Non-invasive Quantification of Absolute Cerebral Blood Volume Applicable to the Whole Human Brain

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Introduction: Cerebral blood volume (CBV) changes are seen across diverse pathologies, and in response to functional challenges providing an important contrast mechanism for functional brain imaging. Non-invasive CBV quantification is desirable for longitudinal studies as well as for patients with contraindications to contrast: VASO has high sensitivity to micro-vessels, but relies on precise blood signal nulling, measures relative changes, and requires baseline absolute CBV for quantification (1). iVASO determines relative arterial contribution to CBV (2), and was later extended to quantify arterial contribution to CBV over a range of arterial transit times (3) similar to iVASO-DS (4) where acquisition of a single-slice needs to be repeated multiple times to extend coverage hindering application to complex paradigms. also, while iVASO (3) fits for arterial transit times, iVASO-DS requires knowledge of individual capillary arrival times for absolute quantification which may vary across subjects and states. Non-invasive absolute CBV quantification was demonstrated using acquisitions varying the extent of blood nulling, where signal changes between VASO images acquired during rest and activation at multiple TIs were fitted to a three-compartment biophysical model to obtain absolute CBV (5). This single-slice approach was expanded to five slices (6) but inefficiencies in spatial coverage permitted only a moderate increase in slices which are fit separately to different portions of the model, resulting in spatially varying errors.

Methods: We introduce and demonstrate on 13 normal volunteers, an extension to the biophysical model with efficient slice coverage and consistent, balanced TI ranges and fitting. Our method is also based on IR for non-invasive data acquisition and the three-compartment biophysical model for quantification, however, with the following changes: Multi-slice imaging beyond the previously described five slices (i.e. 20) 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 of the same TI times, with balanced and consistent TI ranges for quantification. Slice acquisition order over successive TRs is shown in Figure 1 for n slices and TIs. 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 the addition of spoiler gradients following inversion, following acquisition of any slice at the longest TI time, and following steady-state saturation. For this acquisition longitudinal magnetization at TI is given by $M0\,(1 - 2\exp(-TI/T1) + \exp(-(TR - TS + TI)/T1))$ and signal evolution over time is simulated for a sample slice of a multi-slice acquisition over multiple TRs in Figure 2. Steady state is established after the first TR period, and different TI values for each slice are acquired in successive TRs. Signals are characterized with the three-compartment model (5,6) considering contributions from a voxel containing CSF and brain parenchyma based on volume fractions, water proton densities, transverse relaxation rates of individual compartments, and longitudinal magnetization including effects of longitudinal relaxation rates; and where functional challenges influence the voxel signal through changes in blood oxygenation and tissue fractions. Data was acquired at 3T (Tim Trio, Siemens, Erlangen, Germany) using a 32 channel head coil and 20 transverse slices covering the whole brain including the calcarine fissure with: TE/TS/TR=11ms/1.2s/3s, gradient echo EPI, 192x256mm FOV, 4x4x4mm, 60 TI values over 400-1158ms, 3 repetitions in ascending interleaved order on 12 volunteers, and 2 repetitions in both ascending and descending interleaved orders in one volunteer. Visual stimulation consisted of a flashing checkerboard of 3 OFF/ON cycles of 78s duration each, 18s of each transition was allowed for settling of the hemodynamic response. Motion and drift corrected data was averaged over blocks and processed in MNI space. Fitting followed the procedure in (5), however, calculations were done for the whole brain rather than one slice; 20-60 TIs were used rather than 14; and T1 of blood was also fitted in our case following the procedure in (6). All results were reported in Brodmann areas 17 and 18.

Results and Discussion: The stimulus resulted in bilateral activation in occipital lobes. The increase in CBV observed upon visual stimulation is depicted in Figure 3, on a composite image of all volunteer data in a region with significant differences between CBV values at rest versus during activation (p<0.05). CBV increased by 37.88% from 7.18 ml blood/100 ml brain at rest to 9.9 ml blood/100 ml brain during activation across 12 volunteers; with average blood oxygenation of 76.19%; longitudinal relaxation time of 1611ms; and CSF volume fractions varied from 12.55% to 22.51% covering approximately 15% on average. Recent iVASO methods reported resting gray matter absolute arterial CBV of 2.04 ± 0.27 and 0.76 ± 0.17 ml blood/100 ml tissue on 11 healthy volunteers without and with crusher gradients (3); and 1.605 ml blood/100 ml brain (average of right and left hemispheres) on 8

healthy volunteers (4). Considering baseline CBV consisting of 21% arterial/arteriolar, 33% capillary, 46% venous contributions (7, 8), our results for resting CBV in the occipital lobe correspond to an arterial CBV of 1.51 ml / 100 ml brain, well within the range of iVASO results. Our resting CBV results are also very consistent with occipital cortical GM CBV reported as 6.67 +/- 1.07 ml/100 g of tissue (7ml/100 ml tissue with brain tissue density of 1.05 g/ml) using posterior cerebral artery territory bolus tracking (9). Changes in CBV during visual activation in humans have previously been reported as 18.2 +/- 2.8 % (10) and 27+/- 4% (11) using bolus tracking; as 32.4 +/- 11.9% (5) and 31 +/- 3.4% (6) using the biophysical model; and 56+/- 1% using multi-echo VASO (12), and our study found an comparable increase of 37.88%. A final evaluation was done to test whether moving blood spins might experience multiple excitation pulses as they traverse through multiple slices during the proposed acquisition, and confirmed negligible error through acquisition of multiple slices in ascending versus descending orders (no significant differences, p<0.05).

Conclusion: We have demonstrated feasibility of non-invasive quantification of absolute CBV applicable to the whole human head, building on previously described methods using IR for data acquisition and a biophysical model for quantification, improved to enable multi-slice acquisition by rotation of the slice order for balanced and consistent TI ranges across all slices. The proposed method produced physiologically expected absolute CBV values in healthy controls, consistent with prior publications. This provides a method for investigating the relationship between neural activity and hemodynamic regulation under normal, pathological and neuronally active conditions, potentially a new clinical approach for improving diagnosis in disease and monitoring treatments, and holds great potential for whole brain fMRI calibration.

References: [1] Lu et al MRM.2003;50 [2] Hua et al MRM.2011;66 [3] Hua et al. NMR Biomed. 2011 [4] Donahue et al. JCBFM.2010;30 [5] Gu et al. Neuroimage.2006;30 [6] Glielmi et al. MRM.2009;61 [7] Sharan et al. Ann Biomed Eng.1989;17 [8] van Zijl et al Nat Med.1998;4 [9] Grandin et al. Neuroimage.2005;26 [10] Li et al Neuroimage 2000;12 [11] Francis et al. MRM.2003;50 [12] Lu and van Zijl PC. MRM.2005;53.