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Isoflurane and sevoflurane decrease entropy indices more than halothane at equal MAC values

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Abstract
Recently, bispectral index (BIS) values were demonstrated to be different for various anesthetics as a result of differential effects on electroencephalographic (EEG) signals. Entropy is similar to the BIS monitor, as both process raw EEG to derive a number. We hypothesized that entropy may also be anesthetic agent-specific. Thirty adult patients undergoing spinal surgery were randomized to receive halothane, isoflurane, or sevoflurane. Entropy indices were recorded at various minimum alveolar concentration (MAC) values—0.5, 0.75, 1.0 and 1.5—both during wash-in and wash-out of the agent. Heart rate (HR), mean arterial blood pressure (MAP), response entropy (RE), and state entropy (SE) were noted. Statistical analysis was done using a one-way analysis-of-variance test. *P* values less than 0.05 were considered significant. Ten patients in each group completed the study. The demographics and baseline values of HR, MAP, RE, and SE were comparable in all three groups. During the study period, for a given MAC value, both RE and SE remained low in the isoflurane and sevoflurane groups compared to the halothane group. For a given MAC, the RE and SE were comparable during wash-in and wash-out phases. Halothane produced higher entropy values as compared to isoflurane and sevoflurane at equivalent MAC levels.

Key words Anesthetic gases · Monitoring · Depth of anesthesia · Equipment · Entropy

Traditionally, the minimal alveolar concentration (MAC) has been used to measure the potency of inhalational anesthetics. It is supposed that equi-MAC concentrations of different anesthetics have a similar potency in suppressing responses to painful stimuli. Recently, attempts were made to see whether equi-MAC concentrations of various anesthetics produced similar bispectral index values [1,2]. However, no such data are available for the use of entropy. We hypothesized that similar data may hold true for the entropy indices, response entropy (RE) and state entropy (SE). To date, there has been no study that compares the three anesthetics halothane, isoflurane, and sevoflurane, in terms of their equi-MAC entropy values. The aim of this prospective and randomized preliminary study was to compare entropy indices (RE and SE) at equi-MAC concentrations of these three commonly used anesthetics.

After approval was obtained from the Institute's Ethics Committee and informed consent was obtained from the patients, 30 adult patients (American Society of Anesthesiologists [ASA] physical status I and II) aged 18–60 years, undergoing lumbar spine surgery, were enrolled for the study. Exclusion criteria included patients with body weight more than 20% of ideal body weight, patients on hypnotics and antidepressants, patients with cardiac diseases and neurological disorders, and those receiving beta-blocker drugs. All patients were premedicated with intramuscular glycopyrrolate 0.2 mg 1 h prior to surgery. In the operation theater, standard monitoring of ECG, pulse oximetry, and noninvasive blood pressure was started. The spectral entropy electrode was applied on the forehead of the patient in accordance with the manufacturer's instructions and connected to the entropy monitor (Datex-Ohmeda S/5 Entropy module; Instrumentarium, Helsinki, Finland). The indices RE and SE were read manually and recorded. Intraoperatively, end-tidal carbon dioxide (Et_{CO_2}) concentration, inspired and expired concentrations of anesthetic gases, and invasive blood pressure were also recorded. Before the induction of general anesthesia, the baseline heart rate (HR) and mean arterial blood pressure (MAP) were recorded along with the RE and SE. General anesthesia was induced with fentanyl 2 $\mu g \cdot kg^{-1}$ and thiopentone sodium 4–5 $mg \cdot kg^{-1}$. Tracheal intubation was facilitated with

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rocuronium 1 mg·kg^{-1}. On the basis of a computer-generated randomization table, patients received either halothane, isoflurane, or sevoflurane for the maintenance of anesthesia, in an oxygen and air mixture (fractional inspired oxygen; $F_{I_{O_2}}$, 0.4). A constant fresh gas flow of 3 l·min^{-1} was maintained throughout the study period. Mechanical ventilation was started to adjust Et_{CO_2} between 34 and 36 mmHg. Intermittent boluses of fentanyl 1 μg·kg^{-1}·h^{-1}, whenever HR and MAP exceeded 20% of baseline, and rocuronium 0.05 mg·kg^{-1} were administered to assist ventilation. The study data were collected at the end-tidal concentration of inhaled anesthetics at 0.5, 0.75, 1.0, and 1.5 MAC (wash-in) and again during 1.0, 0.75, and 0.5 MAC (wash-out). The HR, MAP, RE, and SE were noted as the end-tidal concentration of inhaled anesthetics increased from 0.5 to 0.75, 0.75 to 1.0, and 1.0 to 1.5 MAC (wash-in). The values were again noted when MAC decreased from 1.5 to 1.0, 1.0 to 0.75, and 0.75 to 0.5 (wash-out). A steady state of 10 min was allowed at each target concentration before data were recorded, to ensure equilibration of the anesthetic to the brain. Arterial blood pressure (from the dorsalis pedis artery) was increased with bolus injection of mephentermine sulfate if values decreased by 20% from the initial MAP.

Data were analyzed using STATA 9.0 software (STATA, College Station, TX, USA). Data values are expressed as means (SD). Mean age and the body weight and sex of the patients and the values for HR, MAP, RE, and SE in the three groups were compared by one-way analysis of variance followed by Bonferroni correction. A P value of less than 0.05 was considered significant.

All patients completed the study and none were excluded from the final analysis. The demographic characteristics and the baseline values of HR, MAP, RE, and SE were comparable in all three groups (Table 1). Under anesthesia, both RE and SE remained low in the isoflurane and sevoflurane groups compared to the halothane group (Fig. 1a,b). Differences were observed at 1.0 and 1.5 MAC, both during wash-in and wash-out. RE in the halothane group remained high at 0.75 MAC as compared to the isoflurane and sevoflurane groups, both during wash-in and wash-out phases. SE in the halothane group was also high at 0.75 and 0.5 MAC as compared to the other two groups, but only during the wash-out phase. However, for a given MAC concentration, the RE and SE were comparable during wash-in and wash-out phases. The use of mephentermine sulfate did not differ between the groups. Three patients in the halothane group and two patients each in the isoflurane and sevoflurane groups required vasopressor at 1.5 MAC.

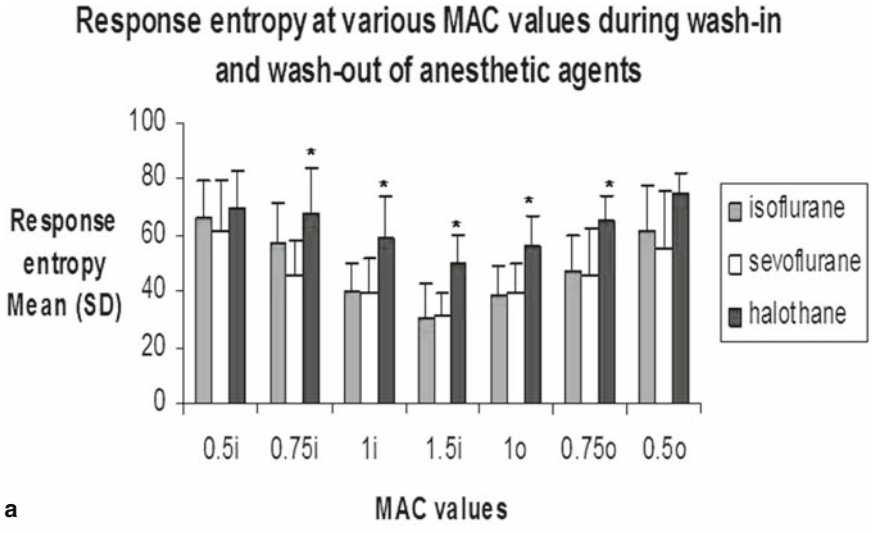
In our study we found that entropy values in the halothane group remained high compared to those in the isoflurane and sevoflurane groups at all MAC values. It was noted that entropy values were comparable in the isoflurane and sevoflurane groups. The difference in entropy values can be explained on the basis of the differential effects of halothane, isoflurane, and sevoflurane on EEG. MAC-awake indicates the concentration required for hypnosis. At larger opioid doses administered with inhalational agents, MAC values are reduced to MAC-awake values. Therefore the MAC-awake/MAC ratio indicates the relative analgesic potency of a given inhalational agent. We also know that halothane has a higher MAC-awake/MAC ratio as compared to isoflurane and sevoflurane; 57% for halothane and 38% and 41% for isoflurane and sevoflurane, respectively.

It is clear that, at equi-MAC concentrations, isoflurane and sevoflurane produce a greater hypnotic effect than halothane. It is known that the MAC indicates the ability of an agent to cause immobility during surgery and has poor correlation with the degree of hypnosis caused by the agent. Anesthetic agents variably affect the spinal mechanisms of immobility and cerebral mechanisms of hypnosis. This may be responsible for the differences in entropy values observed between agents at equi-MAC concentrations. Jinks et al. [3] showed that halothane, through its spinal mechanisms, caused greater degrees of analgesia and immobility when compared with isoflurane. In a study by Constant et al. [4], the authors found that clinical concentrations of halothane produced relatively fast EEG rhythms,

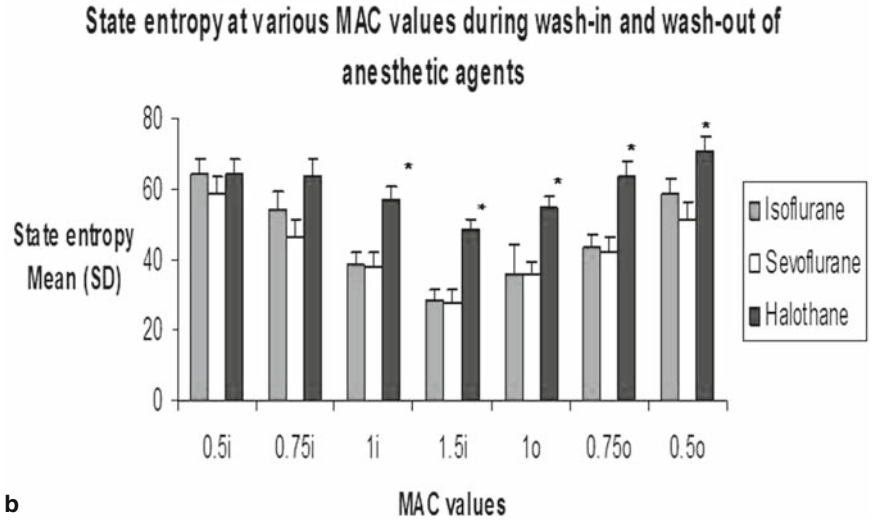
Table 1. Demographics and baseline values measured before induction of general anesthesia

	Isoflurane group (n = 10)	Sevoflurane group (n = 10)	Halothane group (n = 10)	P value
Age (years)	38.1 (16.5)	38.2 (16.8)	38.2 (10.5)	NS
Weight (kg)	55 (10.6)	56.9 (7.6)	62.7 (13.6)	NS
M:F	8:2	6:4	7:3	NS
HR	88.8 (12.3)	84.4 (12.6)	81.0 (12.3)	NS
MAP	99.8 (8.1)	102.8 (9.5)	105.4 (8.2)	NS
RE	97.7 (1.5)	98.1 (0.7)	97.8 (1.4)	NS
SE	87.6 (2.5)	89.8 (0.9)	87.0 (2.7)	NS

Data values are means (SD)
HR, heart rate; MAP, mean arterial pressure; RE, response entropy; SE, state entropy; NS, not significant



a



b

Fig. 1a,b. Graphical trends showing **a** response entropy values during various minimum alveolar concentration (*MAC*) concentrations and **b** state entropy values during various MAC concentrations. *i*, values recorded during wash-in phase of the given MAC value; *o*, values recorded during wash-out phase of the given MAC value. $*P < 0.05$, as compared to isoflurane and sevoflurane

whereas sevoflurane produced progressively slower EEG activity with relatively few fast rhythms.

Our work is different from earlier studies in that we recorded the entropy values of three volatile agents for comparison. Through entropy, we measured two indices; SE, which quantifies cortical cerebral activity (hypnosis) and has been shown to be similar to the BIS value, and RE, which evaluates electromyography (EMG) activity (subcortical component). It was observed that, under anesthesia, the difference between RE and SE remained at less than 10, indicating adequate analgesia. The possibility of incomplete equilibration of anesthetics between brain and blood during assessment cannot be ruled out. To minimize this, we measured RE and SE once a stable MAC value was achieved for no less than 10 min, and we carried out these measurement during both wash-in and wash-out phases.

The clinical implication of our study is that adjusting the administration of anesthetic agents based on entropy values may be inappropriate, as halothane results in higher entropy of EEG compared to sevoflurane or isoflurane at equivalent MAC values. As halothane produces higher entropy values compared with sevoflurane and isoflurane, clinicians may administer excessive halothane in an attempt to achieve adequate entropy values. This may indirectly affect systemic and intracranial hemodynamics. In previous similar studies using a BIS monitor, the absence of a surgical stimulus was a limitation [2]. Ropcke et al. [5] have shown that surgical stimulus shifts the EEG concentration-response relationship of desflurane and therefore affects BIS values. We therefore recorded all parameters after the surgery started.

A limitation of our study could be that we did not adjust the MAC values of the inhaled anesthetics to the age of the patient. However, it must be mentioned that the age-corrected MAC values as suggested by Eger et al. [6] were derived from a metaanalysis, which may

not be clinically relevant for individual patients. We are of the same opinion as Schwab et al. [2] in this regard. In conclusion, the results of our study are consistent with the findings in other studies using the BIS as the monitor. Halothane produced higher entropy values compared to sevoflurane or isoflurane at equivalent MAC values.

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