Quantitative CBF MRI of Anesthetized Baboon using Pseudo-continuous ASL

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Introduction Cerebral blood flow (CBF) is an important physiological parameter. Under normal physiological conditions, cerebral blood flow (CBF) is tightly regulated to meet the brain's metabolic demand and is intricately coupled to changes in neural activities (1). Many neurological diseases often exhibit perturbations to basal CBF and its responses to physiologic and task-induced stimulations in their early stages. CBF and its responses to stimulations could thus serve as non-invasive early imaging biomarkers for these diseases. Non-human primates (NHPs) are important animal models because of their overall similarities to humans compared to the more commonly used rodent models, resulting in better recapitulation of many human diseases. Although arterial spin labeling (ASL) techniques to image CBF have been widely applied in humans and rodents, similar studies on primates remain sparse (2,3). The goal of this study was to implement pseudo-continuous ASL (pCASL) (4) to improve CBF sensitivity on a Siemens 3T TIM-Trio clinical scanner, and applied to image CBF in anesthetized baboons, which offer comparatively larger brain size and are widely utilized in stroke, genetic and obesity studies. We further analyzed CBF of gray matter (GM) and white matter (WM) under two commonly used anesthetics: isoflurane and ketamine. Our long term goals are to apply CBF MRI in stroke and epilepsy studies.

Methods Six studies (N = 6) were performed on three normal female baboons (14 ± 4, 10-20kg). Each study involved typically two repeated measurements for each condition. Studies were done first under 0.7~1.0% isoflurane, followed by 6-8mg/kg/hr ketamine drips (isoflurane discontinued) in the same session under mechanical ventilation with and without paralytics (vecuronium 0.1mg/kg). End-tidal CO_2, heart rate, respiration rate, and rectal temperature were monitored continuously and maintained within normal ranges. At the end of the MRI experiments, neostigmine (0.5-2 mg) was administered to reverse paralytic effects.

CBF images were acquired using single-shot gradient-echo EPI with TR/TE = 3500/16 ms, labeling duration = 2.1 s, 10 imaging slices, matrix = 64×64, FOV = 12.8×12.8 cm (2x2x5mm resolution), and labeling gradient of 0.6 G/cm. Paired images were acquired alternating between labeled and non-labeled images. Each basal CBF measurement took 3.5 mins (N = 6). Each hypercapnic challenge included 2 mins baseline and 2 mins 5% CO_2 inhalation (N = 6). Each post-labeling delay (PLD) measurement took 2 mins. PLD were evaluated from 300-2200 ms under isoflurane only (N = 4 studies). Typical T1-weighted MRI was performed on the same slices. WM and GM segmentation was performed based on T1-weighted MRI.

Results and Discussion Under isoflurane and ketamine, respectively, the heart rates were 101 ± 42 and 119 ± 19 bpm; respiration rates were 11.7 ± 1.0 and 11.4 ± 0.9 bpm; tidal volumes were 169 ± 38 and 169 ± 38 ml; $ETCO_2$ values were 36 ± 5 and 36 ± 4 mmHg; and rectal temperatures were 99 ± 2 and 99 ± 2 ^oF. None of the measured parameter was statistically different between the two anesthetics.

Figure 1 shows the ΔS/M0 as a function of PLD for vessel, GM and WM ROI's. The arterial transit times (ATT) for vessel, GM and WM ROI's were 500, 800, and 1100 ms, respectively. These PLD values are consistent with those reported previously of 800 ms (GM+WM) (*2*), 742 ms in GM and 985 ms in WM (*5*) in anesthetized rhesus and are shorter than those reported in humans GM (1000 ms) (7).

Figure 2 shows the basal CBF images under isoflurane and ketamine at 2x2x5 mm resolution obtained in 3.5 mins. Basal CBF images showed excellent contrast between GM and WM. The group-averaged basal CBF under GM and WM and their ratios for the two anesthetics are summarized in **Table 1**. The GM:WM CBF ratio of 1.8 (isoflurane) and 1.9 (ketamine) are within the ranges (1.7-3.0) reported in the literatures. Quantitative CBF in NHP is sparse and to our knowledge none has been reported in baboon. In isoflurane-anesthetized macaques, GM and WM CBF has been reported to be of 104±3 and 45±6 ml/100g/min, respectively (2), and 98±38 (GM) and 43±20 (WM) ml/100g/min of remifentanil-anesthetized macaques. A PET study reported GM CBF of 56-68 ml/100g/min and WM CBF of 34 ml/100g/min in ketamine anesthetized rhesus (6). CBF values in awake human are 56 ± 5 (GM) and 33 ± 3 ml/100g/min (7).

Hypercapnia induced large and heterogeneous CBF change over the entire brain (data not shown). Group-averaged hypercapnia-induced CBF changes were 31±15% (GM) and 24±6 (WM) under isoflurance, and 20±8% (GM) and 18±6% (WM) under ketamine. Hypercapnia-induced CBF increases in isoflurane-anesthetized rhesus have been reported to be 59±10% (GM) and 37±4% (WM) (2).

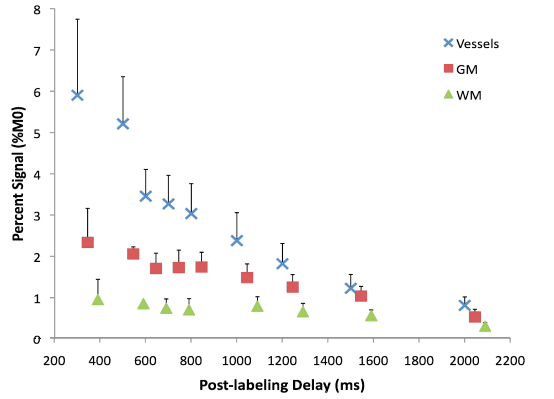

Figure 1. Percent signal (%M0) vs. PLD (ms). Mean ± S.E.M (N = 4 animals).

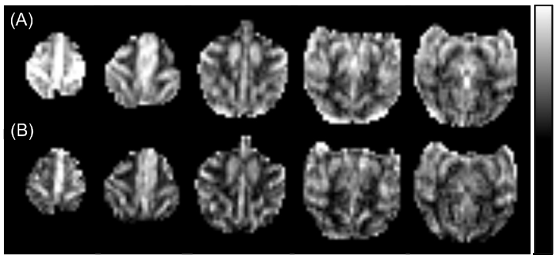

Figure 2. Baseline CBF (N = 1) under (A) isoflurane and (B) ketamine from a representative animal (scale bar = 0~120 mL/100g/min).

Table 1. Quantitative CBF of whole brain, grey matter (GM), and white matter (WM) were summarized with mean ± SD (N = 6) for the two anesthetics.

	Whole Brain	GM	WM	GM/WM ratio
Isoflurane	67 ± 9	81 ± 10	45 ± 9	1.8 ± 0.3
Ketamine	59 ± 17	73 ± 18	38 ± 10	1.9 ± 0.4

Conclusion We implemented and optimized a pseudo-continuous arterial spin labeling technique for NHP studies on a Siemens 3T TIM TRIO. This study established a robust non-human primate model for perfusion imaging studies. Basal CBF and hypercapnia-induced CBF responses were studied under two commonly used anesthetics isoflurane and ketamine. Future studies will improve the spatial resolution and investigate stimulus-evoked neurovascular couplings in non-human primates in diseased states.

References 1. Roy & Sherrington, J Physiol 1, 85 (1890). 2. Zhang et al., Neuroimage 34, 1074 (2007). 3. Zappe et al., MRI 25, 775 (Jul, 2007). 4. Wu et al., MRM 58, 1020 (2007). 5. Zappe, et al., JCBFM 28, 640 (2008). 6. Enlund, et al, Acta Anaesthesiol Scand 41, 1002 (1997). 7. Talagala et al., MRM 52, 131 (2004). This work is funded by EIA 0940104N, R21 NS 065431-01, and CTSA imaging supplement (UL1RR025767)