

CLINICAL PRACTICE

# Advance of age decreases the minimum alveolar concentrations of isoflurane and sevoflurane for maintaining bispectral index below 50

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**Background.** We investigated age-related differences in the minimum alveolar concentration (MAC) of isoflurane and sevoflurane for maintaining bispectral index (BIS) below 50 (MAC<sub>BIS50</sub>).

**Methods.** One hundred and twenty young ( $\leq 40$  yr), middle-aged (41–69 yr), and elderly ( $\geq 70$  yr) patients were randomly allocated to one of the six groups. Anaesthesia was induced with isoflurane or sevoflurane in oxygen. After tracheal intubation, we arbitrarily started maintenance of anaesthesia in each group with end-tidal isoflurane and sevoflurane concentrations of 0.8 and 1.2 vol%, respectively. After 10 min at predetermined end-tidal isoflurane or sevoflurane concentrations, BIS was measured for 1 min. MAC<sub>BIS50</sub> of isoflurane or sevoflurane for each group was determined by up–down methodology.

**Results.** MAC<sub>BIS50</sub> of isoflurane in young, middle-aged, and elderly patients was 0.82% end-tidal (95% confidence intervals 0.76–0.88), 0.67% (0.61–0.73), and 0.56% (0.51–0.61), respectively, and that of sevoflurane in young, middle-aged, and elderly patients was 1.28% (1.24–1.32), 0.97% (0.89–1.05), and 0.87% (0.84–0.90), respectively. For both isoflurane and sevoflurane, the MAC<sub>BIS50</sub> was significantly higher ( $P=0.002$  and  $0.001$ , respectively) in young patients and significantly lower ( $P=0.02$  for both) in elderly patients than those in middle-aged patients.

**Conclusions.** Advance in age significantly decreased the concentrations of isoflurane and sevoflurane required to maintain BIS below 50. BIS correctly reflected age-associated decrease of end-tidal concentrations of isoflurane and sevoflurane required for maintaining adequate depth of anaesthesia during resting state.

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The minimum alveolar concentration (MAC) of volatile agents decreases with advance in age.<sup>1–3</sup> Additionally, a decrease in the MAC to suppress patients' response to commands (MAC<sub>awake</sub>) is also observed in older patients.<sup>4–5</sup> As such, it can be hypothesized that the concentration of anaesthetics required to suppress cerebral electrical activity sufficiently to maintain a given depth of anaesthesia decrease with advance in age. Bispectral index (BIS), a proprietary algorithm based on EEG, correlates significantly with the level of responsiveness and is a reliable marker indicative of the depth of anaesthesia, thereby being widely used.<sup>6–9</sup> We hypothesized that concentrations of isoflurane and

sevoflurane required for maintaining BIS below 50 (MAC<sub>BIS50</sub>) would decrease with increasing age.

## Methods

After obtaining approval from the institutional ethics committee and written informed consent, 40 young ( $\leq 40$  yr), 40 middle-aged (41–69), and 40 elderly ( $\geq 70$  yr) patients with ASA physical status I or II, undergoing elective orthopaedic or gynaecological surgery, were randomly included. The study was conducted in a double-blind fashion. Patients with

abnormal ECG, cardiovascular, respiratory, or psychological diseases or with predicted difficulty in tracheal intubation were excluded from this study. Other exclusion criteria included a regular use of hypnotic medication, drug or alcohol abuse, and obesity with BMI  $>30 \text{ kg m}^{-2}$ . Patients were allocated to one of the following six groups according to age and anaesthetics they received: young-isoflurane, young-sevoflurane, middle-aged-isoflurane, middle-aged-sevoflurane, elderly isoflurane, and elderly sevoflurane groups ( $n=20$  each). Random allocation to these groups was made using a computer-generated random number table.

No premedication was used. Before anaesthesia, a venous catheter was inserted and lactated Ringer's solution was infused at a rate of  $10 \text{ ml kg}^{-1} \text{ h}^{-1}$  throughout the study. Intraoperative monitoring consisted of a five-lead ECG, non-invasive measurement of arterial pressure, and pulse oximetry. Carbon dioxide tensions and concentration of anaesthetics were measured with a gas analyzer (Capnomac Ultima; GE Healthcare, Helsinki, Finland) which was calibrated before each experiment. The anaesthetic system used was a semi-closed system with a total gas flow of  $6 \text{ litre min}^{-1}$ . Anaesthesia was induced using a face mask with isoflurane in oxygen (young-isoflurane, middle-aged-isoflurane, and elderly isoflurane groups) or sevoflurane in oxygen (young-sevoflurane, middle-aged-sevoflurane, and elderly sevoflurane groups). End-tidal carbon dioxide tension was maintained at 35–40 mm Hg throughout the study. The concentrations of isoflurane and sevoflurane were initially set at 0.3 vol% and then increased slowly until the end-tidal concentration reached 1.1 and 1.7 vol%, respectively. The concentrations of these two anaesthetics were determined according to their MAC and our previous study outcomes.<sup>10</sup> After loss of consciousness, vecuronium  $0.1 \text{ mg kg}^{-1}$  was given and assisted ventilation was started followed by controlled ventilation. Twelve minutes after induction of anaesthesia, the trachea was intubated and the lungs were mechanically ventilated. Induction of anaesthesia and tracheal intubation were performed by one of the authors (Y.O.) who was able to know only the end-tidal concentration of anaesthetics and carbon dioxide tensions but blinded as to EEG and BIS.

We arbitrarily started in each group with end-tidal concentrations of isoflurane of 0.8 vol% and sevoflurane of 1.2 vol% (corresponding to 0.75 MAC) according to the previously reported MAC<sub>BIS50</sub> of sevoflurane.<sup>11</sup> A pre-determined target end-tidal concentration of isoflurane or sevoflurane was maintained for 10 min, followed immediately by a 1 min assessment of BIS consisting of six recordings taken at 10 s intervals by an observer blinded to the patients' groups (T.M.). If a given patient had an average BIS of  $<50$ , the concentration of isoflurane or sevoflurane was reduced by 0.1 vol% in the subsequent patient randomized to the same group, whereas if a given patient had a BIS  $\geq 50$ , the concentration was increased by 0.1 vol% in the subsequent patient in the same group. The mean (with 95% confidence interval) MAC<sub>BIS50</sub> of isoflurane and

sevoflurane was calculated from the midpoints of pairs of concentrations from consecutive patients in which a negative response was followed by a positive one according to the up–down method with back-up probit analysis.<sup>11 12</sup>

EEG data were continuously observed by a monitor (A-2000, version 3.34; Aspect Medical Systems, Norwood, MA, USA). The impedance of each electrode was maintained at  $<2 \text{ k}\Omega$ . The smoothing window was set at 15 s, which was used for interpreting the data. All binary data packets, containing raw wave data and BIS, were recorded on a personal computer (LB500/J2, NEC Corporation, Tokyo, Japan) using Bispectrum Analyzer for BIS developed by Hagihira and colleagues<sup>13</sup> and analysed later by one of the authors who was unaware of the group allocation (K.T.).

### Statistics

Sample size was determined based on our preliminary study, where MAC<sub>BIS50</sub> of sevoflurane was measured in young, middle-aged, and elderly patients with mean ages of 28, 55, and 74 yr, respectively ( $n=12$ , each group). MAC<sub>BIS50</sub> measured by the up–down method was 1.2 (0.1), 1.0 (0.1), and 0.9 (0.2) vol% in young, middle-aged, and elderly patients, respectively. Power analysis on the assumption of a type I error protection of 0.05 and a power of 0.80 to detect a 0.1 vol% change in MAC<sub>BIS50</sub> showed that 20 patients were required for each of the three groups. Patient characteristics data were expressed as the mean (SD). The end-tidal concentrations of isoflurane and sevoflurane were expressed as the mean with 95% confidence intervals. Patient characteristics data were compared among the six groups with  $\chi^2$  test. One-way analysis of variance was used to test the differences of MAC<sub>BIS50</sub> among the three groups receiving the same anaesthetics, followed by the Student–Newman–Keuls test for multiple comparisons.

### Results

Similar patient characteristics among the six groups with respect to sex ratios, weight, and height were found. Similar age distribution was found between young-isoflurane and young-sevoflurane, middle-aged-isoflurane and middle-aged-sevoflurane, and elderly isoflurane and elderly sevoflurane groups (Table 1). For each anaesthetic agent, the end-tidal concentrations before and after tracheal intubation were similar (data not shown). Body temperature and the carbon dioxide tensions at the beginning of 1 min measurement of BIS were similar among the six groups with no difference being found.

The MAC<sub>BIS50</sub> of isoflurane and sevoflurane significantly decreased with advance in age. Sequences of individual patients in the isoflurane and sevoflurane groups and measured MAC<sub>BIS50</sub> values according to up–down methodology are shown in Figure 1 and Table 2. For both isoflurane and sevoflurane groups, the MAC<sub>BIS50</sub> of young

**Table 1** Patient characteristic and physiological data. Data are expressed as mean (range) or mean (SD) of 20 experiments. There were no differences among the six groups except age. There were no differences in age between young-isoflurane and young-sevoflurane, middle-aged-isoflurane and middle-aged-sevoflurane, or elderly isoflurane and elderly sevoflurane groups. Body temperature and end-tidal carbon dioxide tensions were measured at the beginning of 1 min measurement of BIS

	Young-isoflurane	Middle-aged-isoflurane	Elderly isoflurane	Young-sevoflurane	Middle-aged-sevoflurane	Elderly sevoflurane
Age (yr)	30 (20–39)	56 (44–67)	75 (70–88)	30 (20–40)	55 (41–66)	75 (71–86)
Weight (kg)	56 (7)	59 (5)	55 (6)	55 (8)	58 (8)	59 (5)
Height (cm)	162 (6)	161 (6)	160 (4)	163 (4)	162 (5)	162 (5)
Sex (male/female)	8/12	9/11	9/11	8/12	8/12	9/11
Body temperature (°C)	36.5 (0.2)	36.4 (0.2)	36.5 (0.2)	36.5 (0.2)	36.4 (1)	36.4 (0.3)
End-tidal CO <sub>2</sub> (mm Hg)	37 (1)	36 (1)	37 (1)	37 (1)	36 (1)	36 (1)

patients was significantly higher ( $P=0.002$  and  $0.001$ ) and that of elderly patients was significantly lower ( $P=0.02$  for both) than middle-aged patients.  $MAC_{BIS50}$  values calculated with probit back-up analysis were similar to those derived by up–down methodology (Table 2). No patients had a systolic arterial pressure  $<80$  mm Hg or a HR slower than  $50$  beats  $\text{min}^{-1}$ . None complained of intraoperative awareness on the follow-up queries in the hospital.

## Discussion

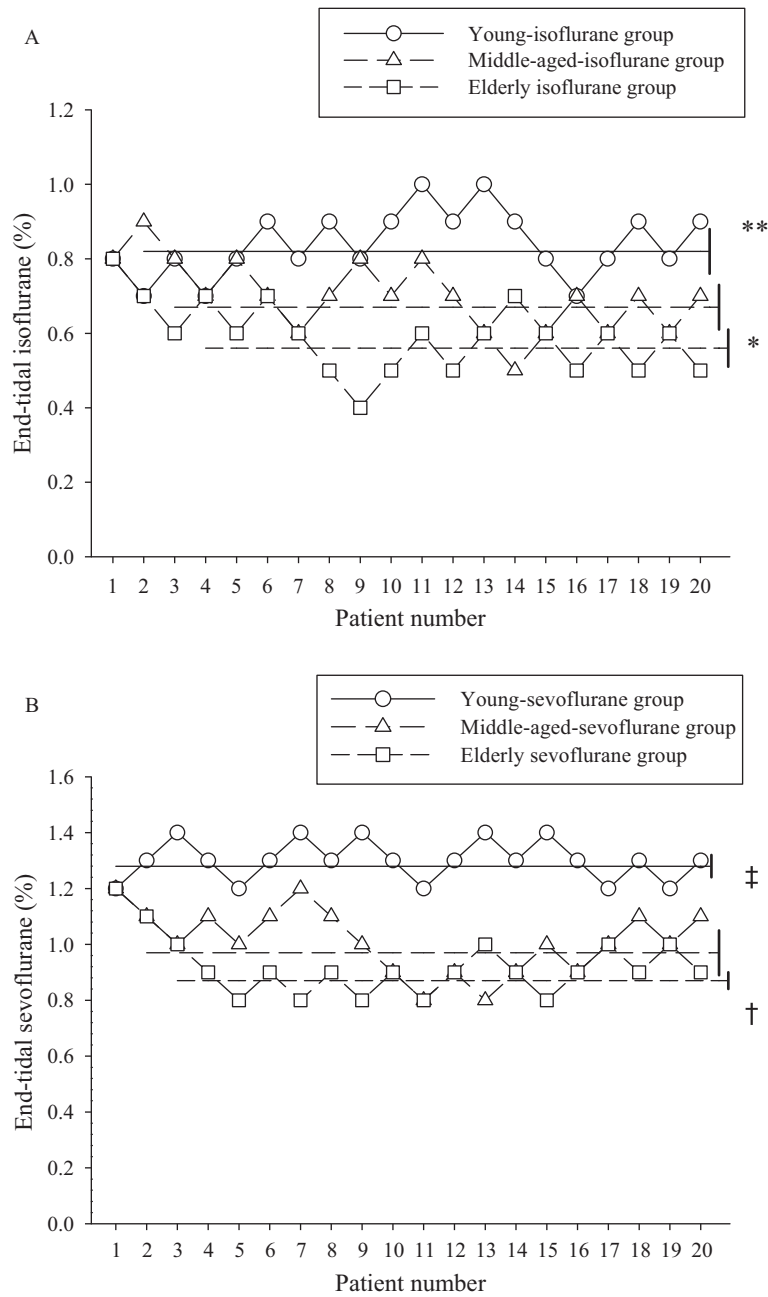
The  $MAC_{BIS50}$  of isoflurane and sevoflurane was found to decrease with advance in age in the present study. After tracheal intubation, the end-tidal concentration of anaesthetics was adjusted to the predetermined value by decreasing the inspiratory concentration of those and then the predetermined end-tidal concentrations of isoflurane and sevoflurane were maintained constant for 10 min before assessment of BIS. BIS was stable in all patients during assessment. Since equilibration half-lives ( $t_{1/2k_{e0}}$ ) of isoflurane and sevoflurane derived from the BIS data are 3.2 and 3.5 min, respectively,<sup>8</sup> the equilibration time including the time for adjusting the end-tidal concentration was more than three times the values of  $t_{1/2k_{e0}}$ . As such, the effect-site concentrations for both anaesthetics were considered sufficiently reaching steady-state conditions. Since MAC and  $MAC_{\text{awake}}$  of volatile agents decreased with advance in age,<sup>1–5</sup> the required concentrations of those to suppress the cerebral electrical activity to the same degree would also decrease with advance in age.

In this study, the relative ratios of  $MAC_{BIS50}$  of the young-isoflurane and elderly isoflurane groups to that of the middle-aged-isoflurane group were 1.22 and 0.85, respectively. Likewise, the relative ratios of  $MAC_{BIS50}$  of the young-sevoflurane and elderly sevoflurane groups to middle-aged-sevoflurane group were 1.32 and 0.89, respectively. The relative ratios of MAC for isoflurane at 30 and 75 yr to that of 55 yr calculated by regression analysis based on previously reported data are 1.22 and 0.85, respectively.<sup>4</sup> And the counterparts of MAC for sevoflurane are 1.21 and 0.86, respectively. These values

are found to be similar to those of  $MAC_{BIS50}$  we measured, which is the  $MAC_{BIS50}$  decreased at the similar rate of decrease in MAC with advance in age. The ratios of  $MAC_{BIS50}$  to MAC of isoflurane and sevoflurane were  $\sim 0.64$  and  $0.60$ , respectively. On the other hand,  $MAC_{\text{awake}}$  of isoflurane and sevoflurane also decreases with advance in age.<sup>5</sup> It does so in a manner parallel to the influence of age on MAC.<sup>4,5</sup> For both isoflurane and sevoflurane, the ratio of  $MAC_{\text{awake}}$  to MAC is  $0.34$ .<sup>5</sup> The  $MAC_{BIS50}$  we measured was situated between  $MAC_{\text{awake}}$  and MAC, suggesting that  $MAC_{BIS50}$  would be a concentration of these anaesthetics required to produce hypnosis.

We used BIS value below 50 as an index of the depth of anaesthesia. Glass and colleagues<sup>7</sup> suggested that a BIS value  $<50$  could attain loss of consciousness and adequate depth of anaesthesia for a variety of clinically used anaesthetics. MAC is defined as a concentration at which 50% of patients do not move in response to a skin incision; however, it is not recognized as an index of appropriate hypnotic concentration. We considered the end-tidal concentrations to maintain BIS below 50 as an appropriate concentration to achieve hypnotic responses; as supportive evidence, this value has been used previously by other researchers.<sup>11</sup> Given these findings, we investigated the relationships between anaesthetic concentrations and single value of BIS at 50 and did not investigate other BIS values such as 40 or 60. Assessment of the relationships between anaesthetic concentrations and a variety of BIS values would warrant further study, but BIS value below 50 is supposed to play a role as an index indicative of adequate depth of anaesthesia; however, BIS values more than 60 would entail a risk of awareness during procedure.<sup>14</sup>

We administered vecuronium to all patients in this study for facilitating tracheal intubation, preventing body movement, and eliminating the contamination of EMG activity which could be interpreted as a high-frequency, low-amplitude fraction of EEG and could falsely increase the BIS. Various studies<sup>15–17</sup> examined the influence of neuromuscular blocking agents on the depth of anaesthesia indices, especially of BIS; however, their results are controversial. A recent study by Ekman and colleagues<sup>17</sup> using sevoflurane 1.2%, being similar to our study,



**Fig 1** Sequences of individual patients in the young, middle-aged, and elderly groups receiving (A) isoflurane and (B) sevoflurane at predetermined end-tidal concentrations. When a patient showed BIS <50, the isoflurane or sevoflurane concentration was decreased by 0.1% in the following patient. When a patient showed BIS ≥50, the isoflurane or sevoflurane concentration was increased by 0.1% in the following patient. MACs of isoflurane and sevoflurane in young, middle-aged, and elderly patients for maintaining BIS below 50 were calculated by the up–down method (*n*=20, each group) and shown as horizontal bars with 95% confidential intervals (vertical line right to the horizontal bar). \**P*<0.05 and \*\**P*<0.01 compared with the middle-aged-isoflurane group. †*P*<0.05 and ‡*P*<0.01 compared with the middle-aged-sevoflurane group.

**Table 2** MACs of isoflurane and sevoflurane for maintaining BIS below 50 (MAC<sub>BIS50</sub>). All values are expressed as end-tidal percentage of isoflurane and sevoflurane (95% confidential interval). \**P*<0.05 and \*\**P*<0.01 compared with the middle-aged-isoflurane group. †*P*<0.05 and ‡*P*<0.01 compared with the middle-aged-sevoflurane group

	Young-isoflurane	Middle-aged-isoflurane	Elderly isoflurane	Young-sevoflurane	Middle-aged-sevoflurane	Elderly sevoflurane
Up–down method	0.82** (0.76–0.88)	0.67 (0.61–0.73)	0.56* (0.51–0.61)	1.28‡ (1.24–1.32)	0.97 (0.89–1.05)	0.87† (0.84–0.90)
Probit analysis	0.84	0.70	0.57	1.31	1.0	0.89

showed that 95% depression of the first twitch in a train-of-four response did not affect BIS or auditory-evoked potential index during resting condition without noxious stimuli, suggesting that neuromuscular blocking agent would not disturb the assessment of BIS in this study.

We assessed  $MAC_{BIS50}$  without noxious stimuli. The anaesthetic concentrations to maintain BIS below 50 during operative procedures are likely to be higher, although this effect would be attenuated if analgesic agents or neuraxial anaesthesia were used.<sup>13</sup> However, extensive diversity of operative stimuli is responsible for the difficulty to assess BIS during operation. Further study will be required to assess the end-tidal concentrations of isoflurane and sevoflurane for maintaining BIS below 50 with the presence of noxious stimuli such as a skin incision and tetanic stimulation.

In summary, concentrations of isoflurane and sevoflurane required to maintain BIS below 50 ( $MAC_{BIS50}$ ) decreased with advance in age. The magnitudes of change in  $MAC_{BIS50}$  with ageing for isoflurane and sevoflurane were parallel to those in MAC and  $MAC_{awake}$  with age. These results indicate that BIS correctly reflects age-related end-tidal concentrations of isoflurane and sevoflurane required to maintain a level of anaesthesia during resting condition.  $MAC_{BIS50}$  of isoflurane and sevoflurane is indicative of a certain hypnotic concentration between  $MAC_{awake}$  and MAC of those.

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