^{18}F-fluorodeoxyglucose and ^{18}F-sodium fluoride for imaging atherosclerotic plaque activity

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While nuclear cardiology is dominated by myocardial perfusion imaging, beyond assessment of the downstream effects of coronary artery disease, molecular imaging with positron emission tomography (PET) provides an opportunity to non-invasively evaluate atherosclerotic disease activity complementing multimodal assessments of anatomic, morphologic, and hemodynamic disease severity. The processes which drive atherosclerotic plaque progression and are implicated in plaque rupture, namely macrophage infiltration, active calcification (or microcalcifications), and inflammation (increased metabolic activity) can be efficiently depicted with ^{68}Ga-DOTATATE, ^{18}F-sodium fluoride, and ^{18}F-fluorodeoxyglucose PET, respectively.

^{18}F-fluorodeoxyglucose PET imaging of atherosclerosis provides a reliable and reproducible measure of vascular inflammation as it indicates increased metabolic activity of macrophages and probably also reflects contributions from local hypoxia and efficiency of tracer delivery by the microcirculation. Unfortunately, coronary ^{18}F-FDG imaging is hampered by problems related to tracer uptake in the myocardium. Despite stringent dietary recommendations suppression of myocardial activity is typically achieved in 57-85% of patients.[1-3] Often suboptimal suppression results in a patchy distribution of myocardial uptake that can obscure activity in one or more coronary vessels.[3]

Given the limitations of ^{18}F-fluorodeoxyglucose coronary imaging, it was proposed that tracers with established roles in cancer imaging (^{68}Ga-DOTATATE, ^{11}C-PK11195, and ^{18}F-fluoromethylcholine) might be more specific for vascular inflammation and better suited to atherosclerotic plaque imaging than ^{18}F-fluorodeoxyglucose.[4] Especially ^{68}Ga-DOTATATE which binds to the somatostatin subtype-2 receptor (SST2) on the surface of activated macrophages is particularly promising. ^{68}Ga-DOTATATE PET offers measurement of both generalized atherosclerotic disease activity and detailed information about local plaque functional phenotype distinguishing culprit from non-culprit coronary lesions.[5]

Aside from inflammation, active calcification processes play a central role in plaque progression and rupture. While established coronary calcifications are largely a hallmark of stable lesions, developing microcalcifications are an established marker of plaque vulnerability.[6] Such small foci of hydroxyapatite (or the bone mineral) which are beyond the resolution of non-invasive CT imaging can be depicted with ^{18}F-sodium fluoride PET. This imaging modality has been shown to distinguish culprit from non-culprit lesions and stable high risk from bystander plaques.[3,7] More recently in the field of coronary artery imaging, ^{18}F-sodium fluoride has been established as a predictor of plaque progression and it was shown that a whole-vessel ^{18}F-sodium fluoride uptake measure (the coronary microcalcification activity) acts as a strong independent predictor of myocardial infarction.[8-12] These important studies position ^{18}F-sodium fluoride ahead of other vulnerable plaque tracers as its clinical utility for risk stratification is particularly promising.[13]

To date we lacked dual-tracer PET studies targeting plaque imaging with dual-time-point imaging. The study by Reijrink et al provides important insights into atherosclerotic plaque progression in the context of baseline ^{18}F-fluorodeoxyglucose and follow-up ^{18}F-

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sodium fluoride PET.[14] On a small cohort of type 2 diabetes patients participating in the RELEASE trial the authors have performed ^{18}F-fluorodeoxyglucose PET and, at 5 years after the baseline scan, an ^{18}F-sodium fluoride acquisition. Since both these emission scanning sessions we performed along with a low-dose computed tomography scan obtained for anatomic reference and attenuation correction purposes, aside from evaluating PET tracer activity it was also possible to assess the extent of atherosclerotic plaque within the great vessels. Interestingly the authors observed a strong correlation between baseline ^{18}F-fluorodeoxyglucose and 5-year follow-up and ^{18}F-sodium fluoride uptake ($r = 0.709$, $P = 0.022$). Additionally, similar to previous studies, plaque progression as evidenced on CT was more pronounced in patients with higher ^{18}F-sodium fluoride uptake.[8,9] The current study has some limitations. It was based on a small population and the assessments of atherosclerotic plaque burden were based on low-dose, thick-slice CT acquired for attenuation correction purposes which does not provide optimal image resolution and quality for quantifying the extent of atherosclerosis. Additionally, ^{18}F-sodium fluoride and ^{18}F-fluorodeoxyglucose uptake were expressed as single SUVmax or TBRmax measured within a relatively large volume of interest (such as the entire ascending aorta and the aortic arch)—yet it was recently proposed that measures of uptake which consider both the extent and intensity of uptake might be superior to characterize atherosclerotic disease activity in the great vessels.[15]

On the molecular level, the association between osteogenesis and inflammation in atherosclerosis was widely reported, and the study by Reijrink et al supports these findings at a non-invasive imaging level.[16,17] This association was also explored in histological assessment of carotid endarterectomy specimens and preclinical models. It was demonstrated that plaques with increased ^{18}F-sodium fluoride uptake not only showed increased microcalcification but also showed more pronounced macrophage infiltration and apoptosis.[6,16,17]

The interplay between inflammation and microcalcification was recently reinvigorated also due to the invention of a CT-derived surrogate measure of plaque inflammation—the pericoronary adipose tissue (PCAT) attenuation. In outcome studies it turned out that by measuring the attenuation of the adipose tissue that is immediately adjacent to the vessel wall it is possible to distinguish culprit from non-culprit plaque in subjects with an acute coronary syndrome and to risk stratify stable coronary artery disease patients.[18,19] In the coronary arteries ^{18}F-sodium fluoride uptake, whether expressed with the SUVmax or TBRmax, was associated with lesion PCAT density again confirming a close association between residual inflammation and active calcification process in the coronary vasculature.[20]

Given the wealth of information that can be derived from atherosclerotic plaque PET imaging there are great both clinical and research potentials in this advanced non-invasive imaging modality. Firstly, given the fact that PET depicts processes directly involved in plaque progression and rupture it is plausible that it could help identify patients at the highest risk of adverse cardiovascular events. While to date we only possess data which support the use of ^{18}F-sodium fluoride in this context, future studies might broaden our armamentarium of tracers which can enhance risk stratification. Secondly PET imaging could facilitate establishing new medication targeting atherosclerosis or elucidate the beneficial effects of existing medication on plaque, thus further improving the management of atherosclerosis and ultimately providing a hope for reducing the burden of cardiovascular disease.

Disclosure

The authors declare that they have no conflict of interest.

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