Innovative atherosclerosis imaging using ^{18}F -NaF PET/CT: Its clinical potential

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Atherosclerosis is a major cause of critical cardiovascular disorders, including myocardial infarction, stroke, and peripheral arterial disease. ^{18}F -sodium fluoride (^{18}F -NaF) positron emission tomography (PET) has recently gained attention in the field of cardiovascular diseases and data have shown its usefulness in identifying high-risk atherosclerotic lesions with active calcification.^{1,2} Lee et al. demonstrated that coronary plaques with high-risk characteristics on intravascular imaging (intravascular ultrasound and optical coherence tomography) had higher ^{18}F -NaF uptake than those without such characteristics.³ Kitagawa et al. assessed the relationship between the ^{18}F -NaF signal on PET and the appearance of coronary atherosclerosis on cardiac computed tomography (CT) examination⁴ and found the following: (1) The coronary calcium score was positively correlated with coronary arterial ^{18}F -NaF uptake per patient; (2) patients with a history of myocardial infarction or unstable angina had higher coronary arterial ^{18}F -NaF uptake; (3) focally increased ^{18}F -NaF uptake in coronary atherosclerosis was independently correlated with the heterogeneous (partially calcified) plaque component; and (4) coronary plaques with high-risk features on coronary CT angiography (CCTA) had a higher ^{18}F -NaF uptake on PET than those without. In addition, intense ^{18}F -NaF uptake was shown in recently ruptured coronary plaques in patients with acute

myocardial infarction.⁵ These points highlight the potential of ^{18}F -NaF PET imaging as an innovative approach to monitoring atherosclerosis.

Why does ^{18}F -NaF uptake indicate ruptured or high-risk atherosclerotic plaques? The ^{18}F -NaF tracer reacts with hydroxyapatite, which is the central component of vascular calcification and is deposited during the earliest and most active stages of mineralization. Atherosclerotic calcification is described as a cellular response to acute and chronic inflammatory stimuli, and the association between osteogenesis and inflammation in atherosclerosis is well described.^{6,7} Therefore, atherosclerotic inflammation precedes vascular calcification, and the presence of microcalcifications are associated with inflammatory cell infiltrate that coexists with other high-risk features of atherosclerotic plaque, including a large lipid core, outward remodeling, and thin fibrous cap. ^{18}F -NaF uptake is thus a comprehensive imaging marker of high-risk atherosclerotic plaques (Figure 1). In imaging of coronary arteries, ^{18}F -NaF tracer, unlike ^{18}F -fluorodeoxyglucose (^{18}F -FDG), is not taken up physiologically in the myocardium; therefore, coronary atherosclerotic lesions can be specifically detected and assessed using ^{18}F -NaF PET/CT.

Fiz et al. conducted an interesting analysis on the correlation between ^{18}F -NaF uptake in the vessel walls and a successive increase in the calcium burden.⁸ They focused on (1) the significance of ^{18}F -NaF uptake with regard to the CT density of noncalcified arterial lesions and new occurrence of calcification, (2) the significance of ^{18}F -NaF uptake with regard to subsequent calcified plaque progression represented by CT density and calcium score, and (3) the significance of ^{18}F -NaF uptake in the whole aorta with regard to the increase in calcium burden. Patients who underwent two consecutive ^{18}F -NaF PET/CT scans were enrolled in their study, and lesions on the abdominal aorta were evaluated. They found that in noncalcified arterial walls, ^{18}F -NaF uptake is colocalized with an increased CT density and related

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Figure 1. Schema and CCTA image of high-risk atherosclerotic plaque with enhanced ^{18}F -NaF uptake on PET. CCTA, coronary computed tomography angiography; ^{18}F -NaF, ^{18}F -sodium fluoride.

to the presence of initial calcium deposition, whereas in calcified plaques, ^{18}F -NaF uptake is a harbinger of future lesion growth. Accordingly, they suggested that ^{18}F -NaF-PET/CT can be used to capture the early stages of arterial calcification and to predict the progression of calcified plaques.

Whether an increased ^{18}F -NaF uptake in arterial walls and lesions correlates with a subsequent increase in the calcium content has been studied elsewhere. Ishiwata et al. showed that ^{18}F -NaF uptake at calcification sites in the arterial wall is positively correlated with temporal changes in calcification volumetric score (Spearman's $\rho = .734$, $P < .0001$) and Agatston unit score (Spearman's $\rho = .587$, $P < .0001$) but not with the changes in mean and maximum CT density.⁹ Li et al. also reported a subsequent increase in both ^{18}F -NaF uptake and calcium CT density in atherosclerosis and found that most noncalcified lesions (86%) had

concordant development of osteogenesis-derived ^{18}F -NaF uptake and inflammation-derived ^{18}F -FDG uptake.¹⁰ Fiz et al.'s study has provided new evidence to support these previous findings.⁸ A key feature of that study is that it focuses on noncalcified arterial lesions with focal ^{18}F -NaF uptake (hot spot), in which CT density is higher than that in lesions without tracer accumulation. As Fiz et al. suggested, this finding could reflect microscopic amounts of calcium within a growing atherosclerotic plaque (increased mineral metabolism within the arterial wall) even if no morphological calcium is visible on CT. In addition, the strong association between whole aorta ^{18}F -NaF uptake and calcium score progression should be of clinical interest because it suggests that ^{18}F -NaF PET/CT may help clinicians manage the overall risk of calcifications in main arteries.

However, as the authors acknowledge, the study has several limitations.⁸ The intervals between the first and second ^{18}F -NaF PET/CT scans varied substantially. Although some normalized analyses were applied, there was no such analysis for the appearance of new calcifications. In fact, the interval between the first and second scans was longer in patients with new calcifications (19.2 ± 12.5 months) than in those without (12.8 ± 6.2 months; $P < .05$). This indicates that new calcifications may be affected by the length of time interval. A prospective study with a fixed interval between the first and second scans is needed to confirm the significance of ^{18}F -NaF uptake (hot spot) on new calcifications. Additionally, two different PET/CT imaging devices were used, which could have introduced differences in the analyses. With regard to image quality, ^{18}F -NaF uptake within atherosclerosis is a lower-grade phenomenon than the physiological mineral metabolism in bone, and so it may be affected by possible spillover signals from vertebrae. Improvement in the spatial resolution of PET/CT images would decrease spillover signals from nearby structures.

In the field of cardiovascular diseases, ^{18}F -NaF PET/CT has been used widely and has great potential for diagnosis and monitoring. The prognostic significance of ^{18}F -NaF signals in atherosclerosis is of interest and value to most physicians. Kitagawa et al. investigated the utility of ^{18}F -NaF uptake for predicting coronary events and evaluated the effective combined use of CCTA and ^{18}F -NaF PET/CT in coronary artery disease risk assessment.¹¹ They demonstrated that higher coronary ^{18}F -NaF uptake is predictive of the occurrence of coronary events over the next 2 years. Furthermore, they confirmed that higher coronary ^{18}F -NaF uptake was correlated with advanced coronary calcification, and that the presence of high-risk plaque on CCTA was a predictor of higher coronary ^{18}F -NaF uptake in both patient- and lesion-based analyses. These results support the implementation of a step-by-step approach using CCTA and ^{18}F -NaF PET/CT for noninvasive identification of high-risk coronary artery disease. Most recently, Kwiecinski et al. assessed whether ^{18}F -NaF PET helps predict myocardial infarction and provides additional prognostic information to current methods of risk stratification.¹² They measured coronary microcalcification activity (CMA) as total coronary ^{18}F -NaF uptake, which was based on both the volume and intensity of ^{18}F -NaF activity within the vessel. They found that ^{18}F -NaF CMA was better for predicting fatal or nonfatal myocardial infarction (area under the receiver operator curve: .76) than coronary calcium scoring, the modified Duke coronary artery disease index, and Reduction of Atherothrombosis for Continued Health (REACH) and Secondary Manifestations of Arterial

Disease (SMART) risk scores (area under the receiver operator curves: .54, .62, .52, and .54, respectively; $P < .001$). The use of ^{18}F -NaF PET/CT for assessing heart valve calcification is an interesting topic. Aortic valve calcification (AVC) is the main etiological mechanism of aortic valve stenosis. Dweck et al. studied various populations with aortic sclerosis (peak aortic valve velocity < 2.0 m/s on echocardiography) and mild, moderate, or severe aortic valve stenosis and demonstrated that ^{18}F -NaF uptake in AVC was positively correlated with aortic valve calcium score on CT.¹³ Moreover, in a study of patients with aortic valve stenosis, Dweck et al. demonstrated that valvular ^{18}F -NaF uptake was correlated with histological markers of active calcification and was a good predictor of subsequent worsening of the aortic valve calcium score over 1 year.¹⁴ Nakamoto et al. simultaneously evaluated ^{18}F -NaF uptake in subclinical AVC (peak aortic valve velocity < 2.0 m/s on echocardiography) and in coronary atherosclerosis as assessed by CT.¹⁵ They found that (1) ^{18}F -NaF uptake in AVC was positively correlated with the extent of calcification in AVC as assessed by CT; (2) increased ^{18}F -NaF uptake in AVC was related to the presence of high-risk coronary plaques as seen on CT; (3) ^{18}F -NaF uptake in AVC was closely correlated with that in coronary atherosclerosis; and (4) in the follow-up cohort, higher ^{18}F -NaF uptake was correlated with AVC progression. Nakamoto et al.'s data suggested that there are relationships between calcification activity in subclinical AVC and characteristics of coronary atherosclerosis and that ^{18}F -NaF PET/CT may provide new information regarding molecular conditions and future progression of subclinical AVC. Finally, simultaneous assessment of coronary arterial ^{18}F -NaF signal and CT-based epicardial adipose tissue (EAT) findings provides clinically significant information. A large cohort study demonstrated that higher attenuation of pericoronary EAT on CT predicted all-cause and cardiac mortality over and above the clinical risk factors and CCTA-derived high-risk plaque features,¹⁶ which highlighted the pathogenicity of inflammatory EAT represented by higher CT density. Kwiecinski et al. recently reported that increased CT density of pericoronary EAT was associated with focal ^{18}F -NaF uptake in patients with high-risk plaques on CCTA.¹⁷ Kitagawa et al. also assessed the relationships between coronary arterial ^{18}F -NaF uptake on PET and EAT parameters based on cardiac CT examination and found that (1) EAT density around coronary atherosclerotic lesions was positively correlated with coronary arterial ^{18}F -NaF activity both per patient and per lesion and (2) higher EAT density around coronary atherosclerotic lesions remained a significant predictor of coronary arterial ^{18}F -NaF cutoff level to predict future coronary events, even

Figure 2. A proposed new flowchart for the use of cardiac CT and ^{18}F -NaF PET/CT for identifying coronary atherosclerotic lesions and patients at high risk for coronary artery disease. CT, computed tomography; PET, positron emission tomography; ^{18}F -NaF, ^{18}F -sodium fluoride.

after adjustment for EAT volume or high-risk plaque on CT.¹⁸ Kitagawa et al.'s results indicated that higher pericoronary EAT density may identify patients and individual lesions that are likely to have clinically meaningful coronary lesions with ^{18}F -NaF uptake.

The results of these previous studies indicate the importance of applying this innovative imaging to the assessment of atherosclerotic disease. Nuclear imaging methods are not practical for use in the general population, and criteria are needed to identify patients in whom it could be beneficial. For example, the step-by-step approach using coronary CT and ^{18}F -NaF PET/CT may be useful for identifying coronary atherosclerotic lesions and patients at high risk for coronary artery disease, and ^{18}F -NaF PET/CT would play a role as molecular imaging modality for coronary artery disease (Figure 2). Further studies in a larger cohort are warranted to clarify the clinical utility of this new imaging option.

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Disclosures

Toshiro Kitagawa and Yukiko Nakano have no conflicts of interest to disclose.

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