Does Global Cerebral Oxygen Metabolism Change During Hypercapnia and Hypocapnia in Awake Humans?

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Introduction

Carbon dioxide (CO_2) is a potent vasodilator, and its effect on cerebral metabolism is of great interest. Notably, hypercapnia is routinely used in calibrated BOLD for estimating changes in oxygen metabolism ($\Delta CMRo_2$), but the latter methodology is contingent upon the assumption of negligible $\Delta CMRo_2$ during hypercapnia-induced cerebral blood flow (CBF) increase [1,2]. While the extent of $CMRo_2$ invariability under end-tidal CO_2 ($ETCO_2$) manipulations has been investigated previously in animals [3,4], the sampling intervals (between 15 min and 1 hour) were generally too long to capture functional $CMRo_2$ changes, and the end-tidal manipulations too severe to be directly interpreted for calibrated BOLD. Thus, $CMRo_2$ invariability has yet to be established for the range of $ETCO_2$ values relevant for functional imaging, and remains little explored in humans. Recent efforts at verifying the assumption of $CMRo_2$ invariability involved measurements of CBF, blood oxygenation and neuronal activity in animals during short hypercapnic challenges. However, these studies reported $\Delta CMRo_2$ increases [5] as well as decreases [7]. Given that the levels of $ETCO_2$ manipulation used in these works were not equivalent, and that the types of anesthetic agent used were different, it is difficult to draw definitive conclusions about applications in human fMRI studies. In this study, we used arterial spin labeling (ASL) and in vivo MR oximetry to measure flow and $CMRo_2$ non-invasively in awake humans during graded hypercapnia and hypocapnia. We show that under the levels of $\Delta ETCO_2$ commonly used in calibrated BOLD, there is no significant change in $CMRo_2$.

Methods

All acquisitions were performed using a Siemens Trio 3 T system and 10 healthy adult subjects (age = 26.8 ± 3.9 years, 5 females) who gave informed consent. The body and neurovascular coils were used for transmission and reception, respectively. Venous blood oxygenation (Y) was obtained *in vivo* for each subject at the internal jugular level using a magnetization-prepared segmented EPI sequence [7]. In addition, ΔCBF changes were measured using QUIPSS II arterial-spin labeling with BASSI saturation/inversion [8] and ASSIST background suppression [9]. The imaged slab was positioned approximately parallel to the AC-PC line, and contained the visual and somatosensory areas as well as sub-cortical nuclei. It was covered in 8 slices of 5 mm (separated by 1 mm gaps), with FOV = 256 mm, matrix size = 64 x 64, TR = 5 s, TI_1 = 700 ms, TI_2 = 1300 ms, TE = 25 ms, labeling thickness = 150 mm, labeling gap = 5 mm. Mild and moderate levels of hypercapnia and hypocapnia were induced through the administration of various mixtures of CO_2 and medical air using the Respiract breathing circuit (Thornhill Research, Toronto, Canada), designed to provide computerized targeting of ETO_2 and $ETCO_2$ independently based on the sequential gas delivery method [10]. This device provided higher accuracy and stability in end-tidal pressure targeting than previous methods, and these features are crucial to the accurate quantification of $CMRo_2$ changes due solely to $ETCO_2$ change. A 3D 1 mm isotropic resolution T_1-weighted scan served as anatomical reference for each subject, from which grey matter (GM) masks were extracted using parametric Bayesian segmentation (the subject-specific training sets each containing 50 manually selected voxels for each tissue species) at an a posteriori probability threshold of 80%. The resultant grey matter mask was used in estimating the average global ΔCBF for each subject, an approach that was found to agree with 2D cine phase-contrast arterial flowmetry measurements of total ΔCBF made at the neck (data not shown).

$$Y = \left[\Delta CBF \cdot (1-\Psi)(Y_a - Y_0)\right]/(\Delta CBF + 1) + Y_0 \qquad [1]$$

Thus, in conjunction with the venous Y measurements, the ratio between $\Delta CMRo_2$ and ΔCBF was estimated based on Eq. [1], derived from first principles as per ref. [11], and where $\psi = \Delta CMRo_2/\Delta CBF$, Y_a and Y_0 are arterial and baseline venous oxygenation levels, respectively, the former assumed to remain at approximately 98% [12]. Unconstrained non-linear least-square curve-fitting was used to fit the data to the model, with weightings proportional to the inverse standard deviation of the data points.

Results

The average baseline venous oxygenation (Y_0) was estimated at 58.2 ± 8.2%, corresponding to an average baseline $ETCO_2$ of 39.9 ± 1.4 mmHg. Hypercapnia produced $\Delta ETCO_2$ of 4.4 ± 0.8 and 9.2 ± 1.0 mmHg under mild and moderate challenges, respectively. These corresponded to average global ΔCBF of 21.6 ± 8.7% and 53.3 ± 10.2%, as well as Y of 62.1 ± 5.7% and 75.3 ± 7.3%, respectively. Conversely, moderate hypocapnia produced $\Delta ETCO_2$ of -5.2 ± 1.8 mmHg, resulting in global ΔCBF of -15.1 ± 4.8% and Y of 50.1 ± 12.9%. Lastly, mild hypocapnia produced $\Delta ETCO_2$ of -3.2 ± 1.0 mmHg, resulting in global ΔCBF of -8.9 ± 5.0% and Y of 50.2 ± 8.0%. Stability in ETO_2 was maintained in all cases. The model offered a good fit to the data, as seen in Fig. 1. Using the whole-brain GM ΔCBF to approximate global ΔCBF, the global ψ value was -4 ± 18% across all subjects and conditions, not distinguishable from zero (P = 0.99). Cortical and sub-cortical GM ψ estimates were examined separately, and were found not to be different statistically (P = 1.00). Finally, assuming ψ = 0, and using the measured ΔCBF, the expected venous oxygenation was calculated based in Eq [1] for all hypercapnic and hypocapnic conditions. The resulting Y values were not different to the corresponding measured values (P = 0.72).

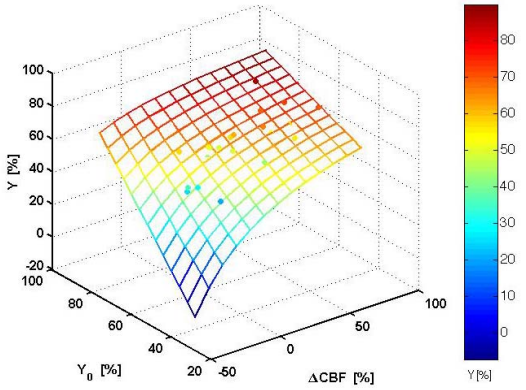

Figure 1. The modeled (grid) venous blood oxygenation (Y) as a function of the baseline oxygenation (Y_0) and ΔCBF, well represents the measured data (points), for graded hypercapnia and hypocapnia. The best fit to the model resulted in a $\Delta CMRo_2$ of -4± 18%, with no significant difference between mild and moderate conditions.

Conclusion

For the first time, we report on global $\Delta CMRO_2$ measurements in awake humans during graded levels of hypercapnia and hypocapnia using in vivo MR flow and oxygenation measurements. The use of the Respiract device enabled us to obtain stable and robust $ETCO_2$ manipulation while keeping ETO_2 constant, a challenge that has not been fully addressed by other methods in the literature. Such stability and robustness permitted more accurate quantification of $CMRo_2$ changes resulting from $ETCO_2$ change. Our results demonstrate a negligible $\Delta CMRO_2$ for $ETCO_2$ variations ranging from -5 to +9 mmHg. These results validate the use of hypercapnia (at the levels explored in this work) for BOLD calibration [1,2], which is widely applied in the assessment of Δ $CMRo_2$ due to neuronal activation.

References:

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