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Effect of high dose isoflurane on cerebral blood flow in macaque monkeys

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ABSTRACT

The effect of high dose isoflurane on cerebral blood flow (CBF) was investigated in adult macaque monkeys receiving 1% to 2% isoflurane with the pseudo continuous arterial-spin-labeling (pCASL) MRI technique. High concentration (2%) of isoflurane resulted in significant increase in the mean CBF of the global, cortical, subcortical regions and the regional CBF in all subcortical structures and most cortical structures (such as motor cortex, anterior cingulate cortex, but not media prefrontal cortex). In addition, the changes of regional CBF in the affected regions correlated linearly with increasing isoflurane concentrations. The study demonstrates region-specific CBF abnormal increase in adult macaque monkeys under high dose (2%) isoflurane and suggests that the brain functionality in the corresponding structures may be affected and need to be taken consideration in either human or non-human primate neuroimaging studies.

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1. Introduction

Isoflurane is an inhalational anesthetic and generally utilized in humans and animals [1,2]. This popular anesthetic agent is found to interfere with normal physiology of subjects, causing cerebral vasodilatation [3], cerebral metabolism decrease [4,5], functional activity reduction [6], mean arterial pressure (MAP) decline and cerebral blood flow (CBF) increase [7–10], and CBF autoregulation disruption [5,11,12]. In general preclinical and clinical studies, the maintenance dose (~1%) of isoflurane is normally applied for sedation purpose [1,2]. High dose isoflurane (2% or above) is usually used for rapid induction or surgery [13]. The dose-dependent effects of isoflurane on CBF, autoregulation, brain metabolites, brain functional performance, et al, are observed in various animal and human studies. It has been demonstrated abnormal CBF increase occurred under mild or high dose isoflurane in non-human primates, and humans [5,9–11,14]. In addition, high isoflurane doses could abolish the coupling between CBF and cerebral metabolites and impair CBF autoregulation in primate and human [5,11,12].

Previous CBF measurements in human are mainly conducted with the Xenon-133 SPECT technique [5,15–17]. Because of the limited spatial resolution of the Xenon-133 technique, the dosage effect of isoflurane on regional CBF of different brain structures is poorly understood. Due to the tight coupling between local CBF and brain neural activity, the functionality of affected brain structures can be misinterpreted due to the region-specific dose-dependence effect of isoflurane. The arterial-spin-labeling (ASL) MRI technique is a non-invasive approach to measure CBF quantitatively by using intrinsic blood water as a freely diffusible tracer [18]. Continuous ASL (CASL) technique with separate labeling coil is an optimal setting for CBF measurements in preclinical research scanners and has been implemented successfully in clinic scanners [19,20]. However, the CASL technique with separate labeling coil is not accessible in most clinical scanners as it requires additional RF hardware. In contrast, the pseudo-continuous arterial-spin-labeling (pCASL) MRI technique allows measuring CBF with a standard clinical setting without requirement of any additional hardware [21–23]. Accordingly, the pCASL technique provides a robust means to measure CBF in a conventional clinical scanner. Non-human primates (NHPs) resemble most aspects of humans in brain anatomical and vascular structures and functionality and are widely used in cerebral neural system (CNS) related disorder studies [24,25]. In the present study, the region-specific effect of high dose isoflurane on CBF of rhesus monkeys was examined with the pCASL technique on a clinical 3T scanner.

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2. Methods

2.1. Animal preparation

Adult female rhesus monkeys (n = 4, 7–11 years old) were employed in this study. The animals were initially anesthetized with ketamine (5–10 mg/kg, IM), then orally intubated. An IV catheter was placed for delivering lactated ringers solution (3.5–10 ml/kg/hr). The anesthetized and spontaneously breathing animals were immobilized with a custom-made head holder and immobilized in the "supine" position during MRI scanning. The physiological parameters such as Et-CO_2, inhaled CO_2, and respiration rate were monitored with an anesthesia machine (GE Datex-ohmeda Cardiocap/5, GE Healthcare.), O_2 saturation and heart rate with a Nonin pulse oximeter (Nonin Medical, MN, USA), the systolic blood pressure (SBP) and diastolic blood pressure (DBP) (recorded every 5 minutes) with a SurgiVet non-invasive blood pressure monitor (Smiths Medical ASD Inc., Ohio, USA), and body temperature with Digi-Sense Temperature controller (Cole-Parmer, IL, USA). Those parameters were maintained in the normal ranges [9]. The animals were given three different isoflurane doses with random order: 1.0%, 1.5 % and 2.0% (or 0.8. 1.2 and 1.6 minimum alveolar concentration (MAC) (end-tidal), respectively), mixed with ambient air. Fifteen-minute or more transition time was applied during each dose change. All procedures followed the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of Emory University in accordance with the NIH Guide for Care and Use of Laboratory Animals.

2.2. MRI examination

MRI was performed on a Siemens 3T Trio whole body scanner (Siemens Medical Solutions, Inc., PA, USA) with an 8-channel transceiver array knee coil (Invivo, Inc., FL, USA). Animal heads were placed in the supine position with the AC-PC line of animals kept almost perpendicular to the B0 field in each scan. The single-shot, gradient-echo planar imaging (EPI) was applied for CBF measurement with the pCASL technique [21]. The MRI parameters were: TR/TE = 4000 ms/25 ms, FOV = 96 mm × 96 mm, data matrix = 64 × 64, 16 slices with slice thickness = 1.5 mm, labeling-offset = 55 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. Corresponding T_2 weighted images were acquired with the same slice positions by using fast spin-echo sequences with TR/TE = 5900 ms/125 ms, FOV = 96 mm × 96 mm, matrix = 128 × 128, slice thickness =1.5 mm, 16 slices, 2 averages. The CBF measurement was started at least 30 minutes later after the animal was moved into the scanner.

2.3. Data analysis

The procedure for CBF calculation and data analyses was basically as same as reported previously [9]. However, the labeling efficiency coefficient was modified accordingly to adapt to the current pCASL technique [22]. Motor cortex, medial frontal cortex (mPFC), anterior cingulated cortex (ACC), caudate, thalamus, cerebellum, and global, cortical, sub-cortical regions were identified on the raw EPI images and corresponding T2-weighted structural images by referring to a macaque monkey atlas [26] and selected for region of interest (ROI) analysis (Fig. 1). For each animal, CBF of each ROI was normalized to its mean CBF value of the three-dose levels to reduce the inter-subject variation. Meanwhile, MAP was calculated based upon a standard formular (MAP = (SBP + 2*DBP)/3). The MAP data at each dose had at least two records and were averaged. The mean MAP readings of each animal at different isoflurane doses were normalized to reduce the inter-subject variation. Repeated ANOVA was performed to analyze the CBF differences statistically across the different doses. Spearmen correlation analysis was used to study the dose-dependence effects on CBF. SPSS 20.0 was used for statistical analysis. P-values less than 0.05 were considered statistically significant.

3. Results

The dose-dependent effect of isoflurane on regional CBF is illustrated in Figs. 2 and 3. Mean CBF in the global, cortical and subcortical regions increased significantly when the isoflurane concentration changed from 1% to 2% and correlated linearly (R^2 = ~0.5) with applied isoflurane doses (Figs. 2 and 4). Regional CBF in thalamus, cerebellum, caudate, motor cortex, and ACC increased 55%, 86%, 79%, 62%, 52%, respectively (Fig. 3), and correlated linearly (R^2 = 0.5–0.8) with the isoflurane doses (1.0%, 1.5%, 2.0%) (Figs. 3 and 5). The MAP (mean ± SD) at 1%, 1.5%, and 2% isoflurane was 67.0 ± 13.4 mm Hg, 52.3 ± 10.4 mm Hg, and 43.3 ± 6.8 mm Hg,

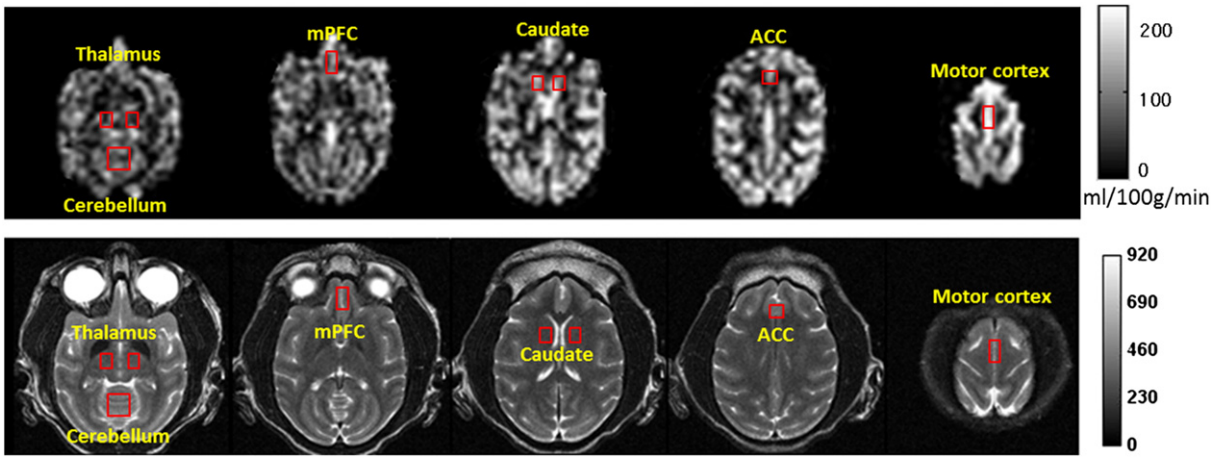

Fig. 1. CBF maps of an adult macaque monkey acquired with the pseudo continuous ASL (pCASL) technique at 3 T. Regions of interest (ROIs) for data analysis are illustrated on the CBF maps (top) and corresponding T2-weighted structural images (bottom). mPFC: medial frontal cortex; ACC: anterior cingulated cortex.

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