Spatial Distribution of Sevoflurane in the Human Brain Revealed by In-vivo 19F Imaging at Clinical-Relevant Concentrations: Preliminary Results

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 ($C_4H_3F_7O$) can provide important information about the pharmacokinetics of this inhalational agent such as its cortical distribution. Together with the pharmacology studies[1,2], this approach may provide better insight into the neuronal mechanisms of general anesthesia. However, the extremely low cortical concentrations at clinically-relevant levels make in-vivo ^{19}F imaging of Sevoflurane in humans very challenging[3,4]. This study aims to examine the sensitivity of ^{19}F imaging in detecting cerebral Sevoflurane concentrations in humans during 0.5MAC anesthesia and to investigate the spatial distribution during Sevoflurane anesthesia. Preliminary results demonstrate the non-uniformity of Sevoflurane distribution in the human brain and provide new insights by directly measuring cortical concentrations during anesthesia.

Methods ^{1}H/^{19}F imaging was performed on Siemens Tim Trio 3 Tesla scanner with a ^{1}H/^{19}F dual-tuned CP head probe (Stark Contrast). Six consenting (ASA I healthy) subjects were recruited for ^{1}H/^{19}F imaging during administration of 0.5MAC Sevoflurane anesthesia. ^{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. The RF frequency for ^{19}F imaging was set at ~150.09ppm; and the bandwidth was chosen to minimize the chemical shift artifacts from the single non-magnetic equivalent Fluorine nucleus that generates a small peak at 69.82ppm. Two control experiments were performed in this study: ***Phantom control*** : ^{1}H and ^{19}F images of water and Sevoflurane (0.2mM in pure Ethanol) phantoms were collected; 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***: ^{19}F imaging was performed in four subjects for the awake condition (without Sevoflurane delivery) while 2 Sevoflurane samples, 0.2mM and 5mM in pure Ethanol, were placed near the temples; the purpose of this experiment was to demonstrate during ^{19}F imaging in the brain there were no confounding signals detected and the noise level in the brain was the same as that in the background. For ***in-vivo ^{19}F imaging in subjects***, ^{1}H and ^{19}F image data were collected and group analysis of the ^{1}H and ^{19}F image data included 5 subjects (one was excluded due to motion). ^{1}H brain anatomical images were collected to facilitate multi-subject group analyses using BioImageSuite. The t-maps of ^{19}F images from group analysis were used to generate a mask of the cortical regions of significant ^{19}F levels induced during anesthesia (t>5, uncorrected). The mean ^{19}F signals within these regions are shown in Fig 1. Results of ROI analysis based on cortical Brodmann Areas (BA) are shown in the Table.

Results Our control experiments demonstrated ***1)*** for ^{19}F imaging of the phantoms, there was no significant difference between the observed image intensity values inside the water phantom (14.9) and the background (15.2) and the intensity for the Sevoflurane phantoms was 166.5. ***2)*** For ^{19}F imaging of the awake condition in 4 of the subjects, 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 probably because of the voxel size and partial volume effects. Compared to the results from the control experiments, group analyses of ^{19}F subject data for the anesthesia condition showed, during 0.5MAC Sevoflurane anesthesia, the global mean image signal intensity within the brain increased significantly to 70.5±4.3. The image signal intensity from the ROIs examined ranged from 53 to 100; 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 values in these ROIs ranged accordingly from 0.09mM to 0.16mM (Table, right column), by assuming similar T_1 for the 0.2mM phantom and the brain. For the whole brain, a global Sevoflurane concentration in the brain at 0.5MAC anesthesia would be ~0.11mM, which is much lower than reported in the literature[3,4].

ROI	V(mm^3)	Mean	Std	Max	Conc
PrimSensory	30716	90	38	212	0.15
PrimMotor	19331	80	36	204	0.13
SensoryAssoc	6750	60	10	160	0.10
BA6	56825	90	33	197	0.15
BA7	41281	70	17	171	0.11
BA8	23099	93	23	176	0.15
BA9	14344	88	18	179	0.14
BA10	32042	69	11	105	0.11
BA11	29852	62	12	127	0.10
Insula	16406	61	8	96	0.10
BA14	1398	61	6	97	0.10
PrimVisual	14382	59	10	109	0.10
VisualAssoc	30193	63	14	217	0.10
BA19	29796	68	24	261	0.11
BA20	16703	72	17	121	0.12
BA21	27632	84	26	229	0.14
BA22	21726	87	27	212	0.14
BA23	19226	59	3	68	0.10
BA24	13107	57	8	87	0.09
BA25	2488	54	5	82	0.09
BA30	4296	58	4	67	0.09
BA31	20195	58	4	71	0.10
BA32	9579	60	7	84	0.10
BA34	657	64	8	93	0.10
Parahip	11449	62	12	132	0.10
Fusiform	41175	60	14	222	0.10
BA38	17140	89	20	164	0.15
BA39	28082	100	52	280	0.16
BA40	32594	98	38	222	0.16
PrimAuditory	10553	73	19	160	0.12
BA44	11087	99	33	160	0.16
BA45	2762	87	21	157	0.14
BA46	6860	86	12	126	0.14
BA47	14147	83	18	156	0.13
Caudate	11932	59	4	82	0.10
Putamen	10528	53	6	75	0.09
Thalamus	14810	62	5	148	0.10
GlobPalidus	1571	59	4	70	0.10
NucAccumb	568	59	7	70	0.10
Amygdala	3181	70	6	91	0.11
Hippocampus	6440	60	7	91	0.10
Hypothalamus	1383	59	4	65	0.10

Discussion The signal intensity showed considerable spatial variability across the brain. Regional Sevoflurane levels could be affected by several factors. Molecular drug-brain interactions involving different types of neurons, specific receptor distributionss, or even the spatially varying vascular structure of the brain. Cortical Sevoflurane concentrations were directly measured in normal human subjects and the results indicated the cortical level was much lower than reported in the previous animal studies. In these animal studies the cortical Sevoflurane concentration was usually measured in-vitro or indirectly calculated with mathematic models. In this study, we also observed significantly elevated Sevoflurane signal intensity of 197.2±21.1 in the scalp/skull (between the brain and the skin). The scalp had the highest ^{19}F signal due to the high affinity of Sevoflurane to the fatty tissue, which was consistent with results from previous animal studies[5]. The Sevoflurane concentration was ~0.32mM in the scalp/fatty tissue at 0.5MAC.

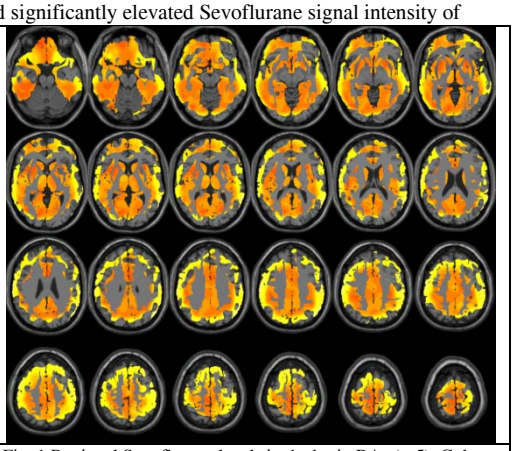

Fig. 1 Regional Sevoflurane levels in the brain BAs (t>5). Color bar (red-yellow): 20-300.

Conclusion We have successfully conducted the first ^{19}F imaging study in humans to assess the cortical distribution of the inhalational anesthetic agent – Sevoflurane at clinically-relevant concentrations and demonstrated the possibility of directly mapping the regional Sevoflurane concentration in the brain using ^{19}F imaging with a ^{1}H/^{19}F dual-tuned CP head coil even though the cortical concentration is extremely low.

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.

Acknowledgment: This work is supported by the NIH under grant NIH R01 NS052344-02A; We thank Dr. Himanshu Bhat from Siemens for his technical assistance in this work.