Stimulus-evoked CMRO2 Changes in Non-human Primate (Baboon): Isoflurane versus Ketamine

H-Y. Wey[1,2], and T. Q. Duong[1,2]

[1]Research Imaging Institute, UT Health Science Center at San Antonio, San Antonio, TX, United States, [2]Radiology, UT Health Science Center at San Antonio, San Antonio, TX, United States

Introduction Brains of large non-human primates (NHPs) are highly evolved with extensive gyrations that are most similar to humans compared to other species, resulting in better recapitulation of many human diseases. While fMRI and metabolic imaging studies have been well published in humans and rodents, similar NHP studies remain sparse. Under normal and resting physiological conditions, the cerebral metabolic rate of oxygen ($CMRO_2$) is tightly coupled to cerebral blood flow (CBF) and cerebral metabolic rate of glucose ($CMR_{glucose}$) (1). However, the magnitude of stimulus-evoked $CMRO_2$ changes remains controversial. Stimulus-evoked $CMRO_2$ changes had been reported to be negligible, substantial to very large up to 200-400%.

In this study, we developed a robust NHP baboon model for MRI studies and investigated stimulus-evoked $CMRO_2$ changes. Visual and somatosenory stimulations were employed. BOLD and CBF were measured simultaneously using the pseudo-continuous arterial-spin-labeling technique on a Siemens 3T TIM-Trio. Davis' biophysical BOLD model was used to calculate $CMRO_2$ changes via hypercapnic calibration (3). The couplings among BOLD, CBF and $CMRO_2$ under the two anesthetics were also analyzed. Moreover, multiparametric fMRI comparisons were made under isoflurane versus ketamine anesthetics. Findings were compared with those reported in literatures on rodents and humans. This study set the stage for future multiparametric fMRI applications in stroke, seizure and other neurological disorders on large NHPs.

Methods Six fMRI sessions were performed on 3 normal baboons (10-20kg). Animals were first studied under 0.8~1.0% isoflurane followed by ketamine (6-8mg/kg/hr) drips in the same session with and without paralytics (vecuronium 0.1mg/kg). Animal was positioned supine in an animal holder and ventilated. End-tidal CO_2, O_2 saturation, heart rate, respiration rate, and rectal temperature were monitored and maintained within normal ranges. Neostigmine was used to reverse paralytic.

Somatosensory/motor stimulation via a pneumatic stimulator was applied to the animal's right hand. Achromatic light flickering at 10 Hz delivered via fiber optics was applied to both eyes. Stimulation paradigm used a block design of three 70s-on/off epochs. Hypercapnic challenge (5% CO_2) was used for $CMRO_2$ calculation.

MRI studies were performed on 3T Siemens TIM TRIO. Pseudo-continuous arterial spin labeling was used to acquire simultaneous BOLD and CBF changes during stimulation. Imaging parameters are TR/TE=3500/16 ms, matrix = 64x64, field of view (FOV) = 12.8x12.8 cm, with a resolution of 2x2x5, 10 slices. Typically, 2 or 3 repeated fMRI stimulation trials were measured in each session. Data were processed using FMRIB Software Library (FSL). Activation maps were threshold to $Z>2.3$ ($p<0.01$) and registered to a high-resolution anatomical template. BOLD and CBF percent changes were tabulated for region-of-interests the primary (S1) and secondary (S2) somatosensory cortex, motor cortex (M), and primary visual (V1) cortex.

Results **Figure 1** shows representative BOLD and CBF fMRI maps associated with simultaneous visual and somatosensory stimulation. The whole-brain hypercapnia-induced BOLD and CBF changes were, respectively, 0.5±0.2% and 41±22% under isoflurane and 0.5±0.3% and 28±13% under ketamine. The average M value for the whole brain was 1.6±0.6% and 2.2±0.8% (mean ± SD) under isoflurane and ketamine respectively. Note that the BOLD % changes and M values were smaller than typically reported in the literature because a short TE was used to achieve comparable BOLD and CBF SNR. With hypercapnic calibration, $CMRO_2$ calculation should not be affected.

Figure 2 plots ΔBOLD versus ΔCBF, and $\Delta CMRO_2$ versus ΔCBF for different brain regions (S1, S2, M, and V1) under isoflurane and ketamine. ΔCBF:ΔBOLD and ΔCBF:$\Delta CMRO_2$ ratios for all regions were, respectively, 122.6±57 and 2.5±1.4 under isoflurane, and 120±36 and 2.8±1.9 under ketamine.

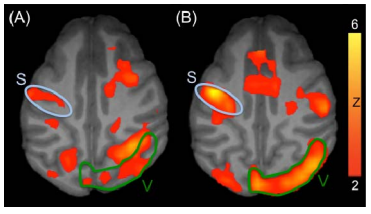

Figure 1. (A) BOLD and (B) CBF fMRI map during simultaneous visual and somatosensory stimulation under isoflurane anesthesia of a representative subject.

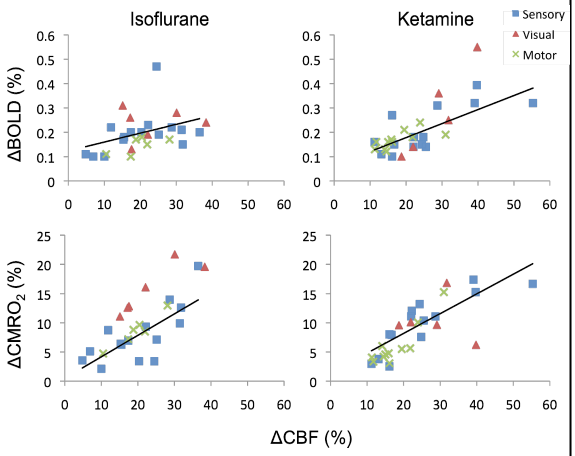

Figure 2. BOLD vs. CBF changes and CMRO2 vs. CBF changes were plotted for somatosensory, visual and motor cortex under isoflurane and ketamine anesthetics.

Discussion Robust and similar BOLD, CBF and $CMRO_2$ responses were detected in NHPs under both isoflurane and ketamine. $CMRO_2$ changes ranged from 2.2% to 21.7% (average = 9.8±5.2%) under isoflurane and 2.5% to 17.4% (average = 8.6±4.6%) under ketamine. CBF:$CMRO_2$ change ratios are consistent with those reported previously in human [2.8:1 (3), 2.0:1 (4), and 2.8:1 (5)] and anesthetized rodents [3.2:1 (6) and 2.2:1 (7)].

$CMRO_2$ imaging could have many applications. One application is in fMRI of disease states where neural-vascular coupling is perturbed, such as in stroke (2). In such cases, the BOLD response may no longer scale with neural activity and, thus, becomes difficult to interpret. $CMRO_2$ changes could be a better indicator of the underlying changes in brain functions associated with stroke. Another application of $CMRO_2$ imaging is in pharmacological fMRI. Following drug administration, the baseline physiologic states of the brain are likely to be different regionally or globally due to drug-induced changes in respiration rates, blood pressure and/or volume, which markedly affect the fMRI signals. $CMRO_2$ imaging could provide the means to differentiate non-neural from neural drug effects in pharmacological fMRI.

In conclusion, this study establishes a NHP model for multi-parametric fMRI studies on a 3T human scanner. This approach can be used to study neural development, aging, epilepsy and stroke, among others.

References: 1. Siesjo, Brain Energy Metabolism (1978). 2. Shen et al. J Cereb Blood Flow Metab (2005). 3. Davis et al. PNAS 95, 1834 (1998). 4. Hoge et al. MRM (1999). 5. Kim et al, MRM (1999). 6. Mandeville et al. MRM (1999). 7. Liu et al. MRM (2004).