Measuring Absolute Arteriolar Cerebral Blood Volume (CBVa) in Human Brain Gray Matter (GM) without Contrast Agent

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Introduction: Arteriolar cerebral blood volume (CBVa) is an important physiological parameter regulating tissue perfusion. We demonstrate a novel approach to measure absolute CBVa (CBVa) based on a variant of vascular-space-occupancy (VASO) MRI (1). VASO is a contrast-agent-free MRI technique that is sensitized to micro-vascular CBV changes through nulling of blood signal. Instead of the spatially non-selective inversion used in the original VASO method, a new approach, dubbed *inflow VASO (iVASO)* (2), was designed in which a spatially non-selective inversion is followed immediately by a spatially selective inversion to flip back the water spins in the imaging slice and the brain above. Thus only the blood water spins below the imaging slice remian inverted. Images are then acquired when the inverted spins flowing into the slice are nulled. As the arterial transit time in human brain gray matter (GM) (400-1400 ms) (3,4) is in the range of inversion times (TI=300-1150 ms) used for blood nulling in VASO MRI (5), iVASO is expected to achieve predominantly arteriolar-selective blood nulling. A control scan can be performed with two consecutive spatially non-selective inversion pulses and identical imaging parameters. By subtracting the inflowing blood nulling scan from the control scan, CBVa values in units of milliliters of blood per 100 milliliters of tissue can be quantified by normalizing the difference signal with an additional normalization factor. We demonstrate this method in healthy human brain GM.

Methods: The difference signal can be derived as: $\Delta S = S_{control} - S_{null} = CBV_{a,GM} \cdot ((TI-\Delta)/\delta_a) \cdot C_{blood} \cdot A \cdot (1-e^{-TR/T_{1,art}}) \cdot e^{-TE/T^*_{2,art}}$, where δ_a is the time for blood to traverse the arteriolar compartment, Δ is the delivery time for the leading edge of the inverted blood to reach the arterioles in the imaging slice, C_{blood} is the blood water density (0.87 ml water/ml blood), $T_{1,art}$ = 1627ms (5) and $T_2^*{}_{,art}$ = 54.9ms (6) are T_1 and T_2^* values for arteriolar blood reported in the literature. When the blood nulling time (TI) is equal to the mean arterial transit time ($\tau_a = \Delta + \delta_a$), ΔS is linearly related to CBVa and can by itself be used as a relative CBVa map. The scaling factor A can be obtained from a pure CSF voxel using a reference scan similar to (7). The fundamental difference between this method and arterial spin labeling (ASL) is that, as arterioles are impermeable vessels, the exchange between blood and tissue is assumed to be negligible for the blood-nulling based inflowing waiting time used in this method. A hyperbolic secant adiabatic inversion pulse is used for non-selective inversion and a frequency offset corrected inversion (FOCI) pulse that is known for its better inversion profile is used for slab-selective inversion. The flip back slab was 80mm and its bottom edge was 7mm inferior to the imaging slice. Experiments were conducted on 7 healthy subjects on a 3T Philips MR scanner (informed consent was obtained according to IRB guidelines). Two different TR/TIs were used: TR/TI=5000/1054ms and 2000/711ms. For each TR, seven inflowing blood nulling scans were performed that were followed by seven control scans with identical imaging parameters. Averages were computed after image acquisition and motion correction. A relatively high resolution (2mm isotropic) was used to reduce partial volume effects. Multi-shot gradient echo (GE) echo planar imaging (EPI) was used (EPI factor=9) to achieve a shorter TE (10ms) for better image quality. Fat suppression was applied to reduce fat shift artifacts in GE-EPI. Volume shimming was employed to ensure homogeneity in the whole brain. Other imaging parameters: flip angle=90°, matrix=96x96, single-slice, SENSE=2.5. A reference image acquired at the GM nulling time after non-selective inversion (8,9) with identical geometrical parameters was used to generate GM and white matter (WM) masks for each subject. A reference scan through the ventricle was acquired to determine the scaling factor "A" (TR=20s, TE=20ms, single-shot EPI, 2 averages, other imaging parameters the same). All images for each subject were acquired using identical scaling factor on the scanner and were co-registered using AIR software before averaging and subtraction. A SNR threshold of 10 was applied.

Results&Discussion: Figs. 1a,b show a representative pair of nulling and control images, respectively, for TR of 5s. Since the water spins in the brain above the imaging slice are all flipped back in the nulling scan, the blood flowing in from superior brain in big draining veins should not be nulled. The reason that the saggital sinus region is still dark is that T_2^* for venous blood is very short so that MR signal has decayed over TE (10ms). Figs. 1c,d show the CBVa maps for TR of 5s and 2s, respectively. The gray scale bar on the right indicates the scale to be from 0 to 5ml blood/100ml tissue. The average CBVa in saggital sinus region was negligible (0.03 ± 0.21ml/100ml), which verifies that venous blood flowing in from superior brain is flipped back in the nulling scan. In white matter (WM), estimated CBVa values were not significantly different from zero (P<0.05), which may largely be due to the much longer arterial transit time in WM that does not allow the inverted blood to reach the imaging slice within TI. Therefore WM CBVa cannot be estimated in this inflowing-blood-nulling-based method. Meanwhile, the almost zero difference signal in WM region implies that off resonance magnetization transfer (MT) effects caused by the inversion pulses, which may result in an overestimate of CBVa, are negligible in GM, as MT effects in WM are about double those in GM. The average GM CBVa values for all subjects are summarized in Table 1. The intra-subject standard deviation (SD) is large, which may be a result of variable CBVa in different cortex regions. The inter-subject SD for the mean CBVa values is much smaller, manifesting a good reproducibility of this method. The CBVa values from TR of 2s are smaller than the ones from TR of 5s (P<0.01). This indicates that with a shorter inflowing time (TI), fewer inverted blood water spins reach the imaging slice and get nulled when the images are acquired, which results in underestimation of CBVa. Accurate estimation of CBVa requires the blood nulling inversion time (TI) to be the same as the average arterial transit time, which can in principle be achieved by selection of an appropriate gap between the inversion slab and the imaging slice. For the inversion scheme used in this study, the arterial transit time in cortical GM in human brain has been reported to be 996±95ms (3). Therefore, we believe that the CBVa values from TR of 5s (TI=1054ms) are more accurate, which is confirmed by the fact that they agree well with literature values (0.93ml blood/100ml tissue in GM (10) and 0.74ml blood/100ml tissue for average of GM and WM (11)).

CBVa (ml/100ml)	TR=5s	TR=2s
Subject 1	0.97±1.01	0.74±1.07
Subject 2	1.01±0.97	0.81±0.65
Subject 3	0.76±1.12	0.65±0.79
Subject 4	0.86±0.77	0.55±0.88
Subject 5	1.18±1.02	0.84±1.02
Subject 6	0.78±0.99	0.69±1.01
Subject 7	1.19±0.99	0.85±0.76
Average (n=7)	**0.96±0.18**	**0.73±0.11**

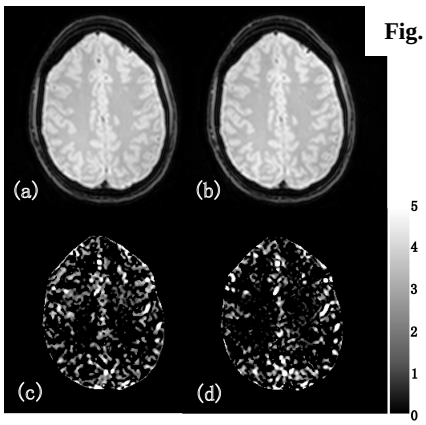

Fig. 1

Conclusion: We presented a contrast-agent-free MRI technique for determining GM absolute arteriolar CBV in physiological units (ml blood/100ml tissue) with high spatial resolution and reproducibility. The measured average GM CBVa were in line with literature values. This approach has potential for mapping GM CBVa in normal subjects and patients with altered tissue perfusion. The value of the measured CBVa may be affected by transit times therefore imaging parameters should be carefully chosen based on the arterial transit time in different brain regions or pathological conditions. On the other hand, this approach may provide information on transit times under conditions of unchanged CBVa.

(1) Lu et al. MRM 2003;50:263. (2) Hua et al. Abstract at this meeting. (3) Francis et al. MRM 2008;59:316. (4) Gonzales et al. MRM 2000;44:739. (5) Donahue et al. MRM 2006;56:1261. (6) Zhao et al. MRM 2007;58:592. (7) Lu et al. MRM 2005;54:1403. (8) Shen et al. JCBFM 2008;1-13. (9) Wu et al. JMRI 2008;28:219. (10) Petersen et al. MRM 2006;55:219. (11) An et al. MRM 2002;48:583. **GRANT SUPPORT**: NIH: P41RR015241, R01EB004130