Dosage-dependent effects of isoflurane on cerebral blood flow in rhesus monkeys

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Introduction: Isoflurane is commonly used as a volatile anesthetic in animal studies [1]. The cerebral blood flow (CBF) effects of isoflurane have been investigated in several studies on human and small animals with PET, laser Doppler flowmetry, or hydrogen clearance technique [1-7]. Non-human primates (NHP) have most of human similarity and widely used as various disease models for pre-clinic study and drug development [8]. However, the dosage effect of isoflurane on regional CBF (rCBF) in NHP brains remains poorly understood. The continuous arterial-spin-labeling (CASL) technique provides a unique mean to measure the CBF of monkey whole brain at high resolution [9]. In this study, the dosage effects of isoflurane on CBF in monkeys were investigated with the CASL technique.

Methods: Adult rhesus monkeys (n=4, 6-10 years old) were studied. The animals were given three different isoflurane dosages (0.6, 0.8 and 1.2 MAC). 15 minute transition time was applied during the dosage changes. O2 saturation, blood pressure, heart rate, respiration rate, and PaCO2, etc, were monitored continuously during each scan session. Body temperature was kept at ~37℃. Isofluence dosage was measured continuously with an anesthesia monitor (GE Datex-ohmeda Cardiocap/5). CBF data were acquired on a setting reported before except a phase-array knee coil was used for imaging [9]. The MRI parameters were: TR/TE = 4000/25 ms, FOV= 96 mm × 96 mm, data matrix =64 × 64, 16 slices with slice thickness = 1.5 mm, Labeling duration= 2 s. 70 pairs of control and labeling images were acquired and repeated 3 times at each dosage. The caudate, frontal cortex, anterior cingulated cortex (ACC), thalamus, cerebellum and the motor cortex (Fig. 1) were selected for ROI analysis. Analysis of variance (ANOVA) for repeated measures was performed to check the differences across time points; SPSS 17.0 was used for statistical analysis. P-values less than 0.05 were considered statistically significant.

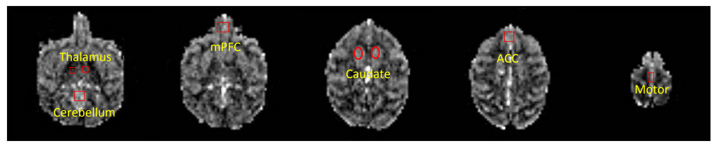

Fig 1, Monkey cerebral blood flow map acquired with CASL. ROIs were illustrated.

Results: The dosage effects of isoflurane on rCBF were illustrated in Fig 2 and Fig 3. In the cingulate cortex, CBF was observed reduced significantly at the dosage from 0.8 to 1.2 MAC (Fig 2), but no significant changes were observed from 0.6 to 0.8 MAC. CBF in thalamus and cerebellum was found progressively increasing from 0.6 to 1.2 MAC. The significant correlation between MAC and CBF indicated the strong dosage-dependence of CBF exists in these two ROIs (Fig 3). No significant CBF changes were observed in the caudate, frontal cortex, ACC and motor cortex at dosages from 0.6 to 1.2 MAC.

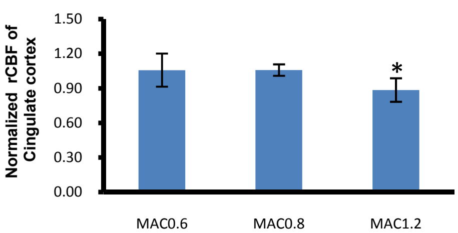

Fig 2. rCBF changes in cingulated cortex (mean±SD).
* p<0.05 vs MAC 0.8.

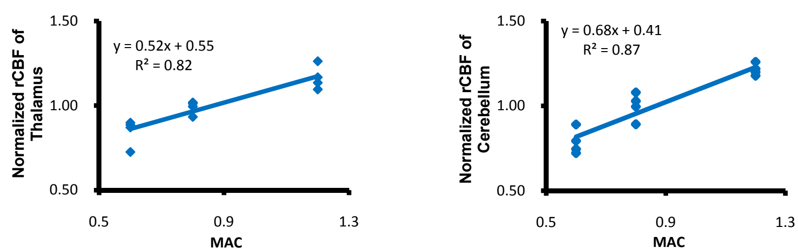

Fig 3. The correlation of isoflurane dosage and rCBF change in Thalamus (left) and Cerebellum (right).

Discussion and conclusion: Human study demonstrated that isoflurane redistributed CBF differently at different dosage (0 vs 0.2, 0.2 vs 0.4, 0.4 vs 1.0 MAC) [4], and CBF was found increased in the insula and decreased in the thalamus and lingual gyrus (0.4 vs 1.0 MAC). Also, it was found CBF was decreased in the cortical areas including frontal, occipital, and parietal cortex in human brain [2-7], while our findings indicated no significant changes were observed in these brain regions in monkeys. In the isofluane dosages of 0.6 to 1.2 MAC, which are usually used in monkey anesthesia, the CBF in the thalamus and cerebellum was found increasing with the isoflurane dosage, while the CBF in the cingulated cortex was decreasing. The results demonstrated that the CBF in the caudate, frontal cortex, ACC, and motor cortex was not affected significantly. Most likely the species difference and the isofluane dosage difference in the studies of human and monkey may be responsible for inconsistency of the dosage effects.

In conclusion, the CBF of monkeys was found redistributed during the isofluane dosage change from 0.6 MAC to 1.2 MAC. The CBF response on isoflurane dosage in different regions may result in non-neglectable effect on cerebral-vascular relative and functional studies.

Reference: [1] Ori C et al, Anesthesiology (1986); [2] Holzer, A. et al, European Journal of Anaesthesiology (2000); [3] Kimme, P., et al, Acta Anaesthesiol Scand (2007); [4] Schlunzen, L., et al, Acta Anaesthesiol Scand (2007); [5] Reinstrup, P., Anesthesiology (1995); [6] Chi, O. Z., Anesth Analg (2010); [7] Lorenz et al, Journal of Neurosurgical Anesthesiology (2001); [8] Dudkin et al, NBP (2006); [9] Zhang, X., Neuroimage (2007)