Cerebral MR Signal Changes Induced by Ferumoxytol and Saline Dilution Boluses: Initial Human Experience

Wendy W Ni[1,2], Deqiang Qiu[1], Thomas Christen[1], Heiko Schmiedeskamp[1], Roland Bammer[1], Michael E Moseley[1], and Greg Zaharchuk[1]

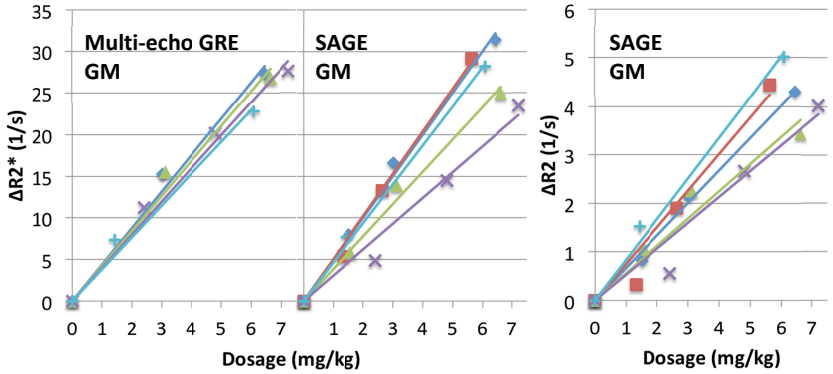
[1]*Department of Radiology, Stanford University, Stanford, California, United States,* [2]*Department of Electrical Engineering, Stanford University, Stanford, California, United States*

Introduction: Contrast-enhanced MRI is widely used in evaluating brain perfusion. In particular, steady-state measurements can be made using blood pool contrast agents, including the class of ultrasmall superparamagnetic iron oxides (USPIOs) [1]. In this study, we describe our initial human experience with the USPIO ferumoxytol as a T2* agent in steady state, and specifically, the dependence of ΔR2* and ΔR2 on dosage. We also present preliminary findings of using saline as a dilution bolus to map relative cerebral blood volume (rCBV) in humans.

Material and Methods: With IRB approval, five healthy volunteers (ages 26-60) were scanned before and after injections of ferumoxytol (Feraheme, AMAG Pharmaceuticals) as described below. Imaging was performed at 3T (MR750, GE Healthcare). Fractions of one full dose (510mg Fe in 17mL) up to approximately 7mg Fe/kg were injected at 1mL/s followed by saline flush. R2* measurements were performed using multi-echo GRE (resolution 0.9×0.9×1mm^3, TR 68ms, 15 echoes, TE range 3-64ms) pre-contrast and after each injection. In addition, Spin- And Gradient-Echo (SAGE) [2] images (resolution 2.9×2.9×5mm^3, TR 1800ms, 5 echoes, TE range 17-97ms, repeated 60 or 90 times) were also acquired at the same timepoints, and R2* and R2 were calculated using 4-parameter fitting [2]. Finally, the time course of saline boluses (40mL or 60mL at 5mL/s) were imaged with SAGE. For analysis, all images were co-registered to the pre-contrast SAGE image, and one 5mm-thick slab was selected to compare across dosages and methods. Values were analyzed in gray matter (GM), white matter (WM) and whole brain ROIs.

Results and Discussion: ΔR2* and ΔR2 were plotted against dosage for each subject to separate the effects of inter-subject variability (due to differences in blood volume per weight, which relates dosage to concentration) and linearity of dose dependence. Plots for GM data are shown in Fig 1 and demonstrate the trends common to the other ROIs. Values of slope and R^2 (for goodness of fit) from linear regression are averaged across subjects and summarized in Table 1. There is clear distinction between the slopes of the ΔR2*-dosage curves (i.e. dΔR2*/dD, s^{-1}/(mg Fe/kg)) in GM and WM, due to the higher GM CBV. On the other hand, dΔR2/dD was an order of magnitude smaller, and there was little difference between its value in GM and WM (likely due to low SNR). This indicates that ferumoxytol has relatively little impact on T2 decay.

Experimentation with saline boluses produced mixed results. We found that it was vital to thoroughly flush the power injector tubing before the saline boluses to avoid contamination by remnant ferumoxytol, which produced a negative response in the first saline bolus. One 60mL bolus (equivalent to 1.2mL/kg for the subject, compared with 0.44-0.72mL/kg for the others) produced a significant signal increase during bolus passage (Fig 2). By integrating the signal-time (first echo) and ΔR2*-time curves under the bolus, removing the post-bolus baseline and eliminating voxels showing negative response, we generated two sets of multi-slice rCBV maps (Fig 3). The ratio between the rCBV values in GM and WM was calculated to be 1.44±2.31 using signal intensity and 1.53±2.88 using ΔR2*. These values are consistent with ratios of 1.64 and 1.57 calculated from [3], though the uncertainties indicate that low SNR is a significant problem. The ΔR2*-based method is especially affected by weak negative responses due to low SNR. In addition, physiological responses to the saline bolus may contribute to a strong negative response observed in many voxels, though the exact mechanism is unclear. While these results demonstrated the use of a saline dilution bolus to measure rCBV, the required saline volume may render this technique infeasible for humans, consistent with extrapolation of prior murine studies [4].



		Slope	R^2
dΔR2*/dD s^{-1}/(mg/kg) GRE	GM	4.11±0.25	0.99±0.00
	WM	2.99±0.22	0.99±0.00
	Brain	3.42±0.19	0.99±0.00
dΔR2*/dD s^{-1}/(mg/kg) SAGE	GM	4.35±0.99	0.99±0.01
	WM	3.53±0.65	0.99±0.00
	Brain	3.85±0.72	0.99±0.00
dΔR2/dD s^{-1}/(mg/kg) SAGE	GM	0.67±0.13	0.97±0.02
	WM	0.65±0.10	0.95±0.05
	Brain	0.66±0.11	0.97±0.03

Table 1: Mean and standard deviation of slope and R^2 values across all subjects.

Figure 1 (left to right): a) Multi-echo GRE data in GM show good linearity and little inter-subject variability. b) SAGE ΔR2*-dosage slopes varied significantly across subjects, though linearity is still similar. c) SAGE R2 data show inter-subject variability and reduced linearity.

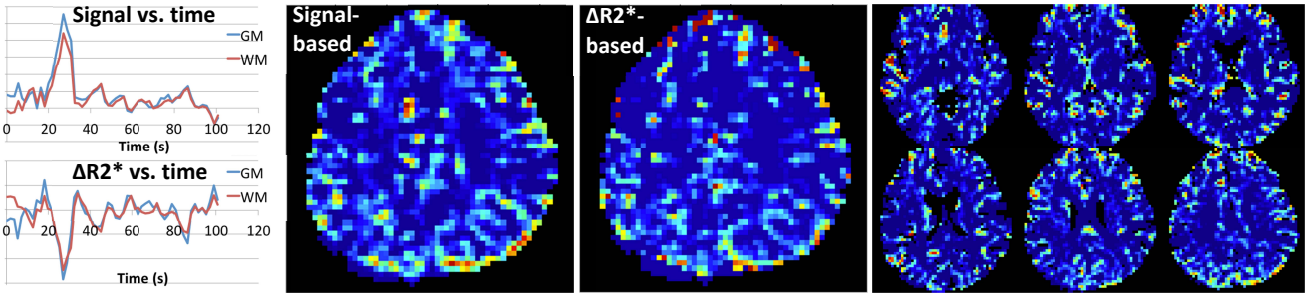


Figure 2: The saline bolus is evident as the peak in signal intensity and the dip in ΔR2* between 20 and 35s.

Figure 3 (left to right): rCBV maps for one 5mm slice calculated from a) signal intensity and b) ΔR2* over time. The color scale is arbitrary. Eliminated voxels (due to negative response) appear as 0. c) rCBV maps for six contiguous 5-skip-2 slices, calculated from signal intensity.

References: [1] J Weinstein *et al.*, JCBFM, 2010. [2] H Schmiedeskamp *et al.*, MRM 2011, in press. [3] T Christen and G Zaharchuk, MRM 2011, in press. [4] M Albert *et al.*, MRM, 1993. **Acknowledgements**: NIH 1R01NS066506, NIH 2RO1NS047607, NCRR 5P41RR09784.