High-Resolution Quantitative Cerebral Blood Volume Imaging in Humans Using the Blood Pool USPIO Contrast Agent Ferumoxytol

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Introduction: Cerebral blood volume (CBV) maps can be used to identify hemodynamic abnormalities in patients with stroke [1], tumor [2] or Alzheimer's disease [3]. CBV maps are usually obtained using Dynamic Susceptibility Contrast by acquiring the time course of the MR signal during a bolus administration of a contrast agent (CA) [4]. This approach requires a fast acquisition protocol, which inherently limits the spatial resolution and signal to noise ratio (SNR) of the maps. An alternative approach is the steady-state susceptibility contrast method [5] that consists of acquisitions of T2* or T2 maps before and after CA injection. This approach has previously been limited to use in animals due to the lack of available long half-life intravascular CA in humans. In the present study, we used ferumoxytol (AMAG Pharmaceuticals, Inc., Cambridge, MA) an FDA-approved ultra-small paramagnetic iron oxide (USPIO) compound, to obtain steady-state high-resolution quantitative CBV maps in 5 healthy volunteers.

Materials and methods: Imaging was performed at 3T (MR750, GE Healthcare Systems, Waukesha, WI) and an 8-channel head coil. All studies were approved by the local IRB committee. Five subjects were scanned using the following protocol:
A 3D T1-weighted fast spoiled gradient echo brain volume (SPGR BRAVO) sequence was used to acquire high-resolution structural information of the whole brain. T2* maps were acquired using a 3D multi-echo gradient echo sequence (TR=75ms, 16 echoes, TE=3.3 to 63.8ms, ΔTE=4ms, FOV=22*22, slice thickness (ST)=1mm, 256*256, 12 slices, acq. time=4min) before (**T2* pre**) and after (**T2* post**) injection of ferumoxytol (approx 7 mg/kg at a rate of 1mL/s). CBV maps were derived using $\mathbf{CBV=\Delta R2^*_{tissue} / (\Delta R2^*_{sag.sinus})^{0.5}}$ assuming a linear relationship between ΔR2* and CBV in tissues [5], and a quadratic relationship between ΔR2* and contrast agent concentration in the sagittal sinus [6]. Data were imported into Matlab (MathWorks Inc., Natick, MA) and SPM8 (Wellcome Department of Imaging Neuroscience, UCL, London, England) was used to co-register the parametric maps and the anatomical scan. To increase the SNR and allow a comparison with standard acquisitions of CBV maps, 5 mm ST maps were also computed by averaging slices of ST=1mm. A whole brain region-of-interest was manually delineated on the anatomic T1-weighted images. An Otsu's 3-thresholding approach was used for white matter (WM), gray matter (WM) and cerebrospinal fluid (CSF) segmentation. Each ROI was transferred to all parametric maps. Then, all voxels with T2*>150ms were excluded from the analysis to remove residual effects of CSF.

Results

Fig 1: Images obtained in one subject.

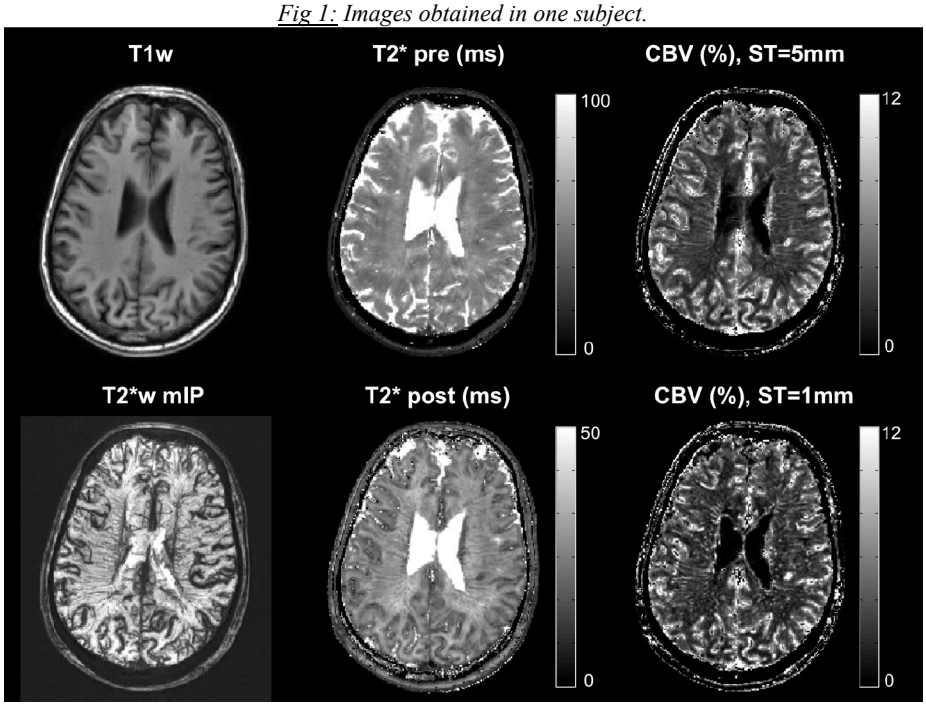

Fig 2: CBV (%) values of all subjects.

Subject	*Gray*	*White*	*Brain*
#1	*5.5±2.8*	*2.9±1.7*	*3.9±2.5*
#2	*5.6±2.8*	*3.1±1.8*	*4.0±2.6*
#3	*5.7±3.0*	*3.3±1.5*	*4.1±2.5*
#4	*5.6±2.7*	*3.5±2.2*	*4.3±2.6*
#5	*4.4±2.4*	*2.9±1.8*	*3.5±2.2*
Total	*5.4±0.5*	*3.1±0.3*	*4.0±0.3*

Parametric maps from one subject are presented in Figure 1. One can notice the strong T2* effect induced by the presence of the CA in the vasculature (T2* pre vs T2* post). The CBV maps show a good contrast between gray and white matter. At this resolution, vascular structures in the WM (seen in the minimum intensity projection map of the 16 echoes of the 3D gradient echo sequence) become visible in the CBV maps. The quantitative CBV values for all subjects are reported in Table 1. A significant difference was found between white and gray matter values. An averaged CBV of 4.0±0.3% was found in the whole brain. These values agree with literature reports using MR [7] or PET [8].

Conclusion: This study demonstrates that quantitative high-resolution CBV maps can be obtained in the human brain using a steady-state approach using a blood pool USPIO agent. This method is superior to the limited spatial resolution CBV maps obtained with DSC, and should enable the evaluation of small lesions and allow comparison of intra and inter-patients blood volume changes during treatment or challenges.

References: [1] RH Wu, Neuroradiology, 1998. [2] AP Pathak et.al, MRM, 2001. [3] GJ Harris et al, AJNR, 1998. [4] EL Barbier et al, JMRI, 2001. [5] I Troprès et al, Magn Reson Med, 2001. [6] A Bjørnerud et al, MRM 2002. [7] Christen et al., MRM 2011. [8] KL Leenders et al, brain, 1990.
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