Quantitative Assessment of Ultrasmall Superparamagnetic Iron Oxide (USPIO) Contrast Agent Uptake in Atherosclerotic Plaque by MRI

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Introduction Non-invasive assessment of atherosclerotic plaque progression/regression and response to therapy has long been a goal of cardiovascular researchers. Recent advancements in MRI technology currently allow for high resolution, *in vivo* visualization of atherosclerotic plaque and its complex composition in humans and animals (1). However, recently, there has been a paradigm shift in the therapeutic focus of atherosclerosis from one of plaque reduction to one of plaque stabilization possibly via targeting anti-inflammatory processes (2). Ultrasmall superparamagnetic iron oxide (USPIO) contrast agents have recently been used in conjunction with MRI to qualitatively assess atherosclerotic plaque inflammation. However, in order for a USPIO based MR imaging strategy to be meaningful for pharmacological intervention studies, a thorough, quantitative investigation using both *in vivo* and *ex vivo* MRI, analytical iron determination, and histology is needed in order to establish the relationship between MRI signal and USPIO deposition in plaque. Therefore, the aim of this study was to quantitatively analyze these parameters in a hypercholesterolemic, balloon-injury rabbit model associated with inflammation and rapid plaque development.

Methods NZW rabbits maintained on a high cholesterol/fat diet were subjected to balloon injury to the abdominal aorta and left iliofemoral artery. USPIO (500 μmol/kg, Combidex® or ferumoxytol) was administered at 2 (n=7), 4 (n=7), and 8 (n=6) weeks post-injury. Imaging was performed on a 4.7T Bruker Biospec system. During each imaging session a series of gradient echo (TR/TE = 350/4 ms, FOV = 11×11 cm, matrix = 256 × 256, slice thickness = 4 mm, number of averages =8, and 2D angiographic (TR/TE = 12/6.55 ms, FOV = 15×15 cm, matrix = 256 × 256, slice thickness = 6.0 mm, number of averages = 6) images were acquired throughout the abdominal aorta and iliofemoral arteries. Imaging sessions were performed immediately prior to a bolus administration of *Combidex* or ferumoxytol for a baseline measurement, immediately after USPIO administration for verification of contrast agent delivery, and 6 days post-administration. Additionally, *ex vivo* MRI, histological analysis, and absolute iron measurements were performed on the vessels.

Results Decreased MRI signal intensity (↓30-53%) was clearly observed in the vessel wall in 2, 4, and 8 (Fig 1) weeks post-injury animals with *Combidex*, but little to no signal loss was detected with ferumoxytol. This signal loss was consistent with that measured by *ex vivo* high resolution MRI (r=0.78, P=0.0001) (Fig 2). Absolute iron content in the vessels, as measured by ICP-MS correlated with both *ex vivo* (r=-0.86, P<0.0001) and *in vivo* (r=-0.58, P=0.01) MRI signal intensity. Correspondingly, histological analysis of the vessels indicated that USPIO uptake was primarily associated with smaller macrophage located in the neointima of the plaque.

Conclusions These findings indicate that quantitative assessment of active atherosclerotic lesion development in a balloon injury animal model using USPIO contrast based MRI is feasible. Future studies examining the relationship between USPIO uptake and inflammation are warranted.

References 1) Fayad ZA et al. *Circ. Res*. 89:305, 2001. 2) Libby P et al. *Nat. Med.* 8:1257, 2002.

Fig 1

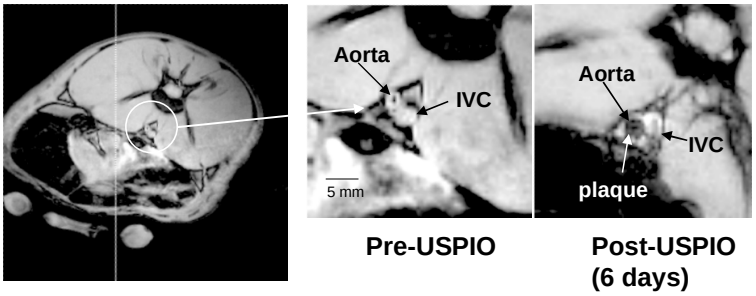

Fig 2