EDITORIAL

^{18}F-sodium fluoride: An old tracer with a new promising clinical application

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Atherosclerosis is among the leading causes of morbidity and mortality in developed countries.[1] It is directly responsible for the majority of ischemic cardiovascular and cerebrovascular events, involved 7.0 and 2.8 million people every year, respectively.[2] Vascular calcification is a complex biological process that is a hallmark of atherosclerosis.[3] However, the complex atheroma pathogenesis process causes a late clinical diagnosis of atherosclerotic cardiovascular disease. Specifically, coronary atherosclerotic plaque rupture is the principal precipitant of acute myocardial infarction and an important cause of sudden cardiac death. Rupture is challenging to predict because most plaques are non-obstructive and are not identified by stress testing or coronary angiography.[4,5] Furthermore, the rapid progression of existing vascular calcium is driven by ongoing microcalcification, carries a poor prognosis, and is not responsive to current medical therapies.[6] Therefore, the early and effective detection, particularly of plaques vulnerable to rupture, of atherosclerotic disease is vital to the effective prevention and management of life-threatening cardiovascular events such as myocardial infarctions and cerebrovascular accidents.[7] Assessment of Framingham risk factors such as dyslipidemia, hypertension, and diabetes can identify patients at risk of developing atherosclerotic disease but cannot clarify the extent or vulnerability of existing plaques. Clinical evaluations performed in symptomatic patients, such as the ankle-brachial index and cardiac stress tests, are useful to investigate the presence of intraluminal stenosis, but the degree of stenosis alone has not been shown to be predictive of plaque rupture.[8,9]

The most reliable method of risk stratification therefore remains radiologic examination, which can visualize not only luminal stenosis but also plaque morphology. Conventional ultrasonography and angiography techniques can be used to examine the extent of luminal stenosis, while cardiac computed tomography (CT) can be used to obtain calcium scores to quantify the calcification of the coronary vessels.[7] Yet, other modalities, including multidetector CT coronary angiography, magnetic resonance imaging, intravascular ultrasonography, and optical coherence tomography, have begun to be implemented with the specific aim of determining plaque composition.[10,11] The plaque composition most strongly associated with rupture includes a thin fibrous cap, a lipid-rich necrotic core, neovascularization, intraplaque hemorrhage, and microcalcifications.[10] Microcalcification is one of the key markers of plaque's instability and degenerative changes in aortic valve stenosis. However, due to the small diameter of the formed calcic vesicles, they cannot be detected on routine CT, which only identifies macrocalcification ($\sim$ 200-500 µm in diameter). Molecular imaging modalities are capable of detecting microscopic processes such as inflammation and microcalcification. These chemical composition changes occur early in the disease process and precede the aforementioned morphologic developments. Foremost among these molecular techniques is positron emission tomography (PET) using the radiotracer ^{18}F-fluorodeoxyglucose (FDG), a radiolabeled glucose analogue that serves as a marker of metabolic activity and, by extension, inflammation. By contrast, ^{18}F-sodium fluoride (NaF) is a specific marker of bone mineralization that has traditionally been used in diagnosing metastatic bone cancer but has recently been applied to vascular calcification.[7]

^{18}F-NaF has also shown considerable promise in allowing the evaluation of patients at risk of atherosclerosis. It differs from ^{18}F-FDG in its molecular binding characteristics and, thus, the manner in which it illustrates disease burden. Whereas ^{18}F-FDG is taken up by metabolically active cells and is considered a surrogate for inflammation, ^{18}F-NaF is incorporated into areas of calcium deposition by exchanging the hydroxyl ions of hydroxyapatite crystals with radiolabeled fluoride to form fluorapatite.[4] The pattern of this tracer uptake depends on differences in regional blood flow, the density of hydroxyapatite as well as exposed crystal surface area. ^{18}F-NaF binds avidly to microcalcification, while areas of macrocalcification show only peripheral uptake thanks to its large volume (low surface-area-to-volume ratio).[6,12,13] Consequently, ^{18}F-NaF PET scans are not affected by the major limitation of myocardial uptake and can be used to assess the coronary arteries in addition to the peripheral vasculature, while ^{18}F-FDG uptake is too intense in the myocardium to enable detection of coronary pathology.[14]

Previous studies evaluated the role of ^{18}F-NaF in the evaluation of coronary artery disease. Dweck et al[14] conducted the first feasibility study on the coronary arteries and found a higher uptake in patients with coronary atherosclerosis. ^{18}F-NaF seems to distinguish between patients with dormant calcific disease, established many months or years previously, and subjects with metabolically active disease where the calcification process is ongoing. Importantly this distinction seems to be of clinical relevance, with higher rates of anginal symptoms, prior major adverse cardiovascular events, and cardiovascular risk factor scores observed in those with active disease.[14] The spatial resolution of PET/CT is sufficient to localize ^{18}F-NaF activity to specific coronary territories, suggesting that ^{18}F-NaF might be able to identify the presence and location of recent plaque rupture.[14] Later, several studies have shown that vascular uptake of ^{18}F-NaF is not only correlated with advancing age, but also with risk factors for atherosclerotic and cardiovascular disease,[15–17] suggesting the evidence that this modality could be diagnostic for atherosclerosis and spurred a series of confirmatory studies. A prospective trial performed by Joshi et al[13] in 40 patients undergoing ^{18}F-NaF PET/CT after myocardial infarction showed that intense tracer uptake localizes to recent plaque rupture in patients with acute myocardial infarction and in those with symptomatic carotid artery disease. Moreover, plaques with high ^{18}F-NaF activity were significantly more likely to demonstrate high-risk morphologic features with positive remodeling, microcalcification, and necrosis of the lipid core, on ultrasonography.[13] Vascular ^{18}F-NaF uptake also correlated with the presence of microvessels seen on optical coherence tomography, suggesting that ^{18}F-NaF avid lesions had increased inflammation.[18] Therefore, ^{18}F-NaF PET imaging might provide the positive predictive value required to consider treatment in patients at high risk for cardiovascular events in the absence of clinical symptoms.

In the current issue of the Journal, Silva Mendes et al[19] conducted a systematic review aimed to summarize and consolidate ^{18}F-NaF PET imaging potentialities to study cardiovascular disease and serve as a diagnostic and prognostic tool in high-risk populations, becoming an assessment method for the early detection of cardiovascular complications. The authors reviewed and resumed 31 articles on the potential use of ^{18}F-NaF in cardiovascular fields. They included studies that used ^{18}F-NaF PET as imaging technique in cardiovascular conditions, performed only on humans. Their results showed that in atherosclerosis, most studies report a positive correlation with the burden of cardiovascular risk factors and vascular calcification. A higher uptake was found in culprit plaques/rupture sites in coronary and carotid arteries and it was also linked to high-risk features in histology and intravascular imaging analysis of the plaques. In aortic stenosis, this tracer displayed an increasing uptake with disease severity. The results of this systematic review highlight the role of ^{18}F-NaF as a promising tool to identify high-risk plaques, which sets ground to a potential use of this tracer in evaluating atherosclerotic disease progression and degenerative changes in aortic valve stenosis.[19]

Some studies tested whether ^{18}F-NaF findings are incremental to conventional imaging techniques such as coronary artery calcium score measurement by cardiac CT, considering that microcalcification is not apparent in the latter. In a prospective analysis of 89 healthy subjects with low cardiovascular risk, Blomberg et al[16] showed that the estimated future risk for cardiovascular disease development increases linearly with coronary ^{18}F-NaF accumulation. ^{18}F-NaF uptake was also a good predictor of aortic valve disease progression by CT calcium score after 1 year, with concordant distribution of new calcic deposits in regions with previous radiotracer accumulation. This technique holds major promise as a means of identifying high-risk and ruptured plaque, and potentially informing the future management and treatment of patients with stable and unstable coronary artery disease. However, the lack of prospective studies, which are essential to the validation of the prognostic value of ^{18}F-NaF, and the lack of a standardized protocol regarding the dose injected and uptake period can sustain significant bias in the results reported by Silva Mendes et al;[19] therefore, the clinical application of ^{18}F-NaF PET in atherosclerosis requires further validation. Additional prospective studies are needed to determine the

prognostic value of this tracer, which based on the ability to identify plaques at risk of rupture. It is also necessary evaluate the possibility of ^{18}F-NaF uptake by other cells that might substantially alter understanding of clinical implications of predictive roles of calcific deposits in the plaques.[20] Calcification is ubiquitous in atherosclerosis and hence its contribution to the plaque behavior and prognostic outcomes needs careful characterization. PET/CT imaging using ^{18}F-NaF can detect active calcium deposition at multiple levels on a single scan, suggesting that whole-body scans can potentially identify high-risk lesions in multiple vascular beds.

It could be useful conducting a meta-analysis on the role of ^{18}F-NaF PET imaging in cardiovascular disease to combine the results from multiple studies in an effort to increase power over individual studies. Outcomes from a meta-analysis may include a more precise estimate of ^{18}F-NaF uptake in patients with cardiovascular disease, than any individual study contributing to the pooled analysis. In addition to evaluation of plaque composition and disease activity, PET/CT also allows for functional assessment of atherosclerotic lesions. The peculiar advantage of hybrid PET combined with CT is the possibility to perform absolute quantification of coronary vascular function and coronary artery calcium, beyond myocardial perfusion evaluation as a part of the same examination.[21] Vulnerable plaque characteristics are associated with hemodynamically significant coronary artery lesions and a combined evaluation of morphological and functional characteristics of vulnerable plaque might provide better identification of culprit lesions with an incremental prognostic definition.

Disclosure

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