Toward a Novel Implantable Contrast Agent for Enhanced MRI Definition of the Vein Graft Wall: Long-Term Stability Assessment of Gd-DTPA Immobilized Contrast-Enhanced (ICE) MRI

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Introduction: Vein bypass graft (VBG) failure occurs in up to 30-50% of the 500,000 grafts implanted annually in the US [1]. Emerging data supports a role for negative vessel wall remodeling in VBG failure, rendering the ability to image their evolving morphology in vivo of paramount importance. Vessel wall MRI has enormous potential of delineating wall and lesion tissue noninvasively based on intrinsic soft-tissue contrast, and thus assess remodeling indices longitudinally to track disease progression. However, it is of limited clinical use due to the high image resolution required to effectively image the vessel wall whose thickness (<1 mm) typically equals the resolution of most clinical MR protocols. This limitation is exacerbated for lower extremity VBGs that can span over 40 cm in length; a state-of-the-art clinical 3T MR protocol (e.g., high sampling efficiency FSE or SSFP) can image 6 cm of the carotid arteries in 6 min. This would still translate to 40 min scan time for a typical VBG. Our long-term goal is the development of an implantable MR contrast agent, immobilized on the outer surface of the vein graft ex vivo at the time of operation, used to enhance both the MR signal and tissue contrast available for subsequent imaging. This work demonstrates for the first time that Gd-DTPA can be successfully immobilized on the vein graft surface and successfully provide long-term MR signal enhancement.

Methods: A previously developed technique for covalent binding to amine groups on the cell surface using *N*-hydroxysuccinamide (NHS) ester coupling chemistry [2] was adopted to immobilize Gd-DTPA on the vein graft adventitia, as previously demonstrated with iron oxide nanoparticles (30 nm) [3]. Briefly, Gd-DTPA is "activated" with NHS in a 3 hr reaction at room temperature. Activated Gd-DTPA (10 mM) is then allowed to bind on vein surface amines during a 30 min incubation period, followed by thorough rinsing. Fresh saphenous vein was obtained from discarded operating room tissue; one half of the donor vein was used for Gd-DTPA labeling and the other half as control. Labeled and control segments were sealed in separate Petri dishes filled with PBS and sodium azide (preservative), and stored at 37°C in a shaker for 122 days. MRI experiments were performed at 3T (GE Excite HDx). Immobilized contrast-enhanced (ICE) T1W MR imaging is demonstrated using 3D SPGR (TE/TR 4/30ms, FA 45°) and an inversion-recovery 3D high sampling efficiency FSE (TE/TR/TI 10/1500/500ms) [4]. ICE MR signal enhancement was assessed using the signal-to-noise ratio at 0, 22, 52, and, 122 days after labeling. In addition, changes in immobilized Gd-DTPA concentration at selected time points were assessed using transverse (R_2) and longitudinal (R_1) MR relaxometric quantitation of the vein graft wall MR signal. R_2 was measured at 0, 22 and 122 days with a Carr-Purcell-Meiboom-Gill multi-echo sequence [4]. R_1 was measured at 0 and 122 days from the signal observed with an inversion-recovery (IR) 3D high sampling efficiency FSE at 5 TIs (50, 250, 500, 750, and 1000ms).

Results: Increased transverse and longitudinal relaxation rates of the labeled portion of the vein compared to the control portion of the vein indicated the presence of Gd-DTPA on the vein graft wall: the transverse relaxation rate of the labeled vein was 1.8 times larger than the control (R_2=14.07±0.23 s^{-1} vs. 7.83±0.04 s^{-1}), while the longitudinal relaxation rate was 1.37 times higher than the control (R_1= 1.93±0.1 s^{-1} vs. 1.41±0.02 s^{-1}). As shown (Figure), the differences in R_1 and R_2 between the labeled and control vein remained stable throughout the 4 month incubation period (one-way ANOVA p=0.78 for lebeled vein R_2 and p=0.97 for control vein R_2 between the three measurement time points; t-test p=0.21 for labeled vein R_1 and p=0.34 for control vein R_1 between the two measurement time points). As is readily seen in the figure, the SNR of the labeled vein was 2.4±0.4 higher than the control vein in 3D SPGR T1W images (and 4.1±1.6 higher in 3D FSE IR images). This SNR increase, demonstrated with ICE MRI, is thus equivalent to a 5.8-fold and 16.8-fold potential reduction in scan time for these two contrasts respectively.

Conclusion: Permanent enhancement of MR imaging efficiency using a novel extrinsic contrast mechanism based on covalent immobilization of Gd-DTPA on the tissue of interest during surgical intervention holds great promise as a strategy for longitudinal studies of vascular biology as well as earlier, more efficient detection of graft failure.

References: [1] Conte MS et. al, J Vasc Surg, 2006;43:742-51. [2] Sarkar D et. al, Bioconjug Chem, 2008;19:2105-9. [3] Ozaki et. al, NESVS 10/2009, Boston, MA. [3] Mitsouras D et. al, MRM 2009;62:607-15. [4] Roebuck JR et. al, MRI 2009;27:497-502.