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EDITORIAL COMMENTARY

NaF uptake in unstable plaque: what does fluoride uptake mean?

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Coronary artery calcification has been used to predict the risk of acute coronary events. Coronary calcification is usually quantified using EKG gated computed tomography (CT) [1, 2]. Recent studies suggest that the predictive value of coronary calcification is not linearly related to risk. For example, a 31% higher progression of coronary artery calcium was demonstrated in patients taking statin medication, despite a lower cardiac event rate [3]. Intravascular ultrasound (IVUS) and CT angiographic studies have demonstrated that although patients with acute coronary syndromes (ACS) had more non-calcified plaques on CT than stable angina patients [4], spotty calcification was frequently observed in the culprit plaques associated with acute events; larger calcific masses did not identify unstable lesions [5, 6]. This observation may be due to the fact that the largest surface area with exchangeable calcium occurs in regions of acute necrosis, where the sizes of lesions are measured in microns. The spatial resolution of clinical CT is ~1–2 mm, to limit patient radiation burden. Ex-vivo studies, on the other hand, where spatial resolution is ~1 μm, demonstrated the presence of microcalcification in lesions that are not seen on clinical CT, but are associated with eventful plaques [7].

^{18}F-sodium fluoride positron emission tomography (NaF) imaging, originally proposed as an agent to identify bone metastasis over 50 years ago [8], has been suggested as an agent to detect microcalcification in atherosclerotic plaques [9–11]. Although spatial resolution of molecular imaging is low, the high affinity of NaF for microcalcification allows visualization of very small lesions.

In this issue of the EJNMMI, Li et al. [12] describe the relationship between ^{18}F-NaF coronary uptake on PET/CT, to coronary IVUS-verified high-risk plaque characteristics and coronary artery calcium distribution based on Electron Beam CT calculation of Agatston score, calcium mass and calcium volume. Li et al. studied 32 symptomatic patients, including 30 with unstable angina and two with stable angina. The investigators used high-frequency IVUS (40 MHz, pullback: 0.5 mm/s) with radiofrequency analysis (Virtual Histology, VH) for target lesions as well as proximal and distal reference segments to characterize coronary plaques. Electrocardiogram-gated ^{18}F-PET-CT was performed within 2 days before IVUS. Sixty minutes after IV administration of ^{18}F-NaF, a 10 min gated, static, PET CT was recorded in one bed position, covering the heart and the aortic arch. Two-dimensional regions of interest (ROI) (diameter: 1–2 mm) were manually set on the target lesion to measure maximum standardized uptake value (SUV max). As a background, the average SUVmax values of three ROIs in the superior vena cava were measured. The lesion SUVmax was divided by the vena cava (SUVblood) to calculate the maximum tissue-to-blood (TBRmax) ratio. The authors set TBRmax of 1.25 as a threshold cut-off value. A total of 69 coronary atherosclerotic lesions were evaluated. NaF uptake ratio was increased in thin-cap atheroma with spotty calcification, thick-cap atheroma and fibrocalcific lesions, but not increased in fibrous plaque. NaF uptake correlated with the severity of plaque burden, positive lesion remodeling, and the extent of necrotic core, but was negatively correlated with fibrotic component of the plaque. In a subgroup analysis of 128 arteries (LMCA, LAD, LCx, and RCA) in the 32 patients grouped by Agatston score, there was no correlation of NaF uptake with calcium burden on EBCT.

High-risk plaques are characterized by: large plaque burden with necrotic core, significant infiltration with cells of monocyte-macrophage lineage, increased density of vasa vasorum, and microcalcification [7]. Atheroma are initiated

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by sub-intimal insudation of LDL cholesterol, followed by infiltration of inflammatory cells to phagocytize the LDL cholesterol, leading to the formation of cholesterol-laden foam cells. The inflamed atheroma is hypoxic, resulting in local release of factors to promote the development of additional vasa vasorum. Early in the life history of an atheroma, the foam cells die by apoptosis and the remnants of the apoptotic cells are phagocytized by surrounding macrophages. In more advanced lesions, inefficient efferocytosis causes apoptotic debris to accumulate, resulting in expansion of the necrotic core and further inflammation. The inflammatory milieu results in collagenolysis and renders the plaque unstable. Microcalcification is initiated in regions of inflammation where cell death is abundant and provides a nidus for calcium seeding [13]. The microcalcific deposits evolve to spotty calcification (SC) easily recognized on CT. If the inflammation is reduced (usually by medication and diet), the lesions stabilize with elimination of foam cells and massive cell death leads to macrocalcification or plate-like calcification (PC) [7, 14–16]. Therefore, micro or spotty calcification or SC may identify at-risk lesions but when extensive (PC), may represent plaque stability. The statin-related calcific progression represents the latter phenomenon. It is therefore important to identify the calcification process rather than calcific fossils that may support the importance of NaF imaging.

The authors have described four types of NaF uptake in plaques and we should try to reconcile the uptake based on the foregoing molecular mechanisms. High NaF uptake of type 1 (thick-cap fibroatheroma with dense necrotic tissue) and type 2 (thin-cap fibroatheroma with dense necrotic tissue) plaques and low uptake of type 3 (fibrotic plaque poor necrotic tissue) seem reasonable. It is also understandable that NaF uptake did not correlate with calcium score but correlated with circulating levels of high sensitivity CRP.

The patients with type 4 fibrocalcific plaques with intensive calcification also showed high NaF uptake, which is more challenging to explain. It might alert us that a simple CTA-based notion of dangerous SC but a guarantee of plaque stability from PC may not be entirely justified. It is hypothetically reasonable to propose that NaF imaging might have the ability to discriminate macrocalcification with or without the inflammatory milieu and hence evil and not-so-evil plaques. On the other hand, it is also possible that NaF uptake seen with extensive CT-verified calcification may mean progression of calcification rather than inflammatory calcification and that NaF uptake in the presence of PC may represent a benign phenomenon. It is also possible that this unexpected finding may be due to the patient population and/or the limited number of patients investigated. This important question could be answered by a multi-center prospective case study to understand the clinical significance of scans that are: PC + NaF+, PC + NaF-, PC-NaF+, PC-NaF-, SC + NaF+, SC-NaF+, SC + NaF-, and SC-NaF-. It is also necessary that we reassess the possibility of NaF uptake by other cells [17] that might substantially alter our understanding of clinical implications of predictive, preventive or punitive roles of calcific deposits in the plaques [18]. Calcification is ubiquitous in atherosclerosis and hence its contribution to the plaque behavior and prognostic outcomes needs careful characterization.

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