A vessel of progress: Aortic microcalcification activity for the quantification of ^{18}F -NaF uptake in the thoracic aorta

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^{18}F -sodium fluoride (^{18}F -NaF) is a positron emission tomography (PET) tracer which has increasingly been shown to be effective for the assessment of cardiovascular diseases. ^{18}F -NaF binds to hydroxyapatite and has long been used to identify active ossification as well as malignancies involving bone. More recently, assessment of ^{18}F -NaF uptake has been harnessed to identify microcalcifications (calcifications less than 50 μm in size) within cardiovascular tissues.¹ Such microcalcifications, which are too small to be detected by computed tomography (CT), represent an earlier stage of biologically active calcium deposition than that represented by macrocalcifications visible on CT (e.g., coronary artery calcium (CAC)).^{1,2} Notably, ^{18}F -NaF uptake provides incremental prognostic information beyond that provided by macrocalcifications alone.^{2–5} For example, higher ^{18}F -NaF uptake predicts progression of calcific aortic stenosis, development of restenosis following peripheral arterial interventions, and future myocardial infarctions (MIs), independent of CAC.^{6–8} Along the same lines, thoracic aortic ^{18}F -NaF uptake has been shown to associate with established clinical cardiovascular risk scores.^{9–12} However, current

approaches to measure ^{18}F -NaF uptake are cumbersome and time-intensive, limiting wider use of the technique. Accordingly, further work is needed to define the optimal, and perhaps simpler, approaches to quantify thoracic aortic ^{18}F -NaF uptake.

Currently-employed assessments of aortic radio-tracer activity involve the laborious assessment of maximum and mean standardized uptake values across sequential axial images of the entire ascending thoracic aorta and aortic arch followed by measurement of background blood-pool activity to yield a tissue-to-background ratio (TBR).¹⁰ An analogous approach has previously been used to measure coronary ^{18}F -NaF uptake. However, investigators recently devised a novel approach to assess coronary ^{18}F -NaF uptake, as coronary microcalcification activity (CMA), that accounts for the extent and intensity of radiotracer uptake throughout the coronary tree. CMA has since been shown to be repeatable and reproducible, to associate with high risk plaque features on coronary CT angiography, and to predict incident MIs over 42 weeks in individuals with stable coronary artery disease (CAD).^{6,13,14} Accordingly, a similar measurement strategy, when applied to ^{18}F -NaF PET imaging of the thoracic aorta, may provide additional diagnostic and prognostic information with potentially important implications.

In the current edition of the *Journal of Nuclear Cardiology*, Fletcher et al. report on an effort to develop and evaluate the effectiveness of such a measurement strategy.¹⁵ To do so, the authors retrospectively leveraged two serial ^{18}F -NaF PET scans (performed within three weeks) in 20 subjects with established multi-vessel CAD from the Dual anti-platelet therapy to Inhibit Atherosclerosis and Myocardial Injury in patients with

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Necrotic high-risk coronary plaque Disease (DIAMOND) clinical trial. The authors employed an approach that is analogous to CMA to simplify and expedite the quantification of aortic ^{18}F -NaF uptake called aortic microcalcification activity (AMA), which represents the ratio of aortic activity to background radiotracer activity. To derive AMA, first, the cumulative voxel intensities of ^{18}F -NaF uptake are measured in two separate volumes of interest spanning the ascending aorta and aortic arch, and then that value is divided by the aortic volume. Next, this measurement is divided by the background activity of the atrial blood pool (corrected for volume) to yield a unitless AMA value. In this manuscript, the authors provide clear verbal and graphical depictions of how AMA is measured. Further, they provide assessments of the reproducibility and repeatability of standard thoracic aortic ^{18}F -NaF uptake measurements as well as AMA and assess each measurement's correlation with standard clinical risk scores.

The authors report that the AMA method was nearly five times faster to perform than standard TBR analyses, yet had similar repeatability and reproducibility compared to the traditional TBR measures. They also demonstrate that, unlike with the coronaries, correction for motion and time delay is not required for assessment of the thoracic aorta. Furthermore, the authors observe that AMA has a stronger association with several clinical risk scores, including the Framingham Risk Score (FRS) for stroke, than other typically employed measurements. Accordingly, the current study shows that AMA is an efficient, reproducible, and repeatable measure that associates with clinical risk scores at the time of imaging and potentially provides a useful imaging biomarker of cardiovascular risk resulting from aortic atherosclerosis.

Nevertheless, the study is not without limitations. Most importantly, the study did not evaluate the relationship between these aortic ^{18}F -NaF measurements and downstream cardiovascular events. While AMA appears to be a promising tool for the evaluation of downstream cardiovascular risk, its true utility cannot be determined without this information. In fact, the authors acknowledge that AMA's effectiveness in predicting downstream events is uncertain, as it is not known if the overall burden of atherosclerotic activity (better measured by AMA) or the most intense focus of atherosclerosis (better measured with standard measurements of ^{18}F -NaF uptake) is more important in the pathogenesis of cardiovascular events related to thoracic aortic disease (e.g., aneurysms, atheroembolic strokes). Additionally, the study population is small; as such, it appears to be underpowered to identify significant relationships between several standard clinical risk

scores and AMA. There also appears to be a somewhat narrow range of AMA values in the population studied, raising the question of whether it will truly be able to distinguish between subtle differences in ^{18}F -NaF uptake that may have clinical implications. Moreover, due to spillover from the adjacent thoracic spine, AMA does not allow for the assessment of the descending aorta, a segment of the thoracic aorta which is strongly associated with cardiovascular risk.⁹ Lastly, the measurement methodology is well-considered and carefully designed to minimize the impact of partial volume effects; however, AMA quantification may remain somewhat influenced by this phenomenon. Even still, the current manuscript provides an important proof-of-concept for a highly reproducible, repeatable, and efficient measurement of aortic ^{18}F -NaF uptake that associates with validated clinical risk scores and offers the potential to predict downstream cardiovascular events.

The study findings also raise several important new questions for subsequent research. First and foremost, a large retrospective study of patients with prior aortic ^{18}F -NaF PET imaging should be performed to determine the relationship between the various imaging endpoints with downstream clinical events and to assess its additive value above conventional risk scores and easily derived measures of arterial macrocalcification. The impact of various therapies targeting atherosclerosis on these measures could also be evaluated to ascertain their effect on imaging findings and clinical outcomes. Additionally, similar methods of ^{18}F -NaF quantification could be applied to other arterial beds (e.g., the carotid arteries) to determine the relationship with clinical risk and events. Finally, it could be informative to evaluate whether a similar measurement to AMA could be applied to other important PET tracers for imaging atherosclerosis of the thoracic aorta, such as ^{18}F -fluorodeoxyglucose and ^{68}Ga -DOTATATE.¹⁶ Importantly, these tracers would also be more effective for the assessment of the descending aorta by minimizing the impact of spillover from the neighboring vertebrae.⁹

AMA is a novel imaging parameter of arterial ^{18}F -NaF uptake, which reports on active aortic microcalcification activity. The parameter can be derived in a fraction of the time needed for standard measurements of aortic ^{18}F -NaF uptake, has good reproducibility, and associates with important clinical risk scores. While the predictive value of AMA remains to be defined, the current study takes an important step in developing this imaging parameter for use in future clinical investigations.

Disclosures

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