Neuronal activity-induced cerebral blood volume changes in humans: measurements with VASO and VERVE

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Introduction: To better understand the BOLD signal, knowledge of the behaviour of its components, namely cerebral blood flow (CBF), metabolic rate of oxygen uptake ($CMRO_2$), and blood volume (CBV), is necessary. In 2003, Lu *et al* proposed vascular space occupancy (VASO), a blood-nulling technique that measures the decrease in grey matter (GM) signal during activation, and associates this decrease to the transfer of water from GM to blood [1]. The change in signal should therefore reflect changes in total CBV. The sequence consists of a non-selective inversion pulse followed by imaging at the blood nulling time. In 2005, Stefanovic and Pike introduced venous refocusing for volume estimation (VERVE), a technique that measures only venous ΔCBV [2]. The venous blood signal is measured following a train of either tightly or sparsely packed CPMG refocusing pulses (the former minimizing the phase offsets caused by the deoxyhemoglobin-induced field heterogeneities), leading to a fast-slow difference that isolates the venous blood signal. In this work, we present ΔCBV results from both of these techniques, and compare their CNR, sites of activation, number of activated voxels and the corresponding time courses.

Methods: 5 healthy adult volunteers (age = 23.2 ± 1.6) were scanned on a Siemens TIM Trio 3T system. A blue-yellow radial checkerboard at 8 Hz was used as a visual stimulus, and bilateral sequential finger tapping at 3 Hz was used for sensorimotor activation. The common imaging parameters for VASO and VERVE were: FOV/matrix/slice-thickness/TR = 224 mm/64x64/5 mm/5 s. A 32 channel receiver head coil was used, along with a body coil for transmission, to maximize inversion uniformity. *VASO*: Non-selective hyperbolic secant inversion was used, and a 5 s TR allowed the blood to recover to more than 90% of its initial magnetization before each inversion, thereby minimizing inflow effects. A 5/8 partial Fourier acquisition allowed for a TE of 8.8 ms, minimizing the BOLD effect. In order to assess and minimize partial volume averaging, voxel-wise baseline cerebral spinal fluid (CSF), GM and white matter (WM) fractions, along with their respective water proton densities, resting CBV and tissue magnetization, were obtained from tissue classification based on a T_1 anatomical scan (1 mm isotropic). The CSF volume and distribution across the slice of interest was considered small enough to neglect effects of changes in CSF volume, in accordance with previous results concerning the visual cortex [3, 4]. *VERVE:* The sequence was CSF-suppressed and used a turbo spin-echo readout to avoid the GE-BOLD effect while increasing the signal-to-noise ratio [5]. B_1 inhomogeneity sensitivity and stimulated echoes were minimized using hard composite 90°-180°-90° refocusing pulses with MLEV phase cycling. The fast train consisted of 64 refocusing pulses separated by 3 ms, whereas the slow train consisted of 8 pulses spaced by 24 ms. The VASO and VERVE runs were composed of an initial 40 s of baseline, followed by four repetitions of 20 s/80 s/90 s OFF/ON/OFF stimulation.

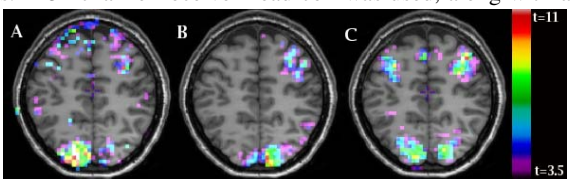

***Figure 1**: Activation map (t>3.5) overlaid onto an anatomical scan for blood-nulled VASO (A), VERVE (B), and BOLD (C).*

Results: Figure 1 shows the distribution of activated voxels (t>3.5) for VASO (A), VERVE (B), and BOLD (C) in one subject. On average, the number of activated voxels from the VASO data was higher, and higher t-scores were observed. The average maximum t-score was 17.8 for VASO, and 9.9 for VERVE. However, the activated voxels in VASO overlapped less with BOLD activated voxels than VERVE. The average VASO overlap was 34.0%, compared to 50.1% for VERVE. The ΔCBV/CBV time courses, averaged over all sessions and all subjects, are illustrated in Figure 2 (VASO in red, VERVE in blue). ΔCBV was calculated from the VERVE data using a calibration factor based on a $\Delta CBF/\Delta CMRO_2 = 3$ and a resting venous blood oxygenation of 65% [2,5]. For VASO, the ΔCBV values were calculated assuming a CBV_{rest} of 0.055 ml/ml in GM and 0.033 ml/ml in WM, a water density of 0.87/0.89/0.73/1.0 ml water/ml blood/GM/WM/CSF, and magnetizations calculated from T_1 values of 1627/1209/758/4300 ms for blood/GM/WM/CSF [4]. Both techniques showed signals which returned to baseline within 30 seconds, with no post-stimulus undershoot. Table 1 summarizes the data for all subjects. The average change found for total CBV based on VASO was 22.0% ± 0.5%, compared to 5.7% ± 0.3% for venous CBV based on VERVE. Previous animal studies reported a two-fold difference between total CBV changes and venous CBV changes [6], but based on CBV measurements made using VASO, a factor of 4 was observed in this study.

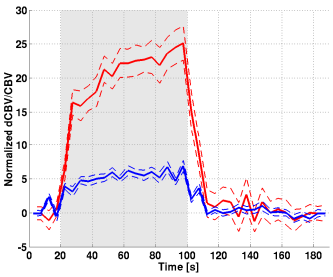

***Figure 2**: Timecourses of CBV changes (%) for VASO (red) and VERVE (blue) in activated voxels, averaged over all runs and subjects. The shaded area represents the stimulus period.*

Conclusion: Both the VASO and the VERVE techniques are potential tools to measure the changes in CBV during activation. Our VASO results were compatible with previous VASO studies which measured changes in CBV in the motor and visual cortices of 17 ± 8 and 18 ± 9%, respectively [7]. The VERVE technique may be more appropriate to investigate the BOLD signal, as it measures the venous CBV, rather than the total CBV. Indeed, the fraction of VERVE activated voxels which overlapped with BOLD activated voxels was 27.5% higher than for VASO. However, its contrast to noise ratio was lower, with a maximum t-score value of only 55% of that obtained with VASO. The VASO technique was easier to implement and had a larger number of activated voxels. On the other hand, the VASO measurements had to be carefully adjusted to remove its BOLD contribution, inflow and steady-state effects, CSF contribution and partial volume averaging.

Subject		1	2	3	4	5	**Average:**
ΔCBV/CBV	VASO	29.1 ± 2.1	19.0 ± 0.7	23.8 ± 1.1	12.5 ± 0.6	25.7 ± 1.0	**22.0 ± 0.5**
(%)	VERVE	6.6 ± 0.3	3.3 ± 0.2	4.9 ± 0.2	6.3 ± 0.3	7.6 ± 0.6	**5.7 ± 0.3**
# activated	VASO	306	193	220	231	189	**227.8 ± 43.8**
voxels	VERVE	105	109	279	110	309	**182.4 ± 119.8**

***Table 1**: ΔCBV/CBV results from VASO and venous ΔCBV/CBV results from VERVE for all subjects, along with the number of activated voxels for each of the techniques. Activation was determined using a threshold of 3.5 on the corresponding t-maps.*

References: [1] Lu *et al.* Magn Reson Med 50:263-274 (2003); [2] Stefanovic and Pike. Mag Reson Med 53:339-347 (2005); [3] Scounten and Constable. Mag Reson Med 58:308-315 (2008); [4] Dohahue *et al.* Magn Reson Med 56:1261-1273 (2006); [5] Chen and Pike, ISMRM 20072008, p 1909; [6] Lee *et al.*Magn Reson Med 45:791-800 (2001); [7] Scouten and Constable. Magn Reson Med 58: 306-315 (2007);