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Meeting abstract

2115 A novel targeted iron oxide nanocolloid agent for rapid detection of fibrin clots via T1 and T2 weighted MRI

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Background

Targeted iron oxide nanoparticles are easily detected with MR by their exaggerated signal dropout. Recent advanced techniques are emerging to visualize iron oxide particles as "hot spots" rather than signal dearth. For background blood pool clearance, a typical delay of 24 hr is required between contrast treatment and imaging. Although targeted USPIO or MION agents bind endothelial cell surface markers, they also further extravasate into plaque, binding macrophages or other intraplaque constituents during the 24-hour wait. This confounds the morphological source of the MR signal. Moreover, in coronary MR imaging_where high temporal and spatial resolution are required and inherent anatomic magnetic susceptibility heterogeneity masks that of the iron oxide agents_dark spot T2-weighted gradient echo imaging of targeted iron oxides is challenging and has not yet been demonstrated. The objective of this research was to develop an intravascular, fibrin-specific iron oxide agent useful for early, rapid detection and quantification of ruptured plaque in coronary arteries with MRI.

Methods

Superparamagnetic nanocolloid particles were developed with the core having multiple magnetite nanoparticles suspended in vegetable oil and encased in a lipid membrane. The MR T1 and T2 properties of the nanocolloid were determined using serial dilutions of the agent from 100% to 1% and MR acquisitions including Look-Locker (inversion recovery) and multi-echo gradient-echo techniques. To assess signal on both T1- and T2-weighted images, functionalized particles were targeted to clot surfaces with biotin and an antibody targeted to fibrin-rich thrombi (n = 7) suspended in saline *in vitro*; one clot served as an untreated control reference. Imaging of the clots was performed at 1.5 T using a high-resolution (0.3 × 0.3 × 1.2 mm^3) 3D T1-weighted turbo spin-echo sequence for ROI analysis and lower-resolution (1 × 1 × 5 mm^3) gradient-echo imaging, both T1-and T2*-weighted, for visual inspection.

Results

The average particle size and zeta potential of the nanocolloid were approximately 140 nm and -23 mV, respectively. The iron concentration, measured by mass spectrometry, was ~2000 μg/g of emulsion. In solution, T1 and T2 effects varied with concentration with minimal T1 effect at 1% dilution. At higher concentrations in solution, the T2* effects dominated and produced dark distorted images typical to iron oxide agents. When bound to the outer surface of the fibrin-rich clots, the nanocolloid produced bright enhancement on T1-weighted imaging (SNR = 26); whereas the control clot, which received no agent, was poorly discerned from surrounding saline (SNR = 10). On T2-weighted images, characteristic "blooming" effects were produced by the bound agent but not on the control. (See Figure 1) Using pharmacokinetic parameters and models for similar lipid-encapsulated

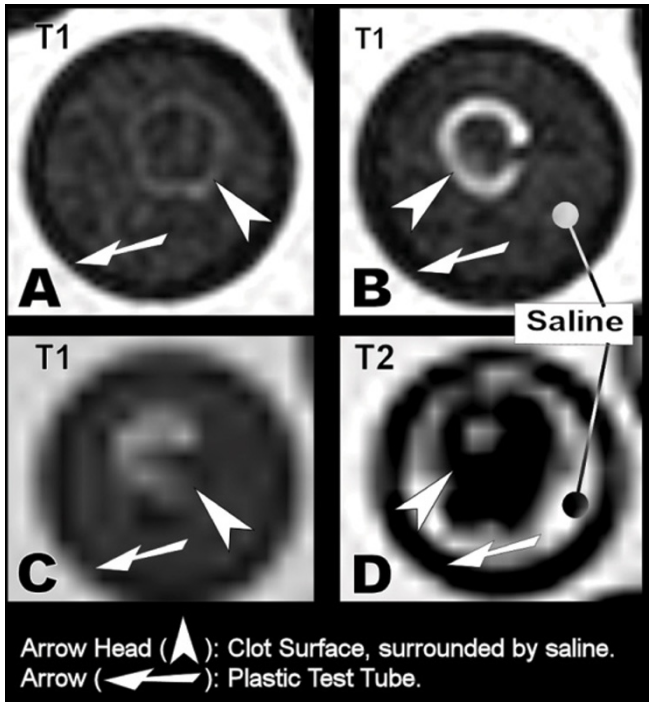

Figure 1
MR images of fibrin-rich clots in saline. (A) the control clot is poorly visualized on high resolution T1 (shown) and T2 (not shown). (B) High resolution, T1-weighted fast spin echo images show the bright enhancement caused by the iron oxid nanocolloid bound to the clot surface. Lower resolution T1-weighted gradient echo imaging (C) also shows enhancement which turns into typical magnetic susceptibility blooming artifact on T2-weighted gradient echo images (D).

emulsion nanoparticles, the systemic concentration of this nanocolloid agent for a typical *in vivo* application was projected to be less than the 1% dilution upon injection and approximately 0.03% of this concentration in 20 minutes, which suggest that, although the particles are constrained to the vasculature, the background levels will be negligible soon after injection leaving only the bound agent visible. Moreover, the dual T1 and T2 contrast features of this agent obviates the need for pre-contrast baseline images.

Conclusion

These larger, fibrin-specific superparamagnetic nanocolloids may provide highly sensitive, bright-contrast detection of microthrombi exposed in ruptured plaque. The combination of high MR sensitivity and the imaging speed advantages of short T1-weighted pulse sequences may overcome the cardiac motion barrier to MR coronary molecular imaging.