Optimizing arterial ^{18}F-sodium fluoride positron emission tomography analysis

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Cardiovascular disease (CVD) remains a leading cause of death worldwide and methods to improve risk stratification and prevention are required. Non-invasive imaging plays an important role in CVD risk stratification, for example the use of CT-coronary calcium scoring to reclassify patients deemed at intermediate risk based on clinical risk scores. However, the quantification of plaque burden often does not distinguish patients with quiescent disease from those who will go on to develop worsening disease manifesting in a cardiovascular disease event. An attractive feature of molecular imaging modalities is the potential to detect and localize active pathophysiological processes that drive progressive vascular disease and subsequent clinical events.

Abdominal Aortic Aneurysms (AAAs) represent a good example of concealed cardiovascular disease that may manifest for the first time clinically with rupture, usually a catastrophic event, which is avoidable with early detection and appropriately timed preventative repair. Current guidelines suggest consideration of operative intervention when the diameter of the aneurysm is larger than 5.4 cm.[1] Frequent screening of patients with a AAA diameter between 3.0 and 5.4 cm[1] is recommended, and screening is often performed using ultrasound. In patients with a AAA $>$ 5.5 cm in diameter, the risk of rupture is more than 5% per year.[2] However, aneurysms do not progress in a predicable manner and as many as 37% of AAAs between 3.0 and 4.4 cm in diameter (which represent the low risk cohort that still require screening) may progress to $>$ 5.4 cm or require surgery in 5 years.[3] In practice this means that the majority of people with AAA receive screening, sometimes for many years, without ever requiring intervention, while a small proportion may have events despite screening at recommended intervals. There is a need for alternative imaging techniques that can improve risk stratification and surveillance and ideally reduce both the logistical burden of repeated tests and associated costs. In this regard, positron emission tomography (PET) has shown promise[4] and the paper by Akerele et al[5] in this edition of the journal addresses an important limitation that will facilitate future research and translation into clinical practice.

^{18}F-Sodium Fluoride (^{18}F-NaF) is widely used for detection of bony metastases but the radiotracer also binds to early and active arterial calcifications,[6] which has generated great interest because of the potential applications in different vascular territories. In the coronary arteries, plaques with ^{18}F-NaF uptake detected by positron emission tomography (PET) are associated with other high-risk plaque features.[7,8] In the carotid arteries, ^{18}F-NaF uptake co-locates with ipsilateral neurological symptoms.[9] In the aortic valve, ^{18}F-NaF uptake may assist in the prediction of progression of aortic calcification.[10] Importantly, in the aorta, the recent SoFIA[3] study has been the first to provide insight on the potential for ^{18}F-NaF PET to predict the rate of progression of AAA.[4]

However, the clinical repurposing of ^{18}F-NaF PET for applications in cardiovascular disease has yet to overcome a number of well-described limitations.[11,12] The analysis of small regions of radiotracer activity, such as in the coronary arteries or small aortic atherosclerotic lesions, is limited by partial volume effects, an inherent drawback of all PET imaging. The

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motion of the coronary arteries, cardiac silhouette, respiratory system and the patient further hinders the confidence in the localization of regional radiotracer uptake. Unique analytical approaches and implementation of specifically designed software are being developed to address these issues (Figure 1). For analysis of AAA, the overspill of ^{18}F-NaF radiotracer activity from the spine is in close anatomical proximity to the aorta, impairing the distinction between vascular and non-vascular radiotracer activity. In order to adjust for this overspill during analysis, regions of suspected non-vascular radiotracer activity are excluded manually, which is time-consuming, requires training and potentially introduces bias and variability into the quantification of the scan, and ultimately limits the ability to automate this aspect of image analysis.

The recent study by Akerele, published in the Journal of Nuclear Cardiology, aimed to address this limitation by utilizing a background correction (BC) technique in the examination of aortic ^{18}F-NaF PET.[5] The BC technique was originally developed for oncological applications[13] and uses a mask of the vertebral bodies, identified on the attenuation correction CT scan, to effectively extract radiotracer activity originating from that region. This leaves only non-vertebral and importantly, aortic specific, radiotracer activity for quantification. The group tested the reconstruction method on the PET data from the cohort from the SoFIA[3] study, which remains the largest dataset of AAA-dedicated ^{18}F-NaF PET scans.[4]

Akerele et al report that background corrected (BC) scans had a significantly lower radiotracer activity than non-background corrected scans ($P = 0.013$) in AAA regions, which suggests that a significant proportion of radiotracer activity within the AAA is from vertebral overspill. When comparing the activity readings from AAA analysis without BC that manually excluded vertebral activity (AAAexc) with an analysis that incorporated the entire diameter of the aorta (AAA), the authors reported that the AAAexc regions had a significantly lower radiotracer reading, regardless of the method of correcting for blood pool activity. However, incorporating BC rendered differences between AAA and AAAexc not significant and this suggests that the BC technique is comparable to AAAexc, which is the current standard method of adjustment. Further comparisons between AAAexc without the BC technique and AAA with the BC technique revealed a good agreement between the two methods (ICC 0.83 to 0.93, depending on method of blood pool correction).

There was no correlation between ^{18}F-NaF PET uptake and aneurysm size in this study and this is not an

Reconstruction methods to improve analysis of arterial ^{18}F-NaF PET
Motion correction of the aortic valve improves signal to noise ration and tissue-to-background ratio compared to current standard approaches [15]
Coronary motion correction technology improves image noise and improves lesion tissue-to-background ratios[16,17]
Partial volume effect correction of atherosclerotic lesions improves tissue-to-background ratios[18]
Compensation for patient motion improves coronary lesion tissue-to-background ratios[19]
Compensation for respiratory motion, cardiac motion and gross patient motion improves test-retest reproducibility of coronary analysis[20]
The current study shows that background correction of vertebral ^{18}F-NaF activity omits the requirement for manual exclusion of vertebral radiotracer activity from aortic analysis [5]

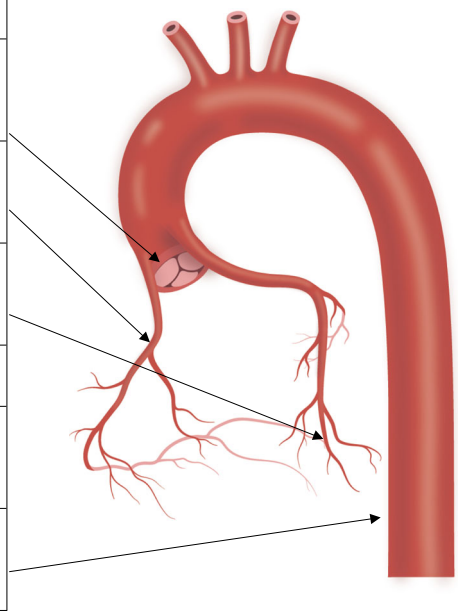

Figure 1. Novel image reconstruction methods to address the limitations of arterial ^{18}F-NaF PET analysis.

unexpected finding. Regions of low or absent radiotracer activity may have arbitrary readings when quantified using standardized methods such as the maximum tissue-to-background ratio, in part due to the disproportionate effects of small variations in blood pool activity among other factors. Also, small regions of increased ^{18}F-NaF uptake may be heavily influenced by image noise, causing a wide variability in readings in positive disease. Therefore, analysis of vascular ^{18}F-NaF PET is moving towards a dichotomous approach and cut-off values for positivity are being refined.[14] When Akerele et al apply a dichotomous definition to AAAs with the BC correction method, the positivity for 5 patients (7% of cohort) changed. Without clinical outcomes, it is not known whether this effect is clinically important, but the data certainly are encouraging and support further development and validation of the technique.

There are two limitations of this study that warrant consideration. Firstly, the reproducibility data are lacking and despite the likelihood that analysis using the BC technique is more reproducible than the AAAexc technique (without BC), validation of this is required. Secondly, it remains difficult to assess the importance of this tool, without clinical outcome data. While the current study is unlikely to be powered to provide the true clinical significance of such a tool, future studies with hard outcomes would benefit from including the BC tool in their workflow in order to provide a better understanding of its efficacy.

The major advantages of the BC technique over the current standard approach of manual exclusion of vertebral overspill are that it is likely to require less training and analysis could be automated using already available technology. Also, the BC tool may also be applied with minimal modification to the analysis of other vascular structures such as the coronary arteries where aortic and annular calcifications impede ^{18}F-NaF PET analysis. With the growing interest in the potential of ^{18}F-NaF PET to improve cardiovascular risk stratification, more tools to address the inherent limitations of the technology are to be welcomed.

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