Inflammation and Neovascularization Intertwined in Atherosclerosis

Imaging of Structural and Molecular Imaging Targets

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Atherosclerosis is a chronic inflammatory disease characterized by lipid-containing inflammatory lesions of large- and medium-sized arteries. It is primarily a disease of the inner layer of the arterial wall, the intima. As the disease advances, the adventitia, however, also participates in the pathogenesis of the atherosclerosis. Herrmann et al have proposed that the development of human atherosclerotic lesions can be considered to involve 3 distinct stages. In the first stage, early alterations in cellular function result from the interaction of environmental risk factors and genetic predisposition. The second stage is characterized by the proliferation of adventitial vasa vasorum with subsequent extension of the neovessels into the inner media and eventually into the enlarging plaque. In vulnerable plaques, vessel density increases from 2- to 4-fold in disrupted plaques, compared with several obstructive stable lesions. Chronic lesions can enter the third stage with further neovascularization, especially in the vulnerable shoulder areas of the plaques. At this stage, the intraplaque neovessels may rupture, leading to intraplaque hemorrhage. This may be because of compromised integrity of the microvascular endothelium and plaque weakening secondary to inflammation. The exacerbation of tightly intertwined plaque inflammatory activity and neovascularization results in plaque rupture, leading to arterial thrombosis with ensuing clinical syndromes.

Revolution in the field of radiology in the last 3 decades has enabled imaging of inflammation and neovascularization within atherosclerotic tissue. In this article, we review advances in various clinical and preclinical imaging modalities aimed at unraveling the pathobiology of atherosclerosis.

Ultrasound Imaging

The use of ultrasound (US) for molecular imaging of the cardiovascular system is an extension of contrast echocardiographic principles already in clinical use. Nontargeted US contrast agents (UCAs) act purely as intravascular blood tracers behaving as red blood cells within the microcirculation. Targeted UCAs decorated with ligands, by affinity-based interaction, localize to a site where a specific target (usually a receptor) is pathologically upregulated. Typically a UCA is composed of microbubbles (MBs) that generally contain a gas core with a stabilizer shell of protein, lipid, or biocompatible polymers. Submicron gas-containing liposomes and acoustically active emulsion-based nanoparticles also exist. On exposure to US waves, MBs vibrate and resonate, creating an acoustic signal different from tissue backscatter, which enables US systems to maximize detection of UCAs.

Nontargeted US Imaging

Using nontargeted UCA, contrast-enhanced US (CEUS) imaging of neovascularization of carotid atherosclerotic plaques is feasible, with CEUS-visualized neovessels (Figure 1) having good histologic correlation with CD31-stained neovessels. However, excellent correlation is unlikely, because tunica adventitia and part of the media is left behind during carotid endarterectomy. The degree of plaque enhancement is not related to the degree of carotid stenosis. High plaque enhancement is prevalent among echolucent plaques, with plaque echogenicity inversely correlated with grade of intraplaque neovascularization. Because plaque echolucency is considered a marker of high-risk lesions, it highlights the ability of CEUS to differentiate between stable and unstable plaques. CEUS can differentiate between patients with symptomatic and asymptomatic carotid disease. An association between the presence and degree of adventitial vasa vasorum and intraplaque neovascularization as graded on CEUS, with a history of cardiovascular disease and previous cardiovascular ischemic events, has also been reported. CEUS has been used to assess the impact of statins on low-density lipoprotein (LDL) levels and CEUS-assessed neovascularization. Plaque...
neovascularization regressed in 46% plaques in patients over a period of 6 months. It was associated with reduction in LDL levels. A prospective clinical study to assess the association of CEUS-quantified neovascularization with future cardiovascular events is awaited.

The above studies relied on subjective assessment of the extent of neovascularization on CEUS. To improve this, the dynamic cine clip-based time-intensity curve for wash-in time of a UCA and intensity of plaque enhancement has been used. Other than being acceptably reproducible, this quantitative approach enabled differentiation between plaques of patients with and without ischemic stroke. By developing an algorithm using cine clip-based ratio of neovascularization area to the total plaque area and applying motion compensation, excellent correlation between this CEUS- and histology-based parameter has also been reported. However, the histologic validation of CEUS-assessed neovascularization has some inherent limitations: data displayed in each US frame are composed of data integrated over a width of a few millimeters rather than from a narrow plane, which is different from the one displayed in the histology sections (in micrometers). Changes in the plaque architecture on histologic processing, such as on fixation, potentially compound this limitation.

In contrast to the use of transcutaneous US for imaging carotid artery, there is severe relative tissue catheter motion (from cardiac contractility) and weak signal strength from the microcirculation in coronary arteries. This renders coronary artery vasa vasorum imaging challenging. UCAs, by enhancing the acoustic signal from the coronary vessel wall, have the potential to overcome such limitations. Carlier et al reported the initial feasibility study in human coronary arteries using nonharmonic intravascular US (IVUS) in vivo. Vasa vasorum was not visualized, but, because plaque perfusion is believed to most likely result from vasa vasorum, enhancement was considered a representation of vasa vasorum density. Unlike the availability of carotid endarterectomy specimens, histologic validation using the coronary atheroma is not possible in clinical studies. Nonharmonic imaging technique assumes linear behavior of the MBs, but it may be difficult to differentiate acoustic signals from the UCA and tissue, reducing the sensitivity and specificity of this technique. By harnessing nonlinear properties of the MBs, it can be stimulated to emit energy higher (harmonic) or lower (subharmonic) than the transmitted central frequency ($f_t$). In a coronary phantom experiment, Goertz et al reported improvement in the contrast: tissue ratio with second harmonic ($2f_t$) and subharmonic imaging ($1/2f_t$).

Magnetic Resonance Imaging

Magnetic resonance (MR) imaging uses the inherent MR relaxation properties ($T_1$ and $T_2$) of different plaque components and the surrounding tissue to characterize plaque components without contrast media (CM). On $T_1$-weighted images, plaque fibrous tissue may appear isointense to hypointense, and the lipid may be isointense to hyperintense. However, fibrous tissue has high signal intensity on $T_2$-weighted images, whereas lipid content appears hypointense. Calcium appears hypointense on $T_1$- and $T_2$-weighted images. The use of CM enables signal enhancement of the tissues, overcoming the issue of limited sensitivity associated with multicontrast MR imaging.

Nontargeted MR Imaging

Contrast-Enhanced MR Imaging

Contrast-enhanced MR imaging involves the acquisition of precontrast images of the tissue of interest, followed by intravenous injection of CM and subsequent acquisition of
of the underlying inflammatory activity associated with acute coronary syndromes. Both studies had some limitations. Both had a small number of patients. There was no comparison with IVUS, which, although invasive, remains the gold standard for coronary plaque assessment. In addition, the presence of calcified plaques makes the assessment of the wall enhancement difficult, particularly when computed tomography is used for coregistration. Larger studies are, however, required to confirm the efficacy of delayed contrast enhancement techniques in the assessment of severity of atherosclerotic activity.

**Dynamic Contrast-Enhanced MR Imaging**

Assessment of the extent and permeability of the plaque neovascularature has become possible by serial acquisition of MR images before and after the administration of gadolinium-based CM and examination of the kinetics of CM uptake in the tissue of interest with appropriate data modeling (kinetic modeling [Figure 3] or with nonmodel-based approaches, such as area under the curve). This technique is called dynamic contrast-enhanced (DCE) MR imaging. It has high temporal and spatial resolution, which allows detailed assessment of activity of various plaque components. Reproducibility of the area under the curve measurements and kinetic modeling parameters has been reported; however, DCE-MR-derived parameters seem to depend on the type of CM used. A strong correlation exists among the transfer constant ($K_{trans}$), a parameter obtained after kinetic modeling, of the CM into the extracellular space, neovascularature area, and plaque inflammation as quantified by macrophage area. Statins, which have the potential to reduce the inflammatory activity of atherosclerotic plaques, significantly reduce $K_{trans}$.

These findings suggest that $K_{trans}$ indirectly represents plaque inflammation. In a rabbit model of atherosclerosis, the relationship of neovessel count in atherosclerotic plaque, neovessel permeability (as determined by area under the curve from DCE-MR), and plaque inflammation (as determined by 18-fluorine-flurodeoxyglucose ($^{18}$F-FDG) has been reported. DCE-MR imaging is therefore a potentially useful technique capable of providing information about the plaque neovascularization and interlinked inflammation.

However, this technique has some limitations. Imaging the microvessels, particularly the ones that are at vulnerable sites, such as at plaque shoulder, requires high in-plane spatial resolution. High temporal resolution, which is important for accurate arterial input function estimation, has to be killed to achieve higher spatial resolution. This can prove further challenging when the arterial wall thickness is only 1 to 2 mm, such as in early atheromatous lesions. The vessel tortuosity and plaque architecture may cause partial volume effects, which can make measurement of parameters (eg, arterial input function) required for kinetic modeling difficult. Area under the curve not only reflects tissue blood flow and vessel permeability, but is also an indirect measure of the interstitial space and, therefore, has no simple physiological meaning. Clinical studies using DCE-MR imaging rely on signal intensities for the calculation of kinetic parameters; it makes it intrinsically difficult to compare studies conducted at different times and different centers unless appropriate calibration measures are taken. More prominent susceptibility effects...
with higher magnetic field strengths can also prove challenging. With the above challenges in mind, development and validation of new acquisition methods are required that would allow accurate, repeatable, and reproducible quantification of physiological parameters for the assessment of inflammatory neovasculature.

**Targeted MR Imaging**

**Iron Oxide–Based MR Imaging**

MR imaging also allows imaging of the cellular mediators of inflammation in atherosclerosis by the use of targeted CM. Although initially devised for imaging the reticuloendothelial system, Kresse et al first reported that superparamagnetic iron oxide particles also get incorporated into cells of aortic atherosclerotic plaques in hyperlipidemic rabbits. Compared with superparamagnetic iron oxide particles, the smaller particle size of dextran-coated ultrasmall superparamagnetic particles of iron oxide (USPIO) and their ability to extravasate via tight capillary pores make them an attractive option for cellular MR imaging. More importantly, USPIO particles are not immediately recognized by the hepatic and splenic reticuloendothelial system, resulting in prolongation of plasma half-life, making them suitable for atheroma imaging. Although the accumulation of USPIO in macrophages is well established, the mechanism of its uptake is not yet well defined. At higher concentrations of USPIO, T2/T2* relaxation effects predominate, with such areas in the tissue appearing hypointense on MR imaging. The areas of signal loss appear initially at 24 hours (Figure 4), becoming obvious at 36 hours until 48 hours after USPIO administration. Relative change in signal intensity in regions of interest between matched post- and pre-USPIO–enhanced MR images was used to quantify the USPIO-induced signal loss. Macrophage staining with CD68 and iron staining with Perls’ stain were used for histologic assessment of USPIO localization within carotid plaques. Correlation between MR and histology was, however, not reported. Trivedi et al observed that, although there was good agreement between the location of Perls’ stain on histology and location of MR signal void, its agreement with the nature of USPIO signal effect was only moderate. Strong correlation existed among the magnitudes of USPIO effect, Perls’ staining, and macrophage count in plaques, which exhibited focal areas of USPIO uptake on MR imaging, compared with plaques with diffuse distribution of USPIO. Plaques with such focal areas were histologically observed to have characteristics of vulnerable plaques. Poor correlation was observed between Perls staining and macrophage localization. Although various possible explanations were given for this observation, such as heterogeneity in the macrophage population in the plaque, authors attributed it to result most likely from the lack of sensitivity of Perls’ stain for USPIO. At low USPIO concentrations, however, T effects predominate, causing signal enhancement. This was observed to be prevalent in asymptomatic carotid plaques with a thick fibrous cap.

![Figure 3. Illustration of vasa vasorum imaging via dynamic contrast-enhanced (DCE) magnetic resonance (MR) imaging.](image-url)

Sequential images after injection of gadolinium contrast agents at different time points (A). L indicates arterial lumen and IJV indicates the internal jugular vein. The sequential images are used in a kinetic model to create parametric images (B) of partial plasma volume (Vp; top left), ECA indicates external carotid artery; ICA, internal carotid artery; and IJV, internal jugular vein) and transfer constant (Ktrans; bottom left). These have been fused into the color-coded image at right (arrows indicate adventitia; J, jugular vein; L, lumen; and P, plaque). A pixel has been drawn in different sections indicated by numbers, that is, a pixel in the lumen (1), adventitial pixels with high (2) and low (3) Ktrans, a pixel with partial volume of the lumen (4), and an interior plaque pixel (5). Demonstration of intensity versus time curves for all of the pixels in the 2-cm² region (all lines) for the set of blood curves extracted by the clustering algorithm (top, green lines) and their average (red line). The bottom curve shows typical fitting results for the kinetic model with corresponding points indicated by numbered pixels shown in B.

![Figure 4. Preultrasmall superparamagnetic particles of iron oxide (USPIO; A) and post-USPIO (B) magnetic resonance (MR) spiral T2*-weighted axial imaging showing atheromatous plaque in the internal carotid artery of a symptomatic patient.](image-url)

L indicates arterial lumen. Focal USPIO uptake can be seen at 24 hours after intravenous injection as an area of signal drop/void (white arrow).
Using serial USPIO-enhanced MR imaging over a 3-month period in asymptomatic patients, a significant reduction in carotid plaque inflammation with high-dose statin-lowering therapy compared with low-dose therapy had also been reported. Post hoc long-term follow-up (median, 4 years) of patients from this trial failed to show any significant association between USPIO signal intensity loss and any subsequent cardiovascular and cerebrovascular events. A limitation of this post hoc study was that it was significantly underpowered to assess the long-term association. The traditional technique of quantifying relative signal loss on MR images as a measure of USPIO-induced changes also has limitations. The differences in patient positioning, magnetic field inhomogeneities, and other artifacts may all induce signal loss and may not be indicative of USPIO uptake. In contrast to such semiquantitative methods, quantitative $T_1$ and $T_2$ MR pulse sequences have been shown to be more robust, particularly quantitative $T_2$ sequences, because of their inherent insensitivity to magnetic field inhomogeneities. Because USPIO and other negative contrast approaches can be difficult to interpret because of a low signal-noise ratio, positive contrast sequences, which can be acquired during the same imaging session, may improve image interpretation and analysis. Despite great potential, so far none of the USPIO products has been approved for atherosclerotic imaging.

Like receptor-targeted UCAs, iron oxide particles tagged with ligands targeted to specific receptors in atheromatous tissue can offer an enhanced nonradiating method of imaging allowing in vivo microscopy. Using VCAM-1–targeted cross-lined iron oxide nanoparticles, Nahrendorf et al initially demonstrated targeting of all cell types within atheroma expressing VCAM-1 in vitro. In vivo MR imaging revealed signal enhancement in the aortic root. VCAM-1 cross-lined iron oxide particles colocalized with endothelial cells and other VCAM-1–expressing cells, such as macrophages in atherosclerotic plaques, on fluoroscopic imaging. By conjugating target-specific peptides with USPIO (cyclic heptapeptide: R8 targeted to VCAM-1 and linear hexapeptide: R826 targeting phosphatidylinerine), contrast enhancement of aortic atherosclerotic plaque in mice (20–30 minutes after CM injection) was observed, which was reproducible. The plaques enhanced by USPIO-R826 contained macromolecules in the cap and a large necrotic core, whereas USPIO-R826 produced a negative enhancement of plaques rich in macrophages and neutral fats concentrated inside the plaque and with lower global collagen content.

Compared with the nonspecific dextran-coated iron oxide particles, significantly shorter optimum imaging time for biofunctionalyzed USPIO is attributed to their specific nature. They can be efficiently rendered stealthy by the covalent conjugation of USPIO derivatives with polyethylene glycol, escaping macrophage uptake. Most recently, other functionalized USPIOs, such as those targeting P-selectin, oxidized LDL, and scavenger receptor A1, have been designed for targeted atheroma imaging. Microparticles of iron oxide dually targeting VCAM-1 and P-selectin in aortic plaques have been reported to have significantly increased binding compared with P-selectin or VCAM-1–only targeted microparticles of iron oxide, with a significantly increased MR signal ex vivo compared with a control agent. By further reducing the size of this microparticle of iron oxide to μ size, efficacy of this CM to image activated endothelium and different stages of development of atheroma has been demonstrated.

Gadolinium-Based CM

Gadolinium-loaded nanoparticles, which act as $T_1$-CM, incorporate phospholipids, surfactants, and lipophilic gadolinium complexes. They were initially used to overcome the limitations of iron oxide–enhanced MR imaging of atheroma in the early days of development of iron oxide–based CM, such as difficulty in differentiating between iron oxide–induced signal void and artifacts, nonspecificity of its uptake, and delays in imaging because of delays in CM penetrating the arterial wall. The use of target-specific, lipid-based nanoparticles allows for delivery of a large number of gadolinium moieties incorporated in the lipid bilayer to the atheromatous tissue, acting as $T_1$-reducing agents that appear bright in $T_1$-weighted MR images. They generally have fast uptake at the target site, rapid clearance, and renal excretion leading to a high target:background signal ratio.

Lipinski et al first reported the use of gadolinium-based immunomimetics specifically targeting macrophage scavenger receptor-A on macrophages in plaques. The development of the Annexin A5–conjugated micellar nanoparticle carrying multiple Gd-labeled lipids for MR imaging and fluorescent lipids for fluorescence microscopy and imaging has also been reported. It was shown to target phosphatidylserine exposed at the surface of apoptotic cells and macrophages in a murine model of aortic atherosclerotic plaque. High-density lipoprotein (HDL) is another native nanoparticle, which, because of its natural interaction with atherosclerotic plaques, has been used as an imaging agent. Using HDL-based gadolinium MR imaging CM, Frias et al observed increased signal intensity in areas of aortic plaques rich in macrophages. However, because of the use of human plasma for manufacturing of such CM, the resulting safety precautions would complicate its clinical translation. This, alongside the pressing interest in HDL and in the treatment of HDL levels, led to the development of HDL-mimicking peptides, with absent immunogenicity and ease of synthesis. Cormode et al reported the first in vivo use of HDL mimicking (with apolipoprotein A-I peptide) gadolinium and rhodamine-loaded nanoparticle for dual modality imaging (MR and fluorescence, respectively) to enhance macrophage-rich areas of plaque in a mouse model. Further modification of the rhodamine-loaded nanoparticle, by incorporation of a cationic and membrane-penetrating lipopeptide (P2A2), showed a more pronounced signal enhancement of the atherosclerotic wall on MR imaging. Confocal laser scanning microscopy revealed rhodamine-loaded nanoparticle-P2A2 nanoparticles colocalized with intraplaque macrophages.

Another exciting development has been the production of chemically engineered substrates, which undergo a physiochemical change after interacting with their intended target (because of enzymatic cleavage, pH change, etc). This physiochemical change would result in a product with
higher relativity and that has high a target:background signal ratio, facilitating easy detection with an imaging modality. Myeloperoxidase enzyme is one such potential target for molecular imaging, which is expressed by neutrophils and macrophages in advanced atherosclerotic lesions. Using such a gadolinium-based probe has been reported to enhance the diseased atherosclerotic thoracic aorta, with enhancement areas correlating with myeloperoxidase enzyme-rich areas infiltrated by macrophages on histologic examination.40

Targeted imaging of angiogenesis in atherosclerotic tissue with an αβvβ3-integrin–targeted, gadolinium-based nanoparticle has been reported.41 αβ3-Integrin is a well-established biomarker of neovascular proliferation. Incorporation of an antiangiogenic agent, Fumagillin, into this imaging probe was used for its localized delivery to the atheroma in a rabbit model. Seven days after treatment, αβvintegrin–targeted nanoparticle-enhanced imaging revealed reduced MR signal enhancement compared with untreated animals. Reduction in the microvessel count was evident in the treatment group.42 Coadministration of αβ3-integrin–targeted fumagillin nanoparticle and atorvastatin was later shown to prolong the antiangiogenic effect of Fumagillin.

Nuclear Imaging
Nuclear imaging relies on its ability to provide quantitative information on a functional level of plaque, such as metabolic activity or expression levels of functional molecules. It is based on the use of radiolabeled biomarkers (usually called radiotracers), with their signal (hot spots) detectable at the target site by means of imaging techniques, such as gamma cameras, positron emission tomography (PET) or single photon emission computerized tomography. To obtain a good quality image, a radiotracer should have a rapid clearance from the bloodstream and a good target:background signal ratio. This is particularly important when imaging a small target, such as atheromatous plaque, where a high background signal can impair the image quality. The use of radiotracers with high target specificity is, therefore, important. Nuclear imaging techniques have high sensitivity but generally lack adequate spatial resolution. The use and further development of multimodality imaging systems, such as PET/computed tomography or PET/MR imaging may help to overcome this limitation because of better spatial resolution.

The feasibility of nuclear imaging in assessing the functional activity of human atherosclerotic tissue was reported as early as the 1980s. Iodine-labeled LDL was used and images were acquired by a gamma camera. Because of relatively poor imaging qualities of iodine, Technetium-99 m was soon found to be a better alternative because of its short half-life and better gamma emission with a low absorbed radioactive dose for the patient. To improve the kinetics of these biomarkers, the discovery that oxidized LDL was readily taken up by macrophages via scavenger receptors led to the formulation of radiolabeled-oxidized LDL. Technetium-99 m–oxidized LDL was observed to have rapid blood clearance and higher sensitivity in detecting symptomatic carotid plaques, localizing at scavenger receptor sites of macrophages. To differentiate between activated and quiescent macrophages, the use of Technetium-99 m–oxidized LDL targeted to folate receptors, which are only expressed on activated macrophages, has been reported,43 thereby potentially enabling precise imaging of unstable atherosclerotic sites. In comparison with lipoproteins, peptides clear from the circulation quickly and theoretically could improve identification of atherosclerotic tissue easier. Their use in humans remains largely unreported. For quantification of macrophage content, radiolabeled monoclonal antibody against amino malonic acid, a molecule vital to monocyte recruitment and foam cell production within atherosclerotic lesions, had significantly higher uptake in atheromatous aortas compared with normal aortas.44 Slow radiotracer clearance from circulation, however, made in vivo imaging of aortic plaque unsuccessful.

Compared with single photon emission computerized tomography imaging, which has a resolution of 1.0 to 1.5 cm, PET-18F-FDG imaging can provide 4- to 5-mm resolution. Using 18F-FDG PET imaging, Rudd et al45 reported efficacy of this noninvasive technique in imaging inflammation within atherosclerotic plaques (Figure 5).46 18F-FDG PET imaging is in fact a readout of vascular glucose metabolism, which is believed to be a surrogate of atherosclerotic plaque inflammation. Preclinical studies in animal models of atherosclerosis (without diabetes mellitus) have largely confirmed that the basis of the signal is inflammation, but not consistently so. Because glucose uptake is higher in macrophages than in other cells within the plaque, it is not surprising when we consider that all cells metabolizing glucose accumulate 18F-FDG. Efficacy of various antiatherosclerotic agents has also been successfully assessed using 18F-FDG PET imaging by measuring the changes that they cause to the 18F-FDG signals.47 The noninvasive read out of inflammation in patients with diabetes mellitus using FDG PET is an attractive option, but its uptake by cells is competitively reduced by the presence of elevated blood glucose levels. This remains a limitation for the use of 18F-FDG PET in clinical studies on diabetic patients. The correlation between 18F-FDG PET quantified arterial inflammation and DCE-MR imaging assessing neovascularization has also been investigated. Taqueti et al48 also observed that, with increasing macrophage count, the FDG PET signal increased and Ktrans value was higher in macrophage-rich plaque areas.

Figure 5. Fluorodeoxyglucose (FDG) magnetic resonance imaging (MRI) of carotid atheroma in the left common carotid artery.46 A, Black-blood MRI, an arrow indicating carotid plaque. B, Superimposed FDG-MRI showing a hot spot (arrow) because of increased FDG uptake in the area of the carotid plaque.
Weak inverse relationship between inflammation measured as $^{18}$F-FDG uptake by PET and plaque perfusion by DCE-MR imaging have also been reported. The likely explanation for the latter observation is that there may be a complex relationship between plaque inflammation and neovascularization during the different stages of plaque development.

PET-computed tomography imaging has also been used recently to investigate calcification within atheromatous tissue, because there is strengthening belief that unstable and metabolically active atheromatous plaques have active calcification, which differs from long-standing dormant calcification. Hydroxyapatite is the central structural component of vascular calcification and is laid down during the earliest and most active stages of mineralization, believed to be associated with plaque inflammation and necrosis. Because fluoride ions are incorporated into the hydroxyapatite by ion exchange with hydroxyl groups at the crystal surface, using this property to advantage $^{18}$F-sodium fluoride (NaF) PET imaging has been used to image atheromatous calcification. Patients with increased coronary $^{18}$F-NaF activity have been observed to have higher rates of previous cardiovascular events and higher overall calcium scores. Quantification of coronary $^{18}$F-FDG uptake is hampered by myocardial activity. This limitation with $^{18}$F-FDG was observed in a most recent prospective clinical trial. $^{18}$F-NaF uptake was, however, observed at all sites of carotid plaque ruptures in patients with previous myocardial infarction and was associated with histologic evidence of active calcification, macrophage infiltration, apoptosis, and necrosis. Patients with stable angina had plaques with focal $^{18}$F-NaF uptakes, which were associated with more high-risk features on IVUS than those without uptake, such as positive remodeling, microcalcification, and necrotic core. These findings highlight the potential benefit of $^{18}$F-NaF in differentiating between stable and unstable atheroma, particularly in coronary arteries where $^{18}$F-FDG PET-computed tomography imaging is limited by myocardial uptake. Further assessment of this imaging technique is required if it were to be used for improving risk stratification, monitoring disease progression, guiding therapeutic interventions, and assessing novel antiatherosclerotic therapies.

Conclusions
Atherosclerosis remains a leading cause of mortality and morbidity in the developed countries despite significant advances in medical diagnostics and therapeutics. A paradigm shift has been witnessed in the past 3 decades from looking at atherosclerotic tissue as mere lipid-laden obstructive lesions to looking beyond the arterial lumen. Novel imaging techniques are enabling us to perform functional imaging and in vivo microcopy of plaque inflammation and neovascularization in much greater detail than ever before. Not only are they unraveling the pathobiology of atherosclerosis but they are also allowing investigation of the efficacy of new antiatherosclerotic and anti-inflammatory agents. Each technique has its strengths and drawbacks. Identification of the atherosclerotic disease process in the earlier stages of development, well before clinical symptoms ensue, with delivery of therapeutic agents to disease-specific targets with the least constitutive expression, to impede or cease the disease process, is the holy grail of functional, cellular, and molecular imaging. This will require careful selection of validated imaging end points in future studies rather than relying on clinical outcome studies, which require a large sample size.

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References


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