Narrowing in on a PET tracer that characterizes coronary atheroma: ^{18}F -NaF uptake is increased in stenotic coronary artery disease

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Received Jul 6, 2020; accepted Jul 6, 2020
doi:10.1007/s12350-020-02279-x

See related article, pp. 3058–3066

A positron emission tomography (PET) imaging tracer that provides a meaningful and clinically deployable risk assessment in coronary artery disease (CAD) has been sought enthusiastically for over a decade. Molecular imaging with PET is uniquely suited for imaging atherosclerosis because it is performed in conjunction with computed tomography (CT) or magnetic resonance imaging as part of a single scan, allowing a simultaneous assessment of disease pathobiology and activity at a molecular level as well as an anatomic evaluation of atherosclerotic plaques. While PET imaging has established itself as a mainstay for the functional assessment of CAD physiology, PET has not yet met its great potential to deliver a measurement of biological activity in coronary atheroma that concurrently provides meaningful clinical risk stratification.

Several PET tracers have been investigated in CAD. Arterial ^{18}F -fluorodeoxyglucose (^{18}F -FDG) uptake provides an index of arterial inflammation that predicts subsequent adverse cardiovascular (CV) events and allows evaluation of an individual's response to CV

therapeutic interventions.¹ Although arterial ^{18}F -FDG uptake is increased in individuals with acute coronary syndromes compared to those with stable angina, its widespread application for the assessment of coronary plaques is limited due to challenges with suppressing the uptake of ^{18}F -FDG by background myocardium as well as its limited spatial resolution for the assessment of smaller vessels.² ^{18}F -sodium fluoride (^{18}F -NaF) offers advantages compared to ^{18}F -FDG with regards to these limitations, and growing evidence supports the utility of ^{18}F -NaF PET imaging for the assessment of several CV diseases.^{3–7} ^{18}F -NaF is incorporated into hydroxyapatite and has long been used to identify areas of bone formation and primary and metastatic osseous malignancies with PET imaging. More recently, it has been increasingly employed to identify biologically active microcalcifications (< 50 μm) in CV tissues (e.g., aortic valve, arterial beds) that are beneath the threshold of detection for macrocalcifications by computed tomography (CT). Accordingly, ^{18}F -NaF PET allows earlier detection of atherosclerotic activity than that permitted by standard CT imaging.^{8,9} Furthermore, it has been shown to predict subsequent macrocalcification as well as progression of coronary artery calcification (CAC) scores.¹⁰ Moreover, ^{18}F -NaF uptake is increased in culprit coronary and carotid plaques in the setting of adverse CV events, predicts restenosis following endovascular intervention for peripheral arterial disease, and predicts progression of aortic stenosis.^{3–6} In a recent study, coronary ^{18}F -NaF uptake was shown to independently predict future myocardial infarctions in individuals with stable CAD beyond standard risk assessment modalities including CAD risk scores, CAC, as well as angiographic burden and severity of CAD. Notably, among those without any coronary ^{18}F -NaF uptake, there were no myocardial infarctions during a

Funding Dr. Osborne is supported in part by United States National Institutes of Health #KL2TR002542.

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J Nucl Cardiol 2021;28:3067–9.

1071-3581/\$34.00

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median 42 months of follow-up.⁷ Collectively, these findings support ¹⁸F-NaF PET's utility to detect an early marker of biologically active coronary atheromatous disease that portends disease progression and heightened CV risk. Nevertheless, its relationship with the degree of coronary stenosis in patients with stable CAD has thus far remained incompletely defined.

That relationship was evaluated by Hayrapetien, et al. in the current edition of *Journal of Nuclear Cardiology* among a cohort of 114 male US Veterans with a history of prostate cancer and known or suspected CAD for which they underwent clinical ¹⁸F-NaF PET imaging as well as ⁸²Rb PET myocardial perfusion imaging (MPI) within a mean interval of 5 months.¹¹ After excluding patients with a history of coronary artery bypass grafting, individuals with inducible ischemia on ⁸²Rb PET MPI had significantly greater coronary artery uptake of ¹⁸F-NaF than those without ischemia. Further, those with visually increased ¹⁸F-NaF coronary uptake, defined in the study as a tissue-to-background ratio (TBR) ≥ 1.5 , had a greater frequency of myocardial ischemia. Among 41 patients who underwent clinically indicated coronary angiography within 3 months of ⁸²Rb PET MPI, those with any angiographic CAD had heightened ¹⁸F-NaF uptake in comparison to those without angiographic CAD. Further, vessels with visually increased ¹⁸F-NaF uptake had a significantly higher frequency of obstructive ($\geq 70\%$) disease than those with less uptake. Importantly, among individuals with an elevated baseline CAC score (Agatston score > 100 in each coronary artery), those with greater ¹⁸F-NaF uptake were significantly more likely to have either non-obstructive or obstructive coronary stenosis than no stenosis on coronary angiography. Accordingly, the authors conclude that greater ¹⁸F-NaF uptake is associated with myocardial ischemia, and it identifies vessels with a greater degree of stenosis among individuals with known or suspected CAD. The latter finding may have important applications among individuals with stable CAD and a highly calcified coronary plaque burden.

The current study has several important limitations. Like many prior ¹⁸F-NaF PET studies, the patient population comprised older men with a history of prostate cancer and known or suspected CAD. Furthermore, given the retrospective nature of the study, there is an inherent selection bias for those who underwent ⁸²Rb PET MPI with further bias superimposed for those who also underwent clinically indicated coronary angiography. The study showed a trend of increased ¹⁸F-NaF uptake in coronary arteries with obstructive ($\geq 70\%$) disease compared to non-obstructive ($< 70\%$) disease; however, it was underpowered to demonstrate that the difference was statistically significant. Finally, the

impact of ¹⁸F-NaF uptake on downstream CV risk was not assessed in this population with stable CAD.

As the clinical implications of findings from ¹⁸F-NaF PET imaging in CAD are increasingly clarified, several key knowledge gaps remain (Table 1). First and foremost, the relationships between ¹⁸F-NaF uptake, CAC, coronary stenosis, myocardial ischemia, and CV events needs to be prospectively and longitudinally assessed in a broad and balanced population of patients with CAD. Whether findings from ¹⁸F-NaF PET provide additive risk stratification beyond the information provided by CT-based or invasive coronary angiography as well as whether these findings should be factored into decisions about revascularization or modifying systemic medical therapy remains unknown. Additional research should refine which patient population would benefit most from a coronary ¹⁸F-NaF PET exam, such as individuals with positive stress imaging and contraindications to intravenous contrast or invasive angiography or those with stable calcified CAD with concern about residual risk on their current therapy. In the same vein, the implications of incidentally identified coronary artery ¹⁸F-NaF uptake on non-cardiac imaging in asymptomatic patients should be studied. Additional research is also needed to identify the most useful measure of ¹⁸F-NaF activity and the cut-off values that optimize test sensitivity and specificity. To date, TBRs and coronary microcalcification activities have both been employed, but the optimal measurement technique is not known. The impact of therapies on ¹⁸F-NaF coronary artery uptake and whether a change in uptake following treatment is clinically meaningful should also be studied. For example, statins reduce adverse events but also increase CAC in patients with CAD; however, their impact on ¹⁸F-NaF coronary artery uptake over time and the clinical implications of that potential impact remain uncertain.^{12,13} Finally, other PET tracers, such as those specific for macrophage-based somatostatin type 2 receptors, also merit further study in CAD.¹⁴ Although growing evidence supports further prospective validation studies of ¹⁸F-NaF in CAD, it is important to recognize that the ideal prospective study would incur significant cost and would require substantial rigor to obtain multiple imaging studies at multiple time points across a large population of CAD patients.

¹⁸F-NaF PET has emerged as a promising modality for the assessment of coronary atheroma that provides novel insights into plaque biology that relate to both CAD severity and CV risk. Nevertheless, several key questions remain that must be answered before ¹⁸F-NaF PET is ready for widespread clinical implementation. We may finally be narrowing in on a highly sought-after

Table 1. Several key remaining questions about the implementation of ^{18}F -NaF PET for coronary artery disease

Does ^{18}F -NaF PET imaging provide risk assessment in a broad population of patients with CAD?
How does ^{18}F -NaF PET imaging of coronary arteries change longitudinally? What is the longitudinal relationship with coronary stenosis, myocardial ischemia, and other plaque features?
Does ^{18}F -NaF PET imaging provide additional risk stratification beyond that which is provided by coronary CT or invasive angiography?
Can ^{18}F -NaF PET imaging be used to evaluate the impact of drug therapy on CAD? Are potential changes that are induced clinically meaningful?
Does intensified therapy or revascularization of patients with coronary plaques with high ^{18}F -NaF PET uptake modify outcomes? Conversely, can therapy be de-escalated in those with lower uptake?
Can incidentally identified CV ^{18}F -NaF PET uptake identify asymptomatic individuals who would benefit from further CV evaluation?
Which population of CAD patients would benefit most from risk stratification provided by ^{18}F -NaF PET imaging?
What is the ideal measurement parameter and cut-off for coronary artery ^{18}F -NaF PET uptake to optimize sensitivity and specificity as well as identify individuals who merit additional testing, intensified therapy, or revascularization?
Would broad implementation of ^{18}F -NaF PET be cost-effective in stable CAD?

CAD, coronary artery disease; CT, computed tomography; CV, cardiovascular; ^{18}F -NaF, ^{18}F -sodium fluoride; PET, positron emission tomography

PET tracer for CAD, but there is still plenty of work left to do.

Disclosures

Dr. Osborne has received consulting fees from Intrinsic Imaging, LLC for unrelated work. The authors Taimur A. Abbasi and Mazen S. Albaghdadi have no disclosures.

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