Positive Contrast MR imaging of in vivo atherosclerosis in a rabbit model using ultrasmall iron oxide particles

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Introduction: Ultra-small iron oxide particles (USPIOs) are currently being evaluated as potential markers of inflammation in atherosclerotic plaque. Long circulating dextran coated USPIOs (such as Combidex) are taken up by the mononuclear phagocytic system with limited uptake into liver Kupffer and endothelial cells. Due to the uptake of iron by plaque macrophages, it is possible to identify inflammation using T_2/T_2* weighted MR techniques. Differentiation between signal loss caused by iron and native low signal in tissue may be problematic because of the negative contrast generated by macrophage uptake of the particles. Recent *in vitro* studies using the GRe Acquisition for Superparmagnmetic Particles (GRASP) sequence show that modifications of traditional GRE sequences to include manually controlled dephasing gradients resulted in significant signal enhancement in gels containing iron particles [1].

Aim: The purpose of our study was to verify the in vivo efficacy of GRASP to produce positive signal in plaques of atherosclerotic rabbits after administration of USPIOs.

Methods: Three atherosclerotic New Zealand White rabbits (balloon injury, high cholesterol diet) and one control rabbit were administered a clinically relevant dose of 4.7 mg Fe/Kg USPIO. The USPIO was prepared by vacuum filtration of Feridex (AMI-25) through a 25 nm filter. The resultant USPIO exhibited the following properties: hydrated mean diameter of 12 nm, r1 of 10 s^{-1} mM^{-1} (60 MHz, 40ºC), and blood half-life in rabbits of 16.7 hours. All imaging was performed at 1.5T using a knee coil. T2* GRE and GRASP sequences were used with TR= 300 ms, TE =5,10, or 25 ms, and variable dephasing gradients (25%, 35% or 100%) both pre and 24 hours post injection of USPIO. After imaging, the rabbits were sacrificed; the aortas were removed and placed in formaldehyde overnight before being transferred to 2% agar gel. The ex vivo aortas were also imaged using similar T2* GRE and GRASP sequences. Immediately after *ex vivo* imaging, the aortas were removed from the 2% gel, fixed in paraffin, and stained for iron used Perls Prussian Blue.

Results: Figure 1A shows cross sectional images of rabbit aorta both pre and 24- hours post administration of USPIO. USPIO uptake was observed (as shown by the signal loss) in the T2* GRE sequence. The atherosclerotic aorta wall was clearly delineated from the background when the GRASP sequence was employed. In addition, the signal enhancement observed using GRASP corresponded well with signal loss observed on T2* GRE sequence. Histology revealed that the iron oxide was taken up by plaque macrophages. In addition the uptake pattern observed by histology was similar to enhancement observed by MRI. Figure 1B shows longitudinal and cross sectional images of the rabbit aorta obtained ex vivo. Positive signal enhancement with GRASP matched negative signal loss on T2* GRE sequences.

Conclusions: This study shows that modified GRE sequences with variable dephasing gradients can be used *in vivo* to generate positive signal enhancement in plaque after administration of USPIO. This sequence may be useful to verify iron oxide uptake in atherosclerotic plaque and for the assessment of macrophage density in vivo.

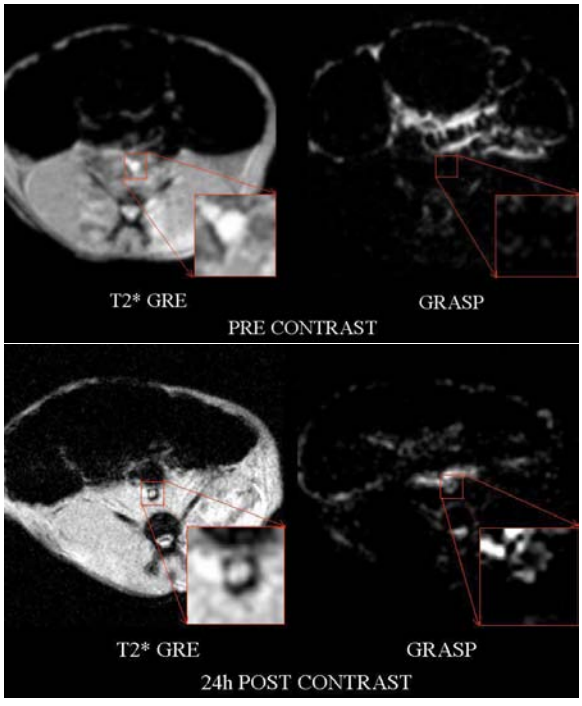

Figure 1A: Cross sectional in vivo images of rabbit aorta

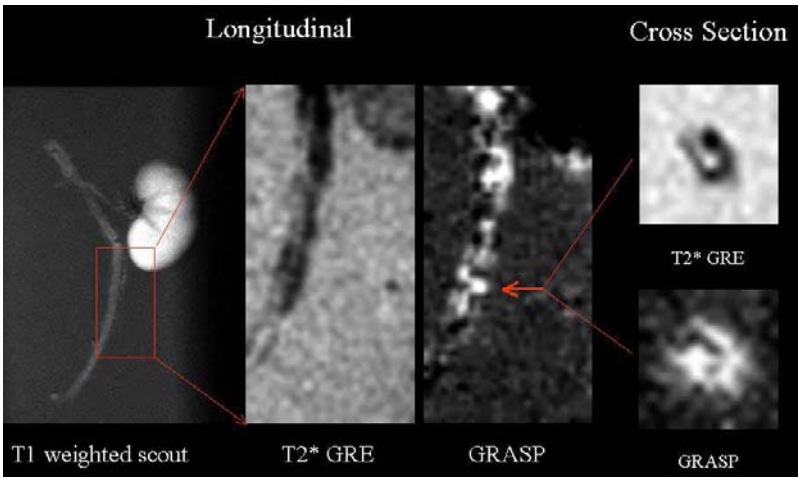

Figure 1B: Ex vivo images of rabbit aorta