MEASUREMENTS OF CEREBRAL BLOOD VOLUME AND BOLD SIGNAL DURING HYPERCAPNIA AND FUNCTIONAL STIMULATION IN HUMANS AT 7T: APPLICATION TO CALIBRATED BOLD

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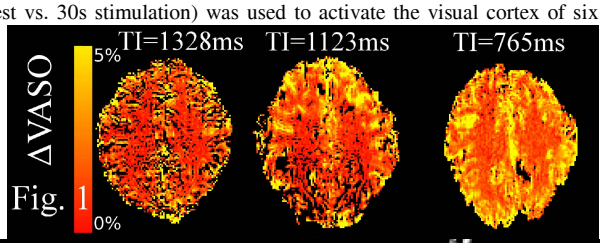
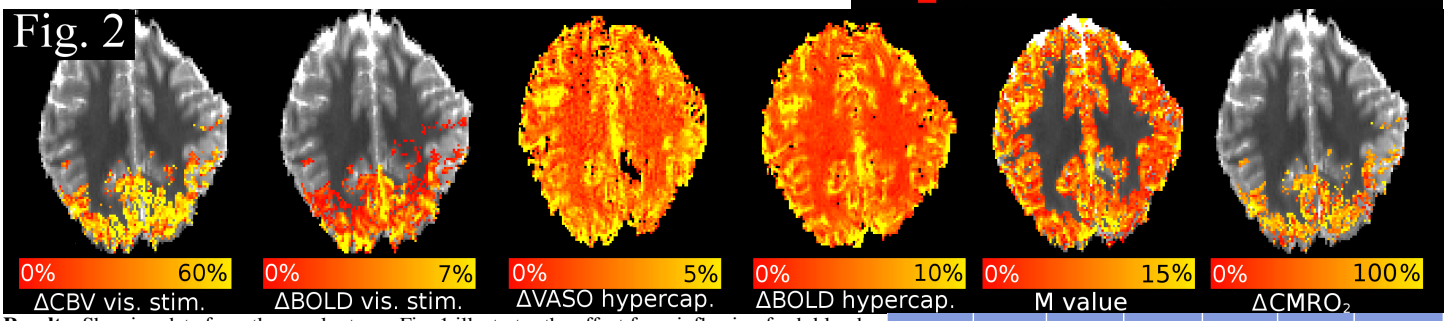
Target Audience: Users of fMRI techniques, fMRI researchers, MRI sequence developers, researchers interested in brain physiology and hemodynamics

Purpose: Hypercapnia is considered to induce changes in cerebral blood supply without significant alterations in metabolism. Many human studies have investigated the relationship between cerebral blood flow (CBF) and blood oxygen level dependent (BOLD) signal. However, the dynamics of human cerebral blood volume (CBV) during hypercapnia and its connection to the BOLD effect have not been fully investigated with a high spatial resolution. Furthermore, to understand how the CBV-BOLD relationship may vary between hypercapnia and neural stimulation has important implications for calibrated BOLD techniques[1,2]. The latter require knowledge of the changes in vascular state during a gas challenge and during stimulation, most often provided by CBF measurements based on arterial spin labeling (ASL). Due to low signal-to-noise-ratio (SNR) of CBF measurements, the resolution of calibrated BOLD techniques remains low, even at high field strengths. A VAscular Space Occupancy (VASO) variant with partial inversion has been developed to obtain high SNR measurement at 7T, enabling comparison of changes in CBV in humans induced by visual stimulation and hypercapnia. Slab-selective, BOLD-corrected VASO increases SNR by manipulating the magnetization of stationary tissue differently from that of flowing blood[3]. Due to the relatively long blood T_1 at high field strengths, the inversion time (TI) for blood nulling can become longer than the blood inflow time from the neck (outside the head coil) into the microvessels of the cortex. The shortening of arterial arrival time during hypercapnia can therefore result in the inflow of fresh (not inverted) blood into the microvessels during the blood-nulling time. To reduce the blood-nulling time below the arterial arrival time, we developed a novel VASO variant with a partial adiabatic inversion. Here, we present results using this VASO variant in human brain at 7T during both hypercapnia and a visual task. This study was performed to investigate whether we can take advantage of the high SNR provided by VASO at 7T as compared with ASL techniques for CBF mapping to obtain voxel-wise estimates of the calibration factor M and maps of changes in the cerebral metabolic rate of oxygen ($CMRO_2$) during a visual task.

Methods: The slab-selective, BOLD-corrected pulse sequence with partial inversion was implemented on a Siemens 7T MRI scanner. Scan parameters were: nominal voxel size =1.5mm isotropic, TE/TR=19/1500ms, inversion efficiencies were 75%, 86%, and 100% with corresponding blood-nulling TI=765/1123/1328ms. Four subjects were scanned with varying TIs. Six subjects were scanned with the optimal TI of 765ms. Imaging data were acquired with a 2D multi-slice single-shot gradient-echo EPI. A tr-FOCI pulse was implemented to achieve slab-selective inversion despite B_1 inhomogeneities and SAR constraints. The pulse was adapted to provide inversion efficiencies of 100%, 86%, and 75%, independently of B_1^+, by means of a phase skip of B_1, introduced during the inversion at the time when the frequency of the adiabatic pulse was exactly on resonance. This opens the "cone of precession" of the magnetization that precesses around the effective magnetic field during inversion and reduces the inversion efficiency. A 10-min. flashing checkerboard (30s rest vs. 30s stimulation) was used to activate the visual cortex of six subjects. The hypercapnia task consisted of 2min/5min/5min breathing air/5%CO_2/air. The heart rate and respiratory gas composition were recorded during the gas challenge. Activated visual areas were identified by using a z-threshold of 2.3 and a cluster significance threshold of p=0.05 (FEAT ver. 5.98, FSL, Oxford, UK) without spatial smoothing. A grey-matter (GM) mask was generated to account for partial volume effects. To compute ΔCBV from ΔVASO, CBV_{rest}=5.5vol% blood within the GM portion was assumed. The Davis-Hoge model[1,2] was used with parameters of α_{total}=0.38, α_{venous}=0.2, β=1 (7T), for calculation of M value and $CMRO_2$ changes. The venous contribution to CBV was assumed to be 40% of total CBV.





Results: Showing data from three volunteers, Fig. 1 illustrates the effect from inflowing fresh blood for TI exceeding the arterial arrival time, which masks the detection of the VASO signal change during hypercapnia (black voxels). This effect can be avoided using shorter blood-nulling times. Fig. 2 summarizes the spatial distributions of VASO and BOLD signal changes in one subject acquired with TI=765 ms where no fresh blood has yet entered the microvessels. CBV changes during visual stimulation are well localized in the GM. Large VASO signal changes during hypercapnia can be found throughout GM. White matter shows a small but significant VASO signal decrease. The contrast-to-noise ratio (CNR) for VASO is approximately half of the CNR for BOLD. Calculated M values averaged over total GM and $CMRO_2$ changes averaged over the stimulated region are given in the Table.

Subject	ΔBOLD hyp.	ΔVASO hyp.	ΔBOLD stim.	ΔVASO stim.	M (TE=19ms)	ΔCMRO2
1	4.4%	57%	2.3%	46%	11.8%	22%
2	3.5%	47%	2.0%	41%	13.9%	25%
3	2.4%	52%	1.9%	42%	15.0%	24%
4	3.1%	37%	2.1%	36%	16.1%	22%
5	3.6%	51%	1.1%	45%	14.6%	12%
Mean	3.4%	48.8%	1.9%	42.0%	14.3%	21%
STD	0.7%	7.5%	0.5%	3.9%	1.6%	5%

Discussion: The decrease in arterial arrival time during hypercapnia can be detrimental to VASO, especially at high field strengths. ΔCBV maps with high resolution and sensitivity can be obtained without the effect of inflowing fresh blood by using shorter blood-nulling times. We expect that this experimental approach might be beneficial in studies beyond visual experiments in humans, e.g. if the RF coil has limited coverage or in an animal model, where arterial arrival times are even shorter. The BOLD signal increase is significantly larger during hypercapnia than for visual stimulation, in contrast with ΔCBV. This indicated that the larger ΔBOLD during hypercapnia compared to visual stimulation results from smaller $CMRO_2$ during the hypercapnia condition. The values for ΔCBV during stimulation are consistent with previous human VASO studies, but they are higher than those from high-resolution studies in rodents. The mean values of M and $CMRO_2$ changes are in agreement with previous literature. Inter-subject variations of the M-value and $CMRO_2$ changes are much smaller than the systematic error arising from uncertainties in the literature values (e.g. α and β) used in the current study. For example, a relative uncertainty of 30% in all physiological parameters assumed results in a relative Δ$CMRO_2$ error of 25%, which is more than the inter-subject variation.

Conclusion: The high SNR of slab-selective, BOLD-corrected VASO with partial inversion efficiency represents a useful tool to investigate the precise relationship of ΔCBV and ΔBOLD during hypercapnia and stimulation. This allows the measurements of M and changes in $CMRO_2$ on a voxel-wise basis. By providing higher SNR vascular measurements, our method could lead to significant improvements in calibrated BOLD measurements from decreased reliance on low-SNR CBF measurements as unique source of vascular information.

References: 1. Davis TL, et al. Calibrated functional MRI: Mapping the dynamics of oxidative metabolism. PNAS:1998;95:1834-1839
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3. Huber L, et al. Slab-Selective, BOLD-Corrected VASO (SS-VASO) in Human Brain at 7T. Proc. ISMRM, 2012:331