Evolution of arterial [^{18}F]-sodium fluoride uptake and calcification

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Ectopic deposition of mineralized calcium plays an important role in a number of chronic age-related cardiovascular diseases. In atherosclerosis, calcification occurs in the remodeled intima *via* an active process initiated by an imbalance of pro- and anti-mineralization factors in presence of local nucleators of mineralization.¹ This process leads to microcalcification, which can be observed on histological examination. Foci of calcification coalesce to form larger deposits, which can be visualized by X-ray computed tomography (CT) as spotty calcification and eventually more extensive, diffuse calcifications.^{2,3} Spotty calcifications have been associated with increased plaque vulnerability⁴ and modeling studies have postulated that microcalcification in the fibrous cap can lead to local increase in wall stress resulting in higher propensity for plaque rupture.⁵

[^{18}F]-Sodium fluoride ([^{18}F]-NaF) is a positron emission tomography (PET) bone tracer. After extraction from blood and chemisorption onto hydroxyapatite, [^{18}F]-fluoride is exchanged with the hydroxyl group of hydroxyapatite crystal. Therefore, [^{18}F]-NaF signal localizes in calcified tissues, and the uptake is increased in sites of bone formation, where the exposed bone surface area is increased.⁶ Similarly, in the atherosclerotic vessel wall, the sites of active calcification with

large surface area resulting from multiple mineralization foci were shown to result in high [^{18}F]-NaF signal.⁷

Vascular [^{18}F]-NaF uptake has been associated with cardiovascular risk factors,^{8,9} markers of plaque vulnerability and culprit lesions.^{10,11} Most of the findings on vascular [^{18}F]-NaF uptake originates from cross-sectional studies and little is known about the evolution and relationship of arterial [^{18}F]-NaF uptake and vascular calcification over time. The study by Nakahara et al.,¹² published in current issue of the *Journal of Nuclear Cardiology*, provides novel insights into this relationship. This retrospective study includes 45 prostate cancer patients followed for at least 1.5 years with multiple [^{18}F]-NaF PET/CT scans to evaluate osseous metastases. Both [^{18}F]-NaF uptake and calcium volume were quantified and reported as an average value for the entire abdominal aorta for each scan. The authors reported that, while the calcification volume either remained constant or increased during the course of the study, [^{18}F]-NaF uptake showed a degree of variability between scans. The authors did not present reproducibility data, however, the methodology chosen for the study and choice of vascular bed were expected to minimize the variability originating from image analysis, as compared to the analysis of individual lesions over time (although the proximity of vertebral bodies to the abdominal aorta might be challenging). The data suggest biological variability in the atheromatous lesion over relatively short period of time, which could be a yet poorly identified pitfall of vascular [^{18}F]-NaF PET imaging. In fact, a recent study of [^{18}F]-NaF PET imaging of coronary artery lesions included the evaluation of scan-rescan reproducibility which showed a degree of variability in the assessment of [^{18}F]-NaF uptake within two weeks. Methodological differences make it difficult to directly compare the variations in the two studies.¹³

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The study by Nakahara et al.¹² also reported a correlation between [¹⁸F]-NaF uptake at baseline and the increase in calcification volume. These data validate the finding by Ishiwata et al.¹⁴ which reported a strong correlation between [¹⁸F]-NaF uptake and calcium volume increase of primarily aortic plaques, over a period of approximately 1 year. Of note, several other studies reported a similar observation,^{15–17} while a retrospective study in a population with low incidence of calcification and with a longer follow-up period did not find a similar correlation.¹⁸ Nakahara et al.,¹² refined this analysis with the evaluation of the relationship between initial [¹⁸F]-NaF uptake and the calcium volume increment over different time intervals. [¹⁸F]-NaF uptake on the initial scan, correlated the best with the increase in calcium volume during the 6-month interval starting 1 year after the initial scan, while the correlation with calcium volume increase during the first 6 months directly after the initial scan was the poorest (albeit also statistically significant). These results are presented as potentially representing a lag period between the evolution from microcalcification to calcification visible on CT images. More intuitively, patient with persistently high [¹⁸F]-NaF uptake (i.e. above the median value of 1.7 SUV_{max}, averaged over the entire abdominal aorta) showed the highest increase in calcium volume. The value of [¹⁸F]-NaF uptake to predict the evolution of calcium deposits has potentially important implications, as it was shown that the rapid increase in calcium volume is predictive of cardiovascular events.¹⁹ This may appear counterintuitive with the data showing low attenuation plaques (as defined on CT angiography, and which may or may not contain microcalcifications) and plaques with spotty calcifications as rupture-prone high risk plaques, while diffuse calcifications are associated with a more stable, fibrocalcific plaque phenotype.³ However, coronary artery calcium score reflects the global burden of the atherosclerotic disease, and is a strong predictor of cardiovascular events and mortality, with an excellent negative predictive value.²⁰ This association extends to other vascular beds, including the abdominal aorta.²¹ Nevertheless, even in a context of more densely calcified vasculature, culprit lesions often have limited calcification.²²

The association between diffuse calcification and [¹⁸F]-NaF uptake remains unclear, with some reports of positive,^{11,15} negative¹⁶ or absence of association.^{8,10,14,17,18} A portion of this variability between the studies may be explained by the differences in methodology. While not presenting a direct correlation, Nakahara et al.¹² showed that the maximal [¹⁸F]-NaF uptake during the follow-up correlated with the calcium volume at the end of the study. Given the postulated underlying biological processes, with a variety of plaque

phenotypes within an individual patient and among the whole population of a given study, a strong association would be surprising and mitigate the interest of [¹⁸F]-NaF imaging as an independent predictor.

The pathophysiology of medial calcification, mainly found in peripheral arteries in older patient with diabetes mellitus and chronic kidney disease, is distinct from intimal calcification found in atherosclerotic plaques.²³ However, on non-contrast low-dose CT acquisition, their presentation could be similar.²⁴ Given the study population (67.0 ± 9.2 years-old, 13/45 patients with diabetes mellitus), it cannot be excluded that a portion of the calcification and related [¹⁸F]-NaF signal observed are related to medial calcification and its distinct pathological process.

Overall, the study by Nakahara et al.¹² provides interesting insights on the temporal association between [¹⁸F]-NaF uptake and arterial calcification. As a single center retrospective study, the present findings require further confirmation, particularly to explore the relevance of those finding to other vascular beds and with more granularity, on a segment to segment basis.

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