Effect of ketamine and isoflurane anesthesia on regional cerebral blood flow of macaque monkeys

Chun-Xia Li[1], Doty Kempf[1], Leonard Howell[1], and Xiaodong Zhang[1]
[1]*Yerkes Imaging Center, Yerkes National Primate Research Center, Emory University, Atlanta, GA, United States*

Target audience: MRI scientists, neuroscience researchers, physiologist and anesthesiologist

Introduction: Ketamine and isoflurane are widely used for maintaining general anesthesia in human and animal studies [1][2]. Both show dose-dependent effects on cerebral blood flow (CBF) [2, 3]. However, it is not clear how they differently affect CBF. In the present study, adult rhesus monkeys were used to examine the effect of ketamine and isoflurane anesthesia on CBF using the continuous arterial spin-labeling (CASL) perfusion MRI [2].

Methods: Adult female rhesus monkeys (n=4, 8-12 years old, 8.8-9.6 kg) were employed. Animals were knocked down with ketamine via intramuscular injection (im, 10-11 mg/kg) then maintained with intravenous infusion (~1.6 mg/kg) and intramuscular injection (2.6-2.8 mg/kg, supplement as needed) every ~15 min to maintain anesthesia. Physiological parameters including O_2 saturation, blood pressure, heart rate, respiration rate, body temperature and PaCO2, were monitored continuously. CBF data were acquired ~15 minutes after animals were moved into the scanner (Siemens 3T Trio with a Tx/Rx volume coil). The perfusion MRI parameters were: TR/TE = 4000ms/25ms, 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 = 2.0s. 80 pairs of control and labeling images were acquired and repeated 6 times [4]. The anesthetic was switched to ~1% isoflurane (~0.8 MAC) mixed with 30 % oxygen and the perfusion measurement was repeated at least 30 minutes later. Isoflurane dosage was measured continuously with an anesthesia monitor (GE Datex-ohmeda Cardiocap/5). Data analyses were performed using home-built Matlab scripts (MathWorks, MA) and Stimulate software (htktp://www.cmrr.umn.edu/stimulate) [2].

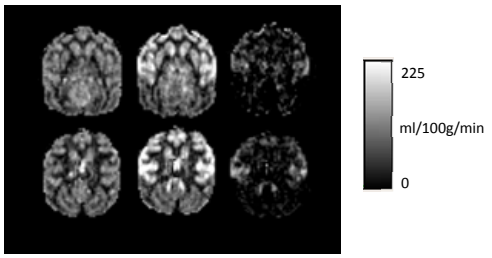

Figure 1. Representative CBF maps of an adult monkey brain under isoflurane (left column), ketamine (middle column) and their subtraction (right column). CBF was acquired with the pseudo continuous ASL (pCASL) technique at 3T.

Results: The CBF maps of ketamine and isoflurane are shown in Fig.1. The bilateral thalamus, insular, putamen, caudate, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), cerebellum, prefrontal cortex (PFC) and middle temporal cortex (MT) were selected as regions of interest (ROIs) for data analysis. Paired t test was performed for statistical analysis. The CBF changes in monkeys under maintenance doses of ketamine and isoflurane are illustrated in Fig 2. Ketamine resulted in higher CBF shown in grey matter, especially in MT, PFC and insular ($p<0.01$), in ACC, PCC, putamen and thalamus ($p<0.05$) (Fig 2). Also, significantly increased mean arterial pressure (MAP) was observed during ketamine anesthesia compared to isoflurane (Table 1). Heart rate showed no obvious difference (Table 1).

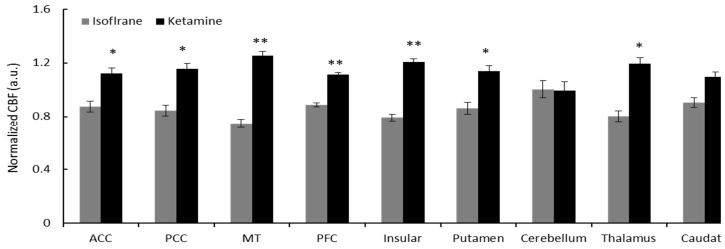

Figure 2. CBF changes in selected ROI after using ketamine or 1% isoflurane in adult monkeys, n=4, error bar is indicated standard deviation error, **, p<0.01; * p<0.05; h, hour.

Table 1. Blood pressure and heart rate changes in monkeys maintained with ketamine and isoflurane. Data are reported as means ± SEM,*p<0.05 compared to isoflurane, MAP: mean arterial pressure. h: hour

	MAP (mmHg)	Heart rate (beat/min)
Ketamine	91±5*	145±6
Isoflurane	73±8	153±11

Discussion and conclusion: Prior studies have demonstrated that ketamine and isoflurane induce a global CBF increase [2, 3]. However, isoflurane has vasodilatory effects and shows dose-related effects on CBF in subcortical areas [2]. In contrast, ketamine increased rCBF mainly in frontal cortex, ACC, thalamus, putamen, insular [3]. The present comparison demonstrates ketamine and isoflurane have very different effects on CBF in grey matter especially in the cortex such as PFC, MT, PCC and ACC and the subcortex including thalamus, putamen of adult monkeys, suggesting ketamine has dominant effects on CBF in the MT, ACC, PCC, insular and frontal cortex. In particular, isoflurane or ketamine is popularly used to anesthetize animals for assessing the functional or therapeutic responses. Their different effects on CBF indicate appropriate anesthetic agents should be applied to minimize the adverse anesthesia interference to experimental results.

In conclusion, the results revealed the different effects of ketamine and isoflurane on CBF in monkeys under maintenance doses, suggesting the use of ketamine or isoflurane might interfere with the experimental outcome in neurovascular diseases and brain function studies.

Reference: [1] White, P.F., et al. Anesthesiology (1982). [2] Langsjo, J.W., et al. Anesthesiology (2003). [3] Li, C.X., et al., Neurosci Lett (2013). [4] Li, C.X., et al., MRI (2014).