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^{18}F-NaF PET and plaque calcification: how complicated can it be?

Sina Tavakoli, MD, PhD[1] and **Mehran M. Sadeghi, MD**[2,3]

[1]Departments of Radiology and Medicine (Vascular Medicine Institute), University of Pittsburgh, Pittsburgh, PA, United States;

[2]Section of Cardiovascular Medicine and Cardiovascular Research Center, Yale University School of Medicine, New Haven, CT, United States.

[3]VA Connecticut Healthcare System, West Haven, CT, United States.

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^{18}F-sodium fluoride (^{18}F-NaF) was introduced as a tracer for imaging skeletal diseases in 1962 and was approved by the FDA in 1972[1]. Recently, with the increased availability of positron emission tomography (PET) scanners there has been a surge in clinical utilization of ^{18}F-NaF imaging for oncological applications. The incidental observation, nearly a decade ago, of ^{18}F-NaF uptake in the vasculature in patients undergoing PET imaging for cancer has led to a growing number of investigations exploring the potential role of this tracer in atherosclerosis[2–4]. However, the biological correlates of ^{18}F-NaF imaging in the vasculature, its potential role in risk stratification of patients and prospective identification of vulnerable plaques remain incompletely characterized. In this issue of the *Journal*, Creager *et al.*[5] address some of these gaps by exploring the relationship between ^{18}F-NaF binding and the size of microcalcifications using a 3D hydrogel platform[6]. In agreement with a previous publication[2], their study finds that smaller and more numerous microcalcifications (i.e., higher surface areas of calcifications) are associated with higher ^{18}F-NaF binding when compared to fewer larger calcifications[5]. The study also provides *ex vivo* proof-of-concept evidence for the correlation between ^{18}F-NaF binding and foci of ongoing calcifications in mouse and human atherosclerotic plaques[5].

Significance of calcification in atherosclerosis

The understanding of the biological significance of calcification in atherosclerosis has evolved from a passive and degenerative phenomenon to a highly dynamic and regulated process with important roles in plaque biology and vulnerability[7]. Elucidating the full picture of the clinical implications of calcification in atherosclerosis has been challenging

Address for correspondence: Mehran M. Sadeghi, M.D., Professor of Medicine (Cardiology), Yale University School of Medicine, 300 George Street, Suite 770G, New Haven, CT 06511, Phone: 203-737 6954, Fax: 203-937 3884, mehran.sadeghi@yale.edu.

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considering the complexity of its underlying mechanisms, its diverse histological patterns and distribution within different regions of plaques, and the intrinsic differences of various imaging modalities used in the detection of calcification. For example, several mechanisms, with potentially different biological implications, may contribute to the pathogenesis of calcification in atherosclerosis. These include the release of extracellular calcifying matrix vesicles from smooth muscle cells and macrophages, apoptosis or death of macrophages and smooth muscle cells, imbalances in local plaque microenvironment promoting mineralization, and chondro- or osteo-genic trans-differentiation of pericytes and vascular smooth muscle cells[7–9]. Also, while the presence of microcalcification in regions of plaques with intense macrophage infiltration suggests a link between inflammation and calcification, macrocalcification is often observed in non-inflamed regions of plaques[7, 8, 10]. The size and location of calcifications are also important determinants of their biological implications. For example, microcalcifications of > 5 μm may contribute to mechanical instability of plaques, in particular in the fibrous cap, by increasing the local mechanical stress and weakening the tensile strength[7, 11]. Conversely, microcalcifications of < 5 μm are reported to have no such effects. On the other end of the size spectrum, the clinical significance of CT-detectable macrocalcification as a marker for global burden of atherosclerosis and a risk predictor is well-established in large population-based studies[12]. While large dense sheet-like calcification is generally thought to confer plaque stability[7], spotty calcifications are believed to be associated with plaque vulnerability[13]. It is important to note that although the spotty calcifications detected by coronary CT angiography or intravascular ultrasound are sometimes referred to as microcalcifications, they are much larger and distinct from fibrous cap microcalcifications described in the context of finite element analysis[11, 13]. Given this complexity, we believe the field would benefit from standardization of terminology (e.g., spotty, speckled, micro-, macro-).

^{18}F-NaF imaging of plaque calcification

Unlike structural imaging modalities such as CT and IVUS, ^{18}F-NaF-based molecular imaging of (micro)calcification may provide unique information on the calcification *process* in atherosclerosis. It is reasonable to assume that the basis for ^{18}F-NaF uptake in atherosclerosis is analogous to its accumulation in areas of bone remodeling, i.e., through chemisorption onto the surface of hydroxyapatite crystals and subsequent exchange of their hydroxyl groups with ^{18}F, which leads to the formation of fluoroapatite[14]. Interestingly, Creager *et al.* showed that in addition to binding to hydroxyapatite, ^{18}F-NaF also binds to pyrophosphate[5]. While the authors did not define the relative affinity of ^{18}F-NaF for hydroxyapatite and pyrophosphate, it is noteworthy that pyrophosphate is a physiologic inhibitor of hydroxyapatite deposition, and can be present at low level in the vessel wall[15]. The significance of this unexpected finding remains to be determined. Furthermore, the differential binding of OsteoSense, a fluorescent bisphosphonate imaging agent used as a surrogate marker of calcification, and ^{18}F-NaF to hydroxyapatite and pyrophosphate[5] indicates that these agents potentially target distinct yet overlapping processes. Having previously demonstrated elegantly that smooth muscle cell-derived extracellular-vesicles coalesce to form microcalcifications in a 3D hydrogel collagen platform and the size of calcified aggregates can be modulated by the hydrogel collagen concentration[6], Creager *et*

al. detected higher ^{18}F-NaF binding in a matrigel composition associated with smaller extracellular vesicle aggregates (and higher total surface area) relative to one with less collagen and larger microcalcifications. This observation strongly supports their hypothesis that ^{18}F-NaF binding correlates inversely with the size of microcalcification[5]. As the authors have previously reported on the size of these aggregates[6], it would have been interesting to explore whether there is a linear correlation between the surface area of the particles and ^{18}F-NaF binding, based on the average size and number of extracellular vesicles under different experimental conditions. Because microcalcifications of <5 μm in diameter do not affect the risk of plaque rupture[11] and larger foci of calcification are thought to be "stabilizing"[7, 8], the correlation between the surface area of the particles and ^{18}F-NaF binding might indicate a complex, non-linear relation between ^{18}F-NaF signal and plaque vulnerability.

High resolution *ex vivo* PET/CT experiments have demonstrated that ^{18}F-NaF binds with high affinity to hydroxyapatite molecules within plaques and co-localizes with foci of nascent and active calcifications in human carotid endarterectomy specimens[2]. As ^{18}F-NaF preferentially adsorbs into microcalcifications that are below the resolution of CT, ^{18}F-NaF PET and CT may unravel distinct aspects of plaque biology, i.e., (ongoing) microcalcification vs. macrocalcifications. This might provide a venue to extend the clinical utility of calcification imaging from a global risk stratification tool, achieved by CT, to a tool for improved plaque characterization. Supporting this, *in vivo* clinical studies have revealed that 88% of plaques with ^{18}F-NaF uptake in large arteries demonstrate concordant calcification by CT[3]. However, in the remaining ~12% of plaques, ^{18}F-NaF uptake does not colocalize with CT-detectable calcifications[3]. To explore the biological correlates of such ^{18}F-NaF^{+}/CT^{-} lesions, Creager *et al.* provide evidence that *ex vivo* binding of ^{18}F-NaF to mouse atherosclerotic plaques and human endarterectomy specimens correlates with the OsteoSense signal[5]. While promising as a proof-of-concept experiment, it would be of interest to further explore the relationship between ^{18}F-NaF binding and histological and biological markers of calcifications. In addition, the strength of the correlation between *in vivo* quantified ^{18}F-NaF uptake and vascular tissue (micro)calcification remains to be determined. Of note, partial-volume effect leading to spill-over of the ^{18}F-NaF signal into adjacent pixels may provide an alternative explanation for the absence of CT-detectable calcifications in at least some ^{18}F-NaF^{+} regions[16].

Clinical perspectives

^{18}F-NaF PET imaging of coronary arteries is challenging and technical and technological issues such as the spatial resolution of PET scanners, cardiac motion, and quantification methodology may adversely affect the quantitative analysis of images[17, 18]. Nonetheless, several small-scale clinical studies have raised the exciting possibility of a role for ^{18}F-NaF PET in assessing disease progression and plaque characterization in patients with coronary and carotid artery disease[4, 19]. Accordingly, it is reported that in over 90% of patients with recent myocardial infarction, the culprit plaques have the highest level of ^{18}F-NaF uptake along the coronary arteries[4]. Similarly, increased focal uptake of ^{18}F-NaF has been detected at sites of plaque rupture in patients with symptomatic carotid artery disease[4]. Despite these promising results, the reproducibility and stability of ^{18}F-NaF signal in coronary and carotid

arteries, and the potential role of ^{18}F-NaF PET in plaque characterization and prospective risk prediction remain to be determined. Indeed, it is possible that the reported high uptake of ^{18}F-NaF in culprit lesions is a consequence of plaque rupture which would facilitate ^{18}F-NaF access and binding to the sites of calcification. In addition, in a major fraction of acute coronary syndromes, the underlying pathology is plaque erosion, where the role of calcification is even less clear than in plaque rupture. Ongoing research and clinical trials such as “Prediction of Recurrent Events With ^{18}F-Fluoride” (Clinicaltrials.gov: NCT02278211) should address these issues, as well as the potential and incremental value of ^{18}F-NaF PET in patients with coronary and carotid artery disease, in near future. Even with these remaining challenges and pitfalls, ^{18}F-NaF PET of atherosclerosis is already a major step toward the transition from structural imaging only, to incorporation of molecular imaging of vessel wall biology in patient management.

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