In-vivo 19F Imaging of Sevoflurane in the Human Brain at Clinical-Relevant Concentrations

Maolin Qiu[1], Ramachandran Ramani[2], and R. Todd Constable[1]

[1]*Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, United States,* [2]*Anesthesiology, Yale University School of Medicine, New Haven, CT, United States*

Purpose Direct Fluorine-19 (^{19}F) imaging of anesthesia induced by Sevoflurane ($C_4H_3F_7O$) will provide important information about the pharmacokinetics of inhalational agents such as drug delivery, cortical drug distribution, and molecular drug-brain interaction. Together with the pharmacology studies[1,2], it may provide the whole picture of the neuronal mechanisms of general anesthesia. However, the extremely low cortical concentrations of Sevoflurane at clinically-relevant levels make in-vivo ^{19}F imaging of Sevoflurane cortical distributions in humans very challenging[3,4]. With the aid of recent advances in imaging, this study aims to assess the sensitivity of ^{19}F imaging in detecting cerebral Sevoflurane concentrations in humans during 0.5MAC anesthesia, to measure the spatial distribution of Sevoflurane during anesthesia, and to investigate the pharmacokinetics of Sevoflurane based on MRI data. Our preliminary results provide new insights of cortical concentrations, cortical distribution, and the delivery of Sevoflurane at clinically-relevant doses.

Methods ^{1}H/^{19}F imaging was performed on Siemens TimTrio 3T with a ^{1}H/^{19}F dual-tuned CP head probe (Stark Contrast). Six consenting (ASA I healthy) subjects have been recruited. ^{19}F imaging data were collected with a TrueFisp sequence: TR=3.38ms; TE=1.68ms; α=56°; In-place resolution=12.5x12.5mm^2; Slice thickness=15mm; Inter-slice spacing=1.5mm; In-plane matrix size=40x40; and Slices=8. Advanced system adjustments and shimming were performed; RF frequency for ^{19}F was set at ~150.09ppm manually, based on the system adjustment results; and the bandwidth was set to avoid the chemical shift artifacts from the single non-magnetic equivalent Fluorine nucleus that generates a small peak at 69.82ppm. Three experiments were performed: ***Phantom control*** (Exp1): ^{1}H and ^{19}F images of water and Sevoflurane (0.2mM in pure Ethanol) phantoms were collected (Fig 1); the purpose of this experiment was to demonstrate the water signal from the water phantom was not picked up during ^{19}F imaging. ***Human awake condition control*** (Exp2): ^{19}F imaging was performed in 4 subjects for the awake condition (without Sevoflurane delivery) while 2 Sevoflurane samples, 0.2mM and 5mM in pure Ethanol, were placed near the temples (Fig 2); the purpose of this experiment was to demonstrate during ^{19}F imaging there were no confounding signals being picked up in the brain and the noise level in the brain region was the same as that in the background. ***In-vivo ^{19}F imaging in subjects*** (Exp3): ^{19}F image data were collected in 5 subjects (one excluded due to motion) to demonstrate the changes in image intensity indeed reflected changes in local Sevoflurane levels during 0.5MAC Sevoflurane anesthesia in the regions of interest. ^{1}H brain anatomical images were collected to facilitate multi-subject integration for group analyses using BioImageSuite (Fig 3 & 4).

Results **Exp1** showed for ^{19}F imaging (Fig 1, bottom row) there was no significant difference between the observed image intensity values inside the water phantom region (14.9) and the background (15.2); the intensity for the Sevoflurane phantoms was 166.5. During ^{1}H imaging of phantoms, the images for the Sevoflurane phantoms were blurred because of the chemical shifts of multiple Ethanol ^{1}H peaks (Fig 1, top row). Group analyses of **Exp2** showed for ^{19}F imaging of subjects for the awake condition (Fig 2), there was no significant difference in image intensity between the head region (15.5±4.8) and the background (16.1±5); the maximum image intensity for the 5mM sample exceeded 4095 and for the 0.2mM sample it was 126.6±13.3, which was lower than expected maybe because of the voxel size and partial volume effect. Compared to the results from Exp2, group analyses of **Exp3** showed, during 0.5MAC Sevoflurane anesthesia, the image signal intensity within the brain increased significantly to 70.5±4.3; Significantly elevated signal of 197.2±21.1 in the scalp (between the brain and the skin) and of 75.8±12.3 outside the head were observed (Fig 3). Fig 4 shows the t-maps (t>8) from the group analysis of Exp3.

Discussion The ^{19}F signal intensity inside the brain was very stable across subjects, when normalized; the changes in the brain became most significant (Fig 4). Together with the control experiments, the t-maps show the observed increased signal in the brain during ^{19}F imaging of anesthesia was indeed induced by Sevoflurane inhaled. The scalp had the highest ^{19}F signal due to the high affinity of Sevoflurane to the fatty tissue[5]. One interesting observation is, Sevoflurane vapor was detected and the level was likely higher than in the brain. Our speculation is, since there is hardly any Sevoflurane affinity to the brain tissues (GM/WM), in order to keep certain level in the brain, a partial pressure gradient must build up from the respiratory gas, alveolar, blood, BBB, to the brain, which is consistent with the observation of the quick recovery from Sevoflurane anesthesia. That also indicates BBB might play an important role in limiting the transfer of Sevoflurane into the brain. Previous in-vitro/animal studies showed clinically relevant concentrations of most commonly-used inhaled anesthetics were in the range of 0.2 to 0.5mM[3,4]. In this study 0.2mM Sevoflurane in pure Ethanol was examined. Based on our measurements of T_2 for the 0.2mM phantom and the brain, which were 3.4ms and 2.1ms, respectively, the T_2-corrected Sevoflurane concentration in the brain at 0.5MAC anesthesia was ~0.11mM, which is much lower than reported in the literature[3,4], by assuming similar T_1. In the scalp/fatty tissue it was ~0.32mM.

Conclusion We have successfully demonstrated in-vivo detecting regional Sevoflurane with a ^{1}H/^{19}F dual-tuned CP head coil during anesthesia at 0.5MAC. Our results not only support the observations from previous animal studies, but have provided new insight into the delivery of this agent. Appreciation of the spatial distribution of this agent in the human brain becomes possible as more subjects are recruited.

References [1] Alkire et al 2008, PNAS 105:1722-7; [2] Qiu et al 2008, MRM 60:987-96; [3] Frank et al 1993, Br J Anesth 71:65-76; [4] Mandal et al 2008, Cell Biochem Biophys 52:31-5; [5] Wyrwicz et al 1987, BBA 927:86-91.

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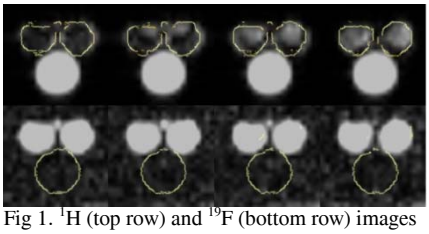

Fig 1. ^{1}H (top row) and ^{19}F (bottom row) images of water and 0.2mM Sevoflurane phantoms. The Sevoflurane phantoms were placed on the top of a water bottle. The scan time was ~30min for ^{19}F.

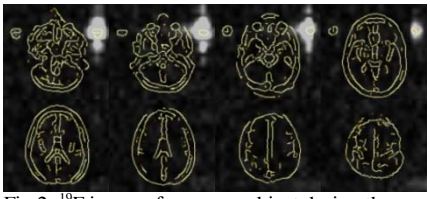

Fig 2. ^{19}F images from one subject during the awake condition. 5mM and 0.2mM Sevoflurane samples were placed near the subject's temples. The scan time was ~30min.

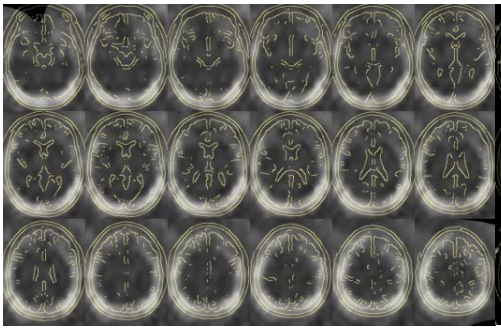

Fig 3. Group mean of the Sevoflurane signals in the head.

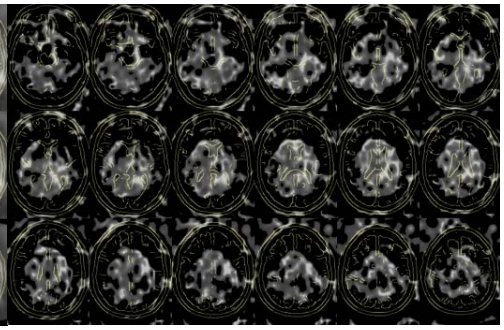

Fig 4. T-maps of Sevoflurane at 0.5MAC (threshold t>8).