Small changes in relative $CMRO_2$ during stepped hypercapnia?

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ABSTRACT The cerebral metabolic rate of oxygen ($CMRO_2$) is a physiological parameter closely linked to neural activation as well as to various disease states. Recently, changes in relative $CMRO_2$ during evoked fMRI responses have been assessed with simultaneous measurements of BOLD, cerebral blood volume (CBV), and blood flow (CBF). The method requires a basal calibration between these parameters, which is commonly performed using hemodynamic responses elicited by systemic hypercapnia (i.e., inhaling CO_2). However, the underlying assumption of no metabolic demand associated with hypercapnia-induced hemodynamic changes has not been clearly validated. In this work, using different CO_2 levels and cross-calibration among hypercapnia-induced responses, we investigated whether inhaling variable levels of CO_2 differently affect the relative $CMRO_2$ in rats.

MATERIALS AND METHODS Four normal healthy Sprague-Dawley rats (~300g) were used to record hemodynamic parameters during stepped CO_2 breathing gas changes. After a 10 minute baseline, we increase the inhaled CO_2 to 2.5%, 5% and 7.5% respectively, every 5 minutes. A cASL sequence with 3000-ms continuous labeling at the carotid arteries, 500-ms delay and EPI read-out was used to acquire CBF with 7.4s temporal resolution [1]; then after bolus injection of MION (36 mg/ml) T_2^* weighted EPI images were acquired continuously and CBV maps were calculated from the T_2* weighted images with 3.7 seconds temporal resolution [2]. We used the hypercapnic calibration approach as outlined by Mandeville et al. [3]. Because the baseline CBF measurement was unreliable, we used the 2.5-5% CO_2 transition to compute the BOLD part of the baseline transverse relaxation rate ($R_{2,0}^{*(BOLD)}$). We then computed the relative $CMRO_2$ index across the entire experiment and averaged its value during the second half of each gas step.

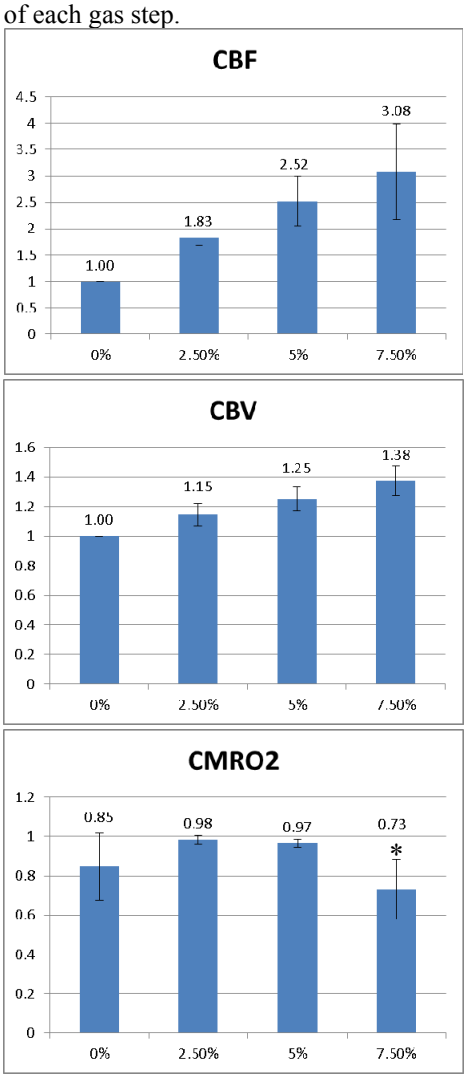

Figure 1.

RESULTS AND DISCUSSION Our hypothesis was that changes in $rCMRO_2$ during hypercapnic challenges are negligible and not CO_2 dose dependent. Thus we expected that if we calibrate the baseline $R_2^{*(BOLD)}$ under the assumption of no metabolic demand during the 2.5-5% transition, we would observe no changes in rCMRO2 at 7.5% CO_2. Figure 1 shows bar charts of relative changes in CBV, CBF and $rCMRO_2$ averaged across the 4 animals used in this study, during the second half of each gas step. We note the expected increasing trends in CBF and CBV. Having assumed the 2.5-5% transition is isometabolic, the average $rCMRO_2$ for 2.5 and 5% is close to unity, but the 7.5% $CMRO_2$ is statistically significantly lower than either 2.5 or 5%. This would appear to indicate that increased CO_2 levels beyond 5% lead to reduced oxidative metabolism. However, it is more likely that several sources of signal contamination are responsible for these results. The effect could rise from the fact that the CBF quantified by ASL is weighted by T_2* which changes during the hypercapnic challenge due to possible changes in the concentration of oxygenated blood in venous compartment of the local brain tissue (especially during 7.5% CO_2 inhalation). Another possible reason is that CBV quantified with the intravascular agent (MION) may be increasingly contaminated by dose dependent BOLD signals, which counter the signal decreases induced by the CBV driven MION concentration increase during the hypercapnic challenge. Furthermore, other unknowns such as differently dilated vascular compartments and compartment dependent blood flow changes may contribute to the apparent decrease of $rCMRO_2$ during 7.5% CO_2 inhalation.. In summary, our results demonstrate limited, if not small $rCMRO_2$ changes during hypercapnic challenges of variable intensity. However, the apparent change of $rCMRO_2$ during 7.5% CO_2 inhalation warrants future studies using different strategies for quantifying metabolism. In particular, we will seek to independently measure relevant parameters such as blood flow and blood volume/oxygenation using methods which are not affected by inherent measurement signal contaminations (e.g., near infrared dynamic optical imaging).

References.

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