# Iron oxide enhancing atherosclerotic plaque: Feasibility of white marker imaging techniques

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**Introduction** It was shown in several studies that macrophages in atherosclerotic plaques accumulate intravenously injected iron oxide nanoparticles from the blood pool and show up as dark spots on $T_2^*$ weighted images [1,2]. However, absence of magnitude signal is ambiguous. It could result from low proton density, fat-water signal cancellation, dephasing due to flow effects or susceptibility induced dephasing caused by iron oxide nanoparticles. For imaging of ex-vivo iron oxide labeled cells the same problem arises. Several so-called "White marker" techniques with reversed contrast have been developed, that generate image signal in the vicinity of the particles only by utilizing the strong magnetic dipole field of iron oxide monocrystals [3, 4]. Aim of this study was to determine how white marker techniques compare with susceptibility weighted imaging in the detection of iron oxide in atherosclerotic plaque.

**Materials & Methods** New Zealand White (NZW) rabbits were fed with a cholesterol rich diet and immunologically stimulated to develop atherosclerotic plaque in the aorta. The animals received iron oxide particles (VSOP-C 184, Ferropharm, Teltow, Germany) at doses of 0, 0.05 and 0.10 mmol Fe/kg, the second corresponds to a dosage used in clinical trials in humans. Twenty-four hours after injection, the animals were euthanized and parts of the aorta were embedded in agarose phantoms for imaging. All experiments were performed on a 1.5 T MR system (Magnetom Sonata, Siemens, Erlangen, Germany). High resolution gradient echo imaging with echo times ranging from 1.9 to 11 ms was performed. Using a linear least squares fit to the magnitude signals, $T_2^*$ relaxation times were determined in the vessel wall. "Dephased MRI" (DMRI) images with correction for partial volume effects as described in [5] were measured with positive and negative dephasing gradients along 3 orthogonal gradient directions. As a third experiment, off-resonance spin echo (ORSE) [3] images using frequency offsets of +800 and -800 Hz were acquired.

**Results & Discussion** Histological staining proved the existence of iron oxide particles in the Tunica intima and media of the extracted aorta segments. In comparison to control animals, the determined $T_2^*$ values show a dose dependent reduction, as figure 1 demonstrates. "White-marker" imaging techniques however failed in detecting the iron. DMRI images were inconclusive as they show signal not only in the iron containing aorta segments, but also in the control animals. We interpret this as residual signal resulting from partial volume effects that did not perfectly subtract. ORSE did not show off-resonant protons above the noise level. Both "White marker" techniques were tested in phantoms containing iron oxide labeled cells where they performed very well in detecting the field disturbance caused by the particles. We conclude that the iron oxide content of atherosclerotic plaque labeled in vivo at a clinical applicable dose is too low to be imaged using off-resonance techniques. More sensitive $T_2^*$ weighted imaging is able to detect the iron; positive image contrast may be obtained with a simple image subtraction technique, as figure 2 shows.

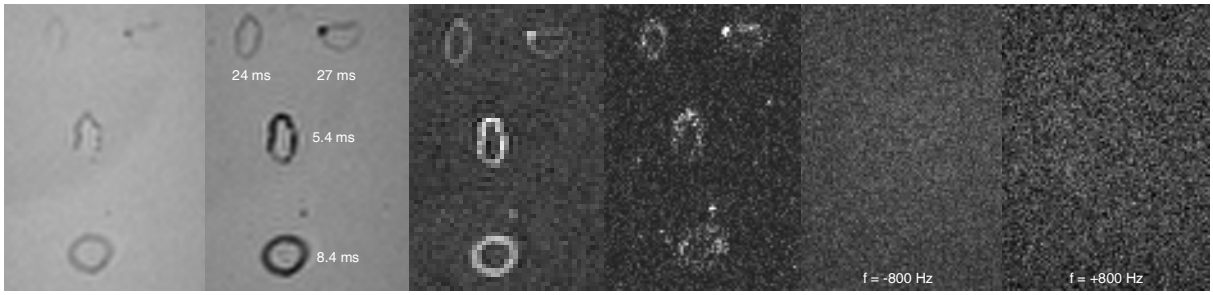


*Figure 1: Images of the embedded aorta of NZW rabbits that received 0 (top), 0.1 (middle) or 0.05 (bottom) mmol Fe/kg. From left: gradient echo image TE 1.9 ms; gradient echo image TE 11 ms with results of the $T_2^*$ fit; "positive contrast" gradient echo image, obtained by subtracting the first two fat-water in-phase images (TE 4.76 ms – TE 9.53 ms); "Dephased MRI" image; off-resonance spin echo images for two offset frequencies*

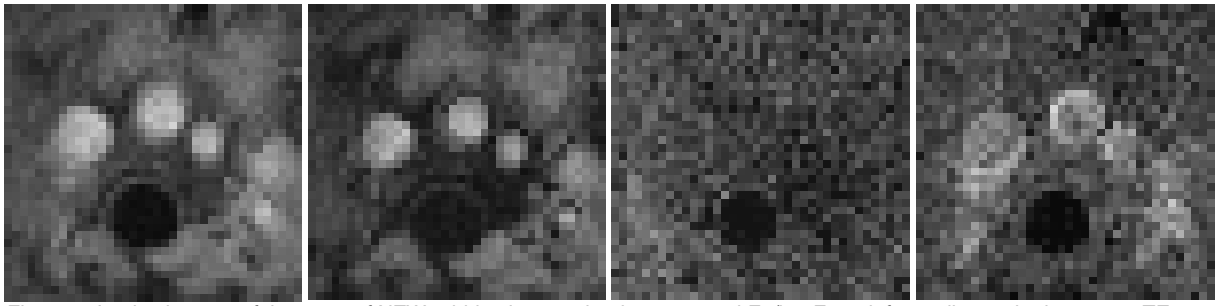

*Figure 2: In-vivo images of the aorta of NZW rabbits that received 0.060 mmol Fe/kg. From left: gradient echo images at TE 4.8 ms and 9.5 ms (in-phase); subtraction prior to injection (control) and after contrast agent administration shows the reduced T2* in the vessel wall as positive contrast*

**References**

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