Steady-State Relationship Between Cerebral Blood Flow and Venous Blood Volume

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Introduction

To understand and predict the blood-oxygenation level-dependent (BOLD) fMRI signal, an accurate knowledge of the relationship between cerebral blood flow (ΔCBF) and volume (ΔCBV) changes is critical [1]. Currently, this relationship is widely assumed to be represented by the Grubb's power-law ($rCBV = rCBF^{\alpha}$), derived from CBF and mean transit time data obtained from anesthetized rhesus monkeys using $H_2{}^{15}O$ and $C^{15}O$-hemoglobin tracers, where rCBV = 1+ΔCBV, rCBF = 1+ΔCBF, and the power coefficient (α) was found to be 0.38 [2]. The validity of this general formulation has been confirmed by several animal and human studies [2-4], and an α of 0.38 has been frequently cited when calculating $\Delta CMRO_2$ from calibrated BOLD and CBF data. However, the value of α has been a subject of debate, especially since it is well established that the BOLD signal is mainly modulated by changes in venous CBV (ΔCBV_v) instead of total CBV, and yet direct ΔCBV_v measurements in humans have been extremely scarce. Preliminary CBV_v measurements have previously been obtained using the venous-refocusing for volume-estimation (VERVE) technique at 1.5 T [5] and 3 T [6]. The goal of this work was to demonstrate an improved design of VERVE, based on magnetization preparation and a turbo spin-echo (TSE) readout, and to report on the resulting steady-state CBV_v and CBF measurements in a group of human subjects using graded visual as well as sensorimotor stimulation.

Methods

The VERVE technique targets ΔCBV of partially deoxygenated blood using the T2 dependence of the latter on the Carr-Purcel-Meiboom-Gill (CPMG) inter-refocusing interval (τ_{180}). The new implementation of the VERVE sequence begins with cerebral-spinal fluid (CSF) suppression at an inversion time (TI) of 1100 ms. This is followed by the VERVE magnetization preparation, composed of a set of non-selective $90°_x$ tip-down and tip-up pulses flanking an MLEV phase-cycled CPMG train made up of non-selective composite $90°_x$-$180°_y$-$90°_x$ refocusing pulses for either fast or slow refocusing. The corresponding $\tau_{180,fast}$ and $\tau_{180,slow}$ are 3 ms and 24 ms, respectively, resulting in an effective TE of 198.8 ms. The TSE readout employs fully spoiled refocusing pulses and readout gradients. The use of TSE improves image signal-to-noise ratio (SNR), and precludes T2* weighting, which becomes increasingly significant in echo-planar imaging (EPI) at higher field strengths. The excitation is phase-chopped, and the readout is bracketed by additional spoiler gradients to maximally suppress alternate echo paths. A slice-selectlve $90_y°$ resetting pulse was used to accelerate signal recovery at the end of each repetition. The difference between the slow- and the fast-refocused images is ΔVERVE. The relationship between ΔVERVE and ΔCBV_v [4] was obtained for each subject using *in vivo* venous blood oxygenation measurements acquired using a magnetization-prepared segmented EPI sequence [7].

All acquisitions were performed using a Siemens Trio 3T system and 20 healthy adult subjects (age = 25.8 ± 2.5 years). The basic imaging parameters were: FOV/matrix/slice-thickness/TR = 200 mm/64x64/5 mm/4000 ms. CBF changes were measured using QUIPSS II arterial-spin labeling [8], and the parameters were: TI_1/TI_2/TE/labeling thickness/gap = 700 ms/1300 ms/25 ms/100 mm/5 mm. Visual activation was induced using a 8 Hz radial yellow/blue checkerboard at 100% and 25% contrast, alternating with a uniform grey field as baseline. Sensorimotor activation was produced through cued bilateral sequential finger tapping at 1.73 Hz and 3.46 Hz. A functional scout was used for slice positioning. The stimulation paradigm employed 2 repetitions of 16 s/96 s/120 s off/on/off blocks, with an additional 32 s initial baseline for resting-state estimation. A 3D T1-weighted scan served as anatomical reference. The region-of-interest (ROI) was delineated for each subject by thresholding the CBF and CBV_v *t*-maps at $p < 0.05$ (corrected for multiple comparisons). The overlap between CBF- and CBV_v ROIs was used to calculate average ΔCBF (%) and ΔCBV_v (%) in the steady-state, defined to begin 52 s after stimulus onset or offset. Finally, α was estimated using unconstrained non-linear least-square curve-fitting weighted by the inverse standard deviation of the data points.

Results

The current TSE-based VERVE demonstrated an SNR improvement of approximately 60% compared to the previous EPI implementation. Sample CBF and CBV_v activation maps for one subject are shown in Fig. 1, with the corresponding *t*-value scales. The activation-induced steady-state ΔCBF and ΔCBV_v are summarized in Table 1, and a scatter plot of $rCBV_v$ vs. rCBF is shown in Fig. 2. The power-law fits for the visual and sensorimotor regions were not significantly different ($P = 0.66$) from each other, and were hence combined in the final weighted fit, which resulted in $\alpha = 0.26 \pm 0.02$, with $P < 0.001$. Linearization of the fit yielded a correlation coefficient of 0.69 and a coefficient of determination of $r^2 = 0.42$.

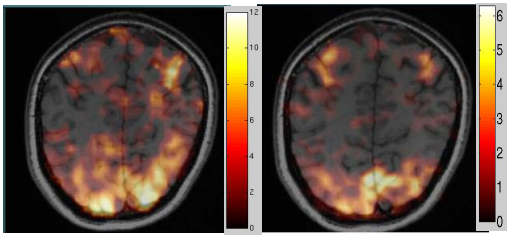

Figure 1. The CBV_v and CBF activation *t*-maps for one subject at 100% visual contrast stimulation and 3.46 Hz bilateral sequential finger tapping.

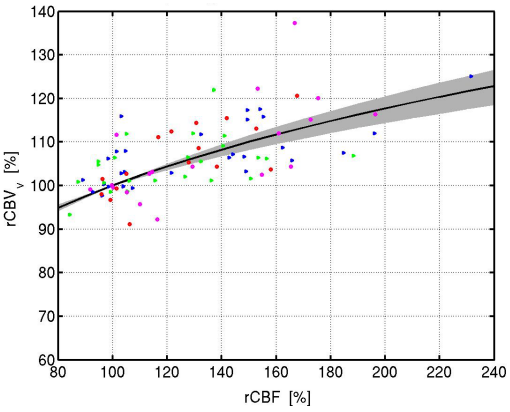

Figure 2. The rCBF and rCBV measurements and the resulting fit to the power-law (dark line), performed on the data from 100% and 25% visual contrast (blue and green, respectively) and for finger tapping at 1.73 Hz and 3.46 Hz (magenta and cyan, respectively). The shaded region represents the 95% confidence interval.

	visual		sensorimotor	
	25% contrast	100% contrast	1.73 Hz	3.46 Hz
ΔCBF (%)	41.3 ± 5.2	51.4 ± 7.8	43.9 ± 5.5	66.4 ± 6.5
ΔCBV_v (%)	8.1 ± 1.7	9.7 ± 1.6	7.2 ± 2.3	11.2 ± 3.9

Table 1. The steady-state CBF and CBV_v estimates.

Conclusion

Both our CBV_v measurements and CBF-CBV_v relationship estimates closely correspond to the findings in the perfluorocarbon tracer animal study from Lee et al [3]. Our ΔCBV_v measurements are substantially lower than measured using techniques targeting all blood compartments [2,9], in good accordance with known venous fractions and prior observations [3]. Since the BOLD signal is dependent primarily upon venous, instead of total, volume change, the relevant ΔCBV in the context of BOLD modeling may be overestimated using Grubb's relationship, leading to the underestimation of $\Delta CMRO_2$ for a given ΔCBF and ΔBOLD. The effect of this underestimation on the flow-metabolism coupling calculations warrants further investigation.

[1] Hoge RD et al. Magn Reson Med 1999;42:849-63; [2] Grubb RL et al. Stroke 1974;5:630-39; [2] Ito H et al. J CBF Metab 2001; 21:608-12; [3] Lee SP et al. Magn Reson Med 2001;45:791-800; [4] Stefanovic B and Pike GB, Magn Reson Med 2005;53:339-47; [6] Chen JJ and Pike GB, Proc. ISMRM 2007; p. 2617; [7] Foltz WD et al. Magn Reson Med 1999; 42: 837-48; [8] Warnking JM and Pike GB, Magn Reson Med 2004; 52:1190-99; [9] Lu H et al. Magn Reson Med 2005;53:808-16.