Combined Spin and Gradient Echo Imaging Following Injection of USPIOs in Humans

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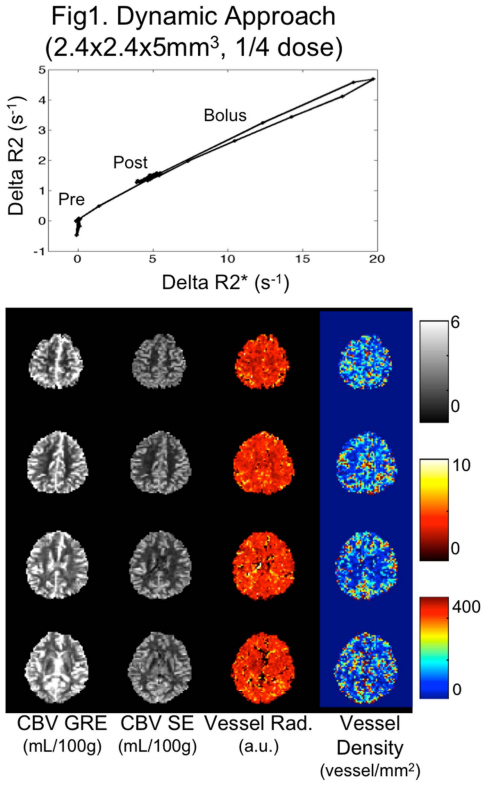
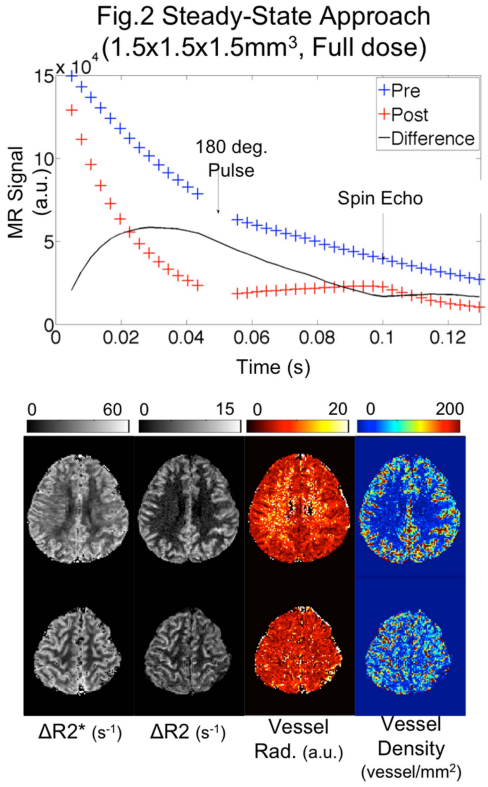
Introduction: Spin-echo (SE) imaging is not commonly used with gadolinium (Gd)-based dynamic susceptibility contrast (DSC) because of a low SNR compared to gradient echo (GRE) imaging. Yet, SE imaging offers a contrast that is more specific to the microvasculature and improves the visibility of hypoperfused regions that may be confounded by large blood vessels [1]. SE can also be combined with GRE to derive quantitative information about vessel diameter [2] or vessel density [3]. The corresponding maps are increasingly used to study angiogenesis in cancer or stroke in small animals [4], but their applications in humans have remained elusive. In the present study, we analysed the spin- and gradient-echo contrast variations following injection of Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc., Cambridge, MA), an FDA-approved ultra-small paramagnetic iron oxide (USPIO) compound in the human brain. The high magnetic susceptibility of ferumoxytol should considerably increase the SNR in the SE perfusion maps and the long half-life should allow high-resolution acquisitions. Two approaches were analysed: (1) a fast multi-echo spin and gradient echo (SAGE [1]) EPI sequence was used to follow a bolus of the contrast agent; (2) a high-resolution gradient-echo sampling of the FID and spin echo (GESFIDE) sequence with 40 echoes was acquired pre and post injection of ferumoxytol (steady-state approach).

Materials and methods: The local IRB committee approved all studies. Nine 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 brain volume (SPGR BRAVO) sequence was acquired to provide high-resolution structural information of the whole brain. Then, two protocols were used:
(1) Dynamic approach (n=9): A 5-echo SAGE-EPI sequence with echo times TE1-5 (ms) = 16.6, 34.0 (gradient echoes), 61.8, 79.2 (asymmetric spin echoes), and 97.0 (spin echo) was used to track the first 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. DSC CBV maps based on the second (gradient) echo (CBV GRE) or the last (spin) echo (CBV SE) were created using automatic AIF detection and delay-insensitive FFT-based deconvolution [5]. R2* and R2 maps were obtained at each TR using a non-linear exponential fit of the 5 echoes to obtain ΔR2* and ΔR2 over time. Then, in each voxels 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 radius size. A similar approach was applied to the function $\Delta R_2^3=f(\Delta R_{2^*}^2)$ to derive a vessel density map.
(2) Steady-State approach (n=5): a GESFIDE sequence (TR=2000ms, 40 echoes, SE=100ms, FOV=20*20cm, ST=1.5mm, 128*128, 12slices, Tacq=4min) was acquired pre- and post-injection of a full dose of ferumoxytol (7 mg Fe/kg). After computing R2* and R2 maps using exponential fit of the echoes, vessel radius was computed as $\Delta R2^*/\Delta R2$ and Vessel density as $\Delta R_2^3/(329x\Delta R_{2^*}^2)$.
Data from the scanner were imported into Matlab (MathWorks Inc., Natick, MA, USA) and SPM8 was used to co-register the parametric maps and the anatomical scan. An Otsu's 3-thresholding approach was used for white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) segmentation.





Results: Fig 1a shows the evolution of $\Delta R2^*=f(\Delta R2)$ within a gray matter ROI during one ferumoxytol injection. Although a general linear trend can be observed, a difference of evolution can be seen when the contrast agent reaches the arterial or venous part of the vasculature during the bolus. Compared to Gd-based agent, the signal does not return to its pre-contrast baseline value after injection (allowing the use of the steady-state approach). The CBV maps show high SNR for both SE and GRE (Fig 1b). The values found in GM (CBV GRE = 4.5±0.2 mL/100g, CBV SE = 2.5±0.6 mL/100g) and WM (CBV GRE = 2.3±0.1 mL/100g, CBV SE=1.4±0.2 mL/100g) are consistent with literature reports [6]. A reduction of the impact of large vessels in the CBV SE maps is clearly observed. Vessel diameter maps show relatively homogeneous values across the brain (VR=3.5±0.3 in GM, VR=3.4±0.3 in WM). Vessel density maps show higher values in GM (VD=218±28 vessel/mm^2) than in WM (VD=130±28 vessel/mm^2). Fig2a shows the signal evolution of the GESFIDE sequence pre- and post-contrast. Parametric maps from one subject are presented as Fig 2. They show similar patterns compared to the dynamic acquisition. However, the high spatial resolution and high SNR of the steady-state maps allows the visualization of finer vascular detail.

Conclusion: This study suggests that spin- and gradient-echo related perfusion maps can be obtained in the human brain using ferumoxytol with both DSC and steady-state approaches. While numerical simulations still need to be performed in order to calibrate the method, high-resolution/high-SNR, quantitative maps of vessel radius, vessel density, and blood volume can be derived and may be useful to study brain disorders.
References: [1] Schmiedeskamp et al, Magn Reson Med, 2012. [2] Dennie et al., MRM 1998. [3] Jensen et al., MRM 2000. [4] Lemasson et al., MRM 2012. [5] Straka et al., JMRI 2010. [5] Christen et al., MRM 2012 **Acknowledgements** Supported in part by the National Institute of Health (NIH 1R01NS066506, NIH 2RO1NS047607, NCRR 5P41RR09784).