fMRI of Anesthetic-Specific Changes in CBF, BOLD and $CMRO_2$

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INTRODUCTION: Despite the frequent use of anesthesia in experimental MRI, an assessment of the effect of commonly used agents on CBF, BOLD and $CMRO_2$ is limited [1]. To make matters worse, comparative analyses of anesthetics are virtually nonexistent despite the fact that experimenters often use an inhalational agent (typically isoflurane or halothane) during surgery and setup then switch to an injectable agent (typically α-chloralose) during imaging [2-4]. Most inhalational and injectable agents have radically different effects on the brain, making it difficult to compare fMRI signal changes between labs or within studies that use multiple anesthetics. A study comparing the cerebral effects of commonly used anesthetics at typical doses within the *same* animal and setting would shed light on these issues.

This study utilized fMRI to investigate the effects of typically administered doses of isoflurane and α-chloralose on basal and hypercapnia-evoked CBF, BOLD and $CMRO_2$. Quantitative CBF and BOLD were simultaneously measured and $CMRO_2$ was calculated from these data using the biophysical BOLD model of Davis *et al.* [5]. Though this fMRI-based model of neural metabolism remains to be validated, it has been recently shown to be reliable during normal and perturbed physiological conditions [6-7]. Five structures were analyzed: whole-brain, cerebral cortex, thalamus, hippocampus and caudatoputamen (CPu).

METHODS: Six male SD rats (300-350 g) were studied. A femoral vein and artery were catheterized for α-chloralose administration, and continuous monitoring of physiology (RR, HR and MABP) and periodic blood gas analysis, respectively. Rectal temperature was continuously monitored and maintained at 37°C. Rats breathed spontaneously throughout and were initially anesthetized with 1.1% isoflurane during which hypercapnic challenges (twice-repeated) were performed. Afterwards, isoflurane was discontinued and α-chloralose injected (55mg/kg bolus then continuous 30mg/kg/h). After injection, a 30 min transition period was given prior to the start of the next set of hypercapnia challenges to allow ample time for recovery from isoflurane [8].

Imaging was performed during 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.* [5]. 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-anesthetic) 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: Relative to isoflurane, α-chloralose decreased MABP, HR, RR and pH, increased $PaCO_2$, but did not significantly alter PaO_2 or SaO_2 (data not shown). Under both anesthetics, hypercapnia 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 similarly anesthetized rats [9-11]. **Figure 1** shows **(A)** representative anatomical images, and **(B)** BOLD and **(C)** CBF activation maps from a rat under α-chloralose anesthesia (blue-purple bar = CBF -10-30%, BOLD -1-6%). Substantial negative basal CBF and BOLD pixels were detected throughout the brain. **Figure 2** summarizes group-average whole-brain baseline and hypercapnia-evoked **(A)** CBF, **(B)** BOLD and **(C)** $CMRO_2$ values during isoflurane (ISO) and α-chloralose (AC) anesthesia (regional data not shown). Whole-brain absolute CBF was substantially lower under α-chloralose (0.81 ± 0.08 ml/g/min) relative to isoflurane (1.02 ± 0.06 ml/g/min). This corresponds to a 26% elevation of CBF under isoflurane which is expected based on its well-known action as a cerebrovasodilator [11]. Whole-brain basal BOLD signal decreased by 4.2 ± 0.9% under α-chloralose, suggesting lower tissue oxygenation presumably due to the lower CBF. Whole-brain $CMRO_2$ was 12 ± 3% higher under α-chloralose relative to isoflurane, consistent with reports demonstrating the former agent to be least depressant of neural functions [2]. Lastly, global hypercapnia-evoked absolute CBF changes were slightly elevated under α-chloralose. These results are in agreement with prior findings of a positive correlation between $CMRO_2$ and cerebrovascular reactivity to CO_2 [12].

Figure 1

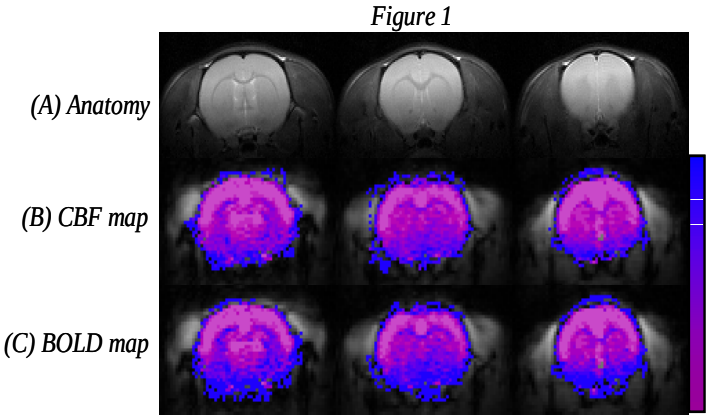
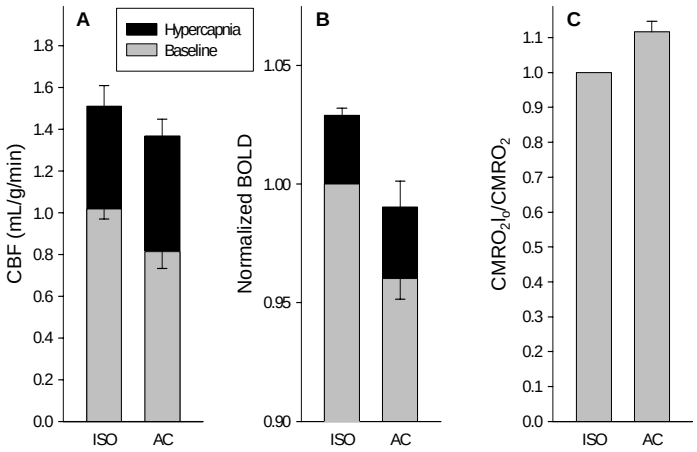


Figure 2



CONCLUSION: fMRI is capable of dynamically tracking regional changes in CBF, BOLD and $CMRO_2$ under various anesthetics in the same subject and setting. Relative to isoflurane, basal $CMRO_2$ was elevated and CBF and BOLD were significantly reduced during anesthesia with α-chloralose. Hypercapnia-evoked CBF and BOLD changes were elevated under α-chloralose. These results are consistent with the distinctly different actions of isoflurane and α-chloralose on cerebral hemodynamics and metabolism, and suggest caution when interpreting data obtained across labs or within studies that switch anesthetics.

REFERENCES: [1] Hyder et al., JCBFM 2000;20:485. [2] Nakao et al., PNAS 2001 ;98 :7593. [3] Ogawa et al., PNAS 2000 ;97 :11026. [4] Silva et al., JCBFM 2000 ;20 :201. [5] Davis et al., PNAS 1998;95:1834. [6] Liu et al., MRM 2004 ;52 :277. [7] Sicard et al., submitted. [8] JAVMA 2001 ;21B ;676. [9] Lee et al., Anesth Analg 1994;79:58. [10] Hirshman et al., Br J Anaesth 1977 ;49 :957. [11] Sicard et al., JCBFM 2003 ;23 :472. [12] Donegan et al., Am J Physiol 1985;249:H4.