Review

MR and Targeted Molecular MRI of Vulnerable Plaques

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Atherosclerotic plaques · Molecular imaging · MRI · Targeted contrast agent · Vulnerable plaques

Abstract

Plaque rupture or erosion represents a major cause of stroke and the acute coronary syndrome. Information on plaque morphology and composition is essential to identify patients at increased risk for acute cardio- and cerebrovascular events, and may play a key role in individualizing therapeutic strategies and monitoring the effect of interventions. The rapidly emerging field of MR and targeted molecular MRI allows to qualitatively and quantitatively characterize plaque features. We aimed to review the literature regarding the current most promising advanced techniques to image vulnerable atherosclerotic plaques.

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Introduction

Plaque rupture or erosion represents a major cause of stroke and the acute coronary syndrome. Information on plaque morphology and composition is essential to identify patients at increased risk for acute cardio- and cerebrovascular events, and may play a key role in individualizing therapeutic strategies and monitoring the effect of interventions. MRI has emerged as the most promising noninvasive imaging technique to estimate the degree of luminal narrowing and to identify plaque components in vivo [1–4]. Recent studies have shown a high sensitivity of MRI in the quantitative characterization of plaque morphology and the classification of the plaque type [1, 5]. Contrast-enhanced (CE) MRI using gadolinium-diethylenetriamine pentaacetic acid has improved the discrimination of the plaque components [6–8]. Furthermore, dynamic CE-MRI has shown that uptake of this agent is correlated

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Fig. 1. MR images of atherosclerotic plaques. **a** 3D-TOF MR angiogram demonstrates lumen stenosis (arrow). **b** T2-weighted image. **c** BB T1-weighted image without fat suppression. **d** BB T1-weighted image acquired with fat suppression yields excellent contrast among the vessel wall, dark lumen and surrounding tissues (arrow) compared with the image acquired without fat suppression (**c**).

with neovascularization and inflammation, both of which are critical indicators of early plaque development and plaque instability [9, 10]. Recent advances in molecular imaging have led to the development of novel paramagnetic and superparamagnetic targeted MR contrast agents that bind exclusively to molecules such as albumin, fibrin, activated platelets, endothelial cells or angiogenesis markers [11–14]. We aimed to review the literature regarding the current most promising advanced MR and targeted molecular MRI techniques in vulnerable atherosclerotic plaques

MRI Techniques

Evaluation of atherosclerotic plaques using MRI includes black blood (BB) and bright blood time-of-flight (TOF) imaging (fig. 1). BB-MRI is commonly performed using fast or turbo spin echo sequences with double inversion recovery preparatory pulses, and yields excellent contrast between the dark lumen and the vessel wall [15]. Using BB-MRI, the combination of the signal intensities in the T1- and T2-weighted images is very helpful for investigators to discriminate lipid deposits, intraplaque hemorrhage, fibrous plaques and calcifications [16]. Bright blood TOF imaging assesses the extent of lumen stenosis and aids in the visualization of the fibrous cap (FC) in the absence of significant flow artifacts [17]. Multiple centers have developed multicontrast-weighted imaging sequences to obtain up to 0.6-mm in-plane resolution [18–24]. These sequences include bright-blood TOF, and pre- and post-Gd contrast-enhanced BB imaging. These studies have shown that MRI can reliably identify FC status [17, 25, 26], plaque composition [17, 27, 28], neovasculature and inflammation [9, 10].

MRI of Plaques

Many studies have investigated the detection of plaque components using MRI. Hatsukami et al. [17] found a high level of agreement between their MR findings and the histological state of the FC by comparing in vivo MRI to histology. The sensitivity and specificity in identifying a thin or ruptured FC was 81 and 90%, respectively [25]. The lipid core was identified with a mean sensitivity of 94% and a specificity of 79% [1, 27, 29], whereas calcifications were identified with a mean sensitivity of 77% and a specificity of 88% [27, 28]. The sensitivity and specificity in identifying the intraplaque hemorrhage was 88 and 80%, respectively [27–29]. In addition, using multiple contrast weightings (T1- and T2-weighted images) improves the detection of soft plaque components with a mean sensitivity of 96% and a specificity of 93% [30]. The Gd-based contrast material can help to differentiate necrotic or lipid-rich components from fibrous components [7, 8]. Dynamic CE-MRI of atherosclerotic plaques has been used to determine the size of the lipid-necrotic core, vascular volume and permeability that strongly associate with plaque inflammation [9, 10]. Ultrasmall superparamagnetic iron oxide (USPIO) agents produce a strong magnetic susceptibility effect on T2*-weighted images [31]. It has been reported that USPIO uptake may be a good marker of the extent of plaque inflammation [31, 32]. Using USPIO particles has allowed the direct visualization of macrophages infiltrating carotid atheroma [33].

MRI of Vulnerable Plaques

It is important to accurately differentiate a stable plaque from an unstable one. Several studies suggest that the key factor determining plaque vulnerability is the plaque composition rather than the degree of luminal stenosis [26, 34–37]. The most possible plaque-related risk factors are the condition of the FC, the size of the necrotic core and hemorrhage, and the extent of inflammatory activity within the plaque [18, 38–45].

Lipids have a high signal intensity on proton density-weighted images and a low signal intensity on T2-weighted images, whereas the fibrous tissues show iso- and slightly high signal intensity on both the proton density and T2-weighted images, which results in significant contrast between lipid cores and fibrous tissues on T2-weighted images [2, 27, 30, 35, 44, 46–50]. Morphologic measurements of the carotid vessel wall with MRI correlate closely with histology [26, 29]. The visualization of FC status with MRI has also shown good agreement with histology [17], and unstable FCs (ulcerated, fissured, disrupted or cap thickness <0.25 mm) were detected with a high sensitivity of 81% and specificity of 90% [25]. Puppini et al. [29] reported that ulceration alone was detected with a sensitivity of 100% and a specificity of 80%. Intraplaque hemorrhage often occurs within lipid cores, and brings the high signal intensity into the lipid cores on both the T1- and T2-weighted images [28, 30, 36, 40]. Yim et al. [40] reported that a fresh or recent intraplaque hemorrhage could be observed as a high signal intensity halo around the carotid artery on the maximum intensity projection images of TOF MR angiography. CE T1-weighted images can differentiate lipid-rich necrotic cores from fibrous tissues, since only the latter show enhancement [40]. Enhancement on the CE T1-weighted images may indicate a fibrous tissue or increased intraplaque vascularity [40]. Increased intraplaque vascularity may indicate a higher degree of inflammation. MRI in conjunction with Gd-based contrast agents has been investigated to detect intraplaque vasa vasorum. A significantly stronger plaque enhancement was seen in plaques with vasa vasorum [51].

Molecular MRI of Vulnerable Plaques

Molecular MRI with targeted contrast agents contributes to a significant improvement in visualizing the characteristics of vulnerable plaques in smaller arteries. Nanoparticle platforms which harbor both (a) molecular probes with affinity for plaques or antibodies directed against plaque antigens, and (b) a reasonable payload of Gd as a T1 shortening agent [52–57] have been used in several experimental studies. Inflammation is an important feature of atherosclerosis, and macrophages play a key role in the atherosclerotic process. USPIO particles can be taken up by activated macrophages in vulnerable plaques and are visible on T2*-weighted sequences as low signal intensity areas [32]. von zur Muhlen et al. [57] reported the use of iron oxide microparticles conjugated to a single-chain antibody targeting activated platelets to image thrombi induced in mouse carotid arteries via MRI. Klink et al. [13] used an activated platelet-targeted MRI contrast agent, P975, which is composed of a peptide targeting $\alpha\text{IIb}\beta_3$ (P977) attached to a Gd chelate (Gd-DOTA). P975 displayed excellent contrast properties, and high resolution and sensitivity in *in vivo* imaging of platelet-rich acute thrombi. Botnar et al. [53] demonstrated the feasibility of *in vivo* molecular MRI for the detection of acute and subacute thrombosis using a novel fibrin-targeted MRI contrast agent in an animal model of atherosclerosis and acute/subacute thrombosis. Rogers and Basu [58] showed that *in vitro* superparamagnetic iron oxide (SPIO) compounds are nonspecifically taken up by macrophages. A number of *in vivo* MRI studies have shown that SPIO compounds localize macrophages and predicted the presence of macrophages in atherosclerotic plaques [33, 59].

Matrix metalloproteinase is predominantly excreted by macrophages. Gd immunomicrospheres targeted at matrix metalloproteinase are capable of increasing the MRI signal both *in vitro* and *in vivo* [14]. Vascular cell adhesion molecule-1 (VCAM-1)-targeted Gd and SPIO compounds have been investigated in atherosclerotic apolipoprotein E knockout mice, and VCAM-1-expressing endothelial cells have been successfully identified *in vivo* [60]. An E-selectin-targeted SPIO compound has been shown to bind to human endothelial cells and consequently cause a clear T2 signal decrease on MRI, demonstrating the feasibility of E-selectin-targeted molecular imaging [61]. McAteer et al. [62] showed that P-selectin-targeted SPIO compounds bind to atherosclerotic endothelial cells *in vitro*. Further study demonstrated the added value of dual-targeted molecular imaging, using a SPIO compound targeted to both VCAM-1 and P-selectin in apolipoprotein E-knockout mice. In the meantime, the dual-targeted compound showed a significantly improved endothelial binding capacity compared to separate VCAM-1- or P-selectin-targeted compounds [62]. *In vivo* MRI using an integrin $\alpha\text{v}\beta_3$ -targeted Gd contrast agent showed a significant increase in the MRI signal in the atherosclerotic vessel wall. Expression of integrin $\alpha\text{v}\beta_3$, proliferation of angiogenic vessels and neointima formation were confirmed by histology [63].

Vulnerable Plaques and Intervention

There is much clinical interest in vulnerable carotid plaques because it is not only a major cause of stroke, but also the most important potentially preventable cause of stroke. Intervention treatment of carotid artery stenosis can reduce the risk of stroke [64]. MRI is well suited for preoperative carotid plaque imaging because it is noninvasive, enables visualization of the carotid vessel lumen and wall, and can quantify plaque components [65]. Therefore, identifying the vulnerable carotid plaques, which probably is clinically more important than the severity of stenosis, is fundamental to the selection of patients for vascular intervention. MR and targeted molecular MRI has demonstrated the ability to identify

morphological features of plaque vulnerability and may provide the pathophysiological information of the plaque pertinent to patient selection for carotid artery stenting. In addition, knowledge of plaque morphology may dictate stent selection and the type of neuro-protection used.

Conclusion

The introduction of targeted molecular MRI may shed more light on the pathophysiological mechanisms of atherosclerosis, and provide a powerful tool to evaluate individualized therapeutic strategies and monitor the effects of therapeutic interventions. The ability of targeted molecular MRI to identify vulnerable plaques may change the management of patients with atherosclerosis.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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