Minimal alveolar concentration of sevoflurane for induction of isoelectric electroencephalogram in middle-aged adults

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Editor’s key points

- Induction of an isoelectric EEG by anaesthetics has been implicated in neuroprotection, and might be clinically useful or detrimental in specific situations.
- The potency of sevoflurane in producing an isoelectric EEG was determined in adult human subjects before surgical incision.
- The minimal alveolar concentration (MAC) of sevoflurane for isoelectric EEG was 3.5 vol%, which is about 2.1 times the MAC for skin incision.

Background. We determined the minimal alveolar concentration (MAC) of sevoflurane inducing an isoelectric EEG in 50% of adult subjects (MACie).

Methods. We included 31 middle-aged subjects; 30 subjects finished the study protocol and received sevoflurane at preselected concentrations according to a modified Dixon ‘up-and-down’ design starting at 1.7 vol% with 0.2 vol% steps size. General anaesthesia was induced and maintained with sevoflurane; tracheal intubation was facilitated with cisatracurium. After a period of 30 min before skin incision, the state of isoelectric EEG was considered as significant when a burst suppression ratio of 100% lasted for 1 min. The haemodynamic responses to skin incision and the vasopressor requirement to maintain stable haemodynamic status were also analysed according to the EEG state.

Results. MACie was 3.5% (95% confidence interval, 3.4–3.7%) in middle-aged subjects. When compared with subjects not in isoelectric EEG state, subjects in isoelectric EEG state received more phenylephrine to maintain stable haemodynamics (10 of 10 compared with 7 of 20 subjects, \( P = 0.001 \)) and experienced less sympathetic responses to skin incision (1 of 10 compared with 11 of 20 subjects, \( P = 0.024 \)).

Conclusions. MACie for sevoflurane was \( \sim 2.1 \) times MAC for immobilization in phenobarbital premedicated middle-aged adults. Sevoflurane-induced isoelectric EEG state is associated with significant cardiovascular depression but reduced haemodynamic responses to skin incision.

Keywords: anaesthetics volatile, sevoflurane; cardiovascular system; responses; monitoring, depth of anaesthesia; monitoring, electroencephalography

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Minimal alveolar concentration (MAC) was introduced to compare the potencies of inhalation anaesthetic agents.1,2 Sevoflurane is a commonly used inhalation anaesthesia agent today. Its effects on motor response (MAC),3 adrenergic reflexes (MACBAR),4,5 reflex pupillary dilatation (MACpup)6 to noxious stimulation, and eye opening to verbal command (MACawake)7 in 50% of subjects have been widely investigated. However, the relation between concentration of sevoflurane and different EEG states is relatively unstudied.8

EEG burst suppression and isoelectric (or persistently suppressed) EEG, typically associated with states of profound brain inactivation, do not appear in normal sleep.9 They are frequently observed in deep general anaesthesia, pathological conditions including hypothermia, hypoxic–ischaemic trauma, coma, and early infantile encephalopathy. Previous studies have demonstrated that burst suppression or isoelectric EEG can be purposely induced by anaesthetic agents to protect the brain during neurosurgery10 or cardiosurgery.11 Although still a controversial issue, low EEG-derived indices might be associated with adverse outcomes after cardiac and non-cardiac surgery.12–16 Understanding the relation between concentrations of volatile anaesthetics and abnormal EEG states including burst suppression or isoelectric EEG might help practitioners avoid excessively deep anaesthesia in vulnerable patients, or achieve transient burst suppression or isoelectric EEG when desired. Hence, this study aimed to determine the MAC of sevoflurane inducing isoelectric EEG (MACie) and burst suppression EEG (MACbs) in 50% of middle-aged adults. In addition, haemodynamic stability and responses to incision in a state of isoelectric EEG were also analysed.
Methods

The study was approved by the local Institute’s Ethical Committee (Huazhong University of Science and Technology) and registered with ClinicalTrials.gov (ref: NCT01662622). After written informed consent, we enrolled 31 subjects aged 45–65 yr, undergoing upper abdominal surgery using general anaesthesia from March to May 2012 at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. All participants had an ASA physical status classification of I or II. Patients were excluded from the study if they had one of the following criteria: any neurological disease or having received central nervous system–active drugs; a cardiac ejection fraction <40%; previous history of difficult intubation or anticipated difficult intubation; daily alcohol consumption; and obesity (defined as a body mass index >30 kg m$^{-2}$). Those without informed consent were also excluded.

As premedication, 0.1 g of phenobarbital and 0.5 mg of atropine were administered by i.m. injection. After arrival in the operating theatre, standard monitoring, including electrocardiography, non-invasive arterial pressure, and pulse oximetry, was established. The i.v. infusion rate of lactated Ringer’s injection was 15 ml kg$^{-1}$ h$^{-1}$ via an 18 G venous catheter. A neuromuscular monitor (TOF-watch SX; Organon, Dublin, Ireland) was placed over the ulnar nerve at the wrist.

Electrical activity of the brain was measured and recorded with a Narcotrend Monitor (unprocessed EEG) and S/5 Compact Anaesthesia Monitor (burst suppression ratio (BSR)). Sensors of the Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany, version 4.0) and Entropy Module (S/5 Compact Anaesthesia Monitor, Datex-Ohmeda, Helsinki, Finland) were attached to the forehead of each subject according to the manufacturer’s recommendation. Impedances were measured for each set of electrodes to ensure adequate electrode contact defined as 6 k$\Omega$ for the Narcotrend Monitor and 7.5 k$\Omega$ for the Entropy Module. To calculate BSR, suppression is defined as periods >0.5 s during which EEG voltage is <5 μV. Time in a suppressed state is measured and BSR is reported as the fraction of the epoch during which the EEG is suppressed. BSR is averaged over at least 15 epochs (60 s). The presence of burst suppression was defined as BSR >0.17. A BSR of 100% implies isoelectric EEG.

General anaesthesia was induced by tidal volume breathing of 8% sevoflurane in 100% oxygen at 6 litre min$^{-1}$ with a semi-closed face mask. Cisatracurium 0.15 mg kg$^{-1}$ was administered after loss of the lash reflex,18 with manual ventilation until the amplitude of T1 decreased to zero. Tracheal intubation was performed and switched to mechanical ventilation with a fresh gas flow of 2 litre min$^{-1}$. Oxygen, carbon dioxide, and sevoflurane were sampled with a 19 G tube connected to the distal end of the tracheal catheter. Gas concentration and partial pressure were analysed by a gas analyser (S/5 Compact Anaesthesia Monitor) with a sample flow rate of 200 ml min$^{-1}$. The end-tidal partial pressure of carbon dioxide was maintained at 4.7 kPa. An oesophageal temperature probe was inserted and a warming unit was used if necessary to maintain 36.5 to 37.5°C. Surgery started at least 30 min after inhalation induction, so that the determined sevoflurane concentration was stable for at least 15 min and the difference of inspired and end-tidal concentrations was <10%.4 A cuff-based continuous arterial pressure monitor was used; an audible alarm was set to indicate mean arterial pressure (MAP) reduction of >20% of baseline values. Phenylephrine 0.1 mg was administered i.v. if necessary to maintain MAP. Neither Entropy nor Narcotrend alarms were set.

MAC was determined using the Dixon up-and-down method. To avoid awareness, the first subject received end-tidal sevoflurane concentration of 1.7% (1 MAC). As shown in Figure 1, the presence or absence of isoelectric EEG of the previous subject determined the end-tidal sevoflurane concentration of the following subject. End-tidal concentration of sevoflurane for the next subject was decreased by 0.2% (isoelectric EEG) or increased by 0.2% (non-isoelectric EEG). A crossover response was defined as the consecutive inclusion of a subject who presented isoelectric EEG, followed by another who did not. The value of a pair was the average of the end-tidal concentration used for the two subjects of this pair. The MACie was determined by averaging the values of six consecutive pairs. For each subject, a 30 min interval was given to allow equilibration between arterial and brain tensions.2 The isoelectric EEG was considered as significant when the isoelectric state lasted >1 min.19 The maximal BSR was recorded if isoelectric EEG was not reached. Then, the end-tidal concentration of sevoflurane was maintained until 3 min after incision. Heart rate (HR) and MAP were recorded at 2 and 1 min before skin incision, and then at 3 min after surgical incision. The pre-incision value was defined as the mean value of the 2 and 1 min before skin incision. Adrenergic reflexes (an increase in either HR or MAP >15% above the pre-incision values)2 cases were counted.

Statistical analysis

Patient characteristic data were collected and presented as mean (SD) or as number (%) where appropriate. The MACie was calculated as the mean of six independent crossovers of end-tidal sevoflurane concentration as shown in Figure 3. Up-and-down sequences were analysed by the probit test (SPSS for Windows 12.0; SPSS, Inc., Chicago, IL, USA), which enabled MACie and MACbs with 95% confidence limits of the mean to be derived.20 Data were also analysed with logistic regression for the probability of isoelectric EEG and burst suppression vs end-tidal concentration, the maximum-likelihood estimation, and goodness-of-fit.

Subjects were divided into an isoelectric EEG (ie+) group and a non-isoelectric EEG (ie−) group. The frequency of phenylephrine injection and incidence of positive adrenergic reflexes were compared between groups by two-tailed Fisher’s exact test. Numerical data were analysed by Student’s t-test or the Mann–Whitney U-tests where appropriate. P-values of <0.05 were considered statistically significant.
Results

As shown in Figure 1, of 40 patients assessed for eligibility, 31 were screened and subsequently enrolled. One subject was excluded because of severe hypotension during the equilibration period. Data analysis was performed on 30 ASA I–II subjects who finished the study.

Grouped patient characteristic data are presented in Table 1. There were more subjects in the ie− group than in the ie+ group (20 compared with 10) because of the experimental design. However, the groups were similar with respect to other characteristics. In addition, the three surgeons who were involved in the study were equally distributed between the two groups, and the surgical incisions were of similar type and length.

Figure 2 shows the Narcotrend index change over the course of anaesthesia from Subject 15, who received end-tidal sevoflurane concentration of 3.7% and showed a representative curve of the ie+ group.

MAC calculation

Figure 3 shows the up-and-down progression. MACie determined by the Dixon method was 3.5 (0.1)%. As the concentration of sevoflurane increased, suppression of the EEG was not all or none. Figure 4 shows the maximal BSR of each subject obtained in the period before skin incision. Twenty-one of 30 subjects displayed burst suppression EEG.

Figure 5 shows the dose–response curve of the probability of isoelectric EEG (Fig. 5a) and burst suppression (Fig. 5a). The 50%
effective dose for isoelectric EEG was 3.5% sevoflurane [95% confidence interval (CI), 3.4–3.7%] and 95% effective dose was 3.7% (3.6–4.9%). The calculated probabilities of the occurrence of isoelectric EEG for other quantiles are detailed in Table 2. Maximum-likelihood estimation showed a \( P=1 \) and goodness-of-fit \( \chi^2 = 0.533 \).

The 50% effective dose for burst suppression EEG was 3.0% (2.1–3.3%). Maximum-likelihood estimation showed a \( P=0.922 \) and goodness-of-fit \( \chi^2 = 3.841 \).

**Vasopressor requirement**

MAP was maintained by repeated administration of phenylephrine. When compared with the ie subgroup (7 of 20), all subjects in the ie+ group (10 of 10) needed phenylephrine (Table 3); the difference was significant (\( P=0.001 \)).

**Adrenergic response to incision**

Only 1 of 10 ie+ subjects showed an increase of >15% in HR or MAP, whereas 11 of 20 ie− subjects showed an increase (Table 3). Compared with ie− subjects, ie+ subjects experienced less adrenergic responses to incision (\( P=0.024 \)).

**Discussion**

The MACie of sevoflurane in 100% oxygen was 3.5% (2.1 times MAC) in middle-aged adults premedicated with phenobarbital. The crossover responses observed were markedly stable between 3.3% (all five subjects ie−) and 3.7% (all six subjects ie+), suggesting high reliability of the target sevoflurane concentration.

Based on the MAC for middle-aged subjects of 1.7%,\(^2\) the MACie was \( \approx 2.1 \) MAC, which was close to MACBAR (2.2 MAC).\(^2\) The EEG recorded by the Entropy Module demonstrates cortical activity,\(^2\) while the autonomic cardiovascular centres are located in the medulla. So MACBAR and MACie represent the sensitivity of different brain structures to sevoflurane. Previous studies showed that burst suppression induced by

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**Table 1** Subject characteristics. Data are presented as mean (SD), mean (range), or number (%). Temperature and \( \text{P}^\prime\text{CO}_2 \) were recorded 2 min before incision. Time interval, time from induction to incision; fluids administered was calculated from entering the room to incision.

<table>
<thead>
<tr>
<th></th>
<th>ie + (n = 10)</th>
<th>ie − (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56 (46–65)</td>
<td>55 (45–64)</td>
</tr>
<tr>
<td>Male gender</td>
<td>5 (50)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (8)</td>
<td>162 (8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57 (11)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.6 (0.5)</td>
<td>36.4 (0.3)</td>
</tr>
<tr>
<td>Time interval (min)</td>
<td>33 (3)</td>
<td>32 (2)</td>
</tr>
<tr>
<td>Fluids administered (ml)</td>
<td>745 (26)</td>
<td>757 (30)</td>
</tr>
<tr>
<td>( \text{P}^\prime\text{CO}_2 ) (kPa)</td>
<td>4.8 (0.2)</td>
<td>5.0 (0.2)</td>
</tr>
</tbody>
</table>
Sevoflurane was synchronous over the whole cortex, but was not synchronous in phylogenetically different brain areas: phylogenetically older areas were more resistant to EEG suppression than the neocortex. In our study, the value of MACie was close to the MACBAR, which could be explained by the approximate requirement of sevoflurane to suppress electric activity in the cortex and medulla. Accordingly, our results demonstrate that the state of isoelectric EEG allows less adrenergic responses to nociceptive stimulation compared with the state of non-isoelectric EEG. Subjects in the state of isoelectric EEG needed more vasopressor to maintain haemodynamic stability in the absence of surgical stimulation. The synchronous inhibition of HR and cortical electrical activity had been demonstrated in humans receiving isoflurane and enflurane anaesthesia. Provided MACie is equal (or close) to MACBAR, we may intentionally produce isoelectric EEG targeted to blunt autonomic reflexes in indicated patients.

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![Fig 4](image_url) Maximal BSR of each subject in per cent. BSR between 0% and 100% shown by bars, 0, no burst suppression EEG; 100, isoelectric EEG. The age and end-tidal concentration of sevoflurane are indicated.

![Fig 5](image_url) (A) The dose–response curve from the probit analyses of end-tidal sevoflurane concentrations and the probability of isoelectric EEG (MACie). MACie is 3.5 vol% (3.4–3.7 vol%). (B) The dose–response curve from the probit analyses of end-tidal sevoflurane concentrations and the probability of the presence of burst suppression (MACbs). MACbs is 3.0 vol% (2.1–3.3 vol%).

### Table 2 Calculated probabilities of isoelectric EEG

<table>
<thead>
<tr>
<th>Probability</th>
<th>End-tidal sevoflurane concentration (vol%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>3.28</td>
<td>2.24, 3.40</td>
</tr>
<tr>
<td>0.05</td>
<td>3.35</td>
<td>2.56, 3.44</td>
</tr>
<tr>
<td>0.10</td>
<td>3.39</td>
<td>2.75, 3.47</td>
</tr>
<tr>
<td>0.20</td>
<td>3.43</td>
<td>2.98, 3.50</td>
</tr>
<tr>
<td>0.30</td>
<td>3.47</td>
<td>3.16, 3.54</td>
</tr>
<tr>
<td>0.40</td>
<td>3.49</td>
<td>3.30, 3.59</td>
</tr>
<tr>
<td>0.50</td>
<td>3.52</td>
<td>3.40, 3.67</td>
</tr>
<tr>
<td>0.60</td>
<td>3.55</td>
<td>3.46, 3.81</td>
</tr>
<tr>
<td>0.70</td>
<td>3.58</td>
<td>3.50, 3.99</td>
</tr>
<tr>
<td>0.80</td>
<td>3.61</td>
<td>3.54, 4.22</td>
</tr>
<tr>
<td>0.90</td>
<td>3.66</td>
<td>3.57, 4.59</td>
</tr>
<tr>
<td>0.95</td>
<td>3.70</td>
<td>3.60, 4.93</td>
</tr>
<tr>
<td>0.99</td>
<td>3.78</td>
<td>3.64, 5.62</td>
</tr>
</tbody>
</table>
Table 3  Haemodynamic parameters. Data are presented as mean (so) or number (%). HR, heart rate; MAP, mean arterial pressure. HR and MAP were recorded on entering the room, 2 min before, and 3 min after skin incision, respectively. NS, not significant

<table>
<thead>
<tr>
<th></th>
<th>ie+ (n=10)</th>
<th>ie- (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative MAP (mm Hg)</td>
<td>92 (7)</td>
<td>95 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-incision MAP (mm Hg)</td>
<td>94 (7)</td>
<td>89 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-incision MAP (mm Hg)</td>
<td>99 (14)</td>
<td>100 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative HR (beats min⁻¹)</td>
<td>72 (9)</td>
<td>69 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-incision HR (beats min⁻¹)</td>
<td>82 (9)</td>
<td>80 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-incision HR (beats min⁻¹)</td>
<td>90 (10)</td>
<td>90 (9)</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine injection [n (%)]</td>
<td>10 (100)</td>
<td>7 (35)</td>
<td>0.001</td>
</tr>
<tr>
<td>MAP or HR increase &gt;15% [n (%)]</td>
<td>1 (10)</td>
<td>11 (55)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

might differentially affect MACBAR and MACie, an interesting direction for further studies.

Preliminary studies of neuroprotection suggested that anaesthetic-associated protection might be mediated by a reduced metabolic demand, such that complete suppression of cortical electric activity would lead to maximal neuroprotection. But, most of the evidence was based on animal experiments since it was hard to do similar experiments with human subjects. Doyle and Matta showed that isoelectric EEG gave more metabolic suppression than 0% and 50% BSR in 11 patients undergoing general anaesthesia. Although still controversial, a growing body of preliminary evidence associates low BIS values and intermediate-term mortality in both cardiac and non-cardiac surgical patients. It is not clear whether the deep anaesthesia-associated adverse outcomes are different between cardiac and non-cardiac surgical patients, or whether the correlation is causal. Our study was not to analyse the cerebral protective or impairing effects of a certain anaesthesia depth, but to find a basis on which a further study can be carried out.

This trial has some important limitations. All subjects were hospitalized middle-aged adults, not healthy volunteers, which might lead to Berkson’s bias. Elderly and critically ill patients, who are more likely to have serious complications under excessively deep anaesthesia, were excluded for safety reasons. Such a cohort needs to be included in further studies to generalize the estimation of MACie to a broader population. We arbitrarily started at 1.7% (1 MAC) with a step size of 0.2% (0.1 MAC) according to previous studies. As the sevoflurane vaporizer output covers a small range from 0% to 8%, a linear rather than logarithmic scale was used. When using the modified Dixon up-and-down method, sample size determination is relatively speculative. In order to balance the interest of accurate MACie estimation and variability estimation, we terminated our experiment after six crossovers were observed to minimize the potential bias. The primary focus of the present study was to determine the concentration of sevoflurane inducing isoelectric EEG in 50% of subjects (MACie); values for other quantities can be estimated with the probit model, but these estimates might not be reliable at both tails of the tolerance distribution. Cerebral blood flow and cerebral oxygen metabolism rate might have influenced the state of isoelectric EEG, but we were unable to collect these data. Volatile anaesthetic induction and maintenance with sevoflurane avoided potential interactions with other anaesthetics that might confound MACie estimation. Patients with known factors that might confound MAC were excluded, and the experiment was strictly controlled to avoid possible confounds such as hypotension, hypothermia, and hyperthermia. Several factors, including age and i.v. anaesthetics, might change the value of MACie of sevoflurane, which should be studied in the next step. All subjects received a single dose of phenobarbital as premedication according to local standards, which could affect the MACie determination; further work is needed to clarify this issue, and to determine the MACie for other currently used volatile agents.

In summary, the MACie of sevoflurane in middle-aged adults premedicated with phenobarbital was 3.5 vol%. The sevoflurane-induced isoelectric EEG state is associated with significant cardiovascular depression but reduced haemodynamic responses to skin incision. These data might be useful in avoiding excessive depth of anaesthesia in vulnerable patients, or achieving transient burst suppression or isoelectric EEG when desired.

Authors’ contributions


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Declaration of interest

None declared.
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**References**

29. Michenfelder JD. The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. *Anesthesiology* 1974; 41: 231–6

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