Advanced Analysis of USPIO Injection in Normal Volunteers

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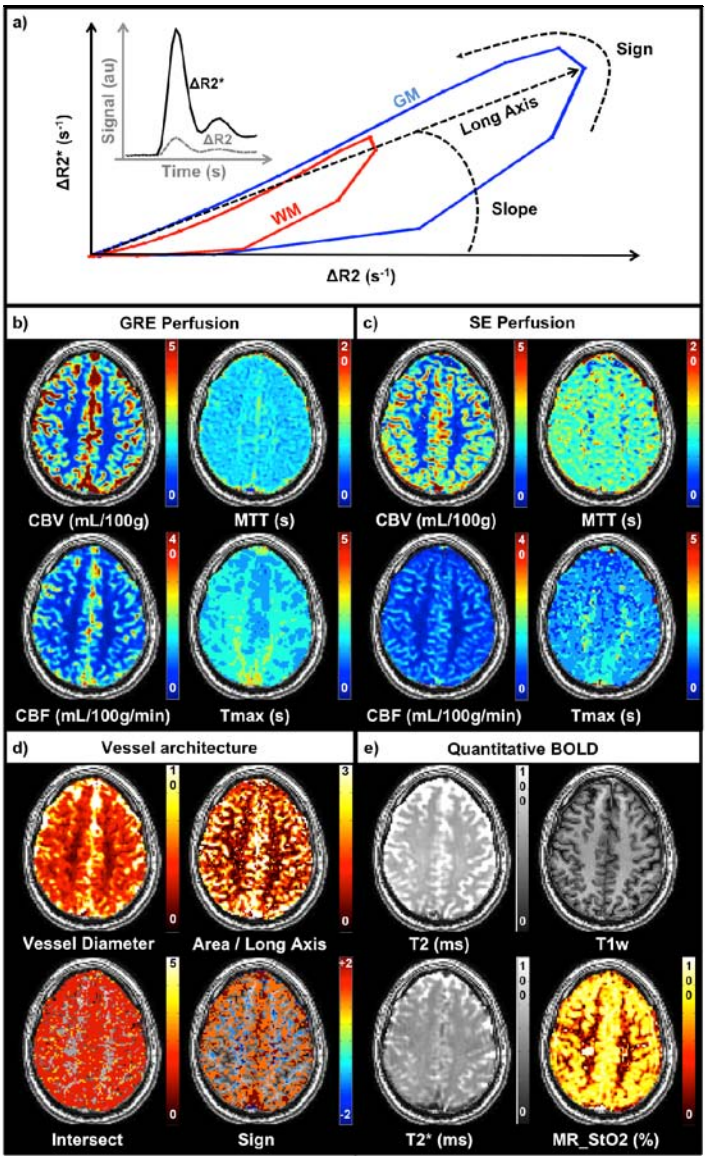
Introduction: It has been recently suggested that following a bolus of contrast agent (CA) with a combined spin-echo (SE) and gradient-echo (GRE) sequence can yield valuable information about vessel architecture and oxygenation [1-2]. The pairwise R2* and R2 data points create a vortex curve whose characteristics can describe the effect of antiangiogenic treatments in patients with brain tumors [1]. More importantly, the method can identify patients who would benefit from therapies. While promising, the approach might, however, suffer from problems related to low signal-to-noise ratio and CA leakage if a gadolinium based CA is used. As an alternative, we propose in the present study to follow an injection of ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc., Cambridge, MA), an FDA-approved ultra-small paramagnetic iron oxide (USPIO) compound, whose large size confines it intravascularly, and creates large magnetic susceptibility effects. We scanned 10 subjects with a multi-echo EPI sequence to study the feasibility of the vortex curve approach and compare the results with bolus perfusion and quantitative BOLD (qBOLD) analyses.

Materials and methods: The local IRB committee approved all studies. 10 subjects were scanned at 3T (MR750, GE Healthcare Systems, Waukesha, WI) with an 8-channel head coil. A 3D T1-weighted fast spoiled gradient echo (SPGR BRAVO) sequence was acquired to provide high-resolution structural information of the whole brain. A 5-echo SAGE-EPI sequence [3] with echo times TE1-5 (ms) = 16.6, 34.0 (gradient echo), 61.8, 79.2 (asymmetric spin echo), and 97.0 (spin echo) was used to track an injection of ferumoxytol (1.75 mg Fe/kg at 1 mL/s). Fifteen 5 mm thick slices with in-plane resolution of 84x84 voxels were acquired with FOV = 24 cm and TR=1800ms.Then, three postprocessing protocols were used:



(1) Dynamic Susceptibility Contrast: DSC maps (CBV, CBF, MTT, Tmax) based on the second echo (GRE) or the last echo (SE) were created using automatic AIF detection and delay-insensitive FFT-based deconvolution as described in [4]. Parameters were optimized for USPIO injection.
(2) Vessel Architecture Mapping: in each voxel, a linear curve was fitted to $\Delta R_2^*=f(\Delta R_2)$ during the bolus passage and the slope was used to create a map of vessel diameter (see Fig1a). The corrected vortex area was computed as the area of the vortex divided by the length of the long axis. The vessel vortex sign is defined by the difference between SE_Tmax and GRE_Tmax. We also computed the number of times the vortex curve intersects with itself.
(3) Quantitative BOLD: Using pre-injection scans (n=15), we computed the baseline R2* and R2 values. We used a combination of these values as well as CBV measurements to create maps of tissue blood oxygenation (MR_StO2) according to the multiparametric qBOLD approach [5].
Data from the scanner were imported into Matlab (MathWorks Inc., USA) and SPM8 was used for co-registeration. An Otsu's 3-thresholding approach was used for white matter (WM), gray matter (GM) segmentation.

Results: Fig 1a shows the evolution of $\Delta R_2^*=f(\Delta R_2)$ within a gray matter or white matter ROI in one volunteer. One can clearly visualize the vortex curves. The corresponding time evolutions are also presented. GRE perfusion maps show similar patterns compared to dynamic acquisitions obtained with Gd injection (Fig1b). Corresponding SE perfusion maps show great SNR with reduction of large blood vessel signals (Fig1c). Vessel diameter maps (Fig1d) show relatively homogeneous values across the brain (VD=6.4± 0.4 in GM, VD=4.9±0.7 in WM) and correspond to results previously obtained with a steady-state approach [6]. The vortex curve present on average 1 self-intersection and the rotation is clockwise (Sign=0.7±0.1%). Yet, some contrast appears in large blood vessels. MR_StO2 values in GM (70±6%) are consistent with literature (Fig1e), while artifactual low values appear in WM (as previously reported in rats and humans [5]).

Conclusion: This study suggests that vessel architecture and function can be mapped with MRI and intravenous injection of ferumoxytol. The maps have high SNR and could be used to study several pathologies such as stroke or cancer. It is worthwhile to notice that the dose used in this study is only one quarter of the maximum dose approved. Numerous parameters can be derived using only one MR sequence but their origins and significance still remains unclear. Application of a complementary technique called 'vascular fingerprinting' [7] where the MR signal time evolution is compared to dictionaries of curves obtained with numerical simulations may bring yet more insights.

References: [1] Emblem et al, Nature Med, 2013. [2] Xu et al, Magn Reson Med, 2011. [3] Schmiedeskamp et al, Magn Reson Med, 2012. [4] Straka et al., JMRI 2010. [5] Christen et al, Magn Reson Med, 2012. [6] Christen et al, ISMRM 2013 #588. [7] Christen et al., ISMRM 2013 #451.

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