Non-invasive Quantification of Absolute Cerebral Blood Volume

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Introduction: Cerebral blood volume (CBV) is a fundamental physiological parameter closely associated with brain activity. CBV changes are seen in diverse pathologic conditions as well as in response to functional challenges and provide an important contrast mechanism for brain imaging[1,2,3]. Nonetheless, absolute CBV measurements have been invasive and difficult especially in humans. VASO detects relative blood volume changes during functional activation, but relies on precise blood nulling and requires knowledge of baseline CBV for absolute quantification[3]. iVASO-DS generates arterial CBV contrast, however, requires knowledge of individual capillary arrival times for absolute quantification which may be subject specific, vary with activation, disease or age[4]. Non-invasive absolute CBV quantification in a single slice was demonstrated using a biophysical model and acquisitions varying the extent of blood nulling at rest and during activation[5]; and expanded to five slices[6], however this expansion results in a different shifted data set for each slice such that each slice must be fit separately to a different portion of the model resulting in spatially varying errors, and permits only a moderate increase in slices. We introduce an extension to the biophysical model and a rotating acquisition of multiple slices with varying contrast weightings, for non-invasive quantification of absolute CBV applicable to the whole human brain.

Methods: Our proposed method is also based on an Inversion Recovery (IR) sequence for acquisition and biophysical model for quantification[5,6], however, with the following changes: Efficient multi-slice imaging is enabled by the rotation of slice order for each inversion, resulting in a data set where each slice location has been acquired at each inversion time (TI), with balanced and consistent TI ranges for quantification. Secondly, steady state is maintained throughout varying inversion and recovery durations by non-selective saturation following completion of acquisition of all slices for each inversion (TS); and by addition of spoiler gradients following inversion, following acquisition of any slice at the longest TI, and following the steady-state saturation (Figure1, top).

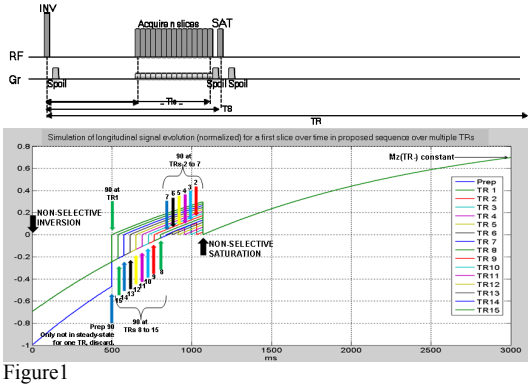

Figure1

Sequence: Steady-state longitudinal magnetization resulting from this sequence is given by $Mz(TI^{-}) = M0\,(1 - 2\exp^{(-TI/T1)} + \exp^{(-(TR-TS+TI)/T1)})$ for TI<TS, and its evolution is simulated for one of multiple slices, during acquisition of multiple TI values over multiple TR's (Figure1 bottom, TIs=500-1014ms, TS =1070ms, TR=3s). At time t=0 in each TR, non-selective inversion inverts all magnetization, which recovers until the excitation at time t = TI. Following the 90° excitation, magnetization recovers to equilibrium until the non-selective saturation at time t = TS. Magnetization again begins recovering to equilibrium, and steady-state is established in 1 TR for any TI.

Model: A voxel in an activated region may contain brain parenchyma (with CBV fraction of blood, and (1-CBV) fraction of tissue), CSF, and WM. Measured signal includes contributions from each compartment depending on their corresponding volume fractions F, water proton densities C, transverse relaxation time constants T2*, a calibration factor K, and longitudinal magnetization at the time of excitation, M=Mz as defined above. $S = K.\mathrm{abs}(\sum_i S\_i)$ and $S,i(TI) = F,i\ C,i\ M,i(TI)\exp^{-TE/T2^*,i}$, TE= echo time, i=CSF,blood,GM,WM. T2* of blood depends on average blood oxygenation fraction Yb[7] (at 3T[8]) as: $1/T2^*\_blood = 18.82 + 188.28.(1-Yb)^2$. T2* of extravascular GM tissue depends on the pure transverse relaxation time, T2_tissue; field inhomogeneity effects, T2'_tissue; frequency shift due to deoxyhemoglobin, dw; susceptibility from blood oxygenation, R(dwTE); gyromagnetic ratio, γ; susceptibility difference between fully oxygenated and deoxygenated blood, $\Delta\chi = 0.2\,ppm$, and microvasculature hematocrit estimate, Hct as [5,9,10]: $1/T2^*\_tissue = 1/T2\_tissue + 1/T2'\_tissue + R(dw,TE)$, where $R(\mathrm{dw,\ TE}) = \frac{F\_blood}{3TE}\int_0^1 du(2+u)\sqrt{1-u}\left[\frac{1 - J_0(3/2\,\mathrm{dw\ TE.u})}{u^2}\right]$ and $dw = \gamma.B_0.\frac{4}{3}.\pi.\Delta\chi.Hct.(1-Yb)$. Functional challenges can influence voxel signals (S) through changes in blood oxygenation (Yb) and tissue fractions (F), causing a slight shift in acquired signal upon stimulation. Absolute CBV at rest and during activation can be estimated in units of mL blood / mL of parenchyma by calculating the fractional signal change between rest and activation, $\Delta S/S = dS/S = (Sact - Srest)/Srest$ and fitting to the biophysical model over a range of TI values[5,6].

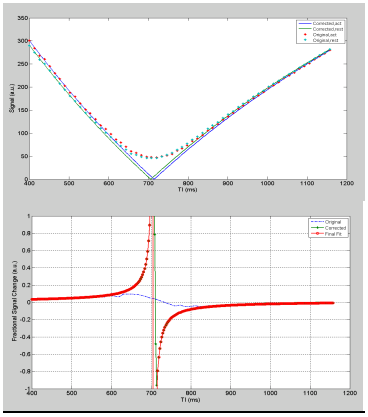

Figure2

Results: Volunteers provided written informed consent in accordance with the ethical review board and were scanned at 3.0T (Siemens) with the proposed sequence (Gradient-echo EPI, TE/TS/TR=11ms/1200ms/3s, 4x4x4mm, 20slices). The TI range of 400-1158ms was covered with 13ms resolution by acquiring three sets of offset TI times. A10Hz checkerboard was used for visual stimulation with 3 OFF/ON cycles of 78s where 18s of each transition was allowed for settling of the hemodynamic response. The acquisition was repeated 3 times each on 3 healthy volunteers. T-tests were used to determine activation regions after smoothing with a 6.4mm kernel; acquired signals were averaged across 3 OFF/ON cycles; corrected for a non-zero noise floor; and normalized change in signal was fitted to the biophysical model as described above. Sample data is shown in Figure 2: a slight curve shift is observed between rest and activation as expected, correction is applied for a non-zero noise floor in the magnitude data (top), and results of fitting the fractional change in signal to the biophysical model are shown (bottom). Repetitions on each volunteer produced consistent results as shown in Table 1. The activated voxels consisted mainly of GM with significant CSF and blood components. On average blood oxygenation increased from 61 to 96% with activation. CBV showed an increase of 67% from 4.95 to 7.27 (ml blood / 100ml parenchyma).

Table1	CBV,rest	CBV,act	Yb, rest	Yb, act	F_CSF, rest	F_CSF, act	Apparent T1,blood	WM fraction
#1	5.13 +/- 0.66 mL	8.03 +/- 2.5 mL	61.78+/-4.3%	95.26+/-2.22%	10.54+/-1.45%	10.91+/-0.7%	1761+/-235s	3.53+/-1.32%
#2	4.43 +/- 0.21 mL	6.5 +/- 0.29 mL	65.67+/-1.16%	94.98+/-0.88%	9.72+/-0.23%	9.99 +/- 0.19%	1616+/-11.7 s	3.74+/-2.06%
#3	5.3 +/- 0.65 mL	7.26 +/- 0.43 mL	56.98 +/- 3.1%	98.13+/-0.09%	27.80+/-0.15%	28.28+/-0.21%	1624+/-3.6 s	0.4+/-0.37%
All	4.95 +/- 0.62 mL	7.27 +/-1.44 mL	61.48+/-4.12%	96.12+/-1.92%	16.02+/-8.88%	16.39+/-8.93 %	1667+/-137 s	2.56+/-2.04 %

Conclusion: We have shown the feasibility of non-invasive quantification absolute CBV applicable to the whole human head, by extending a biophysical model with varying CBV and BOLD contrast weightings for efficient coverage for inherently 3D brain structures and functional areas. The proposed method produced physiologically expected CBV values in healthy controls. This holds great potential for investigating the relationship between neural activity and hemodynamic regulation under normal, pathological and neuronally active conditions, and improving diagnosis and monitoring treatments.

References: [1] Belliveau et al. Science.1991;254. [2] Mandeville et al. MRM.1998;39. [3] Lu et al. MRM.2003;50. [4] Donahue et al. JCBFM.2010;30. [5] Gu et al. Neuroimage. 2006;30. [6] Glielmi et al. MRM.2009;61. [7] Silvennoinen et al. MRM.2003;49. [8] C.Clingman, P. vanZijl communications shared in [5] [9] Yablonskiy et al. MRM.1994;32. [10] Lu et al. MRM.2005;53.