Initial Experience with Ferumoxytol Dynamic Susceptibility MRI in Human Brain at 3T and 7T

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Introduction

Dynamic susceptibility contrast (DSC) MRI techniques are widely used for non-invasive measurement of tissue perfusion. These techniques typically involve the bolus administration of a paramagnetic MRI contrast reagent (CR) which is detected indirectly via a ^1H_2O signal intensity decrease due to a concentration dependent catalysis of ^1H_2O T_2* relaxation. Since the contrast is T_2* based there are important contrast/noise advantages of collecting data at high magnetic field strengths.[1] A central assumption of the standard DSC analysis is that the CR remains within the vascular compartment during the measurement time-series; an assumption often violated and leading to erroneous estimates of blood volume and flow. This is particularly troublesome in brain tumors since the vascular permeability can be increased by a factor of 10^3 or more, and where reliable estimates of blood volumes are crucial for assessment of new antiangiogenic therapies. The ultrasmall paramagnetic iron oxide (USPIO) class of MR contrast agents have a high molecular weight and are much less likely to extravasate even when blood vessels are extremely permeable to low molecular weight CRs. Ferumoxytol (AMAG Pharmaceuticals, Inc) is a USPIO recently FDA-approved as an iron replacement agent.[2] In this study we investigate the use of Ferumoxytol as a T_2* based MRI contrast reagent in human subjects with brain tumors at 7T. Unlike most other USPIOs, Ferumoxytol can safely be injected as a bolus and this greatly facilitates dynamic MRI studies.[2]

Methods

Eleven subjects with primary metastatic brain tumors provided informed consent before participating in this three-day MRI study. All MRI data were collected using 3T (Siemens TIM) and 7T (Siemens MAGNETOM 7T) whole-body instruments. A body transmit and a 12-channel phased-array head receive RF coil pair was used at 3T and an 8-channel phased array transmit/receive RF coil (Rapid Biomedical) was used at 7T. The DSC time-series data were collected with a axial 2D gradient recalled echo-planar imaging (EPI) sequence (TE20/TR1500/FA45; GRAPPA=2 at 7T). A 64^2 matrix was collected over a $(200\ mm)^2$ with a 3 mm (3T) or 2 mm (7T) slice thickness. The total coverage was 27 slices (3T) or 24 slices (7T). The CR injections were accomplished using a power injector that delivered 0.1 mmol/kg gadoteridol (Gd, Bracco Diagnostics Inc) on day 1 and 0.6-2.2 mg/kg Ferumoxytol (FeO, AMAG Pharmaceuticals, Inc) on day 2 at a rate of 3 mL/sec. The FeO was diluted 2x from stock and administered sequentially for a total dose of 4 mg(FeO)/kg. A simple transformation was used to convert from a signal intensity to ΔR_2* time series ($\Delta R_2^* = -\ln(\mathbf{S}(t)/\mathbf{S}_0)/TE$). All DSC data were transferred off-line and processed using JIM 5.0 (Xinapse, Inc) and MATLAB 7.5 (Mathworks, Inc).

Results And Discussion

Figure 1 presents results representative for normal appearing white matter tissue. Fig 1A shows 3T and 7T 0.1 mmol/kg Gd administration ΔR_2^* time-courses sampled from centrum semiovale white matter regions (indicated as white ovals on baseline EPI images in the Fig 1A inset). The maximum ΔR_2* change for the 7T DSC was more than twice that observed at 3T, consistent with expectations. This confirms that a significantly lower CR dose could be administered at 7T to obtain comparable information to that obtained using lower magnetic field MRI instruments. Image quality was similar between the 3T and 7T acquisitions, despite the thinner slice collected (and two-fold parallel acceleration) at 7T, although geometric distortions in some slice regions typically were more significant at 7T. Figure 1B shows 7T ΔR_2* time-courses from different sequential increasing FeO doses and a standard Gd dose. Similar post-CR ΔR_2* behavior was observed with 0.1 mmol/kg Gd and 1.2 mg/kg FeO. **Figure 2** shows ΔR_2* behavior from a brain tumor region with high permeability to Gd. The effect of Gd extravasation is easily appreciated as negative post-first-pass ΔR_2* values - a result of increasing tissue R_1 with Gd extravasation. The FeO ΔR_2* time-course is well-behaved throughout the measurement, and provides a more reliable estimate of tumor blood volume using standard DSC analyses.

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References: **1.** Yacoub, Shmuel, Pfeuffer, Van De Moortele, Adriany, Andersen, Vaughan, Merkle, Ugurbil, Hu. *Magn. Reson. Med.* 45, 588-94. (2001) **2.** Weinstein, Varallyay, Dosa, Gahramanov, Hamilton, Rooney, Muldoon, Neuwelt. *J Cereb Blood Flow Metab.* 2009 Sep 16. [Epub ahead of print]

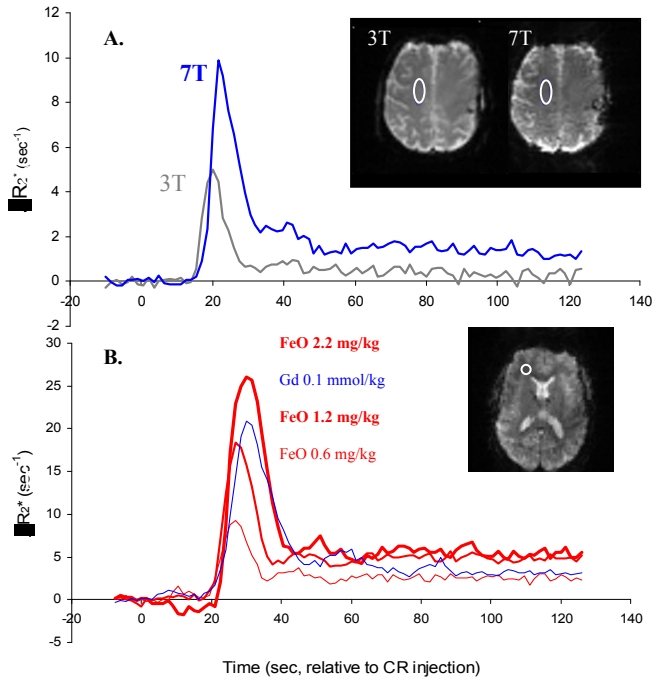

Figure 1. Panel A displays ΔR_2* time-courses from a normal appearing centrum semiovale WM ROI following bolus injections of 0.1 mmol/kg Gd at 3T and 7T in the same 36 y M. The axial images (inset) show baseline GE EPI data. The 3T and 7T DSC studies were performed within 24 hours. The 7T post-CR ΔR_2* peak has more than twice the amplitude observed at 3T. Panel B shows 7T ΔR_2* time-courses from a frontal WM ROI for increasing FeO doses and a standard Gd dose administered to a different 36 y male. The ROI is indicated in the inset. A FeO dose of 1.2 mg/kg provided similar ΔR_2* enhancement as that achieved with 0.1 mmol/kg Gd.

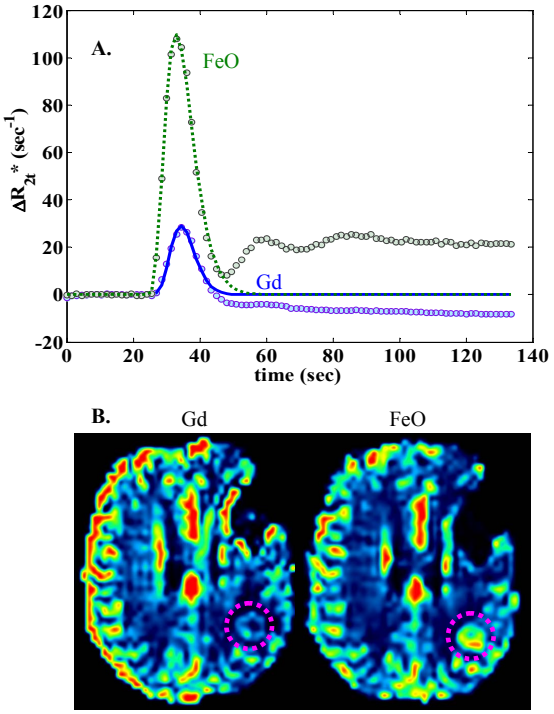

Figure 2. Panel A shows 3T ΔR_2* time-courses from a GBM tumor in a 67 y M for 0.1 mmol/kg Gd and 2 mg/kg FeO CR administrations. The negative ΔR_2* time-course observed for the Gd DSC (blue circles) is a signature of eventual domination by T_1-weighting, resulting from Gd extravasation into the tumor – the blood volume estimate in this case is confounded. The FeO ΔR_2* time-course (olive circles) remains positive over the time-course. The associated blood volume maps are displayed in panel B using the same color scale (red is 10%). A significantly larger blood volume in the tumor (inside dashed circle) is obtained from the FeO DSC measurement.