# Imaging Hypothermia-Induced Global and Regional Changes in CBF, BOLD and $CMRO_2$

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**INTRODUCTION:** The abilty to measure $CMRO_2$ is crucial to understand neural-vascular coupling during changes in neuronal activity and has the potential for greater spatial specificity compared to hemodynamically-based fMRI parameters. Unfortunately, current techniques for measuring $CMRO_2$ have low spatiotemporal resolution, are arduous to perform, or require invasive/lethal procedures [1]. A fully developed fMRI-based $CMRO_2$ technique would circumvent these issues and would likely have a critical impact in neuroscience research.

Our lab recently demonstrated that stimulus-evoked elevations in $CMRO_2$ could be reliably measured in spontaneously breathing rats using the fMRI-based biophysical BOLD model of Davis *et al.* [1-3]. We further showed that moderate perturbations in animal physiology *per se* do not basal and stimulus-evoked $CMRO_2$ as measured by fMRI, further supporting the validity of the Davis model [3]. In this study, we sought *i)* to characterize the effects of normothermia and hypothermia on baseline and hypercapnia induced changes in CBF, BOLD and $CMRO_2$ under spontaneously breathing conditions, and *ii)* to use these findings to test the self-consistency of Davis' $CMRO_2$-MRI technique during a period of metabolic depression. Temperature modulation was chosen because there is a large body of literature on temperature-dependent effects on CBF and $CMRO_2$ (determined using validated techniques) with which our data could be cross-validated. Five structures were analyzed: whole-brain, cerebral cortex, thalamus, hippocampus and caudatoputamen (CPu).

**METHODS:** Six male SD rats (300-350 g) were studied. Femoral artery catheterization was performed for continuous monitoring of physiology (RR, HR and MABP) and periodic blood gas analysis. For the remainder of the study, rats breathed spontaneously under 1.1% isoflurane. A feedback-regulated water pad was used to continuously monitor and alter rectal temperature, which was reduced from 37.0 ± 0.5 °C (normothermia) to 32.0 ± 0.5 °C (hypothermia) over 30 min. Hypercapnic challenges (twice repeated) were performed during 37 and 32°C periods. Blood gases obtained at 32°C were temperature corrected [4].

Imaging was performed during the hypercapnic challenges consisting of a 2min baseline period followed by a 2min stimulation period of breathing 5% $CO_2$. A 15-min break was given between challenges. Combined CBF and BOLD measurements were made on a 4.7 T Bruker scanner using the CASL technique with single-shot, gradient-echo EPI acquisition. An actively decoupled surface coil (2.3-cm ID) was used for brain imaging and a neck coil for perfusion labeling. MR parameters were: data matrix=64x64, FOV=2.56x2.56 $cm^2$, eight 1.5-mm slices, TE=20ms and TR=2s. High resolution anatomical images (128x128, RARE) were also acquired.

BOLD images were derived from the control dataset of the CBF measurements. Cross-correlation analysis was performed on the CBF and BOLD datasets to derive percent-change maps. Calculation of relative $CMRO_2$ used the biophysical BOLD model and methodology of Davis *et al.* [3]. ROI analysis without activation-map mask was performed on aforementioned brain structures. Pair-wise comparisons of parameters between temperatures, and baseline and hypercapnic periods (within-temperature) were made in the same animal. Normalized BOLD and $CMRO_2$ changes were derived by normalizing all values within a structure with respect to their 37°C baseline period value which served as the fixed baseline state. Paired t-tests (two-tailed) were performed with $P < 0.05$ taken to be significant.

**RESULTS & DISCUSSION:** Hypothermia reduced MABP, HR and RR, and did not significantly alter corrected blood gases. At 37 and 32°C, hypercapnia altered RR, $PaCO_2$, pH and $PaO_2$ and did not produce significant changes in other parameters. These physiologic changes are unlikely to have significantly contributed to observed fMRI signal changes as they fell well-within the autoregulatory ranges reported for hypothermic anesthetized rats [5]. **Figure 1** shows **(A)** representative anatomical images, and **(B)** BOLD and **(C)** CBF activation maps from a hypothermic rat (blue-purple bar = CBF -10-50%; red-yellow bar = BOLD +1-10%). Substantial negative basal CBF and positive BOLD pixels were detected throughout the brain at 32°C. **Figure 2** summarizes group-average whole-brain baseline and hypercapnia-evoked **(A)** CBF, **(B)** BOLD and **(C)** $CMRO_2$ values at 37 and 32°C. Consistent with a prior study [6], basal CBF was regionally heterogeneous at 37°C, being highest in the thalamus and lowest in the CPu. At 32°C, whole-brain basal CBF was reduced by 0.24 ± 0.05 ml/g/min (24 ± 5%), basal BOLD increased by 1.7 ± 0.2%, and $CMRO_2$ reduced by 29 ± 6%. This is consistent with the degree of hypothermia-induced metabolic depression and vasoconstrictive reduction of CBF found in other studies [7-9], and supports the validity of Davis' fMRI-based $CMRO_2$ model. Preliminary analysis suggests that these changes were similar across regions, in good agreement with another study [10] but not with Frietsch *et al.* [11] who found regional variations in basal CBF during hypothermia. Differences in results may be due to differences in methodology. Interestingly, hypercapnia-evoked CBF change was reduced (-50 ± 7%) at 32°C, suggesting that cerebrovascular reactivity to $CO_2$ was attenuated by hypothermia. This finding lends indirect credence to the $CMRO_2$ changes reported herein as a positive correlation between $CMRO_2$ and cerebrovascular reactivity to hypercapnia has been well established [12], with Fujishima *et al.* [13] reporting that a $CMRO_2$ reduction of 25% resulted in a 50% reduction in absolute CBF reactivity in anesthetized animals.

*Figure 1*

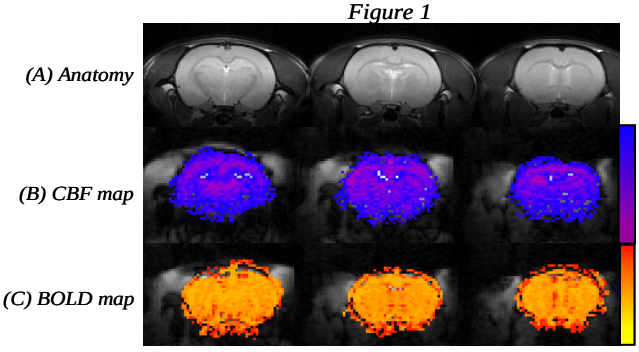
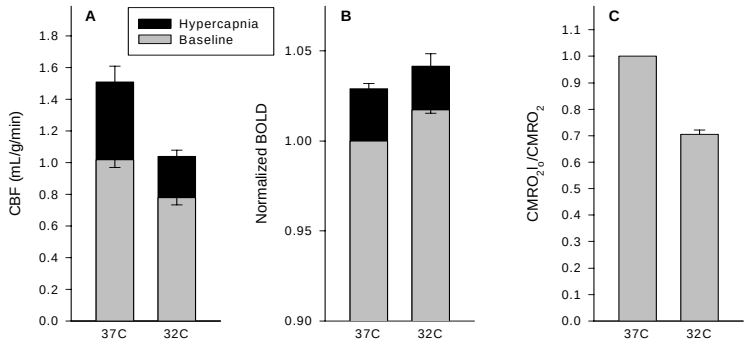



*Figure 2*




**CONCLUSION:** This preliminary study demonstrated the simultaneous measurement of CBF, BOLD and $CMRO_2$ during normothermia and hypothermia. Hypothermia reduced basal CBF and $CMRO_2$, while elevating basal BOLD. Hypercapnia-evoked CBF and BOLD changes were also depressed at 32°C. The magnitudes of hypothermia-induced CBF and $CMRO_2$ changes were in good agreement with published literature employing similar conditions. Together, these results support the validity of the $CMRO_2$ model derived by Davis *et al.*

**REFERENCES:** [1] Liu et al., MRM 2004;52:277. [2] Sicard et al., submitted. [3] Davis et al., PNAS 1998;95:1834. [4] Kelman & Nunn, J Appl Physiol 1966;21:1484. [5] Niwa et al., Brain Res 1998 ;789 :68. [6] Sicard et al., JCBFM 2003;23:472. [7] Hagerdal et al., J Neurochem 1975 ;24 :311. [8] Young et al., Crit Care Med 1989;5:821. [9] Rosomoff et al., Am J Physiol 1954 ;179 :85. [10] Okubo et al., Ped Intern 2001;43;496. [11] Frietsch et al., Anesthesiology 2000;92:754. [12] Donegan et al., Am J Physiol 1985;249:H421. [13] Fujishima et al., Stroke 1971;2:251.