Assessing global cardiovascular molecular calcification with ^{18}F -fluoride PET/CT: will this become a clinical reality and a challenge to CT calcification scoring?

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Published online: 25 January 2012
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The complex biology of atherosclerosis has been approached by functional imaging from multiple directions, each exploring the specific and distinctive etiopathogenetic mechanisms underlying its formation and progression as well as its subsequent complications [1–5]. In a review published in this journal [2], the targets and the radiopharmaceuticals with their targeting characteristics were classified into four major groups: (1) atherosclerotic lesion components (targets include foam cells, lipoproteins, lipids, endothelin); (2) inflammation (targeting metabolic glucose activity, macrophages and monocytes, neutrophils, monocytes and lymphocytes, lymphocytes); (3) thrombosis (targeting platelets, activated platelets, fibrins, etc.); and (4) apoptosis. In addition to these aforementioned enumerated targets, there have been recent endeavors to detect and image active arterial calcification with ^{18}F -fluoride positron emission tomography (PET)/CT [6–9]. This novel approach, which requires further critical evaluation in experimental and clinical studies, opens up the possibility of a new armamentarium of functional imaging in the evaluation of this complex disease process. In this

comment, we explore some demonstrated promises and take a look at future prospects and limitations of this for being translated into a clinical reality.

The association of aortic calcification with cardiovascular events and all-cause mortality has been emphasized in several reports. Inflammation and calcification are two dynamic and complex processes that are integral components in various pathophysiological steps of atherogenesis. Arterial calcification has been traditionally determined by CT, whereas inflammation mainly mediated by macrophage activity has been assessed by ^{18}F -fluorodeoxyglucose (FDG) PET over the last few years. The increasing use of ^{18}F -sodium fluoride (NaF) PET has raised the theoretical possibility of studying active mineral deposition in the atherosclerotic plaque perhaps years or even decades earlier than previously.

To date there have been five clinical studies [6–10] that have explored the feasibility of using ^{18}F -NaF PET/CT in assessing the calcification component of atherosclerosis. Derlin et al., in a retrospective study [6], evaluated the prevalence, location, and topographic relationship of ^{18}F -NaF accumulation and vascular calcification in major arteries. On a patient-specific analysis, ^{18}F -NaF uptake was observed at 254 sites in 76%, and CT calcification was observed at 1,930 sites in 84% of the 75 study patients. On a lesion-by-lesion analysis, colocalization of radiotracer accumulation and CT calcification was observed in 88% of the PET-positive lesions, whereas only 12% of all arterial CT calcification sites showed increased radiotracer uptake. The investigators also observed that a higher prevalence of ^{18}F -NaF uptake visibility is related to a degree of calcification; however, they found no significant correlation between the intensity of radiotracer uptake [maximum standardized uptake value (SUV_{max})] and the calcification score [6]. Interestingly, the per patient colocalization of ^{18}F -NaF uptake and CT calcification was found to be substantially higher than the

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previously reported rates of <2% and 7% concordance of ^{18}F -FDG and CT calcification in other studies, one of which showed a change in the FDG uptake pattern in about half of the patients at repeat imaging 8–26 months apart with virtually no change in CT calcifications [11–13].

In a separate study [7] by the same group of authors, where the correlation between ^{18}F -NaF and arterial wall calcification in the common carotid arteries was evaluated using a semiquantitative SUV_{max} technique [by placing an individual region of interest (ROI) around the lesion on coregistered transaxial PET/CT images], there was a significant correlation between (a) ^{18}F -NaF uptake and arterial wall calcification as well as between (b) the degree of radiotracer uptake (SUV_{max}) and both calcification score and calcified lesion thickness in the atherosclerotic plaque. ^{18}F -NaF uptake in calcifying carotid plaque had significant correlation with cardiovascular risk factors such as age, male sex, hypertension, hypercholesterolemia, and cumulative smoking exposure. The prevalence of carotid ^{18}F -NaF accumulation increased with the number of risk factors.

In a recently published retrospective analysis [8], where the fluoride uptake and calcification in major arteries (including coronary arteries) were analyzed by both visual assessment and SUV measurement, there was evidence of significant correlation between history of cardiovascular events and presence of fluoride uptake in coronary arteries. The coronary fluoride uptake value in patients with cardiovascular events was significantly higher than in patients without cardiovascular events. The authors concluded that ^{18}F -NaF PET/CT might be useful in the evaluation of the atherosclerotic process in major arteries, including coronary arteries, and that an increased fluoride uptake in coronary arteries may be associated with an increased cardiovascular risk.

In an animal study performed at the University of Pennsylvania (unpublished data), the potential of ^{18}F -NaF PET/CT in detecting molecular calcification of heart and major vessels of diabetic pigs was studied. These animals were examined at different stages of the disease with both ^{18}F -FDG and ^{18}F -NaF. Interestingly, the investigators were able to visualize molecular calcification in the heart and lower lumbar aorta of diabetic pigs using ^{18}F -NaF prior to visualization of any visible calcification in the CT images (Fig. 1).

In a novel study by Beheshti et al. [9], the authors introduced a new concept for calculating global calcification as a sensitive biomarker for detection of early molecular and cellular calcification in the atherosclerotic plaques (Fig. 2). The concept was primarily based upon the concept of global disease burden, which had been earlier employed using FDG PET in a different scenario. The feasibility of ^{18}F -NaF PET/CT for the quantification of global molecular calcification of the heart and aorta was examined in this study. Fifty-one patients with a variety of malignancies who

Fig. 1 Upper panel **a** The coronal image on ^{18}F PET, which was generated 1 h after the administration of ^{18}F -NaF, reveals three sites of uptake in the heart which likely represent calcification either in the coronary arteries or in the soft tissues of the myocardium. **b** The CT image shows no or minimal evidence of calcification at these sites. **c** Fused image of PET and CT shows the location of the sites of cardiac calcification. It is our hypothesis that calcification in the myocardium will be detected far in advance of visualization of this pathological state on CT images and this will have prognostic value in forecasting future events. Lower panel **a** The sagittal image on ^{18}F PET, which was generated 1 h after the administration of ^{18}F -NaF, reveals three sites of uptake in the lower lumbar aorta which corresponds to sites of calcification on the CT image (**b**) and their location is further confirmed by the fused image (**c**). In this animal model, this is the most common site for atherosclerosis and calcification as noted in this particular study. There is no evidence of calcification in the descending or upper abdominal aorta either on PET or CT images. Reproduced with permission²³

had undergone ^{18}F -NaF PET/CT for skeletal evaluation were selected for the analysis. Quantitative analysis was performed by drawing an ellipsoid ROI on the cardiac silhouette on each CT slice and corresponding PET slice all over the heart. The molecular calcification score of each particular slice was calculated by multiplying slice volume (calculated by multiplying the area on the ROI by the slice thickness) by the mean SUV of each ROI. The cardiac global molecular calcification score was then obtained by adding the molecular calcification scores among the entire

Fig. 2 *Left panel* This figure demonstrates a typical ROI that was assigned to the cardiac silhouette on each CT slice and the corresponding PET slice. As noted above, the degree of ^{18}F -NaF uptake is quite nonuniform throughout the selected slice and thus is of limited value for accurate assessment of related calcification. Also, please note that the process of uptake is diffused and does not conform to the shape of the ventricle lumen in either ventricle. In this particular slice the volume of the selected ROI was 30.8 cc, and the SUV_{mean} on the corresponding PET slice was 0.5. Therefore, the molecular calcification score for this particular slice was calculated to be 15.4 ($30.8 \times 0.5 = 15.4$). The global calcification score for the entire heart was calculated by adding the individual slice values generated by this approach. *Right upper panel*

Relationship between cardiac global molecular calcification score (GMCS), as measured by ^{18}F -NaF PET/CT and age. The GMCS data points (mean and SD) reflect ^{18}F -NaF uptake in five different age groups as shown above. The *fitted line* shows a statistically significant increase in cardiac molecular calcification with age (Pearson correlation coefficient = 0.92; $p = 0.003$). *Right lower panel* Relationship between aortic SUV_{mean} , as measured by ^{18}F -NaF PET/CT, and age. The aortic SUV_{mean} data points (mean and SD) reflect ^{18}F -NaF uptake in five different age groups as shown above. The *fitted line* shows a statistically significant increase in aortic molecular calcification with age (Pearson correlation coefficient = 0.97; $p = 0.004$). Reproduced with permission⁹

set of calculated ROIs. In this study, the authors observed that ^{18}F -NaF uptake in the heart and aorta increased significantly with advancing age. Hence, they inferred from these preliminary data that ^{18}F -NaF PET/CT may make it feasible to measure the regional and global calcification of the heart and major arteries.

In a recently reported interesting study by Derlin et al. [10], the macrophage activity was determined by ^{18}F -FDG PET and ongoing mineral deposition was measured by ^{18}F -NaF PET in atherosclerotic plaque and these findings were correlated with calcified plaque burden estimated by CT. Both qualitative and semi quantitative analysis was performed, and the ROIs were drawn around the visually assessed lesions on coregistered transaxial PET/CT images manually. The findings of this study suggested the distinctive nature of the pathogenetic processes and hence would indicate complex interactions between them ongoing in an atherosclerotic plaque. Also, the investigators hypothesized that ^{18}F -NaF PET would depict active mineral deposition and provide functional information about the activity of the calcification process,

whereas CT could only demonstrate the presence of mere calcification [10].

As mentioned, one of the major strengths of ^{18}F -NaF PET/CT is its ability to demonstrate and assess what is assumed to be active mineral deposition in the atherosclerotic plaque. CT calcification, on the other hand, is likely to be influenced by both active and passive processes, the latter, associated with necrosis, being presumed to be less important in the study of atherosclerotic plaque, since it is frequently observed in advanced atherosclerotic lesions [14, 15]. Interestingly, though CT calcification is now considered a powerful risk marker, it does not agree very well in asymptomatic subjects with clinical risk score algorithms like the HeartScore [16]. In a screening study involving 1,825 individuals, CT coronary artery calcification (CAC) was found to be common in healthy middle-aged individuals with a low HeartScore, and, on the contrary, high-risk subjects very frequently did not have CAC. It is theoretically possible that ^{18}F -NaF PET/CT may provide highly relevant information about ongoing active molecular calcification in the plaque which might be before

structural calcification is detectable by standard CT techniques. Atheromatosis appears to be a lifelong process of active and passive phases not synchronized, but at different stages at various sites of the arterial system. Thus, it appears reasonable to imagine increased FDG uptake signaling macrophage infiltration as one of the very earliest signs of active local atheromatosis and NaF accumulation as a marker of succeeding incipient molecular calcification, which may or may not result in overt calcification detectable by CT. It is tempting to speculate that here could be a key to the detection, characterization, and quantification of the active atheromatosis process in the individual patient early enough to allow for intervention long before symptoms may appear. The influence of partial volume effect on the visualization of ^{18}F -NaF uptake in the PET/CT may be considered a limitation. However, with the development of sophisticated techniques and software for partial volume correction and adoption of the global molecular calcification score technique, this limitation might be obviated in the future.

The phenomenon of atherosclerosis is a complex and dynamic process that involves various mechanisms ongoing at different time points of its evolution. Functional imaging critically looking into each of these distinctive processes can provide insight into their formation, progression, vulnerability, and resulting atherothrombotic complications. The concept of the vulnerable coronary plaque, i.e., the soft, lipid-filled endothelial swelling with a fibrous cap that may disrupt and cause a cascade of thromboembolic processes leading to occlusion and acute myocardial infarction more often than narrow calcified stenoses, has led to a search for methods that can detect these culprit lesions in the coronary bed [2, 17]. Further, it has served as a basis for the creation of a novel practice guideline for cardiovascular screening in the asymptomatic at-risk population. The main clinical purpose of noninvasive tests for subclinical atherosclerosis in cardiovascular risk assessment is to target intensified preventive care to those at highest risk. Thus, in the opinion of some, men over a certain age with certain cardiac risk factors should be given prophylactic treatment with statins to stabilize potential vulnerable plaques, the net result supposedly being a massive reduction in coronary events [18, 19]. However, these drugs are not without side effects and the consequences of long-term population-based treatment are still not known. Therefore, today's trend toward personalized diagnosis and therapy seems immediately more attractive. For years it has been tried to image coronary lesions by either single photon emission computed tomography (SPECT) or PET. Except for a few promising reports [20, 21], attempts to visualize the vulnerable plaque have on the whole been disappointing due to a series of limiting factors [1, 2, 22]. However, with the idea of measuring global molecular cardiovascular calcification conceptually years, perhaps decades, before it becomes macroscopically

visible, things may change dramatically. Thus, active molecular calcification may be assessed by ^{18}F -NaF PET/CT much earlier than the detectable calcification identified by CT and, hence, provide clinically relevant information in the individual patient at an early stage when medical intervention is likely to have correspondingly greater effect. ^{18}F -NaF PET/CT could provide a bridging gap between the FDG depicted inflammatory component and the CT depicted organized calcification. Further research in this area will hopefully generate more interesting data that will clarify the complex interactions between the various underlying mechanisms involved in this process in a time bound fashion.

Conflicts of interest None.

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