Effect of deep isoflurane anesthesia on cerebral blood flow autoregulation in non-human primates

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Target audience: MRI scientists, preclinical human and animal researchers, physiologist and anesthesiologist

Introduction: Isoflurane is an inhalational anesthetic and generally utilized in humans and animals. Previous human and animal studies have demonstrated that the cerebral blood flow (CBF) autoregulation can be disrupted and CBF of subcortical structures is more susceptible than that of cortical structures under high dose isoflurane [1, 2]. However, the regional specification of the high dose isoflurane on CBF remains poorly understood in humans and animals. Prior baboon study with SPECT has shown that global CBF increases with isoflurane dosage and CBF auto-regulation might be impaired under high isoflurane concentration [2]. Non-human primates (NHP) resemble most aspects of humans and are widely used in preclinical studies and various neuroscience researches [3]. We hypothesized that the effect of deep isoflurane anesthesia on CBF autoregulation would be dose-dependent and regionally specific. In the present study, the effect of deep isoflurane anesthesia on regional CBF of rhesus monkeys was evaluated with the pseudo-continuous ASL (pCASL) technique [4].

Methods: Adult female rhesus monkeys (n=4, 7-11 years old) were employed. The animals were given three different isoflurane doses (1.0% (0.8 MAC), 1.5% (1.2 MAC) and 2.0% (1.6 MAC)) mixed with ambient air. 15-minute transition time was applied during the dose changes. O_2 saturation, blood pressure, heart rate, respiration rate, body temperature and PaCO2, etc, were monitored continuously in each scan session. All the physiological parameters were recorded and maintained in normal ranges. Isoflurane dosage was measured continuously with an anesthesia monitor (GE Datex-ohmeda Cardiocap/5). CBF data were acquired on a Siemens 3T scanner with a Tx/Rx volume coil. The MRI parameters were: TR/TE = 4000/25 ms, FOV= 96 mm × 96 mm, data matrix = 64 × 64, 16 slice with slice thickness = 1.5 mm, post-labeling delay = 0.8 s, Labeling duration= 2.0 s. 80 pairs of control and labeling images were acquired and repeated 3 times at each dosage. The caudate, medial prefrontal cortex (mPFC), anterior cingulated cortex (ACC), thalamus, cerebellum, the motor cortex (Fig. 1), global, cortical and subcortical regions were also selected for data analysis. Analysis of variance (ANOVA) for repeated measures was performed for statistical analysis.

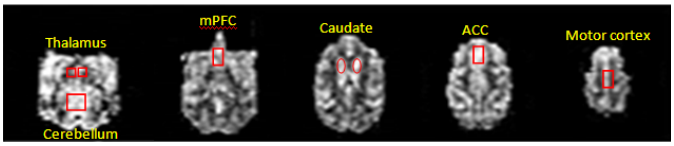

Fig 1. Monkey CBF maps acquired with the pseudo continuous ASL (pCASL) technique at 3T. ROIs for data analysis are illustrated.

Results: The dose-dependent effect of isoflurane on regional CBF was illustrated in Fig 2. CBF was increased significantly at 2.0 % isoflurane in the selected ROIs except for mPFC (Fig 2). CBF in global, cortical and subcortical regions remained progressively increasing with isoflurane concentrations (not shown). CBF in the selected ROIs except for mPFC was progressively increasing with isoflurane doses changed from 1.0 % to 2.0 % (Fig 3). Decreased mean arterial pressure (MAP) and increased heart rate were observed when the dosage increased, but no significant change in either MAP or heart rate was observed.

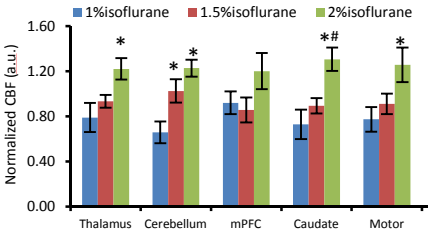

Fig 2. CBF changes in selected ROI, *, # p<0.05 vs 1% or 1.5% isoflurane.

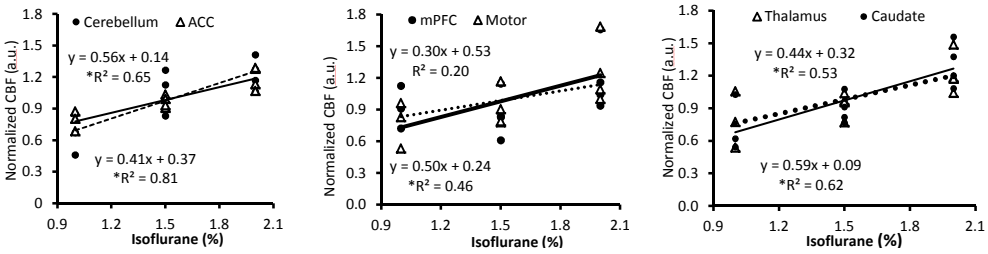

Fig 3. The correlation between isoflurane dosages and regional CBF changes in selected ROIs. *: p<0.05

Discussion and conclusion: Isoflurane results in CBF increase and impairs CBF autoregulation in a dose-related manner [6]. Early human study demonstrated that isoflurane resulted in significant CBF increase at 1.6 MAC [5], and the influence is more evident in subcortical regions [7, 8], in which CBF autoregulation is impaired at ~1 % or higher isoflurane. The present study demonstrated significant and large CBF increase in thalamus, cerebellum, caudate, motor cortex, indicating CBF autoregulation in these regions was impaired at 2% isoflurane. In contrast, the autoregulation was still preserved in mPFC.

In conclusion, the results suggest that the CBF autoregulation is impaired in some cortical structures and all subcortical structures of monkeys maintained under 2% isoflurane. The effect of deep isoflurane anesthesia on CBF should be taken into consideration in related function and physiology studies of non-human primate models.

Reference: [1] K.S. Olsen, L et al, Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man, Br J Anaesth (1994); [2] H. Van Aken, W. et al, Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon, Anesth Analg (1986); [3] Dudkin et al, Disorders of learning and memory processes in a monkey model of Alzheimer's disease: the role of the associative area of the cerebral cortex, NBP (2006); [4] Wu et al, Effects of CBV, CBF, and blood-brain barrier permeability on accuracy of PASL and VASO measurement, MRM (2010); [5] K.E. Murphy FL Jr et al, The effects of enflurane, isoflurane and halothane on cerebral blood flow and metablism in man, Abstracts of annual meeting of the American Society of Anesthesiologists (1974); [6] Strebel S et al., Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia, Anesthesiology (1995); [7] P. Reinstrup et al, Regional cerebral blood flow (SPECT) during anaesthesia with isoflurane and nitrous oxide in humans, Br J Anaesth (1997); [8] P. Reinstrup et al, Distribution of cerebral blood flow during anesthesia with isoflurane or halothane in humans, Anesthesiology (1995);