The BOLD-Specific Flow-Volume Relationship During Hypercapnia and Hypocapnia

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Introduction

Knowledge of the relationship between venous cerebral blood volume (ΔCBV_v) and blood flow (ΔCBF) changes is crucial to understanding the blood oxygenation level-dependent (BOLD) fMRI signal. To date, Grubb's power-law ($rCBV = rCBF^{\alpha}$), where an α of 0.38 was measured in rhesus monkeys under hypercapnic challenge [2], has been extensively used in human BOLD modeling. The equivalence of the flow-volume relationship observed under neuronal activation and hypercapnia has been further investigated using PET [3,4], and is instrumental in calibrated BOLD-based cerebral oxygen metabolism ($CMRo_2$) estimation [1,5]. However, these previous measurements were of total ΔCBV instead of the BOLD-specific venous ΔCBV, and the venous flow-volume relationship under CO_2-induced flow changes needs to be measured for fMRI applications. In addition, the comparability of the venous flow-volume relationship under focal and CO_2-induced hyperemia has yet to be established. We found the former relationship in humans to be characterized by $\alpha = 0.23$ [6], significantly lower than Grubb's value. In this work, we report on the venous flow-volume relationship in humans under graded hyper- and hypocapnia.

Methods

All acquisitions were performed using a Siemens Trio 3 T system, involving 16 healthy adult subjects (age = 25.8 ± 3.5 years, 9 females) who gave informed consent. The body and neurovascular coils were used for transmitting and receiving, with basic imaging parameters: FOV/matrix/#slices/slice-thickness/TR = 256 mm/64x64/1/5 mm/5 s. Changes in venous cerebral blood volume (ΔCBV_v) were measured using the venous-refocusing for volume-estimation (VERVE) technique [6,7], with CSF suppression performed at an inversion time (TI) of 1350 ms. In the VERVE magnetization preparation, τ_{180} = 3 ms and 24 ms, for fast and slow-refocusing, respectively. QUIPSS II arterial-spin labeling (ASL) [8], with scan parameters TI_1/TI_2/TE/labeling thickness/gap = 700 ms/1300 ms/25 ms/150 mm/5 mm, was used to measure ΔCBF (control-tag) and $\Delta BOLD$ ((control+tag)/2). Mild and moderate hyper- and hypocapnia were induced through the administration of various mixtures of O_2, CO_2 and medical air delivered using the Respiract breathing circuit (Thornhill Research, Toronto, Canada) designed to provide computerized targeting of end-tidal O_2 (ETO_2) and CO_2 ($ETCO_2$) pressure independent based on the sequential gas delivery method [9]. This device significantly increases steady-state ETO_2 stability while achieving ETO_2 invariability relative to existing methods, thus enabling us to accurately assess steady-state flow-volume changes. The stimulation paradigm employed 2 repetitions of 60 s/180 s/120 s off/on/off blocks. The calibration from $\Delta VERVE$ to ΔCBV_v [7] was performed for each subject at each $ETCO_2$ using *in vivo* jugular vein oximetry [10]. A 3D T_1-weighted scan served as anatomical reference, from which grey matter (GM) masks were extracted using parametric Bayesian segmentation. The region-of-interest (ROI) was delineated for each subject by thresholding the BOLD *t*-map at $P < 0.05$ (corrected for multiple comparisons). The overlap between these BOLD ROIs and the GM mask was used to calculate average ΔCBF (%) and ΔCBV_v (%) in steady-state, defined to begin 90 s after the onset and offset of the challenge in order to accommodate the slower hypocapnic transition. Finally, α was estimated using unconstrained non-linear least-square curve-fitting weighted by the inverse standard deviation of the data points.

Results

The average baseline venous oxygenation (Y_0) was 60.6±11.4%. The steady-state ΔCBF and ΔCBV_v and BOLD time courses in cortical GM for one subject during a moderate hypercapnia ($\Delta ETCO_2$ = 9±0.8 mmHg) challenge are shown in Figure 1, with each symbol representing one sessional average from each subject. Mild and moderate hypercapnia trials produced average $\Delta ETCO_2$ of 4.6±0.9 and 9.1±1.1 mmHg, respectively, while mild and moderate hypocapnia trials produced average $\Delta ETCO_2$ of -3.4±1.2 and -5.7±2.4 mmHg, respectively, with steady-state stability maintained. A scatter plot of $rCBV_v$ vs. rCBF is shown in Fig. 2. Since the power-law fit for cortical and sub-cortical ROIs ($P < 0.001$ for both cases) were not significantly different ($P > 0.05$), the two regions were combined in the final weighted fit, which resulted in $\alpha = 0.19 \pm 0.04$, with $P < 0.001$. Linearization of the fit yielded $R = 0.52$, $r^2 = 0.38$.

Conclusion

Using venous CBV changes, the estimated power-law coefficient (α=0.19±0.04), in agreement with our previous findings for human neuronal activation (α=0.23±0.05) [6]. Thus, as was in the case of total ΔCBV [3,4], the venous flow-volume relationships observed under hypercapnia as well as hypocapnia were found to be equivalent to that for neuronal activation. However, this α value is significantly lower than Grubb's value of 0.38. Our results are in agreement with animal ΔCBV_v data under hypercapnia [11]. Thus, since BOLD is mainly dependent on venous ΔCBV, the flow-volume relationship given by Grubb's α of 0.38 overestimates the CBV contribution to hypercapnia-induced BOLD. This leads to overestimation of the maximum achievable BOLD signal in calibrated BOLD, resulting in the underestimation of activation-induced $\Delta CMRo_2$.

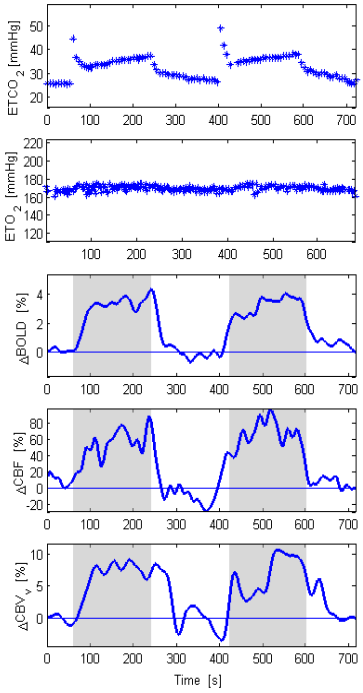

Figure 1. The top 2 plots show $ETCO_2$ and ETO_2 tracings corresponding to the BOLD, CBF and CBV_v measurements (bottom 3 plots) obtained from the grey-matter constrained BOLD *t*-map ROI for one subject during blocks of $ETCO_2$ increase by 9 mmHg, indicated by the shaded regions. ETO_2 remained unchanged during $ETCO_2$ manipulations.

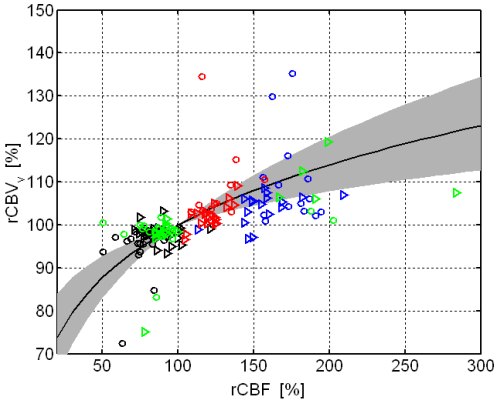

Figure 2. The rCBF and rCBV measurements and the resulting fit to the power-law (black line), where α = 0.19±0.04. Each symbol represents one sessional average from one subject. Triangles and circles indicate cortical and sub-cortical data, respectively, and the colours represent the trial number. Red and blue = low and moderate hypercapnia, respectively, while black = moderate hypocapnia. The shaded region represents the 95% confidence interval of the fit.

References

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