Steady-State and Dynamic Susceptibility Contrast using USPIOs in Humans

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Introduction: CBV maps are usually obtained using Dynamic Susceptibility Contrast (DSC) MRI by acquiring the time course of the MR signal during a bolus administration of a gadolinium based contrast agent (CA) [1]. Yet, the accuracy of the CBV estimates using DSC relies on intravascular localization of the CA and can be compromised in the setting of a leaky blood brain barrier. Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc., Cambridge, MA) is an FDA-approved ultra-small paramagnetic iron oxide (USPIO) compound, whose larger size (compared with gadolinium agents) confines it to the intravascular space, and has the potential to measure CBV more accurately. The long half-life of this agent in the blood also enables alternative approaches, such as steady-state methods [2], to measure CBV with higher resolution and/or signal to noise ratio (SNR). In the present study, we acquired both DSC and steady-state (SS) CBV maps using ferumoxytol in volunteers and compared the quantitative values at different doses and spatial resolutions.

Materials and methods: Imaging was performed at 3T (MR750, GE Healthcare Systems, Waukesha, WI) with an 8-channel head coil. The local IRB committee approved all studies. Four subjects were scanned using the protocol described in Fig 1a. A 3D T1-weighted fast spoiled gradient echo brain volume (SPGR BRAVO) sequence was first used to acquire high-resolution structural information of the whole brain. Then, CBV maps were computed in 4 different ways:
(1) DSC_CBV maps were acquired using a single-shot EPI double GRE sequence (**2DEPI**, TR/TE1/TE2 = 1800/18/34 ms, flip angle 90°, 15 slices of 5mm thickness) during injection of ferumoxytol (1.75 mg Fe/kg at 1 mL/s) [3]. Maps were created using automatic AIF detection and delay-insenstive FFT-based deconvolution [4].
(2) SS_CBV maps were created using R2* maps derived from averaging 15 scans (pre and post injection of the CA) of the **2DEPI** sequence used in (1) (see Fig 1b). Maps were derived using $\mathbf{rCBV=\Delta R2^*_{tissue} / (\Delta R2^*_{sag.sinus})^{0.5}}$ assuming a linear relationship between ΔR2* and CBV in tissues [2], and a quadratic relationship between ΔR2* and contrast agent concentration in the sagittal sinus [5].
(3) SS_CBV_fulldose maps were created using T2* maps derived from averaging 120 time points of the **2DEPI** sequence acquired pre and post injection of a full dose of the agent (approximately 7 mg Fe/kg, max dose as recommended). CBV maps were created using the same process as in (2).
(4) HR_SS_CBV_fulldose maps were created using a 3D multi-echo gradient echo sequence (**3DGRE**, TR=75ms, 16echoes, TE=10 to 55ms, FOV=22*22, ST=1mm, 256*256, 12slices, Tacq=4min) acquired pre and post injection of the full dose of ferumoxytol. The maps were averaged to form images with 5mm thick slices.
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. A whole brain region-of-interest was manually delineated on the anatomic T1-weighted images and transferred into the CBV maps.

Fig 1: MR Acquisition Protocol

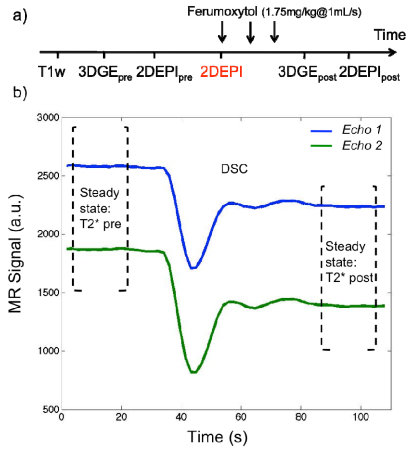


Fig 2: CBV maps in subject 1

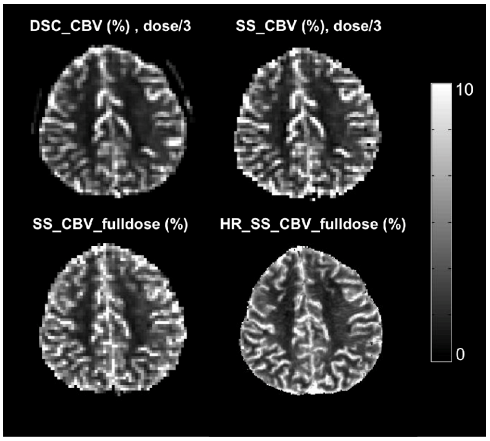
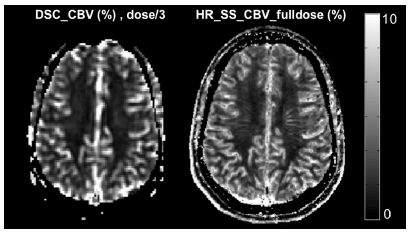


Table 1: rCBV (%) values of all subjects

Subject	CBV(1)	CBV(2)	CBV(3)	CBV(4)
#1	3.5±2.4	4.3±3.1	4.6±3.2	4.4±2.6
#2	3.4±2.4	4.6±3.4	4.7±3.2	4.1±2.7
#3	2.7±2.4	3.1±2.9	4.1±2.7	3.6±2.3
#4	3.3±2.6	3.5±3.0	No acq.	3.8±2.2

Fig 3: CBV maps in subject 4



Results: Fig 1b shows the MR signal evolution within a selected ROI of 2 gradient echoes of the 2D EPI sequence acquired during one ferumoxytol injection (in red fig1a). The bolus induced a significant drop of the signal that remained lower than its pre contrast baseline value (allowing the use of the steady-state approach). Parametric maps from one subject are presented in Figure 2. Similar patterns can be observed for the 4 CBV maps and are consistent with CBV maps acquired with regular DSC experiment using Gadolinium based CA [1]. SS_CBV acquired at dose/3 with an acquisition time of 30s show similar SNR as the DSC_CBV. The maximum rate allowed for the injection of feraheme is 1mL/s, limiting the dose that can be used for DSC experiments. However, the long half-life of the CA allows increasing the dose and SNR with the SS approach (as seen in the SS_CBV_fulldose image). The 3DGE sequence produced a high-resolution CBV map, in which fine vascular detail are visible (Fig.3). The quantitative CBV values for all subjects and the four approaches are reported in Table1. The SS values agree with recent literature reports using a combined Arterial Spin Labeling and DSC approach in normal subjects [6]. The DSC values obtained are lower than those found with the SS approach but stay in the range of previously reported CBV values.

Conclusion: This study suggests that quantitative CBV maps can be obtained in the human brain using both DSC and SS approaches. DSC using ferumoxytol will be useful in determining CBV in lesions where the BBB is damaged. It will also provide maps of the cerebral blood flow and Tmax, though, as with gadolinium-based DSC, the quantification of the values is challenging [7]. As shown in this study, the steady-state approach seems to give similar CBV patterns but can be acquired using either a rapid or high-resolution protocol. CBV quantification using this method is straightforward and the results are not dependent of bolus arrival or transit times. SS CBV measurements using blood pool agents such as ferumoxytol are promising for the detection of small lesions and to compare intra and inter-patient blood volume changes during treatments.

References: [1] Barbier et al, JMRI, 2001. [2] Troprès et al, Magn Reson Med, 2001. [3] Newbould et al., MRM 2007. [4] Straka et al., JMRI 2010. [5] Bjørnerud et al, MRM 2002. [6] Christen et al., MRM 2011. [7] Zaharchuk et al, MRM, 2010. **Acknowledgements** Supported in part by the National Institute of Health (NIH 1R01NS066506, NIH 2RO1NS047607, NCRR 5P41RR09784).