as transient ischemic attacks (TIAs), occur, they may be managed. However, according to a recent report from Massachusetts General Hospital, $\geq 50\%$ of patients who suffered from subsequent ischemic event developed permanent cerebral infarction.¹⁾ If serious cerebral infarction occurs on the first attack, the opportunity of treatment may be lost; therefore, the vulnerability of arteriosclerotic plaque should be carefully evaluated. The incidence of symptomatic lesions is correlated with the percent stenosis, and the event risk in natural history increases with the severity of stenosis. On the other hand, several studies reported that there was no correlation between asymptomatic lesions and the percent stenosis.^{2,3)} In addition to

Comprehensive Stroke Center and Department of Neurosurgery, Chiba University Graduate School of Medicine, Chiba, Chiba, Japan

Received: April 13, 2018; Accepted: August 8, 2018
Corresponding author: Eiichi Kobayashi. Comprehensive Stroke Center and Department of Neurosurgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8670, Japan
Email: papez@xa2.so-net.ne.jp

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives International License.

©2018 The Japanese Society for Neuroendovascular Therapy

morphological information, a modality to evaluate the plaque vulnerability is necessary. Positron emission tomography with ^{18}F -2-deoxy-2-fluoro-D-glucose (FDG-PET), which is primarily used for the diagnosis of malignant tumors, provides valuable information on glucose metabolism, especially inflammation of the arterial wall, and may be applied for the diagnosis of arteriosclerotic lesions. In this article, we review the principle and indication of FDG-PET, quantification, application for the detection of arteriosclerotic lesions/carotid plaque, and future development/issues, and introduce recent findings. The main articles quoted in this article are listed in **Table 1**.

■ Principle and Indication of FDG-PET

Glucose is the only source of energy for the brain in a normal state. Glucose absorbed in the small intestine is transported to the whole body via the portal system, and adenosine triphosphate (ATP) is synthesized through the glycolytic pathway, citric acid cycle, and electron transport chain. FDG is a glucose-like compound in which the hydroxyl group in the C2 position of glucose is substituted for ^{18}F . It is taken into the cytoplasm by glucose transporter, and phosphorylated by hexokinase, as reported for glucose. While phosphorylated glucose is finally decomposed into water and carbon dioxide, the metabolism of FDG stops when it is phosphorylated, leading to intracellular FDG retention, which is termed “metabolic trapping.” As this reaction is proportional to tissue glucose metabolism, images reflecting this can be obtained (**Fig. 1**). Finally, FDG is reduced by glucose-6-phosphatase, returning into blood.

Many clinical studies confirmed the usefulness of FDG-PET in various fields. In Japan, FDG-PET for 12 diseases (epilepsy, ischemic heart disease, lung cancer, breast cancer, colorectal cancer, head and neck cancer, and so on) became covered by health insurance in 2002. In 2005, FDG became commercially available as a radioactive-agent based on the Pharmaceutical Affairs Law. In 2006, three types of cancer, esophageal, ovarian, and uterine cancers, were added as diseases for which FDG-PET may be applied, and compound PET/CT was newly established. During this period, much clinical data were accumulated, and PET and PET/CT for stage/relapse/metastasis diagnosis of all malignant tumors, excluding early gastric cancer, became covered by health insurance in 2010. In 2012, pharmaceutical approval on simultaneous PET/MRI was obtained, and PET/MRI for the diagnosis of the site of

inflammation in patients with cardiac sarcoidosis and evaluation of the treatment response of malignant lymphoma became covered by health insurance.⁴⁾ Currently, health insurance coverage for arteriosclerotic diseases is not approved, and clinical data should be further accumulated.

■ Quantification of FDG-PET

For FDG-PET, it is necessary to secure the safety of apparatus, maintenance of performance, and quality of examination. The “Guidelines regarding imaging techniques on FDG-PET” were published by the Academic Committee, Japanese Society of Nuclear Medicine Technology.⁵⁾ We introduce the quantification of FDG accumulation.

The physical half-life of ^{18}F is 110 minutes. ^{18}F -FDG competes with glucose and is taken into cells. Therefore, the blood glucose level should be reduced to ≤ 130 or ≤ 150 mg/dL; patients must be fasted for ≥ 4 hours before the examination. When collecting 2D data, 185–444 MBq (3–7 MBq/kg) of FDG is intravenously administered. When collecting 3D data, 111–259 MBq (2–5 MBq/kg) of FDG is intravenously administered. For the quantification of glucose metabolism, the intravenous injection of FDG at a constant rate and three-compartment model-based autoradiography (ARG) are routinely adopted. A favorable contrast against normal tissue can be obtained by adjusting the dose and establishing the duration of imaging as 90–120 minutes.⁶⁾

To quantify FDG, the standard uptake value (SUV) or tissue to background ratio (TBR) is used. The SUV refers to the ratio of accumulation to the dose per unit body weight. When FDG is uniformly distributed to the whole body in the absence of excretion, the SUV is 1.00. The TBR refers to the ratio of the SUV for the region of interest for a target blood vessel to the control SUV for the center (blood-pool area) of a large vein free from spill-over effects (**Fig. 2**). Concerning the two parameters, the mean and maximum for the region of interest are calculated. However, Asabella et al. compared the SUV_{max} , SUV_{mean} , TBR_{max} , and TBR_{mean} , and reported that it was difficult to differentiate plaque with marked inflammation from that without it using the SUV_{max} and SUV_{mean} , whereas it was possible to differentiate the type of plaque using the TBR_{max} and TBR_{mean} .⁷⁾ Recently, studies using the TBR has been increasing, but the reference SUV for the blood-pool area depends on the timing of imaging or kidney function; therefore, caution is needed. The standardization of quantification should be reviewed in the future. Various patterns

Table 1 List of main references

Author (year)	Content	No. of patients, No. of samples	Results
Lederman et al. (2001) ⁹⁾	Comparison with pathological specimens using rabbits	11	They reported FDG accumulation in the site of arteriosclerosis for the first time by administering a high-fat diet to New Zealand white rabbits after mechanical injury of the iliac artery.
Aziz et al. (2008) ¹⁰⁾	Comparison with pathological specimens using rabbits	20	In a rabbit model, marked FDG accumulation in the site of arteriosclerosis with thrombus formation was observed, and marked macrophage accumulation at the same site was confirmed.
Rudd et al. (2002) ¹¹⁾	Comparison with pathological specimens collected during CEA	8	Autoradiography of eight specimens resected during CEA showed that the FDG accumulation ratio of symptomatic carotid plaque was 27% higher than that of contralateral asymptomatic plaque.
Rudd et al. (2007) ¹²⁾	Verification of the reproducibility of FDG-PET	11	They compared inter- and intra-subject measurements at the site of carotid artery/aortic arteriosclerosis, and reported the reproducibility of FDG-PET.
Tawakol et al. (2005) ¹³⁾	Comparison with pathological specimens collected during CEA	17	They investigated the association between the TBR at the lesion site before CEA and extent of inflammation on CD68 staining using extirpated plaque specimens, and reported that there was a favorable correlation. There was no correlation with the plaque area, thickness, or smooth muscle cell staining.
Graebe et al. (2009) ¹⁴⁾	Comparison with pathological specimens collected during CEA	10	They investigated mRNA expression in specimens extirpated during CEA using the real-time quantitative PCR method, and reported that there was a strong correlation between FDG accumulation and CD68 gene expression. Its correlations with cathepsin K, matrix metalloproteinase 9, and IL-18 were weak.
Arauz et al. (2007) ¹⁵⁾	Comparison with pathological specimens collected during CEA	13	FDG accumulation was observed in $\geq 80\%$ of patients with symptomatic $\geq 50\%$ carotid artery stenosis.
Tahara et al. (2007) ¹⁶⁾	Comparison with carotid ultrasonography	100	FDG accumulation was confirmed in approximately 30% of relatively slight plaque patients in with a plaque score of ≥ 5 or IMT of ≥ 2 mm. This percentage was significantly higher than in patients without arteriosclerosis.
Abdelbaky et al. (2013) ¹⁷⁾	Long-term cohort study involving patients who underwent FDG-PET/CT	137	They serially examined the progression of calcification of the thoracic aortic wall for 1–5 years in patients who underwent FDG-PET/CT, and reported marked FDG accumulation in new calcification deposition sites at the start of observation.
Graebe et al. (2010) ¹⁹⁾	Comparison with carotid ultrasonography	33	They indicated that FDG accumulation varied among low-brightness-echo plaques on carotid ultrasonography, whereas it was not marked in high-brightness-echo plaques.
Moustafa et al. (2010) ²⁰⁾	Comparison with transcranial Doppler ultrasonography	16	They investigated recent patients with symptomatic carotid artery stenosis and reported that FDG accumulation was marked in plaques with microembolic signals on intracranial Doppler ultrasonography, suggesting the usefulness of FDG-PET for the identification of vulnerable plaque, which may become the source of embolism.
Poredos et al. (2017) ²¹⁾	Relationship with blood markers of inflammation	37	They reported that FDG accumulation was correlated with high-sensitivity CRP, IL-6, and TNF- α in patients with carotid artery stenosis or common femoral artery occlusion.
Lei-xing et al. (2014) ²²⁾	Comparison with plaque MRI	31	They reported that the TBR at the lesion site was high in patients with plaques with a ruptured fibrous capsule, lipid-rich plaques, or intra-plaque hemorrhage.
Figueroa et al. (2012) ²³⁾	Comparison with carotid CTA	34	The presence or absence of three factors characterizing vulnerable plaque on CT (positive remodeling, irregular lumen, and low attenuation) and number of existing factors were correlated with FDG accumulation.

Table 1 (Continued)

Author (year)	Content	No. of patients, No. of samples	Results
Rominger et al. (2009) ⁽²⁴⁾	Cohort study involving cancer-bearing patients	932	A cohort study involving cancer-bearing patients without vascular events (ischemic stroke, myocardial infarction, revascularization). They suggested that FDG accumulation in systemic blood vessels, including the carotid artery, is an independent, potent prognostic factor for subsequent vascular events.
Paulmier et al. (2008) ⁽²⁵⁾	Cohort study involving cancer-bearing patients	101	They investigated cancer-bearing patients. In the marked FDG accumulation group, the incidences of previous cardiovascular events and those within 6 months were significantly higher.
Joseph et al. (2017) ⁽²⁶⁾	Sub-analysis of the dal-PLAQUE trial	42	As a sub-analysis of the dal-PLAQUE trial (RCT of a cholesteryl ester transfer protein inhibitor, dalcetrapib), they suggested that short-term changes in arterial-wall inflammation on FDG-PET reflect the subsequent long-term progression of arteriosclerosis.
Figuerola et al. (2013) ⁽²⁷⁾	Short-term changes in FDG accumulation and long-term changes in the arterial-wall morphology	24	They measured changes in FDG accumulation in the carotid artery at the time of registration and after 6 months, and examined arterial-wall thickening and changes in the wall area on MRI at the time of registration and after 2 years, suggesting that short-term changes in FDG accumulation reflect long-term changes in the arterial wall.
Marnane et al. (2012) ⁽²⁸⁾	Small-scale cohort study involving patients with symptomatic carotid artery stenosis	60	The subjects were 60 patients with stroke, TIA, or retinal embolism within 2 weeks after onset and ≥50% stenosis of the carotid artery. They investigated the relationship between carotid plaque FDG accumulation at the time of onset and subsequent recurrent stroke. The mean SUV was the only prognostic factor for recurrence.
Fernández-Ortiz et al. (2013) ⁽²⁹⁾	Prospective cohort study (PESA study)	1300	A prospective cohort study regarding the progression of systemic arteriosclerosis involving 4000 patients (PESA study). As a sub-analysis, FDG-PET is scheduled in 1300 patients. Ongoing.
Tahara et al. (2006) ⁽³⁰⁾	Evaluation of the therapeutic effects of simvastatin	43	They reported that simvastatin reduced FDG accumulation in the thoracic aorta/carotid artery.
Tawakol et al. (2013) ⁽³¹⁾	Evaluation of the therapeutic effects of atorvastatin	67	The administration of atorvastatin for a relatively short period (12 weeks) reduced FDG accumulation in the ascending aorta/carotid artery in a dose-dependent manner.
Mizoguchi et al. (2011) ⁽³²⁾	Evaluation of the therapeutic effects of pioglitazone	56	The administration of an antidiabetic agent, pioglitazone, for 4 weeks reduced FDG accumulation in the ascending aorta/carotid artery regardless of blood glucose-lowering effects.
Hyafil et al. (2016) ⁽³³⁾	Identification of the source of embolism in ESUS patients	18	They suggested that carotid artery lesions with marked inflammation despite a low percent stenosis are involved in embolism in patients with cerebral infarction in whom the source of embolism was unclear (ESUS) using FDG-PET/MRI.

CEA: carotid endarterectomy; CRP: C-Reactive Protein; dal-PLAQUE: Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging; ESUS: embolic stroke of undetermined source; FDG: ¹⁸F-2-deoxy-2-fluoro-D-glucose; IL: interleukin; IMT: intima-media thickness; PCR: polymerase chain reaction; PESA: Progression of Early Subclinical Atherosclerosis; PET: positron emission tomography; RCT: randomized controlled trial; SUV: standard uptake value; TBR: tissue to background ratio; TIA: transient ischemic attack; TNF: tumor necrosis factor

Fig. 1 FDG and glucose metabolism. Both ^{18}F -FDG and glucose are transported into the cell by GLUT-1, and phosphorylated by hexokinase. While glucose is metabolized into glycogen, CO_2 , and H_2O , FDG stops metabolism and stays as it is in the cell, which is called metabolic trapping. FDG: ^{18}F -2-deoxy-2-fluoro-D-glucose; GLUT-1: glucose transporter-1

● SUV = radioactive concentration of ^{18}F in the tissue / (dose of ^{18}F /body weight)

● TBR = SUV in plaque / SUV in blood pool

Fig. 2 Two methods of quantification of ^{18}F uptake. SUV: standard uptake value; TBR: tissue to background ratio

of accumulation on FDG-PET (**Fig. 3**) and clinical cases (**Fig. 4**) are presented.

FDG-PET for Arteriosclerosis and Carotid Artery Lesions

As glucose metabolism in inflammatory cells, including macrophages, at the site of inflammation, may be enhanced 20- to 30-fold than that in the non-active phase,⁴⁾ the application of FDG-PET for arteriosclerotic diseases,⁸⁾ which are sometimes termed chronic inflammation, has been emphasized. In 2001, Lederman et al. reported FDG accumulation in the site of arteriosclerotic plaque using New Zealand white rabbits fed a high-cholesterol diet for the

first time.⁹⁾ Aziz et al. also indicated marked FDG accumulation in the site of arteriosclerosis with thrombus formation, as well as marked macrophage accumulation, using similar rabbits.¹⁰⁾ In 2002, Rudd et al. performed FDG-PET in eight patients with symptomatic carotid artery stenosis and reported that the FDG accumulation ratio was 27% higher than in the site of contralateral asymptomatic plaque.¹¹⁾ A study verified FDG accumulation in the site of macrophage infiltration using autoradiography of specimens resected during endarterectomy, suggesting the usefulness of FDG-PET for inflammation imaging. The same group reported the reproducibility of FDG-PET.¹²⁾ Thereafter, Tawakol et al. examined histopathological findings in 17 patients in whom CEA was scheduled, investigated the association between the preoperative TBR at the lesion site and extent of inflammation on CD68 staining of extirpated plaque specimens, and reported that there was a favorable correlation between the two parameters.¹³⁾ However, there was no correlation with the plaque area/thickness or smooth muscle cell staining. Graebe et al. investigated mRNA expression in specimens extirpated during CEA using the real-time quantitative polymerase chain reaction method, and indicated that there was a strong correlation between FDG accumulation and CD68 gene expression, whereas its correlations with cathepsin K, matrix metalloproteinase 9, and interleukin (IL) 18 were weak, suggesting the association with macrophages.¹⁴⁾ A study reported that FDG accumulation was observed in $\geq 80\%$ of patients with symptomatic $\geq 50\%$ carotid artery stenosis.¹⁵⁾ However, Tahara et al. indicated that FDG accumulation was noted in 30% of mild patients with a plaque score of ≥ 5 or intima-media thickness (IMT) of ≥ 2 mm as well as severe-status patients.¹⁶⁾ Abdelbaky et al. serially examined the progression of calcification of the aortic wall for 1–5 years in 137 patients who had undergone FDG-PET/CT. They reported that FDG accumulation at the start of observation was marked at sites where calcified deposition newly occurred, suggesting that FDG is useful as a biomarker of the progression of arteriosclerosis.¹⁷⁾ In addition, some studies indicated the association of FDG with the site of calcification,¹⁸⁾ but a consensus has not been reached, possibly because the significance of calcification may differ among the carotid artery, coronary artery, and aorta, and because there are two types of calcification: active and inactive.

With respect to the association with other modalities for arteriosclerosis diagnosis, Graebe et al. indicated that FDG accumulation varied among echolucent plaque areas on carotid ultrasonography, whereas there was less variation

Fig. 3 Various patterns of FDG accumulation on 3D mapping of FDG-PET/CT. FDG: ^{18}F -2-deoxy-2-fluoro-D-glucose; PET: positron emission tomography

Fig. 4 Demonstrable case. A 74-year-old man with symptomatic 92% stenosis of left carotid artery. DSA showed severe long stenosis and contrast-enhanced plaque MRI (T1WI) demonstrated a large necrotic core with fibrous cap rupture (arrow). FDG-PET revealed marked accumulation of FDG at the site of vulnerable components. FDG: ^{18}F -2-deoxy-2-fluoro-D-glucose; PET: positron emission tomography; SUV: standard uptake value; T1WI: T1-weighted image

of FDG accumulation, which was not marked, among echogenic plaque areas.¹⁹⁾ In the echogenic group, most plaques were stable. However, in the echolucent group, plaques, which are generally considered to be vulnerable,

may be heterogeneous by different conditions. They suggested the usefulness of FDG-PET for stratification. Moustafa et al. examined the relationship between a microembolic signal (MES) and FDG accumulation on transcranial

Doppler ultrasonography in patients with symptomatic carotid artery stenosis.²⁰⁾ As a result, they reported that FDG accumulation was more marked in the plaques of patients with MESSs than without (median ipsilateral to contralateral carotid artery SUV ratio: 1.05 vs. 0.76, $p = 0.005$), suggesting that FDG-PET is useful for identifying vulnerable plaque, which may become the source of embolism. Poredos et al. examined the relationship with blood markers of inflammation in 37 patients with carotid artery stenosis or common femoral artery occlusion, and reported that FDG accumulation was correlated with high-sensitivity C-reactive protein (hs-CRP) ($r = 0.417$, $p = 0.010$), IL-6 ($r = 0.603$, $p < 0.001$), and tumor necrosis factor (TNF)- α ($r = 0.374$, $p = 0.023$).²¹⁾ A study compared FDG-PET with MRI findings and indicated that the TBR was high at the sites of plaque with a ruptured fibrous cap, lipid-rich plaque, and intra-plaque hemorrhage.²²⁾ Furthermore, another study compared FDG-PET with carotid CT and reported that the presence or absence of three factors (positive remodeling, irregular lumen, and low attenuation) characterizing vulnerable plaque on CT, as well as the number of factors, were correlated with FDG accumulation.²³⁾

Onset of Vascular Events and FDG-PET

With respect to the association with the onset of vascular events, Rominger et al. conducted a cohort study involving 932 cancer-bearing patients without vascular events (ischemic stroke, myocardial infarction, revascularization), and suggested that FDG accumulation in systemic blood vessels, including the carotid artery, might be an independent, potent prognostic factor for subsequent vascular events (mean TBR: >1.7 , hazard ratio on multivariate analysis: 14.144, 95% confidence interval [CI]: 4.823–41.482).²⁴⁾ Paulmier et al. also investigated 101 cancer-bearing patients and reported that the incidences of old cardiovascular events (48 vs. 15%, respectively, $p = 0.0006$) and cardiovascular events within 6 months (30 vs. 1.8%, respectively, $p = 0.0002$) were significantly higher in the marked FDG accumulation group.²⁵⁾ Joseph et al. performed a sub-analysis of the safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE) (randomized controlled trial [RCT] of a cholesteryl ester transfer protein inhibitor, dalcetrapib), and suggested that short-term changes in arterial-wall inflammation on FDG-PET reflect the subsequent long-term progression of arteriosclerosis.²⁶⁾ In 24 patients, FDG

accumulation on carotid FDG-PET/CT at the time of registration was compared with that after 6 months. Simultaneously, changes in the arterial-wall thickness and area on MRI were examined at the time of registration and after 24 months. As a result, there was an increase in FDG accumulation after 6 months in 18 patients (42.9%). In this group, the rates of change in the arterial-wall thickness and area after 2 years were significantly higher than in the other groups (rate of change in wall thickness: 17.49 vs. 1.74%, respectively, $p = 0.038$, rate of change in the wall area: 25.50 vs. 3.59%, respectively, $p = 0.027$). If the deterioration of wall inflammation in the initial phase of arteriosclerosis can be evaluated, its progression may be reduced by therapeutic intervention. There may be no correlation between one-time-only FDG accumulation and wall thickening, but its chronological changes may be important. In addition, as a long-term study, Figueroa et al. performed FDG-PET in 513 non-cancer-bearing patients without a history of vascular events, and followed them up, with a mean follow-up of 4.2 years.²⁷⁾ In 44 patients, the development of vascular events (stroke, TIA, acute coronary syndrome, revascularization, new-onset angina pectoris, peripheral artery disease, heart failure, and vascular death) was noted, and the TBR of the ascending aorta was an independent prognostic factor for the onset of vascular events (hazard ratio: 4.71; 95% CI: 1.98–11.2; $p < 0.001$). Introduction of FDG-PET to the Framingham risk score, which is a score for predicting coronary events, improved the accuracy. In addition, as a review of acute-stage patients, Marnane et al. reported a small-scale cohort study involving patients with recent symptomatic carotid artery stenosis.²⁸⁾ The subjects were 60 patients with stroke, TIA, or retinal embolism within 2 weeks after onset and $\geq 50\%$ stenosis of the carotid artery. The relationship between carotid plaque FDG accumulation at the time of onset and subsequent recurrent stroke was investigated. In 13 patients (22%), recurrent attacks were observed within 90 days. The mean SUV was significantly higher in the recurrence group (1.85 ± 0.44 g/mL vs. 1.58 ± 0.32 g/mL, $p = 0.02$). In a group with a mean SUV of >2.14 g/mL, the recurrence rate within 90 days was 80%, whereas it was 22.9% in the other group with that of ≤ 2.14 g/mL. Multivariate analysis using Cox's proportional hazard model showed that neither the age nor percent stenosis was involved in recurrence, and that the mean SUV was the only prognostic factor for recurrence (corrected hazard ratio: 6.1; 95% CI: 1.3–28.8; $P = 0.02$). As a future large-scale study, a prospective cohort study (Progression of Early

Subclinical Atherosclerosis [PESA] study) regarding the progression of systemic arteriosclerosis involving 4000 patients was started by a study group in Spain, and the results are being reported. In the study, FDG-PET of the carotid or iliac femoral arteries is scheduled in 1300 patients, and the results may provide important information.²⁹⁾

FDG-PET is also applied to evaluate the treatment response. Several studies reported that simvastatin reduced FDG accumulation in the thoracic aorta/carotid artery,³⁰⁾ atorvastatin reduced FDG accumulation in the ascending aorta/carotid artery in a dose-dependent manner in a relatively short period (12 weeks)³¹⁾, and the administration of an antidiabetic drug, pioglitazone, for 4 weeks more markedly reduced FDG accumulation in the ascending aorta/carotid artery compared with glimepiride regardless of hypoglycemic actions.³²⁾

Future Development and Issues

One of the most important issues regarding FDG-PET is its spatial resolution. The limit is 4–6 mm, which is insufficient for examining the inner structure of carotid plaque. However, FDG-PET/CT and FDG-PET/MRI, which facilitate the visualization of the activity and rough site of inflammatory cells in the arterial wall, provide new information, as described above, beyond the limits of conventional morphological diagnosis. In particular, concerning FDG-PET/MRI, the accuracy of vulnerable plaque detection may be improved by adding PET-based metabolic information to conventional plaque MRI diagnosis using the black blood or contrast-enhanced methods. According to a study, FDG-PET/MRI suggested that carotid artery lesions with marked inflammation despite a low percent stenosis might be the sources of embolism in patients with cerebral infarction in whom the source of embolism was unclear.³³⁾ In the future, FDG-PET/MRI may become a powerful tool for clarifying the pathogenesis of embolic stroke of undetermined source (ESUS). Furthermore, recently, 18-sodium fluoride (¹⁸F-NaF), which is used to detect benign or malignant bone lesions, has been applied for the detection of plaque rupture sites or differentiation of active from inactive calcification.^{34,35)} It may provide new information.

As described above, many animal experiments and clinical studies have demonstrated the usefulness of FDG-PET as a diagnostic imaging method that reflects the instability and activity of arteriosclerosis. However, no long-term, large-scale prospective study excluding cancer-bearing patients

has been conducted. In the future, data must be further accumulated. Concerning carotid artery lesions, there are no data regarding the onset of asymptomatic lesions or prediction of treatment-related risks. Future study results may provide new information.

Acknowledgment

The author expresses sincere gratitude to Dr. Yoshio Uchino (Sousen Hospital and PET diagnosis department of Chiba Ryougo center) for his great cooperation and instructions in this study.

Disclosure Statement

There is no conflict of interest for the first author.

References

- 1) Conrad MF, Boulom V, Baloum V, et al: Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg* 2013; 58: 128.e1–135.e1.
- 2) Walker MD, Marler JR, Goldstein M, et al: Endarterectomy for asymptomatic carotid artery stenosis. Executive committee for the asymptomatic carotid atherosclerosis study. *JAMA* 1995; 273: 1421–1428.
- 3) Halliday A, Mansfield A, Marro J, et al: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004; 363: 1491–1502.
- 4) Japanese Society of Nuclear Medicine and Japan Radiological Society: [Guidelines for the clinical use of FDG PET and PET/CT 2012.] http://jsnm.sakura.ne.jp/wp_jsnm/wp-content/themes/theme_jsnm/doc/fdgpct_guideline2012_120912.pdf (Accessed April 13, 2018). (in Japanese)
- 5) Academic Committee, Japanese Society of Nuclear Medicine Technology: Guidelines about the imaging technique in the examination for FDG-PET. *Jpn J Nucl Med Technol* 2007; 27: 425–456. (in Japanese)
- 6) Eiichi Kobayashi. [Recent carotid plaque imaging]. In: Warou Taki, Ichiro Nakahara, ed. Perfect master: Neuroendovascular therapy. Update of indispensable knowledge. 2nd. ed. MEDICAL VIEW CO., LTD. Tokyo, 2014, 77–89. (in Japanese)
- 7) Niccoli Asabella A, Ciccone MM, Cortese F, et al: Higher reliability of 18F-FDG target background ratio compared to standardized uptake value in vulnerable carotid plaque detection: a pilot study. *Ann Nucl Med* 2014; 28: 571–579.

- 8) Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; 362: 801–809.
- 9) Lederman RJ, Raylman RR, Fisher SJ, et al: Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). *Nucl Med Commun* 2001; 22: 747–753.
- 10) Aziz K, Berger K, Claycombe K, et al: Noninvasive detection and localization of vulnerable plaque and arterial thrombosis with computed tomography angiography/positron emission tomography. *Circulation* 2008; 117: 2061–2070.
- 11) Rudd JH, Warburton EA, Fryer TD, et al: Imaging atherosclerotic plaque inflammation with [¹⁸F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002; 105: 2708–2711.
- 12) Rudd JH, Myers KS, Bansilal S, et al: ¹⁸F-fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. *J Am Coll Cardiol* 2007; 50: 892–896.
- 13) Tawakol A, Migrino RQ, Hoffmann U, et al: Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. *J Nucl Cardiol* 2005; 12: 294–301.
- 14) Graebe M, Pedersen SF, Borgwardt L, et al: Molecular pathology in vulnerable carotid plaques: correlation with [18]-fluorodeoxyglucose positron emission tomography (FDG-PET). *Eur J Vasc Endovasc Surg* 2009; 37: 714–721.
- 15) Arauz A, Hoyos L, Zenteno M, et al: Carotid plaque inflammation detected by ¹⁸F-fluorodeoxyglucose-positron emission tomography. Pilot study. *Clin Neurol Neurosurg* 2007; 109: 409–412.
- 16) Tahara N, Kai H, Yamagishi S, et al: Vascular inflammation evaluated by [¹⁸F]-fluorodeoxyglucose positron emission tomography is associated with the metabolic syndrome. *J Am Coll Cardiol* 2007; 49: 1533–1539.
- 17) Abdelbaky A, Corsini E, Figueroa AL, et al: Focal arterial inflammation precedes subsequent calcification in the same location: a longitudinal FDG-PET/CT study. *Circ Cardiovasc Imaging* 2013; 6: 747–754.
- 18) Laitinen I, Marjamäki P, Haaparanta M, et al: Non-specific binding of [¹⁸F]FDG to calcifications in atherosclerotic plaques: experimental study of mouse and human arteries. *Eur J Nucl Med Mol Imaging* 2006; 33: 1461–1467.
- 19) Graebe M, Pedersen SF, Højgaard L, et al: ¹⁸FDG PET and ultrasound echolucency in carotid artery plaques. *JACC Cardiovasc Imaging* 2010; 3: 289–295.
- 20) Moustafa RR, Izquierdo-Garcia D, Fryer TD, et al: Carotid plaque inflammation is associated with cerebral microembolism in patients with recent transient ischemic attack or stroke: a pilot study. *Circ Cardiovasc Imaging* 2010; 3: 536–541.
- 21) Poredos P, Spirkoska A, Lezaic L, et al: Patients with an inflamed atherosclerotic plaque have increased levels of circulating inflammatory markers. *J Atheroscler Thromb* 2017; 24: 39–46.
- 22) Lei-xing X, Jing-jing G, Jing-xue N, et al: Combined application of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography and magnetic resonance imaging in early diagnosis of vulnerable carotid atherosclerotic plaques. *J Int Med Res* 2014; 42: 213–223.
- 23) Figueroa AL, Subramanian SS, Cury RC, et al: Distribution of inflammation within carotid atherosclerotic plaques with high-risk morphological features: a comparison between positron emission tomography activity, plaque morphology, and histopathology. *Circ Cardiovasc Imaging* 2012; 5: 69–77.
- 24) Rominger A, Saam T, Wolpers S, et al: ¹⁸F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med* 2009; 50: 1611–1620.
- 25) Paulmier B, Duet M, Khayat R, et al: Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events. *J Nucl Cardiol* 2008; 15: 209–217.
- 26) Joseph P, Ishai A, Mani V, et al: Short-term changes in arterial inflammation predict long-term changes in atherosclerosis progression. *Eur J Nucl Med Mol Imaging* 2017; 44: 141–150.
- 27) Figueroa AL, Abdelbaky A, Truong QA, et al: Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. *JACC Cardiovasc Imaging* 2013; 6: 1250–1259.
- 28) Marnane M, Merwick A, Sheehan OC, et al: Carotid plaque inflammation on ¹⁸F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence. *Ann Neurol* 2012; 71: 709–718.
- 29) Fernández-Ortiz A, Jiménez-Borreguero LJ, Peñalvo JL, et al: The progression and early detection of subclinical atherosclerosis (PESA) study: rationale and design. *Am Heart J* 2013; 166: 990–998.
- 30) Tahara N, Kai H, Ishibashi M, et al: Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2006; 48: 1825–1831.
- 31) Tawakol A, Fayad ZA, Mogg R, et al: Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol* 2013; 62: 909–917.
- 32) Mizoguchi M, Tahara N, Tahara A, et al: Pioglitazone attenuates atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetes: a prospective, randomized, comparator-controlled study using serial FDG

- PET/CT imaging study of carotid artery and ascending aorta. *JACC Cardiovasc Imag* 2011; 4: 1110–1118.
- 33) Hyafil F, Schindler A, Sepp D, et al: High-risk plaque features can be detected in non-stenotic carotid plaques of patients with ischaemic stroke classified as cryptogenic using combined ^{18}F -FDG PET/MR imaging. *Eur J Nucl Med Mol Imaging* 2016; 43: 270–279.
 - 34) Dweck MR, Chow MW, Joshi NV, et al: Coronary arterial ^{18}F -sodium fluoride uptake: a novel marker of plaque biology. *J Am Coll Cardiol* 2012; 59: 1539–1548.
 - 35) Joshi NV, Vesey AT, Williams MC, et al: ^{18}F -fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 2014; 383: 705–713.