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

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Introduction

Knowledge of the relationship between venous cerebral blood volume (ΔCBVv) and blood flow (ΔCBF) changes is crucial to understanding the blood oxygenation level-dependent (BOLD) fMRI signal. To date, Grubb’s power-law (rcBF = rCBF)6, 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 hypcapnia has been further investigated using PET [3,4], and is instrumental in calibrated BOLD-based cerebral oxygen metabolism (CMRO2) 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 CO2-induced flow changes needs to be measured for fMRI applications. In addition, the comparability of the venous flow-volume relationship under focal and CO2-induced hyperemia has yet to be established. We found the former relationship in humans to be characterized by α = 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 ms. Changes in venous cerebral blood volume (ΔCBVv) 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, τm = 3 ms and 24 ms, for fast and slow-refocusing, respectively. QUIPSS II arterial-spin labeling (ASL) [8], with scan parameters TI/TE/T/labeling thickness/gap = 700 ms/1300 ms/25 ms/150 mm/5 mm, was used to measure ΔCBF (control-tag) and ΔBOLD ((control+tag)/2). Mild and moderate hyper- and hypocapnia were induced through the administration of various mixtures of O2 and CO2 and medical air delivered using the Respiract breathing circuit (Thorntielli, Research, Toronto, Canada) designed to provide computerized targeting of end-tidal O2 (ETCO2) and CO2 (ETCO2) pressure independent based on the sequential gas delivery method [9]. This device significantly increases steady-state ETO2 stability while achieving ETO2 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 ΔVERVE to ΔCBVv [7] was performed for each subject at each ETCO2 using in vivo jugular vein oximetry [10]. A 3D T1-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 signal with a 95% confidence interval of the fit. This leads to overestimation of the maximum achievable BOLD signal in calibrated BOLD, resulting in the underestimation of activation-induced ΔCMRO2.

Results

The average baseline venous oxygenation (Yo) was 60.6±11.4%. The steady-state ΔCBF and ΔCBV and BOLD time courses in cortical GM for one subject during a moderate hypercapnia (ΔETCO2 = 9±0.8 mmHg) challenge are shown in Figure 1, with each symbol representing one sessional average from each subject. Mild and moderate hypcapnia trials produced average ΔETCO2 of 4.6±0.9 and 9.1±1.1 mmHg, respectively, while mild and moderate hypcapnia trials produced average ΔETCO2 of -3.4±1.2 and -5.7±2.4 mmHg, respectively, with steady-state stability maintained. A scatter plot of rCBV 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 α = 0.19 ± 0.04, with P < 0.001. Linearization of the fit yielded R2 = 0.52, r2 = 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 hypcapnia 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 ΔCBVv data under hypcapnia [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 hypcapnia-induced BOLD. This leads to overestimation of the maximum achievable BOLD signal in calibrated BOLD, resulting in the underestimation of activation-induced ΔCMRO2.

Figure 1. The top 2 plots show ETCO2 and ETO2 tracings corresponding to the BOLD, CBF and CBV measurements (bottom 3 plots) obtained from the grey-matter constrained BOLD t-map ROI for one subject during blocks of ETCO2 increase by 9 mmHg, indicated by the shaded regions. ETO2 remained unchanged during ETCO2 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
