REVIEW ARTICLE

Pet tracers for vulnerable plaque imaging

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Received: 11 February 2020 / Accepted: 10 March 2020 © The Japanese Society of Nuclear Medicine 2020

Abstract
Most of the acute ischemic events, such as acute coronary syndromes and stroke, are attributed to vulnerable plaques. These lesions have common histological and pathophysiological features, including inflammatory cell infiltration, neo-angiogenesis, remodelling, haemorrhage predisposition, thin fibrous cap, large lipid core, and micro-calcifications. Early detection of the presence of a plaque prone to rupture could be life-saving for the patient; however, vulnerable plaques usually cause non-haemodynamically significant stenosis, and anatomical imaging techniques often underestimate, or may not even detect, these lesions. Although ultrasound techniques are currently considered as the “first-line” examinations for the diagnostic investigation and treatment monitoring in patients with atherosclerotic plaques, positron emission tomography (PET) imaging could open new horizons in the assessment of atherosclerosis, given its ability to visualize metabolic processes and provide molecular-functional evidence regarding vulnerable plaques. Moreover, modern hybrid imaging techniques, combining PET with computed tomography or magnetic resonance imaging, can evaluate simultaneously both functional and morphological parameters of the atherosclerotic plaques, and are expected to significantly expand their clinical role in the future. This review summarizes current research on the PET imaging of the vulnerable atherosclerotic plaques, outlining current and potential applications in the clinical setting.

Keywords Atherosclerosis · Myocardial infarction · Positron emission tomography · Stroke · Vulnerable plaque

Introduction
Cardiovascular disorders are currently the leading causes of morbidity and mortality in developed countries [1]. Atherosclerosis represents the main pathophysiological mechanism of cardiovascular disorders. It has a long asymptomatic phase, in which associated changes in the vessel wall have a chronic and progressive character. Rupture of an atherosclerotic plaque initiates clot formation in the vessel lumen, reducing blood flow. Moreover, emboli may break off and lodge in the downstream circulation, leading to acute myocardial infarction or stroke. Therefore, although atherosclerotic plaques may remain quiescent for a long period, atherosclerotic disease can become life-threatening when plaque ruptures [2]. However, vulnerable plaques usually result in non-haemodynamically significant stenosis, which may be underestimated (or even remain undetected) based on anatomical imaging techniques. In current clinical practice, “first-line” examinations for the diagnostic investigation and evaluation of treatment response in patients with atherosclerotic plaques, include mainly ultrasound techniques.

Molecular imaging can be performed in vivo for the visualization, characterization and quantification of both cellular and subcellular physiological processes. Particularly, positron emission tomography (PET) is a molecular-functional imaging technique that is used for the investigation of metabolic processes in the body. Hybrid systems combining PET with computed tomography (CT) or more recently with magnetic resonance (MR) are considered as the “state of the art” technology (PET/CT, PET/MR) for simultaneous morphological and functional imaging. The clinical applications of these techniques to atherosclerotic disease could...
offer valuable information regarding plaque composition, as well as important evidence for the identification of atherosclerotic plaques which are vulnerable to rupture.

In the present review, we aim to present PET imaging probes developed and/or tested for atherosclerotic plaque imaging, outlining current and potential applications in the clinical setting.

**Pathophysiology of atherosclerosis**

Under hyperlipidemic state, low-density lipoprotein (LDL) diffuses through the arterial endothelium, and is prone to oxidation leading to oxidized LDL and glycated LDL. Endothelial cells and macrophages are stimulated by these converted LDLs, promoting inflammatory processes [3]. Several adhesion molecules, proteases, pro-inflammatory cytokines, and receptors, like scavenger receptors on migrated macrophages, are involved in these mechanisms. Notably, in the initial phases of atherosclerosis, lipid-laden macrophages (foam cells) are the characteristic pathologic features in plaques.

Later, due to the loosening of the plaque by a number of macrophage-released proteases, vascular smooth muscle cells migrate into the plaque and produce collagens to fill the extracellular matrix. This fibrous tissue deposition represents an indication of atherosclerosis progression. Various cells, including endothelial cells, macrophages, T-cells, smooth muscle cells, and platelets, contribute to the progressive inflammation process, and are regulated by a number of cytokines.

**The vulnerable plaque**

Acute coronary syndromes are mainly linked to atherosclerotic plaque rupture, combined with the superimposed coronary thrombosis. Prolonged inflammation in the plaque results in neo-angiogenesis, and leukocytes migrate via the newly developed vessels, stimulating further inflammation. On the other hand, these vessels are prone to haemorrhage, leading to sudden plaque enlargement and thrombin generation. Moreover, due to the apoptosis of inflammation-related cells, micro-califications are observed in the plaque, as a type of healing process. Plaque rupture may occur as a result of intra-plaque haemorrhage and necrosis, leading to thinning, erosion, and disruption of the fibrous cap. Afterwards, in the arterial lumen, the contact between the highly thrombogenic plaque with blood promotes thrombus formation, increasing the risk of an embolism.

Thin-cap fibroatheromas (TCFAs) is a type of plaque that has been suggested to be related to plaque vulnerability [4]. TCFA is described as a plaque with a thin fibrous cap (<65 μm thick) infiltrated by a significant number of inflammatory cells and a few smooth muscle cells, a large necrotic core, spotty calcification, and positive outward remodelling [5]. Nevertheless, the presence of a TCFA does not necessarily lead to a clinical event, but various complex interactions between anatomical and physiological factors seem to contribute to plaque rupture. Interestingly, rupture is observed in a small number of vulnerable plaques, whereas most vulnerable plaques (even those that were ruptured) show a silent clinical course [6].

Possibly, there are four crucial rupture-related factors that include fibrous cap micro-califications, cholesterol crystals, apoptosis of intraplaque macrophages, and endothelial shear stress distribution [4–6]. Intimal micro-califications are developed mainly due to the apoptosis of smooth muscle cells and the release of matrix vesicles from the macrophages. Micro-califications aggregate progressively, creating calcified sheets or plates which subsequently form calcified nodules. Notably, calcified nodules are associated with an increased risk for thrombosis, despite the fact that severe calcification results in clinically stable outcomes. Moreover, cholesterol crystallization causes changes in local plaque temperature, pH, and hydration status, which may form the basis of cholesterol crystallization-induced thrombogenesis. In parallel, the large necrotic core represents a key feature of rupture-prone atherosclerotic plaque, which is primarily associated with the apoptosis of advanced lesion macrophages. Finally, endothelial shear stress, as a result of friction on the endothelial surface, has been involved in the pathophysiological mechanisms of plaque formation and vulnerability. In a number of clinical studies, endothelial shear stress has been associated with plaque progression and rupture, expansive remodelling with lumen narrowing, as well as the prediction of myocardial infarction [7].

**Pet molecular imaging of the vulnerable plaque**

Obviously, early identification (at least, before rupture) and proper management of the vulnerable plaques are highly anticipated in the clinical setting. Nevertheless, imaging molecular signals of the atherosclerotic plaques is still challenging in humans, although PET modality may obtain an important role in this field. Functional-molecular evidence, acquired through the performance of PET techniques, could contribute significantly to the assessment of several crucial mechanisms of plaque vulnerability, such as inflammatory cell infiltration, neo-angiogenesis, hypoxia, apoptosis, and calcifying activity.

The main radiotracers related to plaque imaging are presented in Table 1. These probes have been developed and tested in animal and/or human studies, with respect to the
Macrophages-related PET imaging

Activated macrophages can be considered as the most extensively studied targets in vulnerable plaque imaging. In animal models and in human studies, a close correlation between $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) uptake and macrophage accumulation has been reported, despite the fact that almost all inflammatory cells show increased glucose metabolism [8]. Furthermore, arterial $^{18}$F-FDG uptake has been related to markers of systemic inflammation, such as matrix metalloproteinase-1 (MMP-1) levels, and known risk factors for atherosclerotic disease, including carotid intima-media thickness, serum high-density lipoprotein, hypercholesterolemia, C-reactive protein, smoking, arterial hypertension, and age.

$^{18}$F-FDG is an excellent imaging agent for clinical applications, such as the detection of active inflammation, since this tracer is already approved worldwide, mainly for indications related to oncology [9]. Among individuals undergoing cancer surveillance, Figueroa et al. demonstrated that arterial activity on $^{18}$F-FDG PET/CT images could improve the prediction of future cardiovascular events, including acute coronary syndromes, beyond Framingham risk score [10]. Recently, Kafouris et al. demonstrated that $^{18}$F-FDG PET carotid imaging can contribute to plaque characterization using texture analysis, and Kelly et al. reported that $^{18}$F-FDG uptake independently predicted early recurrent stroke [11, 12]. Notably, $^{18}$F-FDG uptake can reflect the present inflammatory process, whereas arterial calcifications on CT images represent the end-products of inflammation (Fig. 1). Based on this background, $^{18}$F-FDG uptake may not coincide with CT evidence, although PET findings could be regarded as a better predictor for future vascular events [13]. The development of hybrid systems, which add the higher CT spatial resolution, permitted a more accurate detection of individual coronary plaques [14]. However, one limitation exists regarding the assessment of coronary plaques, since myocardial $^{18}$F-FDG uptake may vary between patients, leading to differences in background activity [15]. Additionally, given its ability to reflect active inflammation, $^{18}$F-FDG uptake may be a promising tool in therapeutic efficacy monitoring [16, 17]. Statin therapy was found to decrease $^{18}$F-FDG uptake in plaques, a finding that was related to better patient prognosis [16, 17]. Moreover, $^{18}$F-FDG imaging was reported to be useful in the evaluation of the therapeutic efficacy of newer drugs for plaque stabilisation [16, 17]. Finally, a catheter-based intravascular radiation detector has been developed for the detection of vulnerable plaques, using $^{18}$F-FDG [18].

Apart from $^{18}$F-FDG imaging, additional imaging probes have been tested in early studies, such as radiotracers targeting surface receptors expressed on activated macrophages. Liu et al. reported that $^{64}$Cu-DOTA-viral macrophage inflammatory protein II (vMIP-II) was a sensitive tracer for the detection of vascular injury-accelerated atherosclerosis in mice [19]. Similarly, Luehmann et al. developed a targeted nanoparticle for PET imaging of the chemokine receptor 5 (CCR5), using a vascular injury model [19]. Furthermore, since mannose receptors are expressed on activated macrophages, particularly on a subset of the macrophage population in high-risk plaques (M2-subtype), Tahara et al. investigated the use of a labelled compound of this isomer of glucose ($^{18}$F-labeled mannose) in a rabbit model, with promising results [20]. Activated macrophages also express somatostatin receptors on their surface. Notably, since somatostatin receptor imaging has long been implemented in the clinical investigation of neuroendocrine tumours, the corresponding PET imaging probe [$^{68}$Ga-DOTA-(Tyr3)-octreotate (DOTATATE)] has been used in human studies, suggesting

### Table 1: Main radiotracers for PET vulnerable plaque imaging

| Targets                  | PET radiotracer                                                                 |
|--------------------------|--------------------------------------------------------------------------------|
| Activated macrophages    | $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)                                      |
|                          | $^{68}$Ga-somatostatin receptor subtype 2 ($^{68}$Ga-DOTATATE)                 |
|                          | $^{11}$C-translocator protein ($^{11}$C-PK11195)                                |
|                          | $^{18}$F-fluorocholine ($^{18}$F-FCH)                                           |
| Apoptosis                | $^{18}$F-annexin V                                                              |
| Hypoxia                  | $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO)                                     |
|                          | $^{18}$F-HX4                                                                    |
| Micro-calcifications     | $^{18}$F-sodium fluoride ($^{18}$F-NaF)                                         |
| Neo-angiogenesis         | $^{18}$F-fluciclatide                                                           |
|                          | $^{18}$F-arginine-glycine-aspartate ($^{18}$F-RGD)                               |
| Matrix metalloproteinases| $^{18}$F/124I—GGS27023A1f                                                       |
|                          | ($^{18}$F/124I)—GGS27023A1e                                                      |
| Thrombus                 | $^{18}$F-glycoprotein Ib/IIa platelet receptor ($^{18}$F-GP1)                   |

PET positron emission tomography, $^{11}$C carbon-11, $^{68}$Ga gallium-68, $^{18}$F fluorine-18, $^{124}$I iodine-124
a potential role of this tracer for coronary plaque imaging and associations of its uptake with known cardiovascular risk factors (Fig. 2) [21–23]. Tarkin et al. reported that $^{68}$Ga-DOTATATE can better discriminate high-risk vs. low-risk coronary lesions in comparison to $^{18}$F-FDG [21]. On the other hand, no significant difference in $^{68}$Ga-DOTATATE uptake was found between recently symptomatic carotid plaques and contralateral carotids/plaques, not supporting a role of this tracer in the detection and characterization of symptomatic carotid plaques [22]. After the evaluation of three somatostatin receptor-targeting PET tracers, Rinne et al. demonstrated the superior performance of 68 Ga-DOTANOC and $^{68}$Ga-DOTATATE in the detection of mouse atherosclerotic plaques, compared to $^{18}$F-FDRNOC [23]. Finally, in activated macrophages, a membrane protein, called translocator protein (TSPO), is expressed on the outer mitochondria membrane, as well as on the cell surface. PK11195 and other compounds have exhibited affinity for TSPO, and $^{11}$C-PK11195 has been investigated for vulnerable plaque imaging in studies with human subjects [24]. Ammirati et al. demonstrated an inverse correlation between $^{11}$C-PK11195 carotid plaque uptake and circulating monocytes, including classical CD14++ CD16− monocytes expressing HLA-DR [24]. Unfortunately, due to the fact that TSPO is also expressed by normal myocardium, there is a limitation for coronary imaging, as a consequence of high background activity.

Given the role of choline in cell membrane synthesis, the choline metabolism is increased in activated macrophages, and atherosclerotic plaques were found to exhibit enhanced radiolabelled choline uptake [25]. Interestingly, plaque imaging studies using radiolabelled choline have been conducted in human subjects, since $^{11}$C-choline and $^{18}$F-choline are currently available for human applications, particularly PET imaging in prostate cancer patients. Hellberg et al. reported that type 2 diabetes enhances arterial $^{18}$F-fluoromethylcholine in mice, suggesting a potential use of this tracer in vascular inflammation associated with diabetes [26]. Furthermore, because of the avidity of plaque macrophages for polysaccharide-containing supramolecular structures, Nahrendorf et al. developed a non-specific PET agent ($^{64}$Cu-nanoparticle) for the direct detection of macrophages in atherosclerotic plaques, concluding that the agent showed similarities to MR probes in clinical trials [27].
**Neo-angiogenesis, hypoxia and apoptosis PET imaging**

Based on their pathophysiologic significance, neo-angiogenesis and hypoxia represent hallmarks of the vulnerable plaque. A group of cellular trans-membrane proteins, called integrins, has an important role in intercellular attachment and intracellular signal transduction. Among integrin subtypes, integrin αvβ3, a receptor for fibronectin and vitronectin, is expressed on activated endothelium and promotes neo-angiogenesis through interactions with several growth factors receptors [28]. A tri-peptide moiety of Arg-Gly-Asp (RGD) was found to exhibit a high affinity for integrin αvβ3, and has been investigated in PET vulnerable plaque imaging using 68Ga-NOTA-RGD [19]. Other PET imaging probes for neo-angiogenesis detection include 18F-flotegatide and 18F-galactoRGD [19, 29, 30]. Using 18F-fluciclatide PET imaging, Jenkins et al. demonstrated that in vivo integrin αvβ3 expression in aortic atheroma is increased in subjects with recent myocardial infarction [29]. Nevertheless, integrin αvβ3 is also expressed on macrophages; therefore, increased uptake of these radiotracers should be regarded not only as a marker of neo-angiogenesis, but also as an indication of macrophage accumulation in the vulnerable plaque. Neo-angiogenesis imaging may further include other targets on activated endothelium, such as vascular endothelial growth factor (VEGF) receptors. For example, Golestani et al. investigated a 89Zr—labelled monoclonal antibody against VEGF receptor, reporting positive results in carotid plaque imaging [31].

In vulnerable plaques, hypoxia is the result of plaque enlargement and metabolic activation associated with inflammation. 18F-fluoromisonidazole (FMISO) is a derivative of nitroimidazole and is widely used for hypoxia imaging in oncology; however, 18F-FMISO can also be employed for PET imaging of the vulnerable plaques [32]. Shimizu et al. reported that 18F-FMISO uptake in macrophages may depend on their polarization state (M1 or M2 type), in addition to hypoxic condition [32]. In parallel, van der Valk et al. investigated a different tracer (18F-HX4) in advanced atherosclerotic plaques in humans, concluding that it may represent another option for hypoxia imaging [33]. Moreover, active inflammation in plaques leads to apoptosis of macrophages and other cells. Apoptosis can be visualized by radiolabeled...
annexin V, which binds to phosphatidylserine on the surface of the apoptotic cells [34].

Other atherosclerotic plaque PET imaging probes

Since inflammation begins with the endothelial activation, the expression of selectins and vascular cell adhesion molecule-1 (VCAM-1) constitute potential imaging targets on the activated endothelium. Nakamura et al. investigated the use of a $^{64}$Cu labelled monoclonal antibody for P-selectin, while Nahrendorf et al. studied $^{18}$F labelled peptide compounds for VCAM-1 imaging [19]. Both studies were conducted in mice with promising results. Moreover, in another animal study, increased uptake of $^{68}$Ga—fucoidan, a polysaccharidic ligand of P-selectin, was reported in atherosclerotic plaques [19].

During plaque progression, inflammatory cells and smooth muscle cells migrate through the space made after loosening of the extracellular space via proteolysis. Several proteases released by macrophages are involved in this process, including matrix metalloproteinases (MMPs) and cathepsin. Breyholz et al. developed an $^{18}$F-labelled inhibitor of MMPs, demonstrating that this radiotracer was able to specifically depict activated MMPs in vascular lesions in mice [25]. In general, apart from cellular components, the molecular imaging of extracellular matrix may also contribute to the assessment of treatment response in atherosclerosis [35, 36].

Calcification is the final process in inflammation. Although calcified plaques can be detected on CT imaging, current calcifying activity in the plaques may not be reflected on CT. Using the PET modality, the calcifying activity can be detected after the administration of $^{18}$F-sodium fluoride ($^{18}$F-NaF) (Figs. 3, 4) [37–54]. Notably, $^{18}$F-NaF uptake was found to be higher in symptomatic or ruptured plaques compared to stable plaques, and has been associated with other pathologic markers of vulnerability to rupture, such as the necrotic core [37]. Based on the results of recent studies, this tracer may soon become an available tool for the clinical management of atherosclerosis [47–54]. Finally, another promising tracer is $^{18}$F-glycoprotein IIb/IIIa platelet receptor ($^{18}$F-GP1) for the direct imaging of acute arterial thrombosis [55].

Pet vulnerable plaque imaging: future directions in clinical practice

Several characteristics of PET radiotracers, either in clinical practice or after pre-clinical evaluation, indicate that PET modality constitutes a promising tool in atherosclerosis. The functional-molecular evidence, obtained through the performance of PET techniques, could be valuable for a
thorough plaque assessment regarding associated subclinical parameters, such as metabolic status, cellularity, specific biomolecules concentrations, and antigenicity. Additional advantages include the high sensitivity of PET imaging, the combination of acquired radioisotopic and morphological data based on the modern hybrid systems (PET/CT, PET/MR), and the associated quantitative analyses using dedicated software. On the other hand, the main drawbacks of PET modality are the limited availability, the moderate specificity and resolution, the use of ionizing radiation, as well as the intolerance in patients with claustrophobia.

Undoubtedly, based on the use of specific imaging probes targeting in vivo selected biochemical mechanisms, PET is at the forefront of non-invasive imaging modalities, permitting significant target depiction at the molecular level. Various underlying mechanisms responsible for the development of the vulnerable plaques, such as inflammation, neo-angiogenesis, hypoxia, apoptosis, and calcifying activity, have been found to be feasible targets for PET imaging (Table 1). These characteristics of PET imaging are unique in comparison to other imaging techniques, and could allow the clinical practice regarding atherosclerotic plaques to move forward to a higher level, in which structural and perfusion findings would be evaluated in parallel with molecular evidence.

**Conclusions**

The ability of $^{18}$F-FDG PET to provide prognostic information and evidence of treatment efficacy has been already demonstrated, while $^{18}$F-NaF is expected to enter soon in clinical practice. In general, PET techniques, using tracers targeting different aspects of plaque pathophysiology, may provide a more accurate evaluation of the vulnerable plaque in the future, with important consequences for patient prognostication and risk stratification. Moreover, the simultaneous evaluation of functional and morphological data in one examination, combined with quantitative analyses, represent an important benefit of hybrid (PET/CT, PET/MRI) systems. Besides, in the emergence of personalised medicine, more molecular evidence is expected to be needed in clinical decision-making.
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