Imaging pathobiology of carotid atherosclerosis with ultrasmall superparamagnetic particles of iron oxide: an update

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Purpose of review
To provide brief overview of the developments regarding use of ultrasmall superparamagnetic particles of iron oxide in imaging pathobiology of carotid atherosclerosis.

Recent findings
MRI is a promising technique capable of providing morphological and functional information about atheromatous plaques. MRI using iron oxide particles, called ultrasmall superparamagnetic iron oxide (*USPIO*) particles, allows detection of macrophages in atherosclerotic tissue. Ferumoxytol has emerged as a new USPIO agent, which has an excellent safety profile. Based on the macrophage-selective properties of ferumoxytol, there is increasing number of recent reports suggesting its effectiveness to detect pathological inflammation.

Summary
USPIO particles allow magnetic resonance detection of macrophages in atherosclerotic tissue. Ferumoxytol has emerged as a new USPIO agent, with an excellent safety profile. This has the potential to be used for MRI of the pathobiology of atherosclerosis.

Keywords
atheroma, atherosclerosis, carotid, ferumoxytol, MRI, ultrasmall superparamagnetic iron oxide

INTRODUCTION

MRI is a promising technique capable of providing morphological and functional information about carotid atheromatous plaques. MRI can distinguish different plaque components including fibrous cap, lipid core, haemorrhage and calcification [1]. The vulnerable atheromatous plaque, considered responsible for majority of acute ischaemic events, not only has a thin fibrous cap, a large lipid pool, but also has macrophage-dense inflammation on or beneath its surface [2]. In contrast, stable or 'well tolerated' plaque is fibrous, with little lipid and no inflammation. Inflammation within atherosclerotic lesions increases the risk for plaque rupture and subsequent thromboembolism [3] and naturally presents itself for novel plaque stabilization interventions.

ULTRASMALL SUPERPARAMAGNETIC IRON OXIDE ENHANCED MRI OF ATHEROSCLEROSIS

MRI using iron oxide particles, called ultrasmall superparamagnetic iron oxide (*USPIO*) particles, allows the detection of macrophages in atherosclerotic tissue [4–7], thereby enabling noninvasive assessment of the underlying inflammation. USPIOs are taken up by macrophages via surface scavenger receptors, producing a region of signal hypointensity on MRI [5], making it a negative contrast medium. USPIOs accumulate predominantly in macrophages in ruptured and rupture-prone human atherosclerotic lesions and induce significant in-vivo signal drop using T_2^*weighted sequence acquired 24 h after intravenous administration of ferumoxtran-10 (Sinerem;

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KEY POINTS

- USPIO particles allow magnetic resonance detection of macrophages in atherosclerotic tissue.
- Ferumoxytol has emerged as a new USPIO agent, with an excellent safety profile.
- Ferumoxytol has the potential to be used for MRI of the pathobiology of atherosclerosis.

Guerbet, Villepinte, France) but not in the images obtained after 72 h. This suggests an active process of uptake and washout and therefore imaging 24 h after USPIO administration was proposed preferable than imaging after 72 h. Electron microscopy has shown unambiguous clustering of USPIO particles in phagosomes of macrophages. In a separate study conducted by our group, areas of magnetic resonance (MR) signal drop corresponding to USPIO/macrophage-positive histological sections were visualized in all patients optimally between 24 and 36 h, decreasing after 48 h, but still evident up to 96 h after infusion [6]. It was shown by the temporal variability of MR signal loss that the process of in-vivo macrophage visualization is dynamic and not sustained. The size of the visualized area of signal loss varies between the patients for any given time point, but there is a distinct temporal variation in the size of this area between images from any one patient. This has been confirmed with double staining techniques using Perls stain (for iron) and anti-CD68 stain (for macrophages). The temporal change in the resultant signal intensity reduction on MR suggests an optimal time window for the detection of macrophages on post infusion imaging [6]. This study was validated with a larger cohort study on 30 patients with severe carotid stenosis and scheduled for carotid endarterectomy [8].

In a comparative study of symptomatic and asymptomatic patients with carotid artery disease using ferumoxtran-10, a dual contrast effect of this agent was observed with signal enhancement seen in plaques with little inflammation and thick fibrous caps (in asymptomatic plaques) [9]. This was better visualized on T_1 weighted than on T_2^*weighted imaging. Symptomatic patients had more focal areas of signal drop than asymptomatic patients on T_2^*weighted imaging, thus suggesting that their plaques had large inflammatory burden. However, some asymptomatic plaques also showed focal areas of signal reduction, suggesting an occult macrophage burden. Identification of this group by this technique would allow identification of inflammation within otherwise morphologically 'stable' plaques, which would benefit from aggressive medical or surgical management for their carotid artery disease.

The systemic nature of atherosclerosis has been demonstrated in a series of comparative studies by our group. Carotid plaques of truly asymptomatic patients were observed to have Sinerem-identified plaque inflammation of lesser degree than carotid plaques on the contralateral side to the symptomatic carotid artery [10]. Patients with truly asymptomatic carotid artery disease but with active coronary artery disease were observed to have more inflammation in carotid plaques, compared with those in truly asymptomatic patients with no coronary artery disease [11]. The degree of plaque inflammation was observed to have no correlation with severity of carotid artery luminal stenosis [12]. In the ATHEROMA study, Sinerem was used to assess the effectiveness of the anti-inflammatory role of high dose atorvastatin versus low dose atorvastatin in carotid plaques [13]. A greater reduction in USPIO uptake relating to reduced plaque inflammation was identified in patients receiving high dose statins, highlighting the potential of USPIO-enhanced-MRI in conducting pharmacological studies. The relatively small sample size limits the generalization of the dose–response observed in this study [14].

In one study by our group, the efficacy of USPIO was assessed in patients with diabetes compared with people without diabetes as diabetic patients have dysfunctional macrophage activity, which may affect the utilization of USPIO in identifying atheroma inflammation. It was observed that USPIO is equally effective in identification of inflammatory burden in carotid atheroma in both diabetic and nondiabetic patients [15▪].

Recently several studies highlighted the importance of high-resolution MRI of plaque morphology to assess the pharmacological effects of various drugs. Reduced plaque enhancement and reduction in large cortical lesions in patients with intracranial atherosclerotic stroke was observed in the group of premorbid statin usage [16▪]. In another trial, it was observed that continued statin therapy leads to a continuous reduction in lipid core and increase in fibrous tissue, which indicates improvement in plaque stability and long-term statin therapy benefits [17]. It was also demonstrated in an MRI study that high-dose modified-release nicotinic acid if given to the statin-treated patients with low HDL-C significantly reduces carotid atherosclerosis within 12 months. Changes in the carotid wall area were assessed at baseline MRI and follow-up imaging at 1 year [18▪]. Similarly, in another study the effect of rosiglitazone was assessed over 1-year duration in patients with type 2 diabetes and coexisting vascular disease or hypertension. Comparison

was based on the changes in the carotid arterial wall volume at baseline and at 52 weeks of pharmacological intervention. The changes were not statistically significant that suggest that rosiglitazone has no effect on progression of carotid atheroma in patients with type 2 diabetes mellitus compared with placebo [19]. However, all these studies were based on morphological assessment of the carotid plaque and lack information regarding the functional activity within the plaque, that is if there was a decrease in the inflammatory burden of the plaque following these therapies.

Several MRI-based studies highlighted the association of risk factors such as blood pressure [20] and elevated haemoglobin A1c (HbA1c) [21▪] in determining the vulnerability of the carotid plaque. It was observed that elevated HbA1c may have an adverse effect in making carotid plaque more vulnerable particularly those with larger lipid content in hypertensive stroke patients [21▪]. Other studies aimed to investigate the association between the systemic cardiovascular outcomes in patients with established vascular disease based on the MR-identified plaque characteristics such as lipid content, fibrous cap status [22] and plaque haemorrhage [23].

Functional MRI using USPIO is regarded as a better index to measure inflammatory activity in atherosclerosis. Recently Ferumoxytol (AMAG Pharmaceuticals, Lexington, Massachusetts, USA/Takeda Pharmaceuticals, High Wycombe, UK) has emerged as a new USPIO agent. This parenteral drug was developed as a treatment for iron deficiency anaemia in patients with chronic renal failure and was approved by the Food and Drug Administration Agency in 2009 [24,25], the European Medical Agency in June 2012 [26] and the Medicines and Healthcare Products Regulatory Agency in 2014 [27]. It is however gaining recognition for its utility in MRI as a blood pool agent [28,29] and as a marker of inflammation when imaged in a delayed fashion [30,31]. The drug can be visualized intravascularly for up to 72 h but begins to clear within 24 h and can be visualized intracellularly (secondary to macrophage uptake) within 24 h. Previous studies on cerebral aneurysms have indicated that peak visualization occurs at 24–48 h [31]; however, it remained visible at 72 h after administration [30,31].

Another study demonstrated the feasibility of Ferumoxytol-enhanced MRI at 1.5 and 3.0 T in healthy volunteers suggesting a range of expected normal values postferumoxytol in a range of tissues. USPIO was detected by changes in $R2^*$ from baseline ($1/T2^*$) at 24 h in myocardium, skeletal muscle, kidney, liver, spleen and blood. This study also suggested that refinement of the dosage, optimization of imaging protocol, detailed image analysis and development of postprocessing and analysis software capable of excluding common artefacts are crucial to ensure reliable and robust quantification of tissue enhancement [32▪]. Ferumoxytol has an excellent safety profile compared with other contrast media including other iron-based contrast media [23,24].

Based on the macrophage-selective properties of ferumoxytol and the increasing validation of MRI with USPIO as a method to detect pathological inflammation [30,31], it may be speculated that ferumoxytol-enhanced MRI can be used for assessment of the activity of inflammatory response in the atherosclerotic tissue similar to ferumoxtran-10. Our group is currently undertaking clinical research studies to validate these observations. Another ongoing trial is aimed at assessing the role of ferumoxytol-enhanced MRI to provide additional information in risk prediction models in patients with abdominal aortic aneurysm [33▪].

CONCLUSION

USPIO particles allow MR detection of macrophages in atherosclerotic tissue. Ferumoxytol has emerged as a new USPIO agent, with an excellent safety profile. This has the potential to be used for MRI of pathobiology of atherosclerosis.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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