Published in final edited form as:

Q J Nucl Med Mol Imaging. 2020 March ; 64(1): 74–84. doi:10.23736/S1824-4785.20.03228-8.

Clinical imaging of cardiovascular inflammation

Claudia CALCAGNO^{1,2}, Zahi A. FAYAD^{1,2,*}

¹BioMedical Engineering and Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;

²Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Cardiovascular disease due to atherosclerosis is the number one cause of morbidity and mortality worldwide. In the past twenty years, compelling preclinical and clinical data have indicated that a maladaptive inflammatory response plays a crucial role in the development of atherosclerosis initiation and progression in the vasculature, all the way to the onset of life-threatening cardiovascular events. Furthermore, inflammation is key to heart and brain damage and healing after myocardial infarction or stroke. Recent evidence indicates that this interplay between the vasculature, organs target of ischemia and the immune system is mediated by the activation of hematopoietic organs (bone marrow and spleen). In this evolving landscape, non-invasive imaging is becoming more and more essential to support either mechanistic preclinical studies to investigate the role of inflammation in cardiovascular disease (CVD), or as a translational tool to quantify inflammation in the cardiovascular system and hematopoietic organs in patients. In this review paper, we will describe the clinical applications of non-invasive imaging to quantify inflammation in the vasculature, infarcted heart and brain, and hematopoietic organs in patients with cardiovascular disease, with specific focus on [¹⁸F]FDG PET and other novel inflammation-specific radiotracers. Furthermore, we will briefly describe the most recent clinical applications of other imaging techniques such as MRI, SPECT, CT, CEUS and OCT in this arena.

Keywords

Atherosclerosis; Positron-emission tomography; Cardiovascular disease

Cardiovascular inflammation plays a crucial role in the development and aggravation of atherosclerosis.¹ Hypercholesterolemia, and the subsequent deposition and oxidation of low-density lipoproteins (LDL) in the arterial vessel wall, triggers a local maladaptive immune and inflammatory response which is responsible for the initiation and progression of atherogenesis. The migration, infiltration and death of inflammatory monocyte/macrophages in the arterial wall ultimately leads to the formation of vulnerable atherosclerotic plaques at high risk for causing fatal cardiovascular events.²

*Corresponding author: Zahi A. Fayad, BioMedical Engineering and Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, One Gustave L. Levy Place, 10029 New York, NY, USA. zahi.fayad@mssm.edu.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

In addition to its role in the vasculature, inflammation is also key in determining the extent of tissue damage, healing and repair in the heart and brain after myocardial infarction^{3–5} and stroke.^{6, 7} Animal⁸ and human^{9, 10} data indicate that cardio- and cerebrovascular ischemia elicit a systemic inflammatory response that not only affects the infarcted heart and brain, but also aggravates vascular inflammation in sites proximal and distal to the original culprit vascular lesion, thereby increasing the chance of secondary events.⁸ This complex network of interactions is orchestrated by the activation of hematopoietic progenitor stem cells (HPSCs) in the bone marrow, and by the timed release of phenotypically different waves of monocytes from the bone marrow and spleen into the blood stream.⁸ Other conditions resulting in heightened systemic inflammation, such as inflammatory^{11, 12} or autoimmune diseases,¹³ can also accelerate the development of atherosclerosis, independent of lipid levels.

While the ‘inflammatory hypothesis’ of atherosclerosis has been heavily supported by this evidence, final proof of its validity has been only recently provided by the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial.^{14–17} For the first time, this study demonstrated that secondary cardiovascular events can be effectively prevented by using solely specific anti-inflammatory therapies (targeted against inflammatory cytokine IL1 β), without any intervention on patients’ lipid profiles.

In this landscape, non-invasive imaging is becoming more and more essential to support either mechanistic preclinical studies to investigate the role of inflammation in cardiovascular disease (CVD), or as a translational tool to quantify inflammation in the cardiovascular system and hematopoietic organs in patients (Figure 1). Positron emission tomography (PET) with the radiotracer [¹⁸F]fluorodeoxyglucose (FDG) or other novel inflammation tracers, is widely used in clinical studies to monitor vascular inflammation in the carotid, aorta, femoral and even coronary arteries, during plaque progression or regression after therapeutic intervention.¹⁸ PET is also used to probe inflammation in the infarcted heart¹⁹ or brain,²⁰ and hematopoietic organs activation^{9, 10} in the context of CVD. MRI with ultrasmall particles of iron oxide (USPIOs) has also been investigated to measure plaque content of inflammatory cells.²¹ Other non-invasive imaging technologies based on computed tomography (CT),²² single photon emission computed tomography (SPECT),^{23, 24} and contrast enhanced ultrasound (CEUS),^{25–27} or invasive techniques such as optical coherence tomography (OCT)^{28, 29} are also currently being investigated in the clinical and preclinical arenas to improve our understanding of inflammation in CVD.

In this review paper, we will describe the clinical applications of non-invasive imaging to quantify inflammation in the vasculature, infarcted heart and brain, and hematopoietic organs in patients with cardiovascular disease, with specific focus on [¹⁸F]FDG PET and other novel inflammation-specific radiotracers. Furthermore, we will briefly describe the most recent clinical applications of other imaging techniques such as MRI, SPECT, CT, CEUS and OCT in this arena.

Metabolic imaging of cardiovascular inflammation with [^{18}F]FDG PET

PET with the metabolic tracer [^{18}F]FDG is nowadays widely applied for the quantification of vascular inflammation in clinical atherosclerosis studies (Figure 2).^{9, 30} The use of this technique to identify vulnerable plaques in humans was first proposed almost 20 years ago,³¹ when higher uptake of [^{18}F]FDG was demonstrated in patients with symptomatic carotid plaques, as opposed to the asymptomatic contralateral side (27% less uptake) and healthy arteries (no uptake detected). Since then [^{18}F]FDG has been extensively validated as a surrogate marker of plaque macrophage content in both animal models^{32–34} and patients with atherosclerosis³⁵ by several, independent studies and in different vascular beds (carotids, aorta, femoral and coronary arteries).^{36, 37}

The predictive value of [^{18}F]FDG vascular uptake for future progression of atherosclerotic plaques has also been investigated.³⁸ A recent sub-analysis³⁸ including⁴² subjects enrolled in the dal-PIAQUE clinical trial, investigating the safety and antiatherosclerotic efficacy of the cholesterylester transfer protein (CETP) inhibitor dalcetrapib, revealed that individuals exhibiting a significant increase in carotid [^{18}F]FDG uptake over 6 months, also showed significant long term (24 months) structural changes in carotid mean wall thickness (MWT, 17.5%) and mean wall area (MWA, 25.5%) by MRI with respect to control subjects. These results strengthen our notion that heightened [^{18}F]FDG vascular uptake is reflective of functional changes in the arterial vessel wall which may precede and predict structural changes related to progression of atherosclerosis. Furthermore, this study suggests that early targeting of vascular inflammation with appropriate therapeutic regimens may slow down the formation of high-risk, vulnerable plaques.

These results were confirmed and expanded upon by a recent sub-study in 755 subjects participating in the Progression of Early Subclinical Atherosclerosis (PESA) clinical trial, which enrolled participants with documented atherosclerosis by baseline ultrasound or CT.^{39, 40} This sub-analysis revealed that 48.2% of the recruited patient population presented with focal [^{18}F]FDG uptake in either their femoral (24.4%), aorta (19.3%), carotids (15.8%) or iliac (9.3%) arteries. Individuals with increased [^{18}F]FDG hot spots also had overall increased plaque burden, in terms of presence, number and volume. Compared to plaques not showing marked [^{18}F]FDG uptake, “hot” plaques were most often located in the carotid and femoral arteries and were larger in volume. Interestingly, in this patient population, [^{18}F]FDG hot spots were also identified in plaque-free arterial segments (459 out of 746; 61.5%), as opposed to plaques (287 out of 2605, 11%), indicating that arterial inflammation may be highly prevalent in middle-aged individuals with known subclinical CVD, potentially indicating systemic, early stage atherosclerosis.

[^{18}F]FDG PET is nowadays widely used as a surrogate non-invasive imaging endpoint of anti-inflammatory drug efficacy in CVD clinical trials. As an example, a recent meta-analysis⁴¹ identified at least 7 eligible clinical studies that have used [^{18}F]FDG PET to evaluate the anti-inflammatory effects of lipid lowering statins, comprising at least 10 treatment arms and 287 subjects. This analysis found that [^{18}F]FDG PET was indeed able to consistently quantify the anti-inflammatory effect of statins (either high and low-to-moderate dose) in these different trials. Duration of treatment, plasma cholesterol and C-

reactive protein (CRP) levels, as well as baseline [^{18}F]FDG uptake values did not affect these outcomes. We refer the reader to this publication⁴¹ for more details on these important studies. Of importance for the application of [^{18}F]FDG PET in clinical trials, another recent study attempted to calculate a fixed threshold of [^{18}F]FDG uptake in the carotid arteries and aortic arch of subjects with risk factors for CVD (N.=23) and known CVD (N.=35) as compared to healthy controls (N.=25).⁴² This study demonstrated diffuse uptake of ^{18}F -FDG vascular uptake in healthy individuals, and established that a [^{18}F]FDG target-to-background ratio (TBR) of 1.84 for the carotids and 2.68 in the aorta best separated these three groups, with patients at risk for or with confirmed CVD exceeding this threshold 52% and 67% of the time, respectively. Importantly, this study also confirmed the high reproducibility of [^{18}F]FDG vascular measurements, as already reported by other investigators.⁴³ Although limited to a small cohort, these findings are relevant to the planning of adequately powered clinical drug trials using [^{18}F]FDG PET.

In addition to the vasculature [^{18}F]FDG has also been used to probe inflammation in organs affected by ischemia, mainly the infarcted heart (Figure 2). [^{18}F]FDG PET has been historically used in myocardial infarction together with late gadolinium enhancement (LGE) MRI or perfusion imaging to identify viable from non-viable cardiomyocytes.⁴⁴ However, recent mouse studies have demonstrated that it is also possible to utilize this technique to quantify macrophage/monocyte infiltration in the infarcted myocardium,⁴⁵ provided that [^{18}F]FDG physiological uptake in healthy cardiomyocytes can be adequately suppressed.⁴⁵ While in animals this is usually achieved with specific anesthesia regimens (for example ketamine/xylazine *versus* isoflurane⁴⁵), in humans specific measures (dietary restrictions and/or heparin administration) have to be followed to achieve proper suppression of physiological [^{18}F]FDG uptake.⁴⁶ The first reports of spotty, persistent [^{18}F]FDG uptake in patients after myocardial infarction date to more than 10 years ago.⁴⁷ Since then, several clinical studies have confirmed higher uptake of [^{18}F]FDG in the infarct zone of patients after acute MI compared to remote and healthy myocardium.^{48–50} [^{18}F]FDG uptake was higher in segments exhibiting LGE,⁴⁷ and with increased extra cellular volume (ECV) fraction and native T1 relaxation time by MRI,⁴⁹ and was associated with poorer left ventricular functional outcome, independent of infarct size.¹⁰ Interestingly a correlation between [^{18}F]FDG uptake in the infarct zone, and [^{18}F]FDG signal in hematopoietic organs (bone marrow and spleen) has also been found in humans⁹ (Figure 2). These findings suggest a potential association between local myocardial inflammation and the systemic immune/inflammatory response after ischemia. Furthermore, together with other studies in this field,^{9, 51} these findings reinforce the translational value of mechanistic mouse studies implicating the hematopoietic system in the inflammatory response after myocardial infarction.⁸

While [^{18}F]FDG PET is a powerful tool to evaluate vascular inflammation in atherosclerosis, using this tracer in cardiovascular disease still poses specific challenges. Firstly, the use of [^{18}F]FDG to evaluate cardiovascular disease is not fully standardized, in terms of image acquisition and analysis protocols. A recent peer-reviewed publication has acknowledged this lack of standardization and attempted to provide guidelines for the use of this important tracer in CVD.⁵² Furthermore, [^{18}F]FDG is a metabolic tracer whose uptake is proportional to cells' oxidative glucose metabolism. While [^{18}F]FDG vascular uptake has

been consistently linked to the presence of inflammatory cells, and specifically macrophages, in atherosclerotic plaques,^{32–35} in principle this tracer is not specific for this cell type. For example, recent papers have found [¹⁸F]FDG uptake to be comparable in macrophage-rich and -poor regions in preclinical swine models^{53, 54} of atherosclerosis and *in vitro* studies.⁵⁵ High physiological uptake of [¹⁸F]FDG in the healthy heart and brain makes it also challenging to use this tracer to probe vascular inflammation in the intracranial and coronary⁵⁶ circulations. To surpass these challenges, other tracers, either probing other aspects of plaque physiology related to plaque inflammation, or more specific to inflammatory cells, are currently being investigated.¹⁸ Among these [¹⁸F]NaF, targeting microcalcification, and [⁶⁸Ga] 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTATATE), specific for somatostatin receptor 2 (SSTR2) positive plaque macrophages, have been recently receiving increasing attention for their use in clinical atherosclerosis studies.¹⁸

Imaging microcalcification using [¹⁸F]NaF

Since the first reports almost 10 years ago showing higher [¹⁸F]NaF activity than [¹⁸F]FDG in patients with coronary^{57, 58} and carotid^{59, 60} atherosclerosis, the number of studies investigating the role of this tracer to characterize inflammation in cardiovascular disease has increased exponentially (Figure 3).^{30, 61} [¹⁸F]NaF vascular uptake has been validated as a readout of plaque intimal microcalcification,⁶² a feature that in preclinical studies has been associated with the presence of plaque inflammation. Correlations between [¹⁸F]NaF uptake and coronary CT calcium score have led to variable results, with some studies indicating a positive significant correlation (higher for partially calcified lesions than fully calcified and non-calcified plaques)⁶³ and others reporting no correlation at all.⁶⁴ While a definitive relationship with plaque inflammatory cell content has not been established, [¹⁸F]NaF uptake was found to increase in the coronary, aorta and carotid artery with increasing risk for CVD,⁶⁴ and to be higher in ‘soft’ plaques with a high-risk phenotype identified by CT.⁶⁵ Importantly, a prospective study of 32 patients (112 lesions) imaged with [¹⁸F]NaF and then followed for 2 years, showed higher [¹⁸F]NaF uptake in 11 patients experiencing coronary events (defined as acute coronary syndrome and/or late coronary revascularization) with a maximum TBR_{max} cutoff of 1.28 to predict at-risk individuals.⁶⁶ Another recent prospective study of 50 patients investigated whether ¹⁸F-NaF and ¹⁸F-FDG PET could predict the rate of restenosis following lower limb percutaneous transluminal angioplasty (PTA).⁶¹ Of the 40 subjects completing the study, 14 patients (35%) reached the primary endpoint of restenosis within 12 months from PTA. Baseline TBR for both tracers was higher in patients who developed restenosis, with cut-off 2.11 for [¹⁸F]NaF and 1.98 for [¹⁸F]FDG, and excellent predictive value for both tracers. In addition to being a promising marker for the detection of plaque microcalcification and inflammation, a recent study³⁰ has provided the first proof-of-principle indicating that [¹⁸F]NaF also accumulates in the infarct scar area after myocardial infarction (Figure 3), thereby suggesting that this tracer may be a good alternative to [¹⁸F]FDG to detect inflammation in the heart after acute coronary events, without the need of specific protocols to suppress physiological background uptake.

Somatostatin receptor 2 (SSTR2) imaging with [⁶⁸Ga]DOTATATE

[⁶⁸Ga]DOTATATE is a tracer that was originally developed for the improved detection of somatostatin receptor 2 (SSTR2) positive neuroendocrine tumors.⁶⁷ The discovery that SSTR2s are present also on plaque macrophages^{68, 69} has led to significant interest in this tracer as a more specific marker of plaque inflammation than [¹⁸F]FDG, especially for applications in the challenging coronary arteries and myocardium (Figure 4).^{69–71} Concomitantly to studies in mice confirming SSTR2-specific uptake of this tracer in atherosclerotic plaques,⁶⁸ clinical studies started investigating the utility of this tracer in atherosclerosis about 10 years ago. Initial retrospective studies in patients with neuroendocrine tumors focused on the coronaries and other large arteries (carotids, ascending and descending thoracic aorta, aortic arch, abdominal aorta, and iliac arteries) and revealed a significant correlation between [⁶⁸Ga]DOTATATE uptake and the presence of calcified plaques by CT,^{72, 73} prior cardiovascular events,⁷² and risk factors for cardiovascular disease, such as male sex,⁷² hypertension⁷³ and age.⁷³ [⁶⁸Ga]DOTATATE plaque signal was shown to correlate with [¹⁸F]FDG uptake.⁷³ Further investigation of the use of [⁶⁸Ga]DOTATATE in patients with cardiovascular disease has confirmed these results. Two studies in patients with coronary and/or carotid atherosclerosis undergoing carotid endarterectomy (CEA)^{69, 74} demonstrated significantly higher DOTATATE (either ⁶⁸Ga⁶⁹ or ⁶⁴Cu-labeled⁷²) uptake and significant SSTR2 expression in culprit *versus* non culprit lesions. In one of these studies,⁷² *ex-vivo* gene expression analysis of 62 plaque segments using quantitative polymerase chain reaction (qPCR) showed that CD68 (a marker for macrophages) and CD163 (a marker for alternatively activated macrophages) correlated significantly but weakly with [⁶⁴Cu]DOTATATE carotid uptake, with only CD163 being correlated in multivariate analysis. Similarly, other authors⁶⁹ also found a correlation between DOTATATE uptake and plaque macrophages, but with SSTR2 being preferentially expressed in classically activated macrophages. In addition to the vasculature, the uptake of [⁶⁸Ga]DOTATATE was recently demonstrated in the infarcted myocardium of patients with both recent (within 6 months) and old myocardial infarction, with little or no background signal in the non-infarcted tissue.⁷⁰ In these same subjects ¹⁸F-FDG signal was uninterpretable in 42% of the cases, but uptake of the two tracers was in agreement in analyzable patients. Furthermore, [⁶⁸Ga]DOTATATE activity in the bone marrow was correlated with [⁶⁸Ga]DOTATATE signal in the infarct, and with bone marrow metabolic activity by [¹⁸F]FDG. In ischemic stroke, a recent case report⁷¹ also described cerebral [⁶⁸Ga]DOTATATE uptake in a 76 years old man who had underwent PET imaging because of a present neuroendocrine tumor (Figure 4). Presence of a prior recent (1 month) ischemic stroke was indeed confirmed from the hospital chart after imaging.

Emerging cardiovascular inflammation PET imaging tracers

In addition to [¹⁸F]FDG, [¹⁸F]NaF and [⁶⁸Ga]DOTATATE, other PET tracers have been proposed or are currently being investigated to improve the quantification of plaque inflammation in humans.¹⁸ Among these are PET tracers targeting neoangiogenesis and hypoxia, two features of developing and vulnerable atherosclerotic plaques which are closely related to plaque inflammation. The formation of new, leaky neovessels facilitates the extravasation of inflammatory cells in atheromas. This knowledge has prompted the

investigation of plaque neoangiogenesis as a surrogate marker of plaque inflammation. Among the PET tracers targeting neoangiogenesis, [^{18}F]galacto-RGD, binding specifically to the integrin $\alpha_v\beta_3$ expressed on macrophages and endothelial cells, has been investigated in 10 patients with stenosis of the carotid artery. Tracer accumulation was found to be higher in stenotic *versus* non-stenotic segments, and weakly correlated with macrophage and microvessel density in endarterectomy specimens without reaching statistical significance.⁷⁵ PET imaging of α_7 nicotinic receptors, which have also been implicated in plaque neoangiogenesis, is also being actively pursued with a variety of novel tracers.⁷⁶ Somewhat related to plaque neoangiogenesis, imaging of plaque hypoxia has also been investigated, although only in *in-vitro*⁷⁷ and animal studies,⁷⁸ using ^{18}F -fluoromisonidazole (FMISO), a tracer commonly used to measure hypoxia in tumors. A paper in a rabbit model of atherosclerosis showed increased [^{18}F]FMISO accumulation after the development of atherosclerosis, and during atherosclerosis progression in this model.⁷⁸ Other investigators are focusing on imaging of β amyloid, whose deposition is primarily involved in the pathogenesis of Alzheimer's disease, but that has also been found to accumulate in the atherosclerotic vessel wall. Uptake of the Alzheimer's PET tracer [^{18}F]florbetaben, which binds to β amyloid, was found in the carotid arteries of subjects with cognitive impairment, regardless of the presence or absence of cerebral uptake.⁷⁹ In addition, there has also been renewed interest in more specific tracers targeted to plaque macrophages. Among these, the tracers [^{11}C]PK11195, targeted to the macrophage translocator protein (TSPO),⁸⁰ and [^{68}Ga]pentixafor,^{81–83} targeted to the macrophage chemokine receptor CXCR4, have attracted some attention. [^{11}C]PK11195 plaque uptake has been investigated in 32 patients with carotid stenosis, and was shown to exhibit higher uptake in culprit plaques *versus* contralateral vessels.⁸⁰ Several studies have also demonstrated accumulation of [^{11}C]PK11195 in areas of ischemic stroke⁸⁴ and in myocardial infarction.⁸⁵ Following preclinical mouse studies reporting on the feasibility of [^{68}Ga]pentixafor imaging to measure myocardial inflammation after ischemia, the uptake of this tracer in the vessel wall was investigated in a retrospective study of 51 patients that had been referred for imaging for non cardiovascular indications. In this population the authors found focal uptake of [^{68}Ga]pentixafor at 1411 sites in all patients, with uptake correlating with calcified plaque burden and cardiovascular risk factors (age, hypertension, hypercholesterolemia, smoking, and prior cardiovascular events).⁸¹ These results were confirmed by other studies in the carotid arteries, which also found prominent CXCR4 expression in inflamed carotid plaques.⁸³ Similar results were obtained in the coronary arteries of 37 patients after stent-based reperfusion after a first acute myocardial infarction.⁸² In the ischemic myocardium, a study⁸⁶ of 22 patients revealed [^{68}Ga]pentixafor uptake in 17 patients, which correlated negatively with the time elapsed between onset of symptoms and PET imaging (range: 2 to 13 days), and with scar volume at follow-up (evaluated by LGE MRI 1 to 14 months after baseline PET imaging). Tracer uptake was also observed in the bone marrow and spleen. Last but not least the tracer ^{18}F fluorothymidine (FLT), which is used in oncology to measure tumor cells proliferation, has also been investigated to quantify inflammatory and hematopoietic progenitor cells proliferation in the vessel wall and hematopoietic organs. Corroborated by positive findings in atherosclerotic mice and rabbits, [^{18}F]FLT uptake was found to be also increased in the inflamed carotid arteries and aortas of patients with atherosclerosis, in concordance with [^{18}F]FDG signal in these same vessels.⁸⁷

Current challenges to the clinical translation of PET imaging of cardiovascular inflammation

As described in the previous sections, PET imaging of cardiovascular inflammation has been widely adopted in clinical research studies and is also being used as a surrogate imaging endpoint of drug efficacy in several clinical trials. However, there are still several challenges that need to be addressed for its smooth translation into clinical practice to better stratify cardiovascular risk in patients and to monitor treatment response.

As already mentioned, cardiovascular PET image acquisition protocols are not fully standardized across different sites, in terms of injected dose, radiotracer circulation time and duration of imaging itself, all factors that can affect image quality and the kinetics and extent of radiotracer accumulation in target tissues.⁵² In addition, while the reproducibility of vascular PET has been previously assessed with good outcomes,⁴³ this kind of quantitative PET analysis requires a significant level of expertise to reliably obtain accurate SUV and TBR values, or to perform more sophisticated most diseased segment (MDS) analyses.

Last but not least, since PET involves the use of ionizing radiation, there might be some resistance in routinely using this imaging modality for evaluating chronic conditions, such as cardiovascular disease, which require longitudinal follow up imaging over many years to evaluate disease progression or stabilization/regression upon treatment. In order to mitigate these concerns several groups are working on novel PET acquisition and reconstructions protocols to obtain high signal-to-noise PET images while using low-dose injection protocols, including in the field of cardiovascular imaging. As a complement to this strategy, other researchers are also investing in the technical development of cardiovascular PET on combined dual-modality PET/MRI scanners.⁸⁸ This strategy bears two fundamental advantages compared to the more widely used PET/CT, namely, the lack of additional ionizing radiation from CT, and the ability to couple the quantitative, highly sensitive, functional information from PET with the superior soft tissue contrast and multiparametric capabilities of quantitative MRI.

Multimodality imaging of cardiovascular inflammation

In addition to PET, other imaging modalities have been used or are actively being developed and investigated to probe cardiovascular inflammation. Among nuclear medicine techniques, several SPECT tracers are being investigated to provide a better characterization of plaque inflammation.^{23, 24} Some techniques, such as dynamic contrast enhanced (DCE) MRI⁸⁸ or contrast enhanced ultrasound^{25–27} with non-targeted microbubbles, provide an indirect readout of plaque inflammation by measuring plaque enhanced permeability and neovascularization. MRI with iron oxide particles has also been used as a direct readout of plaque macrophages.²¹ Several studies have shown uptake of ultrasmall particles of iron oxide (USPIOs) in the carotid arteries of symptomatic patients scheduled for carotid endarterectomy, and it is colocalization with plaque macrophages.⁸⁹ Higher uptake was found in asymptomatic carotid artery disease with respect to individuals with no documented coronary⁹⁰ or carotid⁹¹ disease. More recently, higher USPIO uptake was confirmed in patients with carotid artery stenosis compared to healthy controls. However, no correlation

with 18F-FDG uptake was found in this cohort.⁹² USPIO MRI has also been used as a readout of antiatherosclerotic therapies. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) study showed a significant reduction in USPIO carotid uptake in patients with carotid stenosis treated with high dose (80 mg/day) of atorvastatin for 12 weeks, indicating a reduction of plaque inflammation, but no effect of a low dose regimen (10 mg/day).⁹³ Other emerging MR-based techniques, such as fluorine 19 (¹⁹F)^{94–98} or deuterium⁹⁹ MRI are actively being investigated to respectively quantify inflammatory cells or immunometabolism, and have already been used or may show potential applications in CVD. Among other imaging modalities, computed tomography (CT) is currently gaining interest not only for the characterization of vulnerable (soft) plaques, but also for the evaluation of the perivascular fat, whose CT attenuation value has been found to correlate with coronary inflammation by [¹⁸F]FDG PET.²² Lastly, invasive optical coherence tomography (OCT) has been showing potential to identify vulnerable, macrophage rich coronary plaques and changes in coronary plaque composition after statin therapy.^{28, 29}

Conclusions

In this review we have provided a summary of the imaging techniques most commonly used in clinical research as read-outs of cardiovascular inflammation, with specific focus on PET imaging with [¹⁸F]FDG, [¹⁸F]FLT, [¹⁸F]NaF and [⁶⁸Ga]DOTATATE, and their use in the vasculature, infarcted heart and brain, and hematopoietic system. Additionally, we have touched upon novel promising PET inflammation tracers which are being investigated in the clinics, or that are still in development in animal models, to improve the quantification of inflammation in cardiovascular disease. Last but not least, we have provided a brief overview of other imaging approaches based on SPECT, MRI, US and CT also geared towards this goal. We foresee that development in each of these areas will improve our understanding of the mechanisms underlying the development and progression of cardiovascular disease, and our ability to identify patients at risk for primary and secondary cardiovascular events. Specifically, we envision that the combination of different approaches in multimodalities scanners, such as PET/MR,⁸⁸ will help exploiting the complementary information from different imaging techniques to further improve our assessment of cardiovascular risk in the near future.

References

1. Libby P Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;32:2045–51. [PubMed: 22895665]
2. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;5:56. [PubMed: 31420554]
3. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. *Nat Rev Cardiol* 2014;11:255–65. [PubMed: 24663091]
4. Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. *Circ Res* 2016;119:91–112. [PubMed: 27340270]
5. Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. *Circulation* 2010;121:2437–45. [PubMed: 20530020]

6. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol* 2016;15:869–81. [PubMed: 27180033]
7. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med* 2011;17:796–808. [PubMed: 21738161]
8. Dutta P, Courties G, Wei Y, Leuschner F, Gorbato R, Robbins CS, et al. Myocardial infarction accelerates atherosclerosis. *Nature* 2012;487:325–9. [PubMed: 22763456]
9. Emami H, Singh P, MacNabb M, Vucic E, Lavender Z, Rudd JH, et al. Splenic metabolic activity predicts risk of future cardiovascular events: demonstration of a cardiosplenic axis in humans. *JACC Cardiovasc Imaging* 2015;8:121–30. [PubMed: 25577441]
10. Joshi NV, Toor I, Shah AS, Carruthers K, Vesey AT, Alam SR, et al. Systemic Atherosclerotic Inflammation Following Acute Myocardial Infarction: Myocardial Infarction Begets Myocardial Infarction. *J Am Heart Assoc* 2015;4:e001956. [PubMed: 26316523]
11. Smilowitz NR, Gupta N, Guo Y, Berger JS, Bangalore S. Perioperative acute myocardial infarction associated with non-cardiac surgery. *Eur Heart J* 2017;38:2409–17. [PubMed: 28821166]
12. Pothineni NV, Subramany S, Kuriakose K, Shirazi LF, Romeo F, Shah PK, et al. Infections, atherosclerosis, and coronary heart disease. *Eur Heart J* 2017;38:3195–201. [PubMed: 29020241]
13. Sanjadi M, Rezvanie Sichanie Z, Totonchi H, Karami J, Rezaei R, Aslani S. Atherosclerosis and autoimmunity: a growing relationship. *Int J Rheum Dis* 2018;21:908–21. [PubMed: 29671956]
14. Baylis RA, Gomez D, Mallat Z, Pasterkamp G, Owens GK. The CANTOS Trial: One Important Step for Clinical Cardiology but a Giant Leap for Vascular Biology. *Arterioscler Thromb Vasc Biol* 2017;37:e174–7. [PubMed: 28970294]
15. Weber C, von Hundelshausen P. CANTOS Trial Validates the Inflammatory Pathogenesis of Atherosclerosis: Setting the Stage for a New Chapter in Therapeutic Targeting. *Circ Res* 2017;121:1119–21. [PubMed: 29074528]
16. Ibañez B, Fuster V. CANTOS: A Gigantic Proof-of-Concept Trial. *Circ Res* 2017;121:1320–2. [PubMed: 29217712]
17. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al.; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017;377:1119–31. [PubMed: 28845751]
18. Tarkin JM, Joshi FR, Rudd JH. PET imaging of inflammation in atherosclerosis. *Nat Rev Cardiol* 2014;11:443–57. [PubMed: 24913061]
19. Kircher M, Lapa C. Novel Noninvasive Nuclear Medicine Imaging Techniques for Cardiac Inflammation. *Curr Cardiovasc Imaging Rep* 2017;10:6. [PubMed: 28357026]
20. Heiss WD. Radionuclide imaging in ischemic stroke. *J Nucl Med* 2014;55:1831–41. [PubMed: 25300599]
21. Tang TY, Muller KH, Graves MJ, Li ZY, Walsh SR, Young V, et al. Iron oxide particles for atheroma imaging. *Arterioscler Thromb Vasc Biol* 2009;29:1001–8. [PubMed: 19229073]
22. Antonopoulos AS, Sanna F, Sabharwal N, Thomas S, Oikonomou EK, Herdman L, et al. Detecting human coronary inflammation by imaging perivascular fat. *Sci Transl Med* 2017;9:9.
23. Na Jager, Westra J, Golestani R, van Dam GM, Low PS, Tio RA, et al. Folate receptor-β imaging using ^{99m}Tc-folate to explore distribution of polarized macrophage populations in human atherosclerotic plaque. *J Nucl Med* 2014;55:1945–51. [PubMed: 25359878]
24. Zanni MV, Toribio M, Wilks MQ, Lu MT, Burdo TH, Walker J, et al. Application of a Novel CD206+ Macrophage-Specific Arterial Imaging Strategy in HIV-Infected Individuals. *J Infect Dis* 2017;215:1264–9. [PubMed: 28204544]
25. Giannarelli C, Ibanez B, Cimmino G, Garcia Ruiz JM, Fata F, Bianchini E, et al. Contrast-enhanced ultrasound imaging detects intraplaque neovascularization in an experimental model of atherosclerosis. *JACC Cardiovasc Imaging* 2010;3:1256–64. [PubMed: 21163454]
26. Coli S, Magnoni M, Sangiorgi G, Marrocco-Trischitta MM, Melisurgo G, Mauriello A, et al. Contrast-enhanced ultrasound imaging of intraplaque neovascularization in carotid arteries: correlation with histology and plaque echogenicity. *J Am Coll Cardiol* 2008;52:223–30. [PubMed: 18617072]

27. Magnoni M, Coli S, Marrocco-Trischitta MM, Melisurgo G, De Dominicis D, Cianflone D, et al. Contrast-enhanced ultrasound imaging of periadventitial vasa vasorum in human carotid arteries. *Eur J Echocardiogr* 2009;10:260–4. [PubMed: 18757860]
28. Scalone G, Niccoli G, Refaat H, Vergallo R, Porto I, Leone AM, et al. Not all plaque ruptures are born equal: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging* 2017;18:1271–7. [PubMed: 28013285]
29. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. *J Am Coll Cardiol* 2014;64:2207–17. [PubMed: 25456755]
30. Marchesseau S, Seneviratna A, Sjöholm AT, Qin DL, Ho JX, Hausenloy DJ, et al. Hybrid PET/CT and PET/MRI imaging of vulnerable coronary plaque and myocardial scar tissue in acute myocardial infarction. *J Nucl Cardiol* 2018;25:2001–11. [PubMed: 28500539]
31. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;105:2708–11. [PubMed: 12057982]
32. Vucic E, Dickson SD, Calcagno C, Rudd JH, Moshier E, Hayashi K, et al. Pioglitazone modulates vascular inflammation in atherosclerotic rabbits noninvasive assessment with FDG-PET-CT and dynamic contrast-enhanced MR imaging. *JACC Cardiovasc Imaging* 2011;4:1100–9. [PubMed: 21999870]
33. Vucic E, Calcagno C, Dickson SD, Rudd JH, Hayashi K, Bucarius J, et al. Regression of inflammation in atherosclerosis by the LXR agonist R211945: a noninvasive assessment and comparison with atorvastatin. *JACC Cardiovasc Imaging* 2012;5:819–28. [PubMed: 22897996]
34. Zhang Z, Machac J, Helft G, Worthley SG, Tang C, Zaman AG, et al. Non-invasive imaging of atherosclerotic plaque macrophage in a rabbit model with F-18 FDG PET: a histopathological correlation. *BMC Nucl Med* 2006;6:3. [PubMed: 16725052]
35. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol* 2006;48:1818–24. [PubMed: 17084256]
36. Chowdhury MM, Tarkin JM, Evans NR, Le E, Warburton EA, Hayes PD, et al. 18F-FDG Uptake on PET/CT in Symptomatic versus Asymptomatic Carotid Disease: a Meta-Analysis. *Eur J Vasc Endovasc Surg* 2018;56:172–9. [PubMed: 29730127]
37. Chaker S, Al-Dasuqi K, Baradaran H, Demetres M, Delgado D, Nehmeh S, et al. Carotid Plaque Positron Emission Tomography Imaging and Cerebral Ischemic Disease. *Stroke* 2019;50:2072–9. [PubMed: 31272325]
38. Joseph P, Ishai A, Mani V, Kallend D, Rudd JH, Fayad ZA, et al. Short-term changes in arterial inflammation predict long-term changes in atherosclerosis progression. *Eur J Nucl Med Mol Imaging* 2017;44:141–50. [PubMed: 27738728]
39. Fernández-Friera L, Fuster V, López-Melgar B, Oliva B, Sánchez-González J, Macías A, et al. Vascular Inflammation in Subclinical Atherosclerosis Detected by Hybrid PET/MRI. *J Am Coll Cardiol* 2019;73:1371–82. [PubMed: 30922468]
40. Blankstein R, Libby P, Bhatt DL. Arterial Inflammation: The Heat Before the Storm. *J Am Coll Cardiol* 2019;73:1383–5. [PubMed: 30922469]
41. Pirro M, Simental-Mendía LE, Bianconi V, Watts GF, Banach M, Sahebkar A. Effect of Statin Therapy on Arterial Wall Inflammation Based on 18F-FDG PET/CT: A Systematic Review and Meta-Analysis of Interventional Studies. *J Clin Med* 2019;8:8.
42. van der Valk FM, Verweij SL, Zwinderman KA, Strang AC, Kaiser Y, Marquering HA, et al. Thresholds for Arterial Wall Inflammation Quantified by 18F-FDG PET Imaging: Implications for Vascular Interventional Studies. *JACC Cardiovasc Imaging* 2016;9:1198–207. [PubMed: 27639759]
43. Rudd JH, Myers KS, Bansilal S, Machac J, Pinto CA, Tong C, et al. Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *J Nucl Med* 2008;49:871–8. [PubMed: 18483100]

44. Rischpler C, Langwieser N, Souvatzoglou M, Batrice A, van Marwick S, Snajberk J, et al. PET/MRI early after myocardial infarction: evaluation of viability with late gadolinium enhancement transmurality vs. 18F-FDG uptake. *Eur Heart J Cardiovasc Imaging* 2015;16:661–9. [PubMed: 25680385]
45. Lee WW, Marinelli B, van der Laan AM, Sena BF, Gorbato R, Leuschner F, et al. PET/MRI of inflammation in myocardial infarction. *J Am Coll Cardiol* 2012;59:153–63. [PubMed: 22222080]
46. Thackeray JT, Bankstahl JP, Wang Y, Wollert KC, Bengel FM. Clinically relevant strategies for lowering cardiomyocyte glucose uptake for 18F-FDG imaging of myocardial inflammation in mice. *Eur J Nucl Med Mol Imaging* 2015;42:771–80. [PubMed: 25389013]
47. Godino C, Messa C, Gianolli L, Landoni C, Margonato A, Cera M, et al. Multifocal, persistent cardiac uptake of [18-F]-fluoro-deoxy-glucose detected by positron emission tomography in patients with acute myocardial infarction. *Circ J* 2008;72:1821–8. [PubMed: 18827373]
48. Wollenweber T, Roentgen P, Schäfer A, Schatka I, Zwadlo C, Brunkhorst T, et al. Characterizing the inflammatory tissue response to acute myocardial infarction by clinical multimodality noninvasive imaging. *Circ Cardiovasc Imaging* 2014;7:811–8. [PubMed: 25049056]
49. Kunze KP, Dirschinger RJ, Kossmann H, Hanus F, Ibrahim T, Laugwitz KL, et al. Quantitative cardiovascular magnetic resonance: extracellular volume, native T1 and 18F-FDG PET/CMR imaging in patients after revascularized myocardial infarction and association with markers of myocardial damage and systemic inflammation. *J Cardiovasc Magn Reson* 2018;20:33. [PubMed: 29792210]
50. Rischpler C, Dirschinger RJ, Nekolla SG, Kossmann H, Nicolosi S, Hanus F, et al. Prospective Evaluation of 18F-Fluorodeoxyglucose Uptake in Postischemic Myocardium by Simultaneous Positron Emission Tomography/Magnetic Resonance Imaging as a Prognostic Marker of Functional Outcome. *Circ Cardiovasc Imaging* 2016;9:e004316. [PubMed: 27056601]
51. Kim EJ, Kim S, Kang DO, Seo HS. Metabolic activity of the spleen and bone marrow in patients with acute myocardial infarction evaluated by 18f-fluorodeoxyglucose positron emission tomographic imaging. *Circ Cardiovasc Imaging* 2014;7:454–60. [PubMed: 24488982]
52. Bucerius J, Hyafil F, Verberne HJ, Slart RH, Lindner O, Sciagra R, et al.; Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis. *Eur J Nucl Med Mol Imaging* 2016;43:780–92. [PubMed: 26678270]
53. Rh Al-Mashhadi, Tolbod LP, Bloch LO, Bjørklund MM, Nasr ZP, Al-Mashhadi Z, et al. 18Fluorodeoxyglucose Accumulation in Arterial Tissues Determined by PET Signal Analysis. *J Am Coll Cardiol* 2019;74:1220–32. [PubMed: 31466620]
54. Libby P, Bhatt DL, Di Carli M. Fluorodeoxyglucose Uptake in Atheroma: Not So Simple. *J Am Coll Cardiol* 2019;74:1233–6. [PubMed: 31466621]
55. Folco EJ, Sheikine Y, Rocha VZ, Christen T, Shvartz E, Sukhova GK, et al. Hypoxia but not inflammation augments glucose uptake in human macrophages: implications for imaging atherosclerosis with 18fluorinelabeled 2-deoxy-D-glucose positron emission tomography. *J Am Coll Cardiol* 2011;58:603–14. [PubMed: 21798423]
56. Robson PM, Dweck MR, Trivieri MG, Abgral R, Karakatsanis NA, Contreras J, et al. Coronary Artery PET/MR Imaging: Feasibility, Limitations, and Solutions. *JACC Cardiovasc Imaging* 2017;10(10 Pt A):1103–12. [PubMed: 28109921]
57. Dweck MR, Chow MW, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. *J Am Coll Cardiol* 2012;59:1539–48. [PubMed: 22516444]
58. Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 2014;383:705–13. [PubMed: 24224999]
59. Quirce R, Martínez-Rodríguez I, Banzo I, Jiménez-Bonilla J, Martínez-Amador N, Ibáñez-Bravo S, et al. New insight of functional molecular imaging into the atheroma biology: 18F-NaF and 18F-FDG in symptomatic and asymptomatic carotid plaques after recent CVA. Preliminary results. *Clin Physiol Funct Imaging* 2016;36:499–503. [PubMed: 26147617]

60. Cocker MS, Spence JD, Hammond R, Wells G, deKemp RA, Lum C, et al.; Canadian Atherosclerosis Imaging Network (CAIN). [18F]-NaF PET/CT Identifies Active Calcification in Carotid Plaque. *JACC Cardiovasc Imaging* 2017;10:486–8. [PubMed: 27318719]
61. Chowdhury MM, Tarkin JM, Albaghdadi MS, Evans NR, Le EP, Berrett TB, et al. Vascular Positron Emission Tomography and Restenosis in Symptomatic Peripheral Arterial Disease: A Prospective Clinical Study. *JACC Cardiovasc Imaging* 2019;S1936–878X(19)30450–4.
62. Irkle A, Vesey AT, Lewis DY, Skepper JN, Bird JL, Dweck MR, et al. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. *Nat Commun* 2015;6:7495. [PubMed: 26151378]
63. Kitagawa T, Yamamoto H, Toshimitsu S, Sasaki K, Senoo A, Kubo Y, et al. 18F-sodium fluoride positron emission tomography for molecular imaging of coronary atherosclerosis based on computed tomography analysis. *Atherosclerosis* 2017;263:385–92. [PubMed: 28528743]
64. Oliveira-Santos M, Castelo-Branco M, Silva R, Gomes A, Chichorro N, Abrunhosa A, et al. Atherosclerotic plaque metabolism in high cardiovascular risk subjects - A subclinical atherosclerosis imaging study with 18F-NaF PET-CT. *Atherosclerosis* 2017;260:41–6. [PubMed: 28349887]
65. Kwiecinski J, Dey D, Cadet S, Lee SE, Tamarappoo B, Otaki Y, et al. Predictors of 18F-sodium fluoride uptake in patients with stable coronary artery disease and adverse plaque features on computed tomography angiography. *Eur Heart J Cardiovasc Imaging* 2020;21:58–66.
66. Kitagawa T, Yamamoto H, Nakamoto Y, Sasaki K, Toshimitsu S, Tatsugami F, et al. Predictive Value of 18F-Sodium Fluoride Positron Emission Tomography in Detecting High-Risk Coronary Artery Disease in Combination With Computed Tomography. *J Am Heart Assoc* 2018;7:e010224. [PubMed: 30371290]
67. Tirosh A, Papadakis GZ, Millo C, Hammoud D, Sadowski SM, Herscovitch P, et al. Prognostic Utility of Total (68)Ga-DOTATATE-Avid Tumor Volume in Patients With Neuroendocrine Tumors. *Gastroenterology* 2018;154:998–1008 e1. [PubMed: 29155309]
68. Li X, Bauer W, Kreissl MC, Weirather J, Bauer E, Israel I, et al. Specific somatostatin receptor II expression in arterial plaque: (68)Ga-DOTATATE autoradiographic, immunohistochemical and flow cytometric studies in apoE-deficient mice. *Atherosclerosis* 2013;230:33–9. [PubMed: 23958249]
69. Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, et al. Detection of Atherosclerotic Inflammation by 68Ga-DOTATATE PET Compared to [18F]FDG PET Imaging. *J Am Coll Cardiol* 2017;69:1774–91. [PubMed: 28385306]
70. Tarkin JM, Calcagno C, Dweck MR, Evans NR, Chowdhury MM, Gopalan D, et al. 68Ga-DOTATATE PET Identifies Residual Myocardial Inflammation and Bone Marrow Activation After Myocardial Infarction. *J Am Coll Cardiol* 2019;73:2489–91. [PubMed: 31097170]
71. Vallée É, Paquet N, Buteau JP, Turcotte É. 68Ga-DOTATATE Uptake in Ischemic Stroke. *Clin Nucl Med* 2018;43:46–7. [PubMed: 29135613]
72. Rominger A, Saam T, Vogl E, Ubleis C, la Fougère C, Förster S, et al. In vivo imaging of macrophage activity in the coronary arteries using 68Ga-DOTATATE PET/CT: correlation with coronary calcium burden and risk factors. *J Nucl Med* 2010;51:193–7. [PubMed: 20080898]
73. Li X, Samnick S, Lapa C, Israel I, Buck AK, Kreissl MC, et al. 68Ga-DOTATATE PET/CT for the detection of inflammation of large arteries: correlation with 18F-FDG, calcium burden and risk factors. *EJNMMI Res* 2012;2:52. [PubMed: 23016793]
74. Pedersen SF, Sandholt BV, Keller SH, Hansen AE, Clemmensen AE, Sillesen H, et al. 64Cu-DOTATATE PET/MRI for Detection of Activated Macrophages in Carotid Atherosclerotic Plaques: Studies in Patients Undergoing Endarterectomy. *Arterioscler Thromb Vasc Biol* 2015;35:1696–703. [PubMed: 25977567]
75. Beer AJ, Pelisek J, Heider P, Saraste A, Reeps C, Metz S, et al. PET/CT imaging of integrin $\alpha v \beta 3$ expression in human carotid atherosclerosis. *JACC Cardiovasc Imaging* 2014;7:178–87. [PubMed: 24412187]
76. Boswijk E, Bauwens M, Mottaghy FM, Wildberger JE, Bucerius J. Potential of $\alpha 7$ nicotinic acetylcholine receptor PET imaging in atherosclerosis. *Methods* 2017;130:90–104. [PubMed: 28602809]

77. Shimizu Y, Motomura A, Takakura H, Tamaki N, Kuge Y, Ogawa M. Accumulation of hypoxia imaging probe “18F-FMISO” in macrophages depends on macrophage polarization in addition to hypoxic state. *Ann Nucl Med* 2019;33:362–7. [PubMed: 30694443]
78. Mateo J, Izquierdo-Garcia D, Badimon JJ, Fayad ZA, Fuster V. Noninvasive assessment of hypoxia in rabbit advanced atherosclerosis using 18F-fluoromisonidazole positron emission tomographic imaging. *Circ Cardiovasc Imaging* 2014;7:312–20. [PubMed: 24508668]
79. Bucerius J, Barthel H, Tiepolt S, Werner P, Sluimer JC, Wildberger JE, et al. Feasibility of in vivo 18F-florbetaben PET/MR imaging of human carotid amyloid- β . *Eur J Nucl Med Mol Imaging* 2017;44:1119–28. [PubMed: 28321471]
80. Gaemperli O, Shalhoub J, Owen DR, Lamare F, Johansson S, Fouladi N, et al. Imaging intraplaque inflammation in carotid atherosclerosis with 11C-PK11195 positron emission tomography/computed tomography. *Eur Heart J* 2012;33:1902–10. [PubMed: 21933781]
81. Weiberg D, Thackeray JT, Daum G, Sohns JM, Kropf S, Wester HJ, et al. Clinical Molecular Imaging of Chemokine Receptor CXCR4 Expression in Atherosclerotic Plaque Using 68Ga-Pentixafor PET: Correlation with Cardiovascular Risk Factors and Calcified Plaque Burden. *J Nucl Med* 2018;59:266–72. [PubMed: 28775206]
82. Derlin T, Sedding DG, Dutzmann J, Haghikia A, König T, Napp LC, et al. Imaging of chemokine receptor CXCR4 expression in culprit and nonculprit coronary atherosclerotic plaque using motion-corrected [68Ga]pentixafor PET/CT. *Eur J Nucl Med Mol Imaging* 2018;45:1934–44. [PubMed: 29967943]
83. Li X, Yu W, Wollenweber T, Lu X, Wei Y, Beitzke D, et al. [68Ga]Pentixafor PET/MR imaging of chemokine receptor 4 expression in the human carotid artery. *Eur J Nucl Med Mol Imaging* 2019;46:1616–25. [PubMed: 31004184]
84. Gulyas B, Toth M, Vas A, Shchukin E, Kostulas K, Hillert J, et al. Visualising neuroinflammation in post-stroke patients: a comparative PET study with the TSPO molecular imaging biomarkers [11C]PK11195 and [11C]vinpocetine. *Curr Radiopharm* 2012;5:19–28. [PubMed: 22074478]
85. Thackeray JT, Hupe HC, Wang Y, Bankstahl JP, Berding G, Ross TL, et al. Myocardial Inflammation Predicts Remodeling and Neuroinflammation After Myocardial Infarction. *J Am Coll Cardiol* 2018;71:263–75. [PubMed: 29348018]
86. Reiter T, Kircher M, Schirbel A, Werner RA, Kropf S, Ertl G, et al. Imaging of C-X-C Motif Chemokine Receptor CXCR4 Expression After Myocardial Infarction With [68Ga]Pentixafor-PET/CT in Correlation With Cardiac MRI. *JACC Cardiovasc Imaging* 2018;11:1541–3. [PubMed: 29454781]
87. Ye YX, Calcagno C, Binderup T, Courties G, Keliher EJ, Wojtkiewicz GR, et al. Imaging Macrophage and Hematopoietic Progenitor Proliferation in Atherosclerosis. *Circ Res* 2015;117:835–45. [PubMed: 26394773]
88. Robson PM, Dey D, Newby DE, Berman D, Li D, Fayad ZA, et al. MR/PET Imaging of the Cardiovascular System. *JACC Cardiovasc Imaging* 2017;10(10 Pt A):1165–79. [PubMed: 28982570]
89. Kooi ME, Cappendijk VC, Cleutjens KB, Kessels AG, Kitslaar PJ, Borgers M, et al. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. *Circulation* 2003;107:2453–8. [PubMed: 12719280]
90. Tang TY, Howarth SP, Miller SR, Graves MJ, U-King-Im JM, Li ZY, et al. Comparison of the inflammatory burden of truly asymptomatic carotid atheroma with atherosclerotic plaques in patients with asymptomatic carotid stenosis undergoing coronary artery bypass grafting: an ultrasmall superparamagnetic iron oxide enhanced magnetic resonance study. *Eur J Vasc Endovasc Surg* 2008;35:392–8. [PubMed: 18171628]
91. Tang TY, Howarth SP, Miller SR, Graves MJ, U-King-Im JM, Trivedi RA, et al. Comparison of the inflammatory burden of truly asymptomatic carotid atheroma with atherosclerotic plaques contralateral to symptomatic carotid stenosis: an ultra small superparamagnetic iron oxide enhanced magnetic resonance study. *J Neurol Neurosurg Psychiatry* 2007;78:1337–43. [PubMed: 17578854]

92. Smits LP, Tiessens F, Zheng KH, Stroes ES, Nederveen AJ, Coolen BF. Evaluation of ultrasmall superparamagnetic iron-oxide (USPIO) enhanced MRI with ferumoxytol to quantify arterial wall inflammation. *Atherosclerosis* 2017;263:211–8. [PubMed: 28662398]
93. Tang TY, Howarth SP, Miller SR, Graves MJ, Patterson AJ, U-King-Im JM, et al. The ATHEROMA (Atorvastatin Therapy: effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol* 2009;53:2039–50. [PubMed: 19477353]
94. Nienhaus F, Colley D, Jahn A, Pfeiler S, Flocke V, Temme S, et al. Phagocytosis of a PFOB-Nanoemulsion for ¹⁹F Magnetic Resonance Imaging: First Results in Monocytes of Patients with Stable Coronary Artery Disease and ST-Elevation Myocardial Infarction. *Molecules* 2019;24:24.
95. Wüst RC, Calcagno C, Daal MR, Nederveen AJ, Coolen BF, Strijkers GJ. Emerging Magnetic Resonance Imaging Techniques for Atherosclerosis Imaging. *Arterioscler Thromb Vasc Biol* 2019;39:841–9. [PubMed: 30917678]
96. Rothe M, Jahn A, Weiss K, Hwang JH, Szendroedi J, Kelm M, et al. In vivo ¹⁹F MR inflammation imaging after myocardial infarction in a large animal model at 3 T. *MAGMA* 2019;32:5–13. [PubMed: 30421248]
97. Bönner F, Merx MW, Klingel K, Begovatz P, Flögel U, Sager M, et al. Monocyte imaging after myocardial infarction with ¹⁹F MRI at 3 T: a pilot study in explanted porcine hearts. *Eur Heart J Cardiovasc Imaging* 2015;16:612–20. [PubMed: 25733209]
98. van Heeswijk RB, Pellegrin M, Flögel U, Gonzales C, Aubert JF, Mazzolai L, et al. Fluorine MR Imaging of Inflammation in Atherosclerotic Plaque in Vivo. *Radiology* 2015;275:421–9. [PubMed: 25496216]
99. de Feyter HM, Behar KL, Corbin ZA, Fulbright RK, Brown PB, McIntyre S, et al. Deuterium metabolic imaging (DMI) for MRI-based 3D mapping of metabolism in vivo. *Sci Adv* 2018;4:eaat7314. [PubMed: 30140744]

Figure 1.—

Overall overview of key organs and tissues involved in cardiovascular inflammation and atherogenesis, together with the most relevant PET tracers used to target these processes.

Figure 2.—.

^{18}F -FDG imaging of cardiovascular immunometabolism. Higher ^{18}F -FDG can be seen in the aortic arch, spleen and bone marrow of patients with acute coronary syndromes, with respect to controls (modified from Emami *et al.*⁹). Prominent ^{18}F -FDG uptake is also present in the infarcted heart after ischemia, indicating the presence of metabolically active inflammatory cells (modified from Marchesseau *et al.*³⁰).

Figure 3.—

^{18}F NaF imaging of microcalcification. High ^{18}F NaF can be seen in concomitance with a calcified lesion in the femoral artery of a patient affected by PAD (modified from Chowdhury *et al.*⁶¹). ^{18}F NaF uptake can also be detected in the infarcted myocardium (modified from Marchesseau *et al.*³⁰).

Figure 4.—

[^{68}Ga]DOTATATE imaging of SSTR2 positive macrophages. [^{68}Ga]DOTATATE uptake is remarkable in a non-calcified coronary plaque (modified from Tarkin *et al.*⁶⁹). Prominent uptake can also be seen in the infarcted heart and brain (modified from Tarkin *et al.*⁷⁰ and Vallee *et al.*⁷¹).