Functional MRI of Graded Barbiturate Anesthesia: Dynamic BOLD, CBF and $CMRO_2$ Imaging

K. M. Sicard[1], N. Henninger[1], Q. Shen[1], T. Q. Duong[2]

[1]Center for Comparative NeuroImaging, University of Massachusetts Medical School, Worcester, MA, United States, [2]Yerkes Imaging Center, Emory University, Atlanta, GA, United States

INTRODUCTION: BOLD fMRI has been extensively applied to map brain activity. However, for BOLD imaging to reach its full potential of quantitatively representing cerebral function, it is necessary to correlate changes in the BOLD signal to changes in CBF and $CMRO_2$ [1]. To this end, Davis *et al.* created a fMRI-based $CMRO_2$ model which has the advantage of being straightforward, noninvasive and capable of being performed multiple times in the same experimental setting. If validated, Davis' model is likely to become a powerful tool for mapping neural metabolism.

The goals of this study were: i) to use fMRI to characterize the effects of graded pentobarbital anesthesia on whole-brain baseline and hypercapnia-evoked CBF, BOLD and $CMRO_2$ in spontaneously breathing rats and ii) to use these finings to support the validity of Davis' $CMRO_2$ model. Pentobarbital modulation of cerebral physiology was chosen because barbiturates have been shown (using validated methods) to have powerful dose-dependent effects on cerebral hemodynamics and metabolism [2] with which our data can be cross-validated.

METHODS: Five male SD rats (300-350 g) were studied. A femoral vein and artery were catheterized for administration of pentobarbital boluses (30mg/kg each), and for continuous monitoring of physiology (RR, HR and MABP) and periodic blood gas analysis, respectively. Rectal temperature was maintained at 37°C. Rats breathed spontaneously throughout under light (1.1%) isoflurane which served as the control period. Rats were exposed to the the following sequential conditions during which imaging was performed: i) hypercapnic challenges under isoflurane anesthesia consisting of a 2min baseline period followed by a 2min stimulation period of breathing 5% CO_2, ii) first pentobarbital challenge consisting of a 5 min baseline period followed by 15 min stimulation period of imaging under pentobarbital anesthesia, iii) post-first dose hypercapnic challenges, iv) second pentobarbital challenge and v) post-second dose hypercapnic challenges. A 15-min break was given between hypercapnic challenges. Blood gases were sampled prior to pentobarbital injections and after the first hypercapnic challenge of each epoch.

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.* [2]. ROI analysis without activation-map mask was performed on whole-brain. Pair-wise comparisons of parameters between baseline and stimulation periods of hypercapnic and pentobarbital challenges were made in the same animal. Normalized BOLD and $CMRO_2$ changes were derived by normalizing all values with respect to that obtained under baseline period of first pentobarbital challenge scan (i.e., values obtained under 1.1% isoflurane control) which served as the fixed baseline state. All reported values in text and graphs are mean ± SD. Statistical tests were performed using paired t-tests (two-tailed) with P value < 0.05 taken to be significant.

RESULTS & DISCUSSION: Both pentobarbital challenges reduced HR, RR and PaO_2 and pH, increased $PaCO_2$, and did not alter MABP or SaO_2. Hypercapnic challenges increased RR, $PaCO_2$ and PaO_2, decreased pH, and did not significantly alter MABP or HR. These physiologic changes are unlikely to have significantly contributed to observed fMRI signal changes as they fell well-within the autoregulatory ranges reported for anesthetized rats [3-4]. **Figure 1** shows **(A)** representative anatomical images, and **(B)** BOLD and **(C)** CBF activation maps from a rat after the first pentobarbital challenge (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 after both boluses. **Figure 2** shows representative whole-brain dynamic CBF, BOLD and $CMRO_2$ responses to the first and second pentobarbital challenges in a rat. Group-averaged data (not shown) demonstrate that BOLD decreased markedly immediately after injection then increased (2.8 ± 0.4%) above baseline value for the duration of the scan. CBF and $CMRO_2$ also dipped markedly just after injection; however, unlike BOLD, their steady-state values remained 24 ± 3% and 31 ± 5% below baseline, respectively. Note that CBF and $CMRO_2$ remained coupled after barbiturate anesthesia. Hypercapnia-evoked changes in absolute CBF and BOLD were significantly reduced after pentobarbital injection (CBF = 0.41 ± 0.02 vs. 0.35 ± 0.05 ml/g/min; BOLD = 4.1 ± 0.5% vs. 2.6 ± 0.8%), as expected based on the relationship between cerebral metabolism and cerebrovascular responsivity to CO_2 [5]. Similar results were observed for the second dose of pentobarbital. Together, these results are consistent with prior studies with similar experimental conditions [6-8] and lend support to the validity of the $CMRO_2$ model of Davis *et al.*

Figure 1

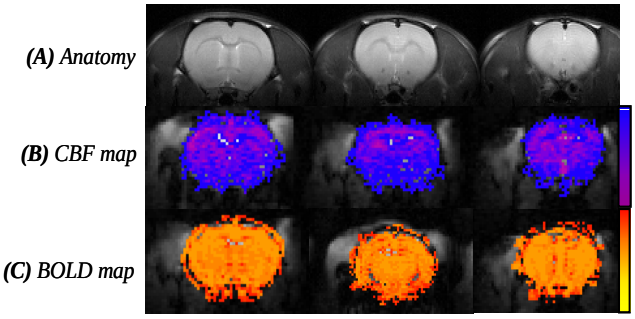
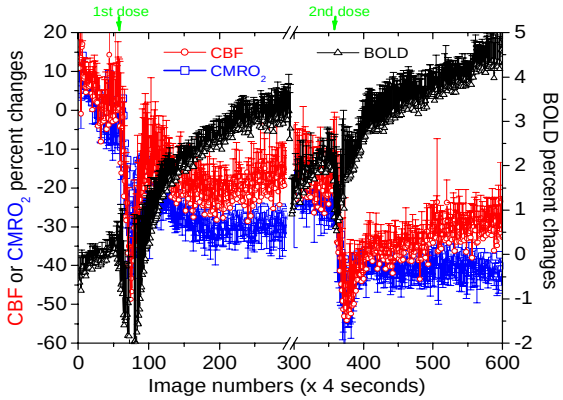


Figure 2



CONCLUSION: This study demonstrated that BOLD, CBF and $CMRO_2$ could be dynamically measured during graded barbiturate anesthesia. Pentobarbital induced an increase in basal BOLD, a reduction of basal CBF and $CMRO_2$, and a reduction of hypercapnia-evoked changes in CBF and BOLD. These findings demonstrate the utility of fMRI for measuring brain activity and lent support to the self-consistency of Davis' fMRI-based $CMRO_2$ model.

REFERENCES: [1] Hyder et al., JCBFM 2000;20:485. [2] Lafferty et al., Anesthesiology 1978 ;49 :159. [3] Lee et al., Anesth Analg 1994;79:58. [4] Hirshman et al., Br J Anaesth 1977 ;49 :957. [5] Donegan et al., Am J Physiol 1985;249:H421. [6] Kida et al., JCBFM 2000 ;20 :847. [7] Albrecht et al., Neuropharm 1985 ;24 :957. [8] Hendrich et al., MRM 2001 ;46 :202.