Aortic ^{18}F-sodium fluoride imaging

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^{18}F-Sodium Fluoride Positron Emission Tomography (^{18}F-NaF PET) depicts active calcification processes in the human body.[1] This imaging modality highlights areas of intense bone turnover in the skeleton and provides an assessment of calcification activity across multiple different cardiovascular disease states, including atherosclerosis, aortic stenosis, mitral annular calcification, abdominal aortic aneurysm, erectile dysfunction, and bioprosthetic valve degeneration.[1-5] While initial studies consistently demonstrated that ^{18}F-NaF activity is more pronounced in patients with an unfavorable risk profile recently, this imaging modality was shown to provide clinically relevant insights into all of the aforementioned cardiovascular diseases. In each of these conditions, ^{18}F-NaF uptake is associated with vascular injury, disease activity, future progression, and clinical outcomes.[1-5] In atherosclerosis, ^{18}F-NaF uptake acts as a strong independent predictor of myocardial infarction in patients with established coronary disease; in patients with peripheral vascular disease it predicts stent restenosis.[6,7] In the context of aorta imaging, ^{18}F-NaF uptake was shown to identify advanced aneurysmal disease and to predict aneurysm growth and clinical events (aneurysm repair or rupture) independent of established clinical risk factors, including aneurysm diameter.[4] It appears that this technique holds major promise for the future management of patients with abdominal aorta aneurysms.[4]

In a retrospective study of patients who underwent serial ^{18}F-NaF PET for oncological purposes, Fiz et al explored the associations between baseline ^{18}F-NaF uptake and evolution of atherosclerotic plaques within the abdominal aorta.[8] In line with prior research focused on coronary atherosclerosis,[9,10] the authors showed that baseline uptake predicts the progression of calcified lesions. Additionally, in their study, focal uptake was often observed in areas without calcification at baseline, which showed an increase in density on follow-up imaging supporting the notion that ^{18}F-NaF activity identifies microcalcifications that are beyond the resolution of computed tomography imaging. In coronary artery disease, multiple studies have demonstrated that ^{18}F-NaF focal uptake is often observed in non-calcified lesions with adverse morphology.[11,12] These so-called high-risk or vulnerable plaques with a large necrotic lipid core are prone to rupture, causing myocardial infarction, ischemic stroke, and thromboembolic events. Importantly, similar to previous studies, Fiz et al. observed that established calcified plaques had low or no ^{18}F-NaF uptake—confirming that this tracer is not merely a marker of calcification at all stages of maturation—but highlights biologically active areas. Burnt out or bystander calcifications do not attract ^{18}F-NaF tracer. In fact (as elegantly shown in the study by Fiz et al.), the intensity of plaque uptake is proportional to the rate of plaque density increase measured in Hounsfield units on non-contrast CT imaging.

The authors rightfully acknowledge that calcification of atherosclerotic plaques is a slow process. Therefore, their study (which clearly shows how ^{18}F-NaF uptake serves as a predictor of calcification and provides a real-time assessment of atherosclerosis activity) can be leveraged in clinical trials. ^{18}F-NaF PET imaging offers an exciting opportunity to evaluate new strategies for slowing down the progression of atherosclerosis. Such studies are already underway in the context of valvular heart and coronary artery disease (NCT02132026—Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (SALTIRE II);

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NCT03689946—Effect of Evolocumab on Coronary Artery Plaque Volume and Composition by CCTA and Microcalcification by 18F-NaF PET).

Given the exciting clinical potential of ^{18}F-NaF aortic imaging by PET, it will be of great importance to standardize image acquisition and quantification methods.[13] Such efforts have already been made in the context of coronary PET—as it was shown that motion (which occurs due to heart contractility, breathing, and patient repositioning) has a detrimental effect on image quality and uptake measurements.[14,15] Likewise, reconstruction settings and the delay from tracer injection to emission scanning also have a profound impact on the measured ^{18}F-NaF activity.[16,17] Nevertheless, it was demonstrated that by performing acquisitions on scanners offering time-of-flight information, applying motion-correction, optimal reconstruction settings, and delaying emission scanning, it is feasible to improve the reproducibility of measurements, enhance the signal to noise ratios, and obtain clinically relevant information enabling enhanced risk stratification.[6,18]

For aortic ^{18}F-NaF PET, studies to date have employed a wide range of acquisition protocols. Fiz et al. performed whole-body imaging with a 2 minutes long acquisition per bed position. In the abdominal aortic aneurysms study by Forsythe et al. patients underwent emission scanning lasting 10 minutes per bed position.[4] While in the coronaries, studies have universally employed 30-minutes single bed position acquisitions, the length of emission scanning for heart imaging is driven by the need for offsetting the detrimental effects of motion and due to the low counts. Such motion effects are less prominent within the aorta, and therefore shorter acquisitions may be warranted, nevertheless, the optimal length of emission scanning remains to be determined.

Most importantly, the optimal uptake measurements for ^{18}F-NaF aortic PET imaging need to be established. Recent studies indicated that for coronary imaging, a measure of tracer activity which encompasses both the intensity and the volume of ^{18}F-NaF activity across the entire coronary vasculature is highly reproducible, more closely associated with established markers of plaque vulnerability and clinical outcomes than the traditional measures of local target-to-background ratio (TBR).[6,18,19] As in coronary atherosclerosis, providing a more global assessment of ^{18}F-NaF activity across the aorta can be advantageous. The maximum TBR values are based upon a single pixel value and provide information only regarding the peak intensity of a lesion. On the other hand, global measures of uptake have the potential to better characterize disease burden.

In the study by Fiz et al., the mean TBR was used within a manually drawn cylindric volume-of-interest, encompassing the whole lumen of the infrarenal aorta. An alternative approach for characterizing activity within the ascending aorta was recently proposed by Fletcher et al.[20] The aortic microcalcification activity (AMA), incorporates both voxel intensity and volume. Compared to tedious averaging of SUV or TBR values, AMA was highly reproducible and more time-efficient than the previous approaches. Additionally, in comparison to SUV/TBR measurements, AMA had the strongest correlation with the Framingham stroke risk score and the revised Framingham stroke risk score.

Whether one of these approaches should be recommended for a wider application remains to be clarified. Ultimately, only studies with hard endpoints shall facilitate definite validation of uptake measures.

Finally, a key peculiarity in aortic ^{18}F-NaF imaging is the proximity of the vertebral column. Bones attract ^{18}F-NaF leading to a significant overspill in the artery of interest. Fiz et al. had to exclude 48 plaques (13%) due to such overspill. Similar measures had to be employed in previous studies, and this fact constitutes a major limitation for aortic uptake quantification.[4] The necessity for excluding plaques (and/or spine-adjacent areas from volumes-of-interest) limits the reproducibility of uptake measures and the clinical utility of the method. In the future, researchers should aim to overcome this key limitation and to develop optimized approaches for characterizing ^{18}F-NaF uptake within the aorta.

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