Improving T1-Weighted "Hot Spot" Imaging with Colloidal Iron Oxide Nanoparticles

S. D. Caruthers[1], A. Senpan[1], D. Pan[1], G. Hu[1], S. A. Wickline[1], and G. M. Lanza[1]
[1]C-TRAIN, Washington University, St. Louis, MO, United States

Background and Introduction: Molecular imaging and nanomedicine approaches to the diagnosis, monitoring and treatment of diseases, *e.g.* cancer and atherosclerosis, could have significant consequence on medical practice and outcomes. Due to the exquisite sensitivity of MR to magnetic field disturbances of iron oxides (IO), a variety of IO-based agents have been utilized. However, despite many elegant new imaging techniques for "hot spot" imaging, the highly-sensitive detection and visualization of IO still depends on the disruption of the local magnetic field and/or the resulting frequency shifts. Contrary to typical IO agents, we have presented a novel colloidal iron oxide nanoparticle (CION) that encapsulates multiple IO nanocrystals suspended in oil within a lipid membrane thereby reducing T2* effects such that T1 effects can be detected[1]. An early version of CION, functionalized to target fibrin, was imaged in atherosclerotic carotid artery specimen from symptomatic patients[2] (Fig. 1). Using "typical" gradient echo techniques (TFE), the expected signal dropout from iron oxides was seen, however, employing high resolution fast spin echo (TSE) with short echo times, bright signal enhancement was evident on T1-weighting. The mechanism by which the T2* is reduced in CION remains under investigation and is hypothesized to be based in the segregation of individual IO nanocrystals within the fluid core of CION in a way that minimizes the synergy between multiple components while still delivering enough copies of IO to the binding site to be detected. The purpose of this work was to develop CION of various core structures so that longitudinal relaxivity (r_1) could be better utilized.

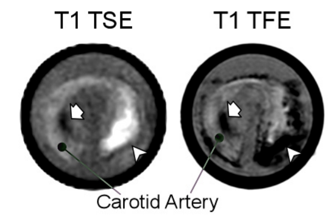

Fig. 1. Carotid Artery with fibrin-targeted iron oxide nanocolloid. Within the plaque (arrow head), bright signal is seen on T1-TSE (Left) but it changes to typical T2* signal void on gradient echo (Right). Some areas (arrow) have low signal on both techniques.

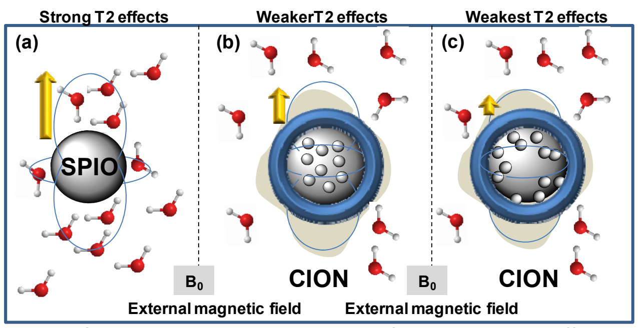

Fig. 2. Cartoon illustrating hypothesis of decreased T2* effects of CION to SPIO. (a) A typical IO particle surrounded by water within a B_0 field. The field dependent dipole moment created is shown (yellow arrow). Protons pass deep within this magnetic flux field and experience strong dephasing effects. (b) The encapsulation of CION iron crystals reduces the effective field experienced by the surrounding protons, such that the relative impact on T2* is greater than the changes of T1 relaxivity. (c) The encapsulation of CION iron crystals with surfactant cross-linking further reduces the effective field experienced by the surrounding protons, such that the impact on T2* is further increased relative to the changes of T1.

Methods: CION were prepared with multiple oleic-acid-coated iron oxide nanocrystals suspended in almond oil and collectively encapsulated with a phospholipid monolayer membrane. To evaluate the role of IO concentration within the almond oil core, CION were created varying the [IO] to 7.5%, 15% and 45% (w/v) Fe_3O_4, both with and without cross-linking the outer lipid membrane. To compare the effect of iron phase, CION was made with mixed-phase maghemite (Fe_2O_3-Fe_3O_4) at 7.5% (w/v). CION were also constructed exchanging the almond oil with sorbitan sesquioleate to evaluate. CION were characterized using dynamic light scattering, vibrating sample magnetometer, atomic force microscopy (AFM) and transmission electron microscopy (TEM). The r_1 was calculated at 1.5T using the Look-Locker technique to measure T1 of serial dilutions of CION.

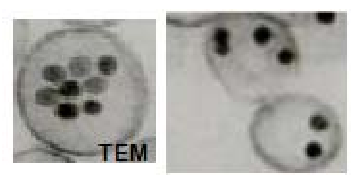

Fig. 3. Electron micrograph of colloidal iron oxide nanoparticles demonstrating the multiple IO crystals incorporated into the oil core of each lipid-encased nanoparticle. Crosslinking (right) appears to discourage aggregation of the particles in the core center as with the non-cross linked version (left).

Results and Discussion: Hydrodynamic diameter and zeta potential of the CIONs ranged from 110-300nm and 23 to 40mV, respectively, depending on composition. AFM revealed an asymmetric (*i.e.,* deformable) particle size of 114±22nm (height) by 228±69nm (diameter). TEM confirmed that the iron nanocrystals were retained in the oil core; but the cross-linked version tended to separate individual nanocrystals and preferentially position them toward the outer shell (Fig. 3). In all cases, r_1 ($[Fe]mMs)^{-1}$ of the cross-linked CION was 2-3x greater than the non-cross-linked version (Fig. 4). Decreasing magnetite loading (45%, 15%, 7.5%) increased r_1 from 1.8, 4.5, to 7.7, respectively. Comparing CION comprising magnetite vs. mixed-phased maghemite/magnetite nanocrystals gave an r_1 of 7.7 vs. 1.3, respectively, the lower susceptibility pure phase performing better. T1-w imaging confirmed r_1 relationships. To simplify manufacture, but retain strong r_1 relaxivity, sorbitan-based CION, which would not require cross-linking, was developed, but requires further evaluation.

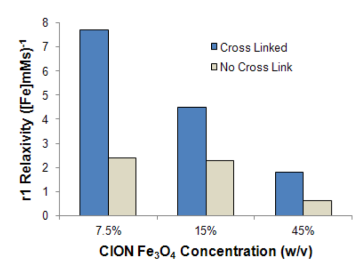

Fig. 4. Longitudinal relaxivity of CION increases with lower [Fe] concentration (horizontal axis) and with cross linking (solid bars).

Conclusion. Site-targeted CION offers a positive-contrast T1 alternative to basic iron oxide approaches. The characteristics of CION which improve r_1 relaxivity are low overall Fe concentration, pure magnetite crystals, and partial cross-linking. Applied to molecular imaging, this novel platform, which can be further developed to deliver drugs, may provide sensitive detection of sparse epitopes via both T2* (FFE) and T1 (TSE) weighted imaging.

References:

1. Caruthers, *et al*., *Proc. ISMRM* 16:3202 (2008)
2. Senpan, *et al*., *ACS Nano*. In press (2009)