HHS Public Access

Author manuscript

Circ Cardiovasc Imaging. Author manuscript; available in PMC 2020 August 06.

Published in final edited form as:

Circ Cardiovasc Imaging. 2019 August ; 12(8): e009591. doi:10.1161/CIRCIMAGING.119.009591.

Hype or hope: ^{18}F-NaF PET for vulnerable coronary plaque imaging

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Keywords

Atherosclerosis; Nuclear Cardiology and PET; PET; Sodium fluoride; Calcification; Imaging; Coronary artery disease

Based on now a classical model, most cases of acute coronary syndrome (ACS) are the consequence of a thrombotic event after rupture of a “vulnerable” atherosclerotic plaque. The vulnerable plaque prone to rupture is characterized by specific structural and biological features, such as a thin fibrous cap, large necrotic core, and abundance of inflammatory cells [1]. The structural features may be detected by imaging techniques such as optical coherence tomography (OCT), virtual histology intravascular ultrasound (VH IVUS), and coronary computed tomography angiography (CCTA), which are now widely available in many centers around the world. In parallel, the key role of plaque biology in ACS has led to growing interest in the development of novel tools to detect plaque biology *in vivo* [2]. Based the role of inflammation in plaque rupture and the value of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in imaging tissue inflammation, several studies have evaluated this technique for detection of plaque vulnerability. The results highlight the potential of ^{18}F-FDG PET as a tool to detect vascular inflammation in the aorta and possibly carotid arteries. The physiological uptake of ^{18}F-FDG in the heart and concerns regarding the specificity of ^{18}F-FDG signal have motivated the search for alternative tracers for coronary plaque imaging. While several new tracers that target different aspects of plaque biology are in the pipeline [3], ^{18}F-NaF has recently emerged as a promising and widely available tracer for plaque characterization. For decades, ^{18}F-NaF has been utilized as a bone tracer. The working mechanism of this tracer is thought to be through the exchange of fluoride with hydroxyl groups on hydroxyapatite, a key structural component in bone and other calcified tissues [4]. A set of elegant studies have linked the uptake of ^{18}F-NaF in atherosclerotic plaques to the presence of microcalcifications, which by virtue of their higher relative surface area compared to foci of macrocalcification, promote ^{18}F-NaF binding and amplify the PET signal [5, 6].

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Conflict of Interest Disclosures: MMS is a consultant for Bracco Research USA.

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Although the high sensitivity of PET is an advantage for molecular imaging, its limited spatial resolution hampers accurate quantification of the signal in coronary arteries, raising concern about the validity and accuracy of coronary artery PET signal quantification. Accordingly, there is controversy regarding the best approach to signal quantification [7]. In this issue of the journal, Moss et al [8] take an important step toward addressing some key issues regarding the reproducibility of coronary plaque ^{18}F-NaF signal in patients with coronary artery disease (CAD). Using the data from thirty subjects [20 with stable CAD and 10 with recent type 1 myocardial infarction (MI)] who underwent two PET-CCTA scans within an interval of 12 ± 5 days, they evaluated the identification, quantification, categorization and scan-rescan reproducibility of ^{18}F-fluoride signal in coronary plaques. Their subjects are enrolled in the DIAMOND (Dual antiplatelet therapy to inhibit coronary atherosclerosis and myocardial injury in patients with necrotic high-risk coronary plaque disease,) and PRE^{18}FFIR (Prediction of recurrent events with ^{18}F-fluoride to identify ruptured and high-risk coronary artery plaques in patients with myocardial infarction,) trials. On visual analysis of co-registered PET and CCTA images, they found on average 3.7 ± 1.8 ^{18}F-NaF-positive plaques in patients with recent ACS and 2.4 ± 2.3 ^{18}F-NaF positive plaques in patients with stable CAD, with good inter-observer reliability (k = 0.66). As expected, the discrepancies were in coronary segments adjacent to high background activity. Interestingly, visual analysis of the images identified a focal coronary ^{18}F-NaF signal in all culprit plaques (n=10), and 13.8% of stable plaques (n=530). Combining visual evidence of focal tracer uptake in a coronary artery with semi-quantitative assessment of the signal led to a comparable scan-rescan agreement. However, the use of pre-specified target-to-background $(TBR)_{MAX}$ thresholds in subjects with recent MI resulted in fewer culprit plaques being classified as positive for focal ^{18}F-NaF uptake (7 out of 10 at TBR_{MAX} 0.9 and 2 out of 10 at $TBR_{MAX} > 1.1$). In visually positive plaques, mixed effects biases were relatively small between observers and between scans. However, the limits of agreement in TBR_{MAX} appeared large, relative to pre-specified TBR_{MAX} intensity thresholds (>0.9 and >1.1) used to define a focal ^{18}F-NaF signal in coronary plaques.

The authors should be congratulated for their carefully planned and executed analysis which adds several key findings to the growing body of evidence on molecular imaging in CAD. Undoubtedly, the implications of this study extend beyond ^{18}F-NaF PET imaging of coronary plaques. While the small size of coronary arteries (~1–3 mm) relative to spatial resolution of PET for ^{18}F-labeled tracers (~5 mm), and cardiac motion are common challenges in coronary plaque imaging, the absence of myocardial uptake is a major advantage for ^{18}F-NaF, and facilitates image analysis. The appropriate image analysis methodology should be considered in the context of the clinical setting and the question addressed. In the case of CAD, the question could be the identification of a plaque which might benefit from percutaneous coronary intervention (PCI), short term and long-term risk assessment, or evaluating the effect of therapeutic interventions. Given the diffuse nature of atherosclerosis and the role of systemic factors, addressing the last two questions probably does not require imaging of individual plaques. Indeed, the positive predictive value of a test seeking to identify high risk plaques must be high enough for future events to justify the identification and treatment of a “vulnerable” plaque. Accordingly, global evaluation of a disease process, such as inflammation, microcalcification, or protease activity, within the

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coronary tree may be more fruitful than focusing on the characteristics of selected coronary plaques. Whether targeting (micro) calcification with ^{18}F-NaF is an appropriate strategy for risk stratification or tracking the effect of therapeutic interventions remains to be determined.

Another issue to consider is the distinction between detecting a plaque prone to rupture and a plaque that has ruptured. It is suggested that ^{18}F-NaF PET may detect the culprit plaque in the setting of acute MI. However, the data by Moss et al [8] raise some concern in this regard, as their most objective and reproducible approach (the combination of visual analysis and TBR_{MAX} thresholds > 1.1) failed to detect the majority of culprit plaques in this study. One caveat to consider here is that no information is available on how many of these plaques had already undergone PCI and stenting at the time of imaging, as this may affect the signal, e.g., by facilitating access of ^{18}F-NaF to its binding sites. There is currently limited evidence to indicate that ^{18}F-NaF imaging can detect a “vulnerable” plaque prone to rupture, or plaque vulnerability in general. Indeed, calcification in its various forms (micro or macro, intimal or medial, inflammatory or metabolic) may be too complicated to be a suitable target for plaque characterization in coronary arteries. As the authors have pointed out, the co-existence of micro- and macro-calcification, which have opposite effects on plaque vulnerability and take up ^{18}F-NaF to different extents, complicates the interpretation of the ^{18}F-NaF signal. In addition, the effect of statin therapy, which reduces the risk of ACS but promotes coronary calcification [9], on ^{18}F-NaF signal remains to be determined. This potentially non-monotonic relation between coronary artery ^{18}F-NaF signal and risk for future events has led the authors to suggest that may be the presence of focal uptake, rather than its magnitude, is most important. Yet, one could contend that the quantitative nature (and reproducibility) are essential attributes of a robust test.

Reproducibility has two components: biological and technical. The report by Moss et al [8] takes into consideration a number of issues related to image analysis, assuming that the plaque biology remains mostly unchanged within the two-week period of repeat imaging. While in the case of stable CAD this may be true, the changes in plaque structure and biology following ACS and possibly coronary interventions may be more significant. In addition, the effect of advances in motion-correction and image reconstruction methodologies [10] on the visualization, categorization and quantification of the coronary plaque signal remains to be determined. The timing of imaging has a major effect on ^{18}F-NaF PET signal, with some studies recommending delayed, 3-hour imaging to allow for blood clearance [11]. Indeed, small differences in the timing of imaging may impact the magnitude of the ^{18}F-NaF signal in coronary arteries and efforts are underway to develop methodologies to compensate for the natural variability encountered in the time of imaging [12]. The subjects enrolled in the study by Moss et al [8] were imaged after 60 minutes with some variation in the actual tracer administration-to-scan time that may have affected the reproducibility analysis. Interestingly, the proximal non-diseased coronary artery segment signal, which has been used to define background activity in a landmark report of ^{18}F-NaF PET/CT imaging for identification of ruptured and high-risk coronary atherosclerotic plaques [13] was found to be inconsistent with a high degree of variability on serial imaging. To identify the best value for background blood activity to calculate TBR, the authors compared image-derived blood activity in several locations and selected the left atrial

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standardized uptake value $(SUV)_{MEAN}$ based on higher values and less variability compared to other locations.

This brings up another issue regarding what the gold standard should be when determining the performance of a new test. While inter-observer and inter-scan reproducibility of the test are critical, the reproducibility of a quantification methodology is not equal to its accuracy. We posit that ex vivo measurements of a signal or its predictive value for an outcome should serve as the standard for accuracy. For background blood activity, it would have been useful to determine in which location image-derive blood activity best corresponds to the actual blood activity measured ex vivo by gamma-well counting. For the plaque, SUV_{MEAN} may best reflect the concentration of the target. However, given the difficulty defining the boundaries of the plaque and the signal, SUV_{MAX} is often used as alternative. Large animal studies to quantify the coronary plaque ^{18}F-NaF signal ex vivo and compare it with TBR_{MAX}, TBR_{MEAN} or any other quantitative measure of in vivo PET images could help address this major gap in molecular imaging of CAD [14]. Indeed, because of the partial volume effect, it is likely that the SUVs measured in vivo in coronary plaques underestimate the true uptake of the tracer, as has been shown in phantom studies [15]. As a possible alternative, if ongoing clinical trials demonstrate a positive predictive value of ^{18}F-NaF PET for any outcome, the question of appropriate quantification methodology will become less critical.

The high number of ^{18}F-NaF-positive coronary plaques per subject reported in subjects with stable CAD by Moss et al [8] and the small difference in the prevalence of such plaques between the MI and stable CAD subjects (who are at considerably different risk for future coronary events) raises concern regarding the utility and predictive value of coronary plaque ^{18}F-NaF PET imaging. Surprisingly, a much higher fraction of “stable” plaques had a $TBR_{MAX} > 1.1$ than in presumably ruptured plaques. It would be interesting to know how many of these plaques have dense calcification or prior stents, and visually compare their attenuation correction (AC) and non-AC images. In addition, the number of stable CAD subjects without focal uptake of ^{18}F-NaF in coronary arteries is informative.

Like inflammation, calcification is a multi-faceted process and it is likely that ^{18}F-NaF is not the optimal tracer for CAD risk stratification, as the relation between calcification and rupture risk is complex. Furthermore, plaque erosion, where the role of calcification is less clear, plays an increasingly important role in ACS [16]. Imaging of a biological process that directly mediates the pathogenesis of atherosclerosis and its complications in conjunction with a global scoring system [17], that considers potential confounders such as blood pool activity and non-coronary tracer uptake, may be more relevant for CAD risk stratification and tracking the effect of therapeutic interventions. This doesn’t reduce the value of coronary plaque imaging as a tool to study the pathophysiology of plaque development and evolution.

Acknowledgments

Funding Sources: This work was supported by grants from NIH (R01- HL138567) and Department of Veterans Affairs (I0-BX004038).

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