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Sevoflurane 0.25 MAC Preferentially Affects Higher Order Association Areas: A Functional Magnetic Resonance Imaging Study in Volunteers

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Abstract

BACKGROUND—Functional magnetic resonance imaging (fMRI) can objectively measure the subjective effects of anesthesia. Memory-related regions (association areas) are affected by subanesthetic doses of volatile anesthetics. In this study we measured the regional neuronal effects of 0.25 MAC sevoflurane in healthy volunteers and differentiated the effect between primary cortical regions and association areas.

METHODS—The effect of 0.25 MAC sevoflurane on visual, auditory, and motor activation was studied in 16 ASA I volunteers. With fMRI (3 Tesla Siemens magnetom), regional cerebral blood flow (rCBF) was measured by the pulsed arterial spin labeling technique. Subjects inhaled a mixture of O₂ and 0.25 MAC sevoflurane and standard ASA monitoring was performed. Visual, auditory, and motor activation tasks were used. rCBF was measured in the awake state and during inhalation of 0.25 MAC sevoflurane, without and with activation. The change in rCBF (δ CBF) with 0.25 MAC Sevoflurane during baseline state and with activation was calculated in 11 regions of interest related to visual, auditory, and motor activation tasks.

RESULTS—The change from baseline rCBF with 0.25 MAC sevoflurane was not statistically significant in the 11 regions of interest. With activation there was a significant increase in CBF in several regions. However, only in the primary and secondary visual cortices (V1, V2), thalamus, hippocampus, and supplementary motor area was the decrease in activation with 0.25 MAC sevoflurane statistically significant ($P < 0.05$).

CONCLUSION—Memory-related regions (association areas) are affected by subanesthetic concentrations of volatile anesthetics. Using fMRI, this study showed that 0.25 MAC sevoflurane predominantly affects the primary visual cortex, the related association cortex, and certain other higher order association cortices.

Functional imaging is a powerful research tool. Its applications in understanding the cortical and subcortical effects of anesthesia are still being explored (1). Functional magnetic resonance imaging (fMRI) and positron emission tomogram are the two most commonly used functional imaging techniques. In 1981, Phelps et al. (2) demonstrated that cerebral glucose use increases in the human visual cortex when the eyes are open (when compared with eyes closed state), and that there was a link between increased neuronal activity and regional metabolism. This

landmark study also demonstrated the feasibility of measuring changes in regional metabolism noninvasively in real-time. Techniques have subsequently been developed to measure both cerebral blood flow (CBF) as well as metabolism. The consistent correlation between neuronal activity and regional CBF (rCBF) on the one hand, and cerebral metabolism, on the other, has been validated in several studies (3).

Sensory input is processed at multiple levels in the central nervous system (CNS) (4). Initially signals from sensory stimuli are relayed to the respective primary cortices (primary visual cortex, primary auditory cortex, somatosensory cortex, etc.). The first level of modulation is the unimodal association areas located in close proximity to the primary cortical regions. These regions give a meaningful interpretation for the stimuli arriving at the primary cortices. For example, the auditory association area located in the superior temporal gyrus, aids in the understanding of the stimuli arriving at the primary auditory cortex located in the Heschl's gyrus. The next level of sensory integration is in the multimodal association area. Anterior, limbic, and posterior association areas are the three well-defined multimodal association areas. Sensory stimuli from various sensory modalities converge in the respective multimodal association areas, where they are analyzed and then integrated with past experiences encoded in long-term memory. Based on the modulation at this level, appropriate corrective action is then planned and initiated.

Memory-related areas [prefrontal cortex (PFC) and hippocampus] are one of the major higher order association regions in the brain. With volatile anesthetics, memory impairment has been observed in subjects within a concentration range (end tidal) of 0.14–0.6 MAC (5–7). In clinical studies with plasma propofol, level of 0.6 $\mu\text{g/mL}$ to 1.0 $\mu\text{g/mL}$ (MAC equivalent of 0.15–0.25) caused memory deficit (8). However, there is no study evaluating the central effects of anesthesia on primary and higher order association areas simultaneously. Our aim in this study was to understand the effects of 0.25 MAC sevoflurane on primary and higher order cortical regions (unimodal and multimodal association areas). Our working hypothesis was that 0.25 MAC sevoflurane causes a decrease in neuronal activity in higher order association regions with minimal effect on the primary cortices. This is based on the understanding that higher order association regions, being polysynaptic pathways, are more sensitive to anesthetic-induced CNS depression when compared with primary regions (9).

METHODS

This study was approved by the Human Investigation Committee of Yale University School of Medicine. Sixteen consenting ASA I volunteers aged between 19 and 30 yr were studied. Subjects receiving psychoactive drugs or any centrally acting medication (such as serotonin uptake inhibitors, gabapentin, etc.) were excluded, to avoid the confounding effect of these medications and sevoflurane. Similarly, subjects with a history of epilepsy or renal disease were also excluded. Subjects with a potentially difficult airway (Mallampatti III or IV, thyromental distance <5 cm) were also excluded. The experimental protocol of imaging, anesthesia, and task activation was described to all subjects before the study. Subjects were asked to fast after midnight on the evening before the study. On arrival at the Magnetic Resonance Research Center, they were first screened for the presence of any ferromagnetic substance and other contraindications for MRI. Electrocardiogram, noninvasive arterial blood pressure, pulse oximetry probe, and end-tidal sampling probe (for ETco₂ and sevoflurane monitoring) were connected and an IV infusion was started with a 22-gauge cannula for maintenance infusion (lactated Ringer's solution infused at 100 mL/h). Subjects were moved into the magnet with the monitors and IV in place. Electrocardiogram, noninvasive arterial blood pressure, oxygen saturation, ETco₂ and end-tidal sevoflurane concentration were monitored continuously. A mixture of oxygen (5 L) and sevoflurane 0.5% ($\approx$ 0.25 MAC) was administered through a semiclosed circuit and a facemask that was held in place with a head-

strap (10). Based on the data generated in a pilot study, 10 min were required for the end-tidal sevoflurane concentration to reach steady-state.

Task Activation

Task activation is an important component of any functional imaging protocol. Visual and auditory tasks and a visually cued motor task were chosen for this study. The visual task was in the form of an 8-Hz reversely flickering black and white checkerboard pattern and the auditory task was a nonspecific tone relayed over the headphones. During the motor task, subjects were instructed to press a specific button in response to a visual cue, and this response was recorded. Nonspecific visual and auditory tasks were chosen in this protocol, to identify and differentiate the activation of primary and secondary regions. The activation sequence consisted of alternating 30-s blocks of task activation and baseline state. Multiple cycles of activation were performed to ensure an optimal signal/noise ratio.

Imaging

Imaging was done in a 3 Tesla Siemens scanner. Five cycles of imaging were performed: Three awake cycles (no anesthesia) with two anesthesia cycles interposed between them, as shown below:

Awake → Anesthesia → Awake
→ Anesthesia → Awake

The three awake cycles were interposed to ensure that the neuronal activity returned to baseline after anesthesia was discontinued and to check that the central effects of anesthesia were reproducible. Each cycle lasted for 25 min with a total imaging time of 125 min (five cycles). In each cycle, 10 min were first allowed to achieve a steady-state end-tidal concentration of sevoflurane (expired alveolar concentration of 0.5%) followed by 15 min of task activation. Fifteen min of activation consisted of 30-s alternating blocks of activation and baseline state. Exactly the same sequence was followed in the awake and sevoflurane cycles. All subjects initially had a sagittal T1-weighted localizer scan (3 min), followed by an axial-oblique T1-weighted acquisition scan. The sagittal scan was for localization of the cortical regions of interest (ROIs). The T1-weighted axial scan was the anatomic scan. During data analyses, the functional images were overlaid on the anatomical scan to identify the ROIs. rCBF was measured by the pulsed arterial spin labeling (PASL) technique.

PASL rCBF Measurement (11,12)

PASL is a noninvasive perfusion MRI technique, in which the protons (hydrogen ions in the water molecule of plasma, referred to as “spins”) serve as the endogenous contrast (Fig. 1). These spins in the feeding artery (hydrogen ions in blood) are periodically exposed to radiofrequency pulses (inversely labeled). This transiently changes the polarity of the protons. The inversely labeled spins, when transported through the capillary bed and the extracellular space, change the spin-lattice relaxation rate and result in a signal change in T1-weighted MRIs when compared with the nonlabeling case. This signal change is proportional to rCBF, and absolute rCBF is calculated from this. When compared with the relatively venous-weighted signal in blood oxygen level dependent contrast (BOLD), in this technique the rCBF in the capillary blood flow is measured, which is spatially closer to the site of metabolic activity and neuronal activity is inferred from this. Multiple perfusion images were acquired every 3 s and the data were averaged. In any fMRI study, acquiring multiple images decreases the noise and improves the signal/noise ratio.

Discharge Criteria

After the last cycle of imaging, subjects were brought out of the scanner. Because the “awake” state was the last cycle, all subjects had fully recovered from anesthesia at this point and were monitored for another 15 min to ensure that they fulfilled the criteria for discharge. Criteria for discharge were the same as those used in the Yale-New Haven hospital ambulatory surgery unit: stable vital signs, awake, alert, talking and able to get dressed, and ambulate without support. At this point the IV cannula was removed and subjects were sent home.

ROIs

The ROIs where the rCBF was measured are listed in Table 1. As hypothesized earlier, our primary aim was to study the effects of 0.25 MAC sevoflurane on the task-induced changes in rCBF (and thereby neuronal activity) in the primary as well as the higher order association cortices, to differentiate the sensitivity to small-dose sevoflurane between these regions. The activation paradigm consisted of simultaneous visual and auditory activation followed by a visually cued motor activation with interposed period of baseline activity. For the visual/auditory activation block, primary and secondary visual and auditory cortices (V1, V2, A1, and A2) were selected as the appropriate primary cortical regions and associated unimodal association area. For the motor activation block, primary motor cortex, premotor area, and supplementary motor area (SMA) were the ROIs selected. PFC, cingulate gyrus, hippocampus, and thalamus were selected as the multimodal association cortices. Although the thalamus is not the component of any of the three defined multimodal association areas, because of its connectivity, we expected the thalamus to respond to an anesthetic like association area. ROIs were identified from the Talairach atlas and were manually marked on the 3D high resolution anatomical image of the individual subjects (13). This was overlaid on the functional images and the rCBF in the ROIs was calculated using the Yale Magnetic Resonance Research Center BioImage Suite (<http://www.bioimagesuite.org>).

Data Analysis

For each subject three sets of data were acquired in the awake state and two sets under 0.25 MAC sevoflurane, for a total of five cycles. In each cycle there were three sets of alternating periods of baseline state followed by activation. rCBF was measured in the baseline state (no activation) and with activation (visual/auditory activation and motor activation). All baseline rCBF data and activation-induced rCBF data in the 11 ROIs were averaged. The difference between the two (δ CBF) was calculated to get the activation-induced increase in rCBF. The δ CBF (activation-induced change in rCBF) in the awake state and under 0.25 MAC sevoflurane was calculated (δ CBF awake and δ CBF sevoflurane). The difference between the two δ CBF (δ CBF awake – δ CBF sevoflurane) would reflect the sevoflurane-induced change in activation. The baseline CBF in all the regions was averaged to calculate the global CBF. The difference between the baseline CBF in the awake state and with sevoflurane (0.25 MAC) was calculated to determine the effect of sevoflurane on baseline activity. Paired *t*-tests were performed between the various data sets, baseline CBF awake versus sevoflurane and activation-induced δ CBF awake versus sevoflurane in the 11 ROIs.

RESULTS

Sixteen healthy ASA I volunteers were studied. There were 11 men and five women and their average age was 26.5 yr. Their mean height, body weight, and body mass index were 174.8 cm, 78.4 kg and 25.96, respectively. The vital signs, heart rate, mean arterial blood pressure, and ETco₂, were within the physiological range during the course of the study in all subjects (Table 2). There was no statistically significant alteration in the vital signs with 0.25 MAC sevoflurane. Spo₂ was above 96% in all subjects (awake state as well as under 0.25 MAC

sevoflurane) during the course of the study. All subjects completed the study successfully without any complications and were discharged within 30 min of completion of the study.

Neurological Status

With 0.25 MAC sevoflurane all subjects were awake, talking and obeying commands. Some subjects reported an inability to perform the motor task despite understanding the visual cue, implying a delayed response or a disconnect between the understanding and execution of the motor task (while being conscious). The lowest Observer Assessment of Alertness/Sedation Scale during 0.25 MAC sevoflurane inhalation was 4/5 (14).

Task Activation

As discussed in Methods, the visual/auditory tasks were presented together and motor task activation was performed separately. Accordingly, the rCBF changes under the two tasks (visual/auditory and motor) conditions are discussed separately.

Effect of 0.25 MAC Sevoflurane on Baseline CBF

Globally, there was a 6.5% decrease in CBF with sevoflurane. The rCBF in the various ROIs during the awake state and with 0.25 MAC sevoflurane (no activation) is shown in Figure 2. The percentage decrease in rCBF with sevoflurane (baseline change – no activation) is presented in Figure 3. δ CBF (the difference between baseline CBF in the awake state and with sevoflurane – no activation) was different in the various ROIs, reflecting the differential sensitivity of the various regions to sevoflurane. However the δ CBF was not statistically significant in any of the 11 ROIs.

Visual/Auditory Task Activation-Induced Covariation in rCBF

The task-induced change in rCBF (δ CBF) in the awake state and with sevoflurane 0.25 MAC is shown in Figure 4. In V1 (primary visual cortex) there was a 38% increase in rCBF with visual activation which decreased to 8.5% with 0.25 MAC sevoflurane. In V2 (secondary visual cortex) there was a 21% activation which decreased to 11% with sevoflurane. The decrease in the activation-induced increase in rCBF (δ CBF) with sevoflurane, in V1 and V2, was statistically significant ($P < 0.05$). In the primary and secondary auditory cortex (A1 and A2) the activation-induced increase in CBF was more or less the same with and without sevoflurane (not significant $P > 0.05$). In the PFC visual/auditory activation induced an 8.8% increase in rCBF in the awake state and a 10.4% increase under sevoflurane (not significant). There was very minimal activation in the hippocampus, cingulate gyrus, and the thalamus (multimodal association areas) with our task and sevoflurane decreased the rCBF in all three ROIs (hippocampus, cingulate gyrus, and the thalamus) in the presence of our tasks. This decrease in rCBF was statistically significant in the hippocampus and thalamus but not in the cingulate gyrus. Figure 5 shows the fMRI of sevoflurane-induced change in rCBF without and with visual/auditory activation.

Motor Activation Task

During the motor activation task, rCBF was measured in the primary motor cortex, premotor area, and SMA. Figure 4 shows the change in rCBF (δ CBF) with motor activation in the three ROIs with and without sevoflurane. There was a $\approx 9\%$ increase in rCBF in all the three motor ROIs in the awake state. However, with 0.25 MAC sevoflurane, the decrease in activation was significant only in the SMA ($P < 0.05$). The fMRI during the motor activation task is shown in Figure 6.

DISCUSSION

To our knowledge, this is the first fMRI study where the PASL CBF technique has been used to compare the alteration in neuronal activity under anesthesia. The PASL technique has several advantages: it has a high spatial and temporal resolution, it is noninvasive and it is done in a nonradiation environment. Because the rCBF is measured at the level of the capillaries, it is a more sensitive reflection of neuronal activity than BOLD, which is heavily weighed toward venous blood flow. The global CBF measured by PASL is slightly lower when compared with what is quoted in the literature. This is because this technique is heavily weighed toward gray matter CBF. However, because most neuronal activity can be localized to the cortex (predominantly gray matter), PASL is a highly sensitive technique for measuring relative changes in rCBF with neuronal activity. Ye et al. found an extremely good correlation in cortical CBF between ^{15}O -labeled positron emission tomogram imaging and the PASL technique (15). Lia et al. (16,17) compared the results of contrast based CBF with PASL techniques in healthy volunteers and found a good correlation between the two techniques.

In summary, our observation in this fMRI study done with 0.25 MAC sevoflurane in healthy ASA I volunteers is:

1. The baseline δCBF (no activation) with 0.25 MAC sevoflurane was not statistically significant in any of the 11 ROIs studied.
2. The activation-induced δCBF was significant in V1 (primary visual cortex) and V2 (unimodal visual association area).
3. Among the multimodal association areas there was a statistically significant decrease in activation with sevoflurane in the thalamus, hippocampus, and SMA.

There was no appreciable effect on the auditory and motor cortices (primary cortex and the related unimodal association area). The activation of the various ROIs is linked to the appropriate sensory/motor stimuli. With task activation, there was a robust increase in rCBF (implying increase in neuronal activity) in the visual, auditory, and motor regions. But with 0.25 MAC sevoflurane, there was a statistically significant decrease in rCBF activation in V1 and V2 and some of the association areas. Our study, therefore, partly supports our hypothesis, because in addition to the association cortices (thalamus, hippocampus, SMA, and V2), the primary visual cortex (V1) is also sensitive to 0.25 MAC sevoflurane.

The relatively higher sensitivity of the visual cortex (V1 and V2) to sevoflurane has been attributed to the higher concentration of γ -aminobutyric acid Type A receptors (50% more) when compared with other regions of the cerebral cortex (18). Volatile anesthetics enhance the activity of the inhibitory γ -aminobutyric acid receptors in the CNS (19). The higher sensitivity of the CNS to an optically evoked response under anesthesia is a well-known and accepted fact. Multichannel electroencephalogram recording during induction and maintenance of anesthesia (volatile as well as IV anesthetics) also has shown comparable results. With the induction of anesthesia " α " wave activity (7–13 Hz) initially decreases in the occipital lobe (visual cortex) (20). This is referred to as the frontal shift of the electroencephalogram.

The sensitivity of the association areas (unimodal as well as multimodal areas) to 0.25 MAC sevoflurane is explained on the basis of the multiple synaptic junctions along these pathways (compared with the primary cortices). Anesthetics act at the level of the synaptic junctions (in contrast to affecting the conductivity of the axons) (9). Hence, pathways with multiple synaptic junctions are expected to be more sensitive to anesthesia when compared with those with fewer synapses. With reference to the visual association area (V2), a decrease in activation in V2 could also be related to a decrease in activation in V1. Clinical studies (with and without imaging) also have demonstrated the selective sensitivity of association areas to anesthetics.

Renna et al. (5) studied the effect of 0.6–1.0 MAC sevoflurane on memory (no imaging). They observed that 0.6 MAC sevoflurane caused memory impairment in all the subjects. In the study by Munglani et al. (6), memory impairment was observed in some of the subjects even with 0.14 MAC isoflurane. Heinke and Schwarzbauer (7) studied the effect of 0.2 MAC isoflurane on visual activation, using BOLD fMRI. A decrease in BOLD activity was observed in the right anterior superior insula and intraparietal sulcus bilaterally, regions linked to visual spatial attention, and visual working memory. There was also an increase in reaction time, indicating some cognitive impairment. At this point all the subjects were conscious and obeying commands. The primary visual cortex, lateral geniculate body, and the thalamus were not affected at 0.2 MAC isoflurane. In our study with 0.25 MAC sevoflurane, the primary visual cortex did show a decrease in activation (and as in Heinke and Schwarzbauer's study (7) subjects were awake, obeying commands).

Functional imaging is an objective way of identifying and understanding the subjective effects of anesthetics in the CNS (21). As a secondary observation, our study also demonstrates that in order to functionally image the central effects of anesthesia, in addition to the baseline neuronal activity, it is essential to study the effect of task activation as well as the appropriate clinical correlation. Task activation increases the regional neuronal activity and rCBF. If the rCBF is measured during activation (with and without anesthesia) the difference between the two reflects the effect of anesthesia. Anesthesia being lack of response to external stimuli, it is imperative to record the change in CBF during activation to understand the clinical significance of the change in CBF induced by anesthesia (22,23). In addition, clinical correlation is also required because any change in neuronal activity does not directly translate to a functional effect. Without activation the global average decrease in CBF was 6.48% and the rCBF decrease varied from 1.2% to 9.49% within the ROIs investigated. These changes were not statistically significant. However with activation, in the primary visual cortex (V1), there was a 38% increase in rCBF which decreased to 8.5% under anesthesia and in V2 it was a 21% increase which decreased to 11%. This decrease in activation in V1 and V2 was statistically significant. Without activation this relatively higher sensitivity in V1, V2 could not have been identified. The hippocampus and thalamus (multimodal association areas) were not activated by our task (visual, auditory, and motor) and yet there was a statistically significant decrease in neuronal activity in these regions with 0.25 MAC sevoflurane.

We observed an increase in baseline activity only in the SMA with 0.25 MAC sevoflurane. Though this change was not statistically significant, this increase in rCBF in the SMA was most probably because of the disinhibitory effect of sevoflurane which totally masked the effect of motor activation (the δ CBF with activation was statistically significant). Disinhibition with increase in neuronal activity has also been reported in other studies. Schlünzen et al. (24) reported an increase in activity in the anterior cingulate gyrus and insula with 0.35 MAC sevoflurane, which also persisted at 1.0 MAC. In the thalamus and cerebellar cortex there was a decrease in activity. Fiset et al. (25) observed an increase in activity in the cerebellum alone, which was attributed to the disinhibitory effects of small-dose propofol.

Our conclusion from this study is that 0.25 MAC sevoflurane predominantly affects the primary visual cortex, the related unimodal association cortex, and other higher order association cortices. However, a more sensitive technique of establishing this sensitivity would be to use an activation paradigm selective for the multimodal association cortex e.g., memory task, and image the changes in neuronal activity with and without anesthesia. Similar techniques could be used to image the end points of general anesthesia and their interaction with anesthetics.

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Figure 1.

Schematic presentation of pulsed arterial spin labeling technique. White circle down arrows emerging from the arterial side represent the magnetized spins (protons). Some of the spins (gray circle arrows) flip back as they pass through the intracranial circulation. This proportion is a direct measure of circulation. Reproduced with permission from Golay X, Hendrikse J, Lim TCC. Perfusion imaging using arterial spin labeling. *Top Magn Reson Imaging*, 2004, 15, 10–27, ©Lippincott Williams & Wilkins.

Figure 2. Baseline regional cerebral blood flow (rCBF) (absolute) in the awake state (blue) and under 0.25 MAC sevoflurane (brown). Error bars indicate the standard deviations.

Figure 3. Percentage decrease in baseline regional cerebral blood flow (rCBF) (no activation) with 0.25 MAC sevoflurane anesthesia. Only supplementary motor area (SMA) shows an increase in rCBF. These changes were not statistically significant. Error bars indicate the standard deviations.

Figure 4. Percentage increase/decrease in regional cerebral blood flow (rCBF) with activation (visual/auditory/motor) in the awake state (blue) and under 0.25 MAC sevoflurane (brown). Error bars indicate the standard deviations. The decrease in activation (rCBF) was significant (marked*) in V1, V2, thalamus, hippocampus, and supplementary motor area (SMA); $P < 0.05$.

Visual-Auditory Activation rCBF

Figure 5.

Shows the δ CBF with visual/auditory activation in the awake state and with 0.25 MAC sevoflurane. Red/orange areas imply an increase in regional cerebral blood flow (rCBF) and purple areas a decrease in rCBF. Decrease in activity in the visual cortex (occipital region) with sevoflurane is seen.

Motor Activation rCBF

Figure 6.

Shows the δ CBF with motor activation in awake state and with 0.25 MAC sevoflurane. Red/orange areas imply an increase in regional cerebral blood flow (rCBF) and purple areas a decrease in rCBF. Except for a decrease in rCBF in the visual cortex (because of the visual cue for motor activation) no other change was observed.

Table 1

Various Regions of Interest (ROIs) Where rCBF was Measured

Regions of Interest	Symbol
Primary visual cortex	V1
Secondary visual cortex	V2
Primary auditory cortex	A1
Secondary auditory cortex	A2
Primary motor cortex	M1
Pre motor area	PMA
Supplementary motor area	SMA
Pre frontal cortex	PFC
Hippocampus	Hip
Cingulate gyrus	Cin
Thalamus	Th

Table 2

Vital Signs Chart

	Awake	0.25 MAC sevo	<i>P</i>
ETco ₂ (mm Hg)	36 ± 2	36 ± 2	0.97
MAP (mm Hg)	87 ± 6	85 ± 5	0.91
Heart rate (bpm)	58 ± 5	58 ± 4	0.50