Vessel Density Imaging in Normal Human Brain using Ferumoxytol

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Background: A method for vivo measurement of blood vessel density and size distribution would be important for assessment of angiogenesis, for example during vascular targeted therapy in oncology (1,2), or regenerative therapies aimed at post stroke rehabilitation (3). Vessel size imaging (VSI, 4) takes advantage of differential tissue T2/T2* relaxation changes close to vessels containing a susceptibility contrast agent. Jensen at al (5) proposed the quantity $Q = \Delta R2/\Delta R2^{*2/3}$ as an estimate of vessel density, where ΔR2 and ΔR2* are changes in T2 and T2* relaxation rates during injection of an intravascular susceptibility contrast agent (e.g. MION). Based on the data of Dennie et al at 2T (6), a Q of 0.72 $s^{-1/3}$ was estimated in rodent gray matter. This group also estimated Q in normal human brain using dynamic imaging at 1.5T and a bolus injection (triple dose) of GdDTPA (7); Q was found to be 1.26 $s^{-1/3}$ in temporal cortex, 0.6 $s^{-1/3}$ in frontal white matter and 0.32 $s^{-1/3}$ in the corpus callosum. The recent FDA approval of ferumoxytol, an iron nanoparticle treatment for anemia which can be used as an intravascular susceptibility contrast agent, enables such measurements to be made in humans using high resolution sequences.

Methods: Five healthy volunteers were enrolled (after informed consent) and scanned on a 3T GE Discovery MR 750HD system. All procedures were approved by our local IRB board. R2 and R2* were measured before and after a bolus injection of 510mg of ferumoxytol using the following sequences: 1) Dual-echo FSE, TE 13/102ms, ETL 8, 2) 2D SPGR, 8-echo TE 3.67 – 41ms, 3) Dynamic SE-EPI, TR 3.65s, TE 60ms. Pre/post relaxation rate maps R2, R2* and $\Delta R2_{EPI}$(dynamic scan) were calculated using MRVision (MRVision Co., Redwood City, CA). Pre/post R2* maps were registered and pre-R2* subtracted from post-R2*, yielding ΔR2* maps (using FSL tools (FMRIB, Oxford, UK). Due to the small signal changes measured in the FSE images, we used pre/post- ROIs rather than voxel based measurements to estimate $\Delta R2_{FSE}$ in different tissues. Q values were derived from ROI measurements ΔR2* and ΔR2 in cortical gray matter, subcortical white matter and the corpus callosum.

Results: Figure 1 shows parametric maps for one subject. Figure 2 plots both ΔR2 measurements against ΔR2* for all subjects for the 3 tissue regions. For gray and white matter there was a high correlation between ΔR2 and ΔR2*. On average $\Delta R2_{FSE}$ values were consistently smaller than corresponding $\Delta R2_{EPI}$ values, as shown in Table 1.

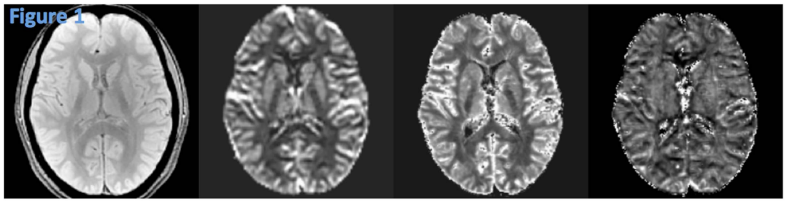
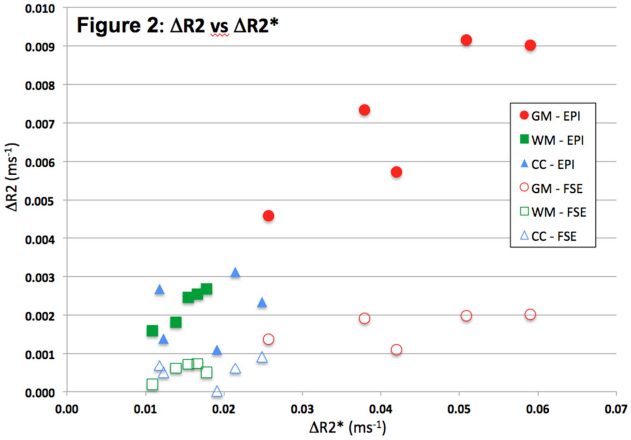


Table 1	ΔR2* (s^{-1})	$\Delta R2_{EPI}$ (s^{-1})	$\Delta R2_{FSE}$ (s^{-1})	Q_{EPI} ($s^{1/3}$)	Q_{FSE} ($s^{1/3}$)
Gray matter	43.1 ± 12.7	7.2 ± 2.0	1.7 ± 0.4	0.58 ± 0.08	0.14 ± 0.03
White matter	14.9 ± 2.7	2.2 ± 0.5	0.5 ± 0.2	0.36 ± 0.04	0.09 ± 0.03
Corpus Callosum	17.9 ± 5.7	2.1 ± 0.9	0.5 ± 0.3	0.32 ± 0.14	0.08 ± 0.05



Conclusions: The FSE based estimates of ΔR2 are likely reduced because of the refocusing of diffusion driven spin dephasing by the echo train. Estimation of the vessel density metric Q in humans is feasible using standard pulse sequences and an i.v. injection of ferumoxytol. Our estimate of Q in cortical grey matter is close to that measured in rodents, using a MION contrast agent, but about half that reported in humans using dynamic imaging of a GdDTPA bolus. Imaging at a steady state contrast agent concentration allows for use of higher resolution sequences; a multi-shot EPI approach would reduce image distortions. This approach can be implemented on any modern scanner and may prove useful for assessing angiogenesis in tumors or during stroke recovery.

References: (1) Batchelor et al. Cancer Cell. 2007;11:83. (2) Fredrickson et al, ISMRM 2012, 1987. (3)Beck et al, Acta Neuropath 2009; 117: 481. (4) Tropes et al, MRM 2001;45:397. (5) Jensen et al, MRM 2000;44:224. (6) Dennie et al, MRM 1998;40:793. (7) Jensen et al, MRM 2006;56:1145.