Dual Agent Relaxivity Cancellation (DARC) Imaging, a Novel Imaging Method for Dark Blood Post-Contrast Imaging: Application to MR Lymphangiography

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Introduction Lymphedema is a highly prevalent chronic disease most commonly related to oncologic surgery and treatment. While there is no cure for lymphedema *per se*, a relatively new microsurgical technique, Lymphaticovenous Anastomosis (LVA), is an increasingly used and efficacious treatment that requires the pre-operative mapping of individual lymphatic channels. In response to this, MR Lymphangiography (MRL), a MRA-like technique in which a small amount of gadolinium contrast is injected intracutaneously between the webspaces of the hand or foot and dynamically imaged as it slowly progresses up the lymphatics, has proven useful for such mapping (1). One big challenge, however, is the simultaneous enhancement of venous structures, making it cumbersome to distinguish between lymphatics and veins, thereby adding considerable time and confusion to study interpretation. We introduce a method of vascular suppression (Dual Agent Relaxivity Cancellation – DARC) for MRL that exploits the blood-pool ($t_{1/2}$ = 14h) and T2*-shortening properties of the ultra-small superparamagnetic iron oxide (USPIO) ferumoxytol.

Methods *Ex vivo* venous human blood was doped with ferumoxytol ranging up to 0.4 mg/ml, and R2* in whole blood and plasma was measured at 1.5 and 3T using a multiecho FFE sequence [TR/TE/ΔTE/α/#echoes = 200/1.5/2.4/35°/32]. Routine clinical MRL examinations are performed using standard intracutaneous Gd injection (4mL gadobenate per extremity imaged) with short echo mDixon high resolution 3D sequences for fat suppression at multi-stations ($TR/TE_1/TE_2/\alpha$ = 4.4/1.5/2.7/20°, true resolution 1.3x1.3x1.6 mm, 1-1.5 min per station). Based on the results (see below), diluted intravenous ferumoxytol 5 mg/kg was administered at different timepoints during the course of clinical MRL examinations and dual-agent 3D MRL's were obtained using longer mDixon echo times (TE_1/TE_2 up to 5.8/7.0 ms) to null blood while preserving signal from the separate Gd-containing intralymphatic compartment and maintaining uniform fat suppression.

Findings R2* of ferumoxytol in *ex vivo* venous blood was near-linear for both whole blood and plasma, showed no significant field effect (1.5T ~ 3T), and was approximately 3 times greater than in plasma (Fig. 1). These data suggest *in vivo* steady-state blood T2* values of 1-2 ms (R2* 1.0-0.5 ms^{-1}) are achievable by dosing ferumoxytol at ~5 mg/kg (assuming 65-75 ml blood/kg, contrast in blood pool only; yielding expected ferumoxytol concentration 0.066 - 0.077 mg/mL).

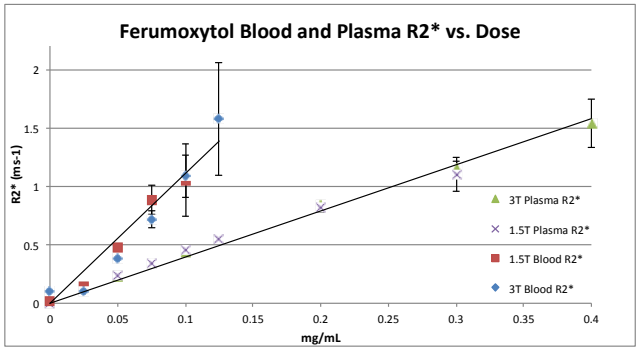

Figure 1. Blood R2* at 1.5 and 3T vs. blood or plasma ferumoxytol concentration. Note no field dependence. R2* in blood was too long to accurately measure much beyond 0.1 mg/mL.

DARC-MRL has been performed on more than 30 patients at 1.5 and 3T without adverse events. In all cases there was complete venous suppression with appropriately lengthened TE's (typically 5.8/7.0 ms, occasionally shorter) (Fig. 2). After administration of ferumoxytol, but prior to imaging, low resolution mDixon images at increasing TE's are performed to find the shortest echo time combination yielding vascular suppression.

We have observed only minimal image degradation due to the longer TE's, with a modest increase in scan time due to the subsequent increased TR. Occasional cases show some mild loss of lymphatic signal at the longer echo times, but in no cases do we believe lymphatics were obscured (based on always performing a final short echo acquisition to ensure no lymphatic signal has been suppressed).

Discussion Interpreting and post-processing MR Lymphangiography can be difficult, largely secondary to venous enhancement (Fig. 2). Ferumoxytol is an FDA-approved USPIO that has gained increased acceptance as an off label alternative for vascular MR in patients with renal failure (2). Typically, the T1 shortening properties of ferumoxytol are carefully exploited to create vascular signal while avoiding associated T2*-related signal loss. In this new dual-contrast technique, however, we utilize a combination T1- and T2*-weighted mDixon sequence to exploit the dramatic blood T2* shortening of ferumoxytol (Fig. 1) to overwhelm any Gd-related venous T1 enhancement. Simultaneously ferumoxytol's blood pool properties ensure that it stays clear of the lymphatic tissues, allowing them to remain bright, thus creating a pure MR Lymphangiogram.

Ferumoxytol can be administered either if/when felt necessary to mask veins as the exam progresses (as per Fig. 2), or can be administered prior to intracutaneous Gd injection such that all MRL acquisitions are performed post ferumoxytol (our preferred technique). Short echo acquisition highlighting the vascular structures can also be obtained at any time during the exam, giving the ability to "turn on/turn off" vasculature as desired.

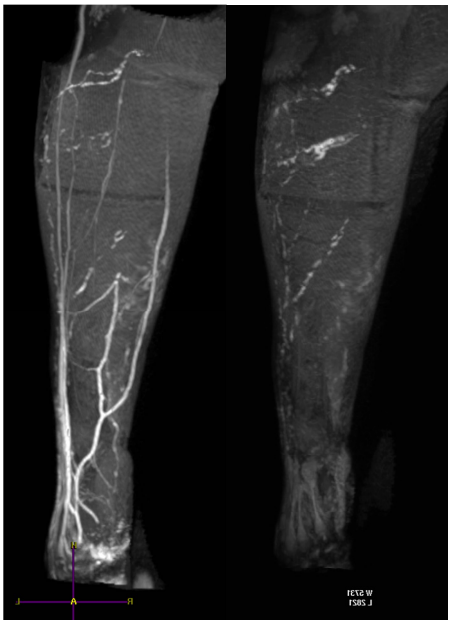

Figure 2. Conventional vs. DARC-MRL. Calf (left) 45' post intracutaneous injection gadobenate. Note significant obscuring venous enhancement. Image 5' after 5 mg/kg i.v. ferumoxytol with TE_1/TE_2 5.8/7.0 ms (right). Note complete suppression of all venous enhancement and much more clear visualization of lymphatics.

References

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2. Li W, Tutton S, Vu AT, Pierchala L, Li BSY, Lewis JM, et al. JMRI, 21(1), 46–52 (2004).