Investigation of Atherosclerotic Plaques at 3T using USPIOs with MR Angiography

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Introduction

Early atherosclerosis cannot be detected by traditional angiographic imaging, because outward vessel wall remodelling can preserve luminal area. MR contrast agents that may detect such plaques are therefore of great interest. Ultra-small superparamagnetic particles of iron oxide (USPIOs) have been suggested as a possible early indicator of atherosclerosis [1–4], since they are accumulated by macrophages in inflammatory plaque. A previous animal study using 'bright-blood' angiographic scans showed strong magnetic susceptibility effects in the aortic lumen, several days after injection of the USPIO agent Sinerem, which accumulated in macrophages in the atherosclerotic vessel wall [1]. We have performed similar studies to assess the uptake and MR detectability of a comparable experimental USPIO agent, DDM43/34, using a higher field strength of 3T which may offer the potential to reduce the administered dose.

Methods

Six Watanabe heritable hyperlipidemic (WHHL) rabbits (Covance, Denver, USA) aged 24–28 months, were anaesthetised and injected with USPIOs (DDM43/34, Schering, Berlin [2]). MR scans were performed over the subsequent five days using MRI. Firstly, four animals were given doses of 0.1, 0.25, 0.5 and 1.0 mmol/kg. Images were acquired before and immediately after USPIO administration, and again after 6 hours and at 1, 2 and 5 days. For histological comparison, two additional animals were given doses of 0.1 and 1.0 mmol Fe/kg, then scanned immediately and after 2 and 5 days. After these animals were sacrificed, aortic slices were stained with HE, Prussian blue and RAM11. These studies were performed, in accordance with all applicable regulations governing animal studies, following approval from the local animal care review board.

The parasagittal MR angiography scans, covering the thoracic aorta, were acquired in a 3T clinical scanner (Philips Medical Systems) using a head array coil, with two 3D gradient-echo sequences at different resolutions. A first sequence used TE/TR = 1.9/4.8 ms, flip angle 25°, 16 NSA, total scan duration 4 min 15 sec. The acquired matrix size was 256×179×15, with a field of view (FOV) 256 mm × 179 mm × 15 mm, giving an isotropic resolution of 1.0 mm (interpolated to 0.5 mm along all three dimensions). This scan was chosen to be similar to Ref. 1 but with a higher SNR.

A second, higher-resolution, MRA scan used a similar sequence but with TE/TR = 2.1/5.6 ms, 35 acquired slices, 12 NSA, total scan time 8 min 23 sec. This scan had 0.7 mm isotropic resolution (interpolated to 0.35 mm). Further scans were acquired perpendicular to the plane of the aorta.

The blood signal is strong only for the narrow range of concentrations in which T1-related enhancement is strong but signal losses due to T2* are weak. To obtain a 'bright-blood' MRA at time zero, the dose was split into two stages: an initial 0.025 mmol Fe/kg was given and bright-blood MRAs were obtained; then the remainder of the dose was administered. Additional 'bright blood' MRAs at later time-points, after substantial USPIO clearance, were obtained with the first MRA protocol (using only 4 NSA) during infusion of gadopentate dimeglumine (Magnevist, Schering, Berlin).

For a quantitative image assessment, changes in blood signal intensity were measured relative to the lipid signal. The images were also assessed qualitatively (by consensus of two reviewers) to determine the presence or absence of susceptibility artefacts in the aortic lumen, and possible causes.

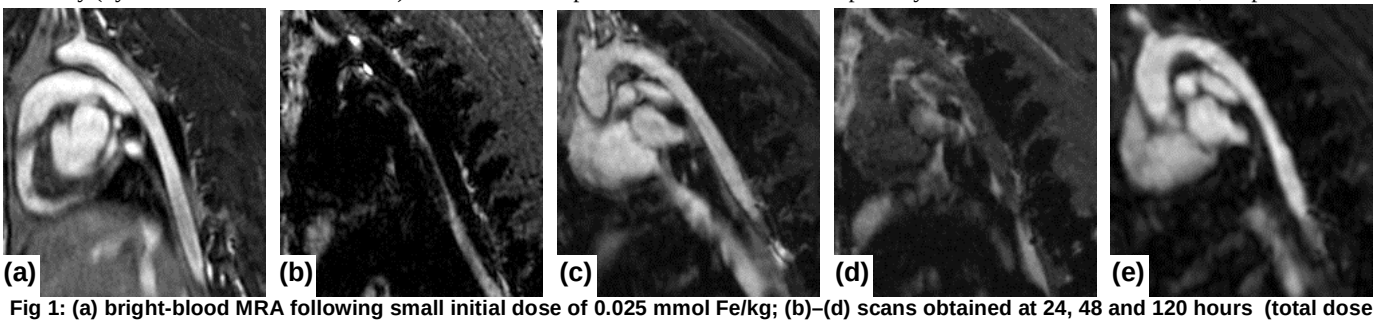

Fig 1: (a) bright-blood MRA following small initial dose of 0.025 mmol Fe/kg; (b)–(d) scans obtained at 24, 48 and 120 hours (total dose 1.0 mmol Fe/kg USPIO); (e) with Magnevist infusion at 120 hours.

Results

Fig. 1 shows representative images of the aorta, initially and over the first five days after administration. Blood signal intensity changes (Fig. 2) suggest a clearance of ≥ 90% after 2 days, somewhat faster than observed in Ref. 1. The images revealed widespread susceptibility artefacts and signal loss, associated with (histologically confirmed) uptake of the USPIOs in liver, spleen, bone marrow and lymph nodes. However no such effects could be associated specifically with the vessel wall, despite some one-sided artefacts which clearly arose from uptake in nearby ribs and spine. Histologically, the two aortas contained active plaques, with low levels of USPIO uptake (Fig. 3) for dose 1.0 mmol Fe/kg and virtually no accumulation for dose 0.1 mmol Fe/kg.

Discussion and Conclusions

The studies of Refs. 1–4 showed USPIO uptake in atherosclerotic aortic plaques, with consequent observation of susceptibility effects using MRI. It is surprising that this study did not demonstrate these effects in any of the animals, despite using a very similar methodology to Ref. 1. Despite the short echo times of the applied sequences, they appear to be sensitive to USPIO uptake elsewhere in the body.

The principal differences between our study and Ref. 1 are the different contrast agent, the greater animal ages and the higher magnetic field strength. Future work will clarify the influence of these and other factors on the results of these experiments.

Despite the potential for plaque detection using USPIOs, we advise caution in interpreting such studies, as the lack of susceptibility effects does not necessarily imply absence of active plaque. The choice of USPIO affects clearance kinetics and possibly their uptake in plaques.

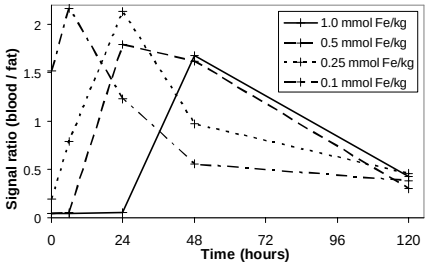

Fig 2: Signals changes over time for the different USPIO doses.

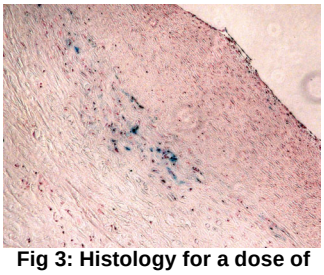

Fig 3: Histology for a dose of 1.0 mmol Fe/kg. Prussian blue reveals little USPIO uptake.

Acknowledgements

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References

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