Molecular Magnetic Resonance Imaging for the Detection of Vulnerable Plaques

Is It Possible?

Brigit den Adel, Mat J. Daemen, Robert E. Poelmann, Louise van der Weerd

Abstract—Recent advances in molecular resonance imaging of atherosclerosis enable to visualize atherosclerotic plaques in vivo using molecular targeted contrast agents. This offers opportunities to study atherosclerosis development and plaque vulnerability noninvasively. In this review, we discuss MRI contrast agents targeted toward atherosclerotic plaques and illustrate how these new imaging platforms could assist in our understanding of atherogenesis and atheroprogression. In particular, we highlight the challenges and limitations of the different contrast agents and hurdles for clinical application. We describe the most promising existing compounds to detect atherosclerosis and plaque vulnerability. Of particular interest are the fibrin-targeted compounds that detect thrombi and, furthermore, the contrast agents targeted to integrins that allow to visualize plaque neovascularization. Moreover, vascular cell adhesion molecule 1–targeted iron oxides seem promising for early detection of atherosclerosis. These targeted MRI contrast agents, however promising and well characterized in (pre)clinical models, lack specificity for plaque vulnerability. (Arterioscler Thromb Vasc Biol. 2013;33:00-00.)

Key Words: atherosclerosis • MRI contrast agent • vulnerable plaques

Over the past decade, much effort has been put in the development of methods to identify vulnerable atherosclerotic plaques with imaging techniques. If vulnerable plaques can be identified, they can be targeted for medical intervention, while avoiding unnecessary treatment of the stable plaques. Virmani et al. defined the fibrous cap as a distinct layer of connective tissue completely covering the lipid-necrotic core. The lipid-necrotic core is frequently surrounded by macrophages and consists of large amounts of extracellular lipid, cholesterol crystals, and necrotic debris. Lesions with a large lipid-necrotic core and a thin fibrous cap are considered to be most likely to rupture. Several invasive methods, such as intravascular ultrasound, palpography, and optical coherence tomography, are clinically applied in patients. Because of their invasive nature, these modalities are not suited to screen patients with subclinical disease.

Noninvasive assessment of plaque vulnerability targets a different population, that is, asymptomatic individuals in whom clinical intervention is not a medical need, yet in whom imaging of vulnerable plaques can be used as risk stratification. MRI has emerged as one of the noninvasive imaging modalities of atherosclerotic disease because of its ability to assess the arterial lumen, plaque burden, and plaque components in an accurate and noninvasive manner. Several in vitro and in vivo studies both in patients and animal models have demonstrated the ability of MRI to differentiate the major components of atherosclerotic plaques, mainly in the carotid artery, without the use of contrast agents. In addition, MRI can accurately and reproducibly measure arterial wall dimensions. This has led to its use as the imaging efficacy end point in therapeutic trials of human carotid artery plaque regression.

In this article, we review recent developments in molecular MRI of atherosclerosis, preview some of the new opportunities molecular MRI offers to atherosclerosis diagnosis, and comment on the challenges faced by the field.

Molecular MRI

High-resolution MRI has emerged as the potential leading noninvasive in vivo imaging modality for atherosclerotic plaque characterization, in particular suitable to detect intra-plaque hemorrhage, cholesterol deposits, and the extent of the lipid core in human carotids. Molecular MRI offers the potential to image events at the cellular and subcellular levels. The introduction of targeted MR contrast agents has enabled the imaging of relatively sparsely expressed biological targets in vivo. During the development of atherosclerotic plaques, many potential biomarkers, such as adhesion molecules, macrophages, and their scavenger receptors (SR), matrix metalloproteinases, oxidized low-density lipoprotein (oxLDL), αβ-integrin, extracellular matrix, and fibrin, are upregulated. It is important to point out that these molecules are often not unique to atherosclerosis...
or cardiovascular diseases but are also upregulated in other diseases as compared with disease-free conditions. Moreover, these molecular targets are often present at relatively low levels. To overcome sensitivity issues, high-payload contrast agent vehicles have been developed for molecular MRI to generate sufficient signal change.

The biological processes described above and their accompanying molecular and cellular events create numerous opportunities for targeting the atherosclerotic plaque. This can be done using nanoparticles carrying an imaging modality and targeting vector. Several novel nanoparticle platforms have emerged in molecular MRI that allows the visualization of atherosclerotic plaques. These contrast agents targeting molecules on different plaque components will be highlighted here in the context of their relevance to plaque vulnerability and summarized in the Table.

### Intraplaque Targeting

#### Lesional Macrophages

In the last years, it has become accepted that classically activated macrophages (or M1) and alternatively activated MØ (or M2) are 2 extremes of a spectrum of macrophage phenotypes that both contribute to plaque development progression and vulnerability.10

#### Macrophages

Myeloid-related protein (Mrp)-8/14 is a member of the S100-family of Ca2+-modulated proteins with a role for the Mrp-complex in the innate inflammatory response to injury. Mrp-8/14 is detected in nonfoam cell macrophages in human and mouse atherosclerotic plaques with rupture-prone lesions.11 Levels of Mrp also have been shown to be an independently prognostic marker of cardiovascular risk.12

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**Table. Targeted MRI Contrast Agents to Detect Atherosclerosis**

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Gd indicates gadolinium; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPIO, microparticle iron oxide; and VCAM, vascular cell adhesion molecule 1.
Recently, Maiseyeu et al\textsuperscript{13} developed a multivalent theranostic agent composed of phosphatidylserine, \textomega-carboxynonanoyl-cholesteryl ester, and gadolinium (Gd) lipids targeted to macrophages using an anti-Mrp14 polyclonal antibody (IgG). Proof of principle of the contrast agent both in vitro on cultured apoE\textsuperscript{−/−} monocytes and in vivo in atherosclerotic mice showed enhanced binding potential to Mrp\textsuperscript{+} monocytes and endothelial cells. This is the first time a contrast agent potentially targeting rupture-prone plaques has been successfully applied, although further optimization of the agent is required for clinical applications.\textsuperscript{14}

**Lipoproteins**

Lipoproteins, such as high-density lipoprotein (HDL) and low-density lipoprotein (LDL), are nanoparticles that are naturally present in most species, and are essential to control lipid metabolism in humans and interact with plaques through a natural conduit. oxLDL plays a key role in the initiation, progression, and destabilization of atherosclerotic plaques and is present in macrophages and the lipid pool.

Targeting oxLDL has been exploited with several compounds. Both Gd-based immunomicelles as well as lipid-coated iron oxide particles containing murine (malondialdehyde [MDA]-lysine MDA2 and oxidized phospholipids E06) or human (IK17) antibodies that bind oxidation-specific epitopes induced significant enhancement in MR images of the aorta of apoE\textsuperscript{−/−} mice (Figure, D).\textsuperscript{15–17} Immunomicelles functionalized with manganese (Mn\textsuperscript{2+}) and MDA were developed to deliver Mn into a cell resulting in \textgreater20-fold increases in MR efficacy compared with the chelated form.\textsuperscript{14} In vivo plaque imaging findings with these Mn-based compounds were comparable with the previous results with iron and Gd; however, background signal from the Mn-based contrast agent in blood was very low allowing a better plaque definition.

Lipoproteins themselves are ideal for the delivery of drug and imaging agents because they circulate in the bloodstream for a significant time, the hydrophobic core facilitates incorporation of poorly soluble drugs or imaging agents, and they are amenable to bioconjugation.

The LDL particle naturally homes to the liver and also to a plaque after intravenous administration. LDL particles that are enriched with a hydrophobic contrast agent, manganese-mesoporphyrin, cause signal enhancement in foam cell pellets.\textsuperscript{18} Despite the potential of these nanoparticles, extensive in vivo MRI of atherosclerotic plaque with these LDL nanoparticles has not (yet) been reported. Yamakoshi et al\textsuperscript{20} recently reported the first in vivo application in both hypercholesterolemic apoE\textsuperscript{−/−} and LDLr\textsuperscript{−/−} mice of an LDL particle functionalized with a GdDO\textsubscript{3}A-monoamide chelate.

Given the key role of LDL in plaque progression, it is debatable whether LDL-based compounds can be optimized for clinical use. Furthermore, the quantitative relation between the amount of oxLDL and lesion progression makes it unlikely to discriminate vulnerable and stable plaques based on oxLDL presence, although a risk stratification of plaques at risk based on LDL quantification would be possible.

In contrast to LDL, HDL forms smaller lipid nanoparticles (5–12 nm) stabilized by the surface apolipoprotein A1 (Apo-A1). HDL nanoparticles have certain advantages for atherosclerotic imaging: HDL binds to SR B type I (SR-BI) and ATP-binding cassette transporters, and thus naturally targets to macrophages expressing these receptors. High-HDL cholesterol levels are associated with reduced plaque burden, whereas LDL promotes the disease.\textsuperscript{21} Second, their small size (\textless10 nm) enables them to penetrate the vessel wall more easily than LDL. This led to the development of a vast array of HDL-based contrast agents.

The first MRI HDL particles contained Gd-chelating phospholipids in the lipid layer (rHDL).\textsuperscript{22,23} In hyperlipidemic apoE\textsuperscript{−/−} mice, these paramagnetic HDL nanoparticles showed enhanced accumulation in atherosclerotic plaques after intravenous administration.

The targeting of rHDL to macrophages was enhanced by the incorporation of P2\textalphaA2, a lipopeptide derived from the LDL receptor–binding domain of apoE.\textsuperscript{24} P2\textalphaA2-modified HDL results in a doubling of the signal in the aortic vessel wall compared with the rHDL particle.

A significant MRI signal change was also observed in the aortic wall of apoE\textsuperscript{−/−} mice in vivo 24 hours after injection of paramagnetic Au-HDL, QD-HDL, and FeO-HDL particles.\textsuperscript{25}

Thus far the potential of HDL particles seems promising, and because of its biological resemblance to autogenous HDL and ease to produce the particle, further development in the near future is likely to occur.

**Scavenger Receptors**

The macrophage SR is a macrophage-specific cell surface protein not expressed on cells in the normal vessel wall.\textsuperscript{26} Both class A and B SR (SR-A and SR-B) are involved in the progression of atherosclerosis and collectively are responsible for binding and uptake of 75% to 90% of modified LDL uptake by macrophages.\textsuperscript{27} SR-A is a high-affinity receptor, with binding affinities in the pico- to nanomolar range. Because macrophages are present through all stages of atherosclerosis, the SR forms an excellent target for molecular imaging of atherosclerosis.\textsuperscript{28}

Amirbekian et al\textsuperscript{29} developed 110-nm-large SR-A targeting immunomicelles containing Gd via the conjugation of a monoclonal CD204 antibody. These micelles showed in vivo detection potential of murine atherosclerosis in the abdominal aorta.\textsuperscript{30} Gd-loaded lipid-based nanoparticles targeting CD36 (SR-B) showed significant uptake by human macrophages in vitro, improved signal intensity in ex vivo aortic atherosclerotic plaque, and were shown to bind to resident macrophages in atherosclerotic plaque (Figure, A).\textsuperscript{31} The CD36-labeled particles created the largest signal in fibrous plaques at the periphery of lipid-rich plaque. These data suggest that lipid-based nanoparticles targeting CD36 may improve the detection and characterization of atherosclerotic plaques and determine the degree of plaque inflammation.

Both CD36 and CD204 targeted contrast agents were successful in the visualization of macrophages. In principle, they can be used as surrogate clinical end point in studies that are aiming to reduce plaque inflammation. Conjugation with a full antibody will, however, hamper repeated application because of an immune response to the antibody. Another limitation in targeting the SRs may be the fact that intravenous administration of this imaging agent will suffer from a large first pass retention in the liver attributed to binding to SRs expressed on...
the surface of Kuppfer cells. Moreover, FluoDeoxyGlucose-PET is currently a very solid clinically applied method to assess macrophage burden in atherosclerosis.

**Vascular Targeting: Cellular Adhesion Molecules**

Dysfunctional endothelium is a crucial pathophysiological factor in atherosclerosis, causing increased permeation of macromolecules, such as lipoproteins, increased expression of chemotactic molecules (eg, monocyte chemotactic protein 1), adhesion molecules (eg, intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1]), as well as E-selectin and P-selectin), and enhanced recruitment and accumulation of monocytes.\(^{32}\)

**VCAM-1 (CD106)**

VCAM-1 is an appealing target because it is differentially upregulated on the endothelium related to atherosclerotic plaque and lesion prone areas of the artery. McAteer et al\(^{33,34}\) have recently reported a microparticle iron oxide approach to...
VCAM-1 imaging that provides quantifiable contrast in mouse vascular inflammation. Because microparticle iron oxide are large they cannot extravasate and are, therefore, useful contrast agents for detection of strictly endovascular molecular targets.

In vivo MRI after injection of monocristalline iron oxides (cross-linked iron oxide) with VCAM-1 targeting peptides showed hypointense (dark) spots in the aortic root of apoE−/− mice, which was confirmed through fluorescence imaging ex vivo and in vitro in macrophages that overexpressed VCAM-1.35,36

Burtea et al37,38 recently developed much smaller Gd-DOTA as well as ultra small particle of iron oxide–based VCAM-1–targeted compounds. Both compounds have shown potential to image atherosclerotic plaques in hypercholesterolemic ApoE−/− mice. The Gd payload may be too low for detection of smaller plaques.

Integrin α3β3

Integrins are a family of heterodimeric cell surface adhesion molecules that mediate cell–extracellular matrix and cell–cell interactions, and are involved in cell adhesion, proliferation, migration, and differentiation. The α3β3 integrin is among others expressed by endothelial cells, VSMCs, platelets, growth factor-stimulated monocytes, and T lymphocytes.39,40 Human atherosclerotic lesions show extensive expression of α3β3 on SMC, endothelial cells, as well as foam cells.41 Most interesting is that α3β3 expression is both an early event in plaque formation42 and is correlated to plaque instability.43

The Wickline group systematically developed several integrin targeting imaging compounds using both different ligands and imaging compounds. Lanza et al44 developed a nanoparticle with a perfluorocarbon core covered with a lipid monolayer, including paramagnetic lipids (Gd-DTPA-bis-oleate) in the monolayer. The nanoparticles targeted to α3β3-integrin detected angiogenesis in a rabbit model of atherosclerosis.45 For imaging of plaque-associated angiogenesis, Winter et al46 have successfully developed a relatively large (273 nm) paramagnetic contrast agent targeted to α3β3 integrins using an Arg-Gly-Asp mimetic (RGD). Although relaxometrically efficient, this agent has the drawback of its large size that limits not only blood clearance but also its diffusion into tissue. A 19F compound targeted to the α3β3-integrin has also been developed by this group, allows to suppress signal from nanoparticles in the blood, and specifically image the contrast agent in vivo (Figure, C).47

A smaller, low-molecular weight nonpeptidic RGD mimetic attached to a Gd-DTPA chelate was developed to image plaque-associated angiogenesis.48,49 This contrast agent was able to penetrate atherosclerotic plaques, allowing visualization of neovascularization. Specificity for angiogenic vessels may be decreased, however, when diffusible rather than pure intravascular imaging probes are used because inflammatory cells and fibroblasts can express many of these integrins.

One of the major drawbacks of the previously mentioned approaches is the nonspecific binding of the used RGD-like peptides to α3β3 integrins.

Selectins

Selectins are proinflammatory endothelial cell adhesion molecules and mediate leukocyte adhesion. When endothelial cells are activated, P-selectin is translocated to the endothelial cell surface. E-selectin expression is linked to the attraction of Ly6C+ immune cells and linked to plaque vulnerability.50

Kang et al51 have functionalized cross-linked iron oxide nanoparticles with E-selectin antibody fragments. A significantly larger cross-linked iron oxide–induced MR signal decrease was observed in activated endothelial cells in mice in response to interleukin-1β treatment, which induces E-selectin expression compared with untreated controls.51

Boutry et al52 targeted E-selectin with a synthetic mimetic of sialyl-Lewis(X), a natural ligand of E-selectin, on the dextran coating of ultrasmall particles of iron oxide. In vitro results on endothelial cells showed high-binding affinity. In vivo experiments have thus far only been performed in a concavalin A-induced hepatitis model, and the application for the detection of atherosclerotic plaques remains to be proven.

Theoretically, the specificity of plaque targeting could be improved by using different ligands for 2 independent targets on the same particle. Such a dual-targeted strategy has been used to image endothelial adhesion molecules in apoE−/− mice, where microparticles of iron oxide were conjugated with monoclonal antibodies against VCAM-1 (VCAM-microparticle iron oxide) and P-selectin (P-selectin-microparticle iron oxide).34 Using ex vivo MR imaging, dual-targeted particles indeed showed higher affinity to the endothelium under flow conditions in comparison with single targeted ones, but no in vivo studies have been published yet.

Luminal Targets for Molecular Imaging

Thrombosis

Plaque rupture resulting in luminal thrombosis plays a central role in myocardial infarction and stroke. Moreover, fibrin plays an important role in atherosclerosis progression. A recent study showed that leakage of plaque neovessels might represent a route for fibrin to enter atherosclerotic plaque before rupture.53

Extensive experience with in vivo MRI of thrombosis has been obtained with EP2104R, currently fibrin targeted contrast agent (FTCA) (Epix Pharmaceuticals, Lexington, KY), a small fibrin-targeted Gd chelate.54 Studies with EP2104R in rabbits and swine reported the ability to detect arterial and venous thrombi.55,56 The contrast agent detected thrombi in vessels and heart chambers in 52 patients with suspected thrombosis in a phase II clinical trial, underlining its translational potential.57 The feasibility of intraplaque and endothelial fibrin detection was also assessed in vivo in ApoE−/− mice.58,59 FTCA selectively visualized the location of atherosclerotic plaque in these mice, whereas surrounding blood and soft tissue signal remained suppressed. Late stage atherosclerotic plaque showed the strongest signal enhancement after FTCA. However, in 2009, the development and clinical trials of FTCA did not proceed.

Another fibrin-targeted contrast agent, a much larger Gd-bis-oleate nanoparticle, with a higher relaxivity, can effectively detect thrombi in vitro and in an animal model, but this particle has not yet been assessed in atherosclerotic mice or patients.60,61 Owing to its size, this agent will be mainly suitable for the detection of luminal fibrin clots.
Moreover, early thrombi can be detected by imaging of activated factor XIII (FXIIIa) that covalently cross-links α2-antiplasmin (α2-AP) to fibrin. Both Tung et al. and Miserus et al. were successful in their approach to image early murine plaques using Gd-conjugated fibrin-binding compounds (Figure B).

**Technical Challenges**

In this review, we have highlighted several contrast agent platforms for molecular imaging of atherosclerosis. Each contrast agent and target has its own advantages and disadvantages in terms of ease of synthesis, toxicity, payload, and biodistribution. These technical challenges are further discussed in the online-only Data Supplement.

**Plaque Vulnerability**

The present review deals with the interplay between the complex vascular biology involved in atherogenesis and plaque vulnerability and the potential use of MR contrast agents in this interplay. The identification of target–ligand combinations specific for a vulnerable plaque is a complex process. Molecular imaging requires the identification of a disease-specific target with high expression levels, and a targeting ligand with favorable binding characteristics (IC50, Kd) for the target. Moreover, the nonspecific binding should be low, pharmacokinetics favorable, and the binding of the contrast agents should generate robust contrast change.

Plaque rupture is a major cause of atherothrombosis; unfortunately, it is not easy to implement mouse models for plaque rupture with clinical events, such as sudden death, brain, or myocardial infarction, and therefore the development validation pipeline for these contrast agents for the detection of vulnerable plaques is complex.

**Discussion**

At this point, multiple MRI contrast agents have been developed that allow the detection of different markers and stages in atherosclerosis. In our opinion, the most promising existing compounds to detect atherosclerotic plaques include the fibrin-targeted compounds that detect thrombi and the contrast agents that allow visualizing plaque neovascularization, although the latter is not specific for the vulnerable plaque. Moreover, VCAM-1–targeted iron oxides seem promising for early detection of atherosclerosis, yet not for vulnerable plaque detection.

These targeted compounds, however promising and well characterized in preclinical models to detect atherosclerotic lesions, still lack disease specificity as well as, and most importantly lack specificity for plaque vulnerability. One particle with atherosclerosis specificity is HDL. However, vulnerable plaques are characterized by the presence of low levels of HDL, which limits its use as vulnerable plaque detection marker.

Novel compounds and new targets are required to further the molecular MRI field to detect vulnerable plaques.

Despite the large hurdles to take, molecular imaging of atherosclerosis may provide more insights in the (temporal) pathophysiological mechanisms of atherosclerosis, aiding in drug selection and monitoring treatment effects.

To conclude, the answer to our main question “Molecular MRI for the detection of vulnerable plaques – Is it possible?” is, at this moment, no, not yet.

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**Disclosures**

None.

**References**

Molecular imaging has gained increasing interest in the research of cardiovascular diseases in the last couple of years mainly because it has become apparent that atherosclerotic plaque composition is an important predictor for clinical events, even more so than the degree of (luminal) stenosis. Molecular MRI holds great potential for detection of different stages of atherosclerosis and differentiation of vulnerable lesions. Its application potential will depend on comprehensive knowledge of the detection possibilities and behavior of targeted and untargeted contrast agents in vivo. In this review, we describe the most promising existing MRI contrast agents to detect atherosclerosis and plaque vulnerability.
Molecular Magnetic Resonance Imaging for the Detection of Vulnerable Plaques: Is It Possible?: Retracted
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