CBV Measurements-Gd DTPA vs. VASO- and Their Relationship with CBF in Activated Human Visual Cortex

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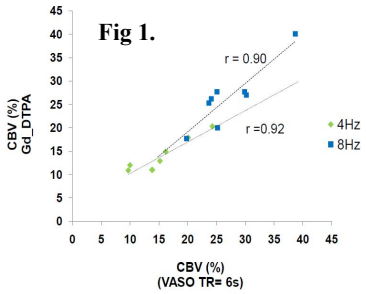
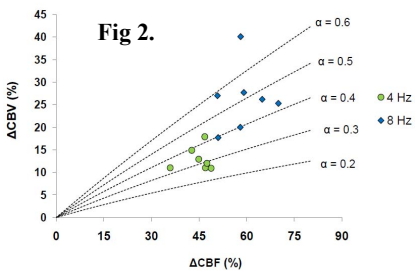
Introduction: The relationship between the task-induced percent changes of cerebral blood volume (CBV) and flow (CBF) ($\alpha = \ln(1 + \%CBV)/\ln(1 + \%CBF)$ is of great interest because it is important for identifying the cerebral vascular resistance (the brain increases CBF by reducing cerebral vascular resistance, corresponding to an increase in CBV) and for calibrating the BOLD contrast for $CMRO_2$ calculation with a fMRI biophysical model (1). Using fMRI, we previously measured CBV changes with the vascular space occupancy (VASO) techniques (2) and demonstrated the frequency-dependent CBF-CBV coupling with multi-rate visual stimulation (3). However, doubts have been casted on the accuracy of VASO for relative CBV determination, particularly the contamination by CBF signals when short repetition time (TR) is used (4) . The purpose of study was to re-visit the CBF-CBV coupling relationship during brain activation with fMRI methods and to investigate the effect of TR on CBV measurement using VASO. The CBV changes were determined with VASO and a contrast agent-based method (Gd-DTPA) (5). Short (2 s) and long (6 s) TR were employed for the VASO approach. Comparison between the three CBV measurement methods (Gd_DTPA, VASO_TR= 2 s and VASO_TR= 6 s), the CBF-CBV coupling under multi-rate visual stimulation and the coupling impact on relative $CMRO_2$ determination were demonstrated and discussed.

Materials and Methods: Seven healthy subjects (4 M and 3 F, age 26 ± 8 yrs) participated in the study. A black-white checkerboard was employed for visual stimulation. The experimental design consisted of 3-min 4Hz/3-min off/3-min 8Hz. Experiments were performed on a 3T Siemens Trio MRI scanner. An intravenous line was inserted for Gd-DTPA contrast agent administration. Four slices (5 mm in thickness) encompassing the primary visual cortex were chosen for fMRI. Images were acquired with a FOV of 24 cm and in-plane matrix size of 64 x 64. Task-induced CBV was measured by VASO acquisition with TR/TE = 6000 ms/9.4 ms and inversion time (TI) of 1086 ms. This was followed by simultaneous measurements of VASO, ASL and BOLD with TR of 2000 ms (3). TE for VASO, ASL and BOLD image acquisition was 9.4 ms, 11.6 ms and 28.1 ms, respectively. The inversion delay times were 610 ms (TI_1) and 1000 ms (TI_2), respectively. 0.1 mmol/kg Gd-DTPA contrast agent was injected per condition (i.e., rest, 4 Hz and 8 Hz) using a power injector with injection rate of 5 ml/s. The images were acquired using a GE EPI sequence with TR/TE = 2000 ms/30 ms. *Data Analysis:* For each condition (rest, 4 Hz and 8Hz), changes in brain signal intensity of Gd-DTPA were converted to contrast agent concentration-time curves. The area under the concentration-time curve is proportional to the local relative CBV. These calculations were performed on a voxel-by-voxel basis to generate images of relative CBV (5). Student's *t* tests were used to compare "baseline" and each frequency "stimulus" signals from contrast agent-based CBV maps, VASO, ASL and BOLD. The threshold was set to $t = 3.0$ ($P < 0.005$). The three functional quantities were then used to calculate α and the $\%CMRO_2$ with the fMRI biophysical model (1, 3) with hypercapnic challenge (5% CO_2). The %CBV determined by the three different strategies were compared with by one-way, repeated-measures ANOVA. Post-hoc testing per condition was done by Newman-Keuls test.

Results: The %CBV measured by the three methods (**M1**: Gd_DTPA; **M2**: VASO_TR = 6s; and, **M3**: VASO_TR = 2s) were shown in Table 1. There was no significant statistical %CBV difference between M1 and M2 ($P > 0.05$). The correlation of the %CBV values obtained by the two methods was further demonstrated in Figure 1. In contrast, a significant difference was found between M1 and M3; M2 and M3 ($P < 0.001$). The %CBV measured by M1 and M2 were used for further α calculation with the measured %CBF. It showed in Table 2 that the α value was stimulus frequency-dependent, with α = 0.35-0.38 at 4 Hz and α = 0.51-0.53 at 8 Hz. The α value distribution (obtained by M1) was further demonstrated in Figure 2. To estimate the impact of %CBV on $\%CMRO_2$ determination, the %CBV obtained by M2 and M3 were used for calculating $\%CMRO_2$. The results were demonstrated in Figure 3. It showed that the $\%CMRO_2$ determined by M3 was significantly lower than that determined by M2 ($P < 0.05$) due to the overestimated %CBV. Nonetheless, the trend of the $\%CMRO_2$ changes (i.e., 4 Hz > 8 Hz) was not altered.

Discussion: Our data demonstrated that VASO signal intensities varied with TR. The high VASO signal changes obtained at short TR was probably due to the contamination of the fresh-blood (non-nulled) fraction (4). At long TR, %CBV obtained at 4 and 8 Hz with VASO (M2) in the study were in good agreement with those obtained by the Gd-DTPA method (M1). We further demonstrated that the task-induced flow-volume coupling (α value) varied with stimulus frequency, ranging from 0.35 to 0.53. Because of the decreased %CBV, $\%CMRO_2$ obtained at long TR were shown significantly higher than those obtained at short TR. Although the $\%CMRO_2$ magnitudes were different between the two measurements, the patterns were similar (i.e., $\%CMRO_2$: 4 Hz > 8 Hz). As a result, a non-linear flow-metabolism coupling relationship (%CBF: 8 Hz > 4 Hz) was observed with both methods. Finally, the $\%CMRO_2$ determination in the study employed the *total* %CBV as measured by either Gd-DTPA or VASO techniques. Collecting evidence has shown that most of the CBV change is on arterial side. Specifically, venous CBV is negligible with short-term stimulation (e.g. < 20 s forepaw stimulation in rats; 6). In the current study, the stimulation period was sufficiently long (3 min) and venous CBV was considered significant (7), but it is suggested to further identify the contribution of arterial and venous CBV increases for task-induced $CMRO_2$ changes in the future studies.





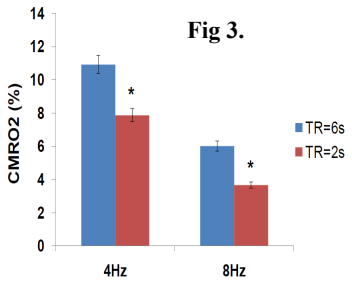


Fig 1. Correlation of the %CBV between M1 and M2. **Fig 2.** Distribution of the α values. **Fig 3.** $\%CMRO_2$ determined with %CBV obtained by VASO at different TR. * $P < 0.05$.

Method	4 Hz (%CBV)	8 Hz (% CBV)
M1. Gd-DTPA	13.9 ± 5.5	25.8 ± 9.1
M2. VASO (TR = 6s)	15.4 ± 4.9	27.1 ± 5.8
M3. VASO (TR = 2s)	20.3 ± 6.0	31.4 ± 5.5
F	3.76 *	1.62
Post hoc	M1 = M2 < M3	M1 = M2 < M3

Table 1. Values are means ± SD (n= 7). * indicates $P < 0.05$. "< " indicates $P < 0.001$ and "=" indicates $P > 0.05$.

Stimulus Rate	CBF (%)	CBV method	CBV (%)	α
4 Hz	45.0 ± 4.1	Gd_DTPA	13.9 ± 5.5	0.35
		VASO (TR = 6s)	15.4 ± 4.9	0.38
8 Hz	57.1 ± 7.8	Gd_DTPA	25.8 ± 9.1	0.51
		VASO (TR = 6s)	27.1 ± 5.8	0.53

Table 2. Values are means ± SD (n= 7).

References: (1) Davis et al., PNAS 1998, 95:1834-9; (2) Lu et al., MRM 2003, 50:263-74; (3) Lin et al., MRM 2008, 60:380-9; (4) Donahue et al., MRM 2006, 56:1261-73; (5) Belliveau et al., Science 1991, 254:716-9; (6) Kim et al., MRM 2008, 60:1518-23; (7) Hua et al., ISMRM 2010, 1127.