Imaging inflammation in atherosclerosis: Exploring all avenues

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Despite remarkable advances in preventive and therapeutic strategies, cardiovascular disease (CVD) remains the primary source of death and disability worldwide.¹ Further, the demographic shift towards an older population will result in increasing numbers of patients, among whom heart disease is the leading cause of death. In view of this global burden, personalized risk-stratification tools and a cost-effective management of CVD are urgently needed. Although rapid innovations in atherosclerosis imaging have widened its applications from anatomical plaque detection to physiological assessment and complex evaluation of vascular biology, non-invasive imaging tools that flag the ‘vulnerable’ patient are still lacking. Indeed, although the presence of coronary artery stenosis is associated with subsequent events, most myocardial infarctions occur in segments with non-obstructive rather than obstructive disease.² As recent landmark trials have further highlighted the fundamental role of inflammation during all stages of

atherosclerosis, the assessment of ‘residual inflammatory risk’ has been proposed as a promising strategy for improving CVD risk prediction and providing guidance for novel precision treatments.^{3,4}

Several molecular imaging modalities including ^{99m}Tc-based single-photon emission computed tomography (SPECT) and ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) have been developed for the non-invasive detection of vascular inflammatory activities^{5,6} (Figure 1). ¹⁸F-FDG-PET has been used to detect macrophage-rich atherosclerotic lesions and as a surrogate endpoint for vascular interventional drug trials.⁷ However, it is limited by its moderate reproducibility and sensitivity for the detection of coronary atherosclerotic changes. In addition, ¹⁸F-FDG-PET has logistical and technical constraints including the need to suppress myocardial and peripheral muscle FDG uptake for the analysis as well as the high FDG uptake in structures close to the vessel wall. Hence, given the small size of the atherosclerotic lesion and the continuous cardiac and respiratory movements during PET acquisition, nuclear imaging of atherosclerosis remains challenging. Therefore, high-sensitivity PET and SPECT imaging probes that specifically target inflammatory cells in the vessel wall would greatly facilitate the non-invasive evaluation of the vulnerable plaque.

In this issue of the *Journal of Nuclear Cardiology*, Meester et al.⁸ analyzed the diagnostic potential of DOTA-JR11, labeled with ¹¹¹indium (¹¹¹In), in a mouse model of atherosclerosis as well as in human carotid endarterectomy tissue. ¹¹¹In-DOTA-JR11 targets the up-regulated somatostatin receptor subtype 2 (SST₂) on activated macrophages and might thus provide functional information about plaque activity and stability. The authors report that aortic plaques were detectable in all atherosclerotic mice, providing a proof-of-concept for the utility of ¹¹¹In-DOTA-JR11 in preclinical

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Figure 1. Molecular targets and selected probes for atherosclerosis imaging by positron emission tomography (PET) and single-photon emission computed tomography (SPECT). (1) ⁶⁸Ga-DOTA-(Tyr³)-octreotate (⁶⁸Ga-DOTATATE), ¹¹¹In-DOTA-JR11. (2) ¹¹C-choline. (3) ^{99m}Tc-RP805, ¹¹¹In-RP702. (4) ¹¹C-PPK11195, ¹⁸F-GE180. (5) ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG). (6) ^{99m}Tc-cAbVCAM1-5. (7) ¹²⁴I-hypericin. (8) ¹⁸F-fluoromisonidazole (¹⁸F-FMISO). (9) ¹⁸F-sodium fluoride (¹⁸F-NaF). (10) ¹⁸F-Galacto-RGD, ⁶⁸Ga-NOTA-RGD. GLUT, glucose transporter; MMPs, matrix metalloproteinases; SST₂ somatostatin receptor 2; TSPO, translocator protein.

atherosclerosis imaging. Further, ¹¹¹In-DOTA-JR11 co-localized with CD68- and SST₂-expressing cells on human carotid tissue sections indicating that the tracer is suitable to detect inflammatory activities in human atherosclerotic plaques. Their data are consistent with previous reports unveiling a close relationship between CVD risk factors, coronary calcium burden, and arterial uptake of ⁶⁸Ga-DOTA-(Tyr³)-octreotate (⁶⁸Ga-DOTATATE)—the most extensively validated SST₂-targeted tracer.⁹ Indeed, in a prospective clinical investigation, Tarkin et al. recently demonstrated that ⁶⁸Ga-

DOTATATE can be used to differentiate between high-risk vs. low-risk carotid and coronary atherosclerotic lesions.¹⁰ Further, ⁶⁸Ga-DOTATATE was superior to ¹⁸F-FDG-PET in discriminating between high-risk vs. low-risk human atherosclerotic plaques, underlining the capability of SST₂-targeted tracers in capturing vulnerable plaque features.¹¹

In contrast to DOTATATE, DOTA-JR11 belongs to the new generation of SST₂ ligands that are based on antagonistic structures and exhibit more favorable receptor binding, pharmacokinetics, and biodistribution

properties.¹² It should be noted, however, that SST₂-directed probes have originally been developed and approved for the detection of SST₂ overexpression on neuroendocrine tumors.¹³ As such, DOTA-JR11 has recently shown promise in exhibiting a several-fold higher tumor uptake than DOTATATE,¹⁴ thereby highlighting its potential for a broad clinical applicability. Meester et al. now extend previous findings by demonstrating that DOTA-JR11, when labeled with indium-111, is sensitive to atherosclerotic plaque detection. Although this is an important finding, the authors did not perform a direct comparison between ¹¹¹In-DOTA-JR11 SPECT and ⁶⁸Ga-DOTATATE PET. Thus, whether second-generation SST₂-based probes will outperform ⁶⁸Ga-DOTATATE in atherosclerosis imaging will have to be tested in future studies. Further, N-terminal radiometal modifications may substantially affect the performance characteristics of DOTA-JR11.¹⁵ Given that gallium-68 labeled DOTA-JR11 (⁶⁸Ga-DOTA-JR11) has not yet been evaluated for the imaging of coronary vascular inflammation, it is unclear how radiometal exchange between ¹¹¹In and ⁶⁸Ga will affect tracer performance. Nonetheless, a recent first-in-man study with ⁶⁸Ga-DOTA-JR11 demonstrated pharmacokinetics and dosimetric data that compared favorably with ⁶⁸Ga-DOTATATE,¹⁶ thus, paving the way for a head-to-head comparison between ⁶⁸Ga-DOTA-JR11 and ⁶⁸Ga-DOTATATE PET in atherosclerosis imaging.

Meester et al. conclude their discussion by stressing the need for future trials demonstrating the clinical utility of DOTA-JR11-based probes in plaque phenotyping. Indeed, provided that an increase in DOTA-JR11 signal is associated with the progression of atherosclerosis and the risk of cardiovascular events, high specific uptake of DOTA-JR11 might not only identify patients with high-risk plaques, but also individuals who could benefit from novel anti-inflammatory treatments. However, pertaining to a wider clinical use of SST₂ imaging, it will be indispensable to consider the influence of sex on the complexity of atherosclerotic plaque morphology and activity. The study by Meester et al. did not address this important issue; nonetheless, sexual dimorphism in the association between inflammation and coronary artery disease has recently been demonstrated.^{17,18} Further, recent advances in coronary computed tomography angiography (CCTA) technology allow to detect coronary inflammation by capturing perivascular fat attenuation.¹⁹ Given the widespread use of CCTA as well as novel CCTA acquisition techniques ranging in a sub-millisievert fraction of effective radiation dose,²⁰ the prognostic performance of SST₂-targeted probes will have to be validated against novel imaging biomarkers derived from CCTA before they may advance from research tools to clinical applications. Future studies

should also address potential synergistic applications of nuclear imaging techniques and CCTA, with the ultimate goal to identify the vulnerable plaque, the vulnerable artery, and, most importantly, the vulnerable patient.

Disclosure

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