

Relationship between Bispectral Index Values and Volatile Anesthetic Concentrations during the Maintenance Phase of Anesthesia in the B-Unaware Trial

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ABSTRACT

Background: Hypnotic depth during anesthesia affects electroencephalography waveforms and electroencephalogram-derived indices, such as the bispectral index (BIS). Titrating anesthetic administration against the BIS assumes reliable relationships between BIS values, electroencephalogram waveforms, and effect site concentration, beyond loss of responsiveness. Associations among BIS, end-tidal anesthetic concentrations (ETAC), and patient characteristics were examined during anesthetic maintenance, using B-Unaware trial data.

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What We Already Know about This Topic

- The relationship during maintenance of anesthesia between end tidal anesthetic concentration and electroencephalography, including derived indices such as the bispectral index (BIS), is relatively unstudied

What This Article Tells Us That Is New

- In more than 1,000 patients, during maintenance of anesthesia, there was a population relationship between end tidal anesthetic concentration and BIS, but there was wide interindividual variability in this relationship; BIS frequently correlated poorly with anesthetic concentration and was often insensitive to changes in anesthetic concentration

Methods: Pharmacokinetically stable ETAC epochs during intraoperative anesthetic maintenance were analyzed. A generalized estimating equation determined independent relationships among BIS, ETAC (in age-adjusted minimum alveolar concentration equivalents), patient characteristics, and 1-yr mortality. Further individual and population characteristics were explored graphically.

Results: A total of 3,347,523 data points from 1,100 patients were analyzed over an ETAC range from 0.42 to 1.51 age-adjusted minimum alveolar concentration. A generalized estimating equation yielded a best predictive equation: $BIS = 62.9 - 1.6$ (if age younger than 60 yr) $- 1.6$ (if female) $- 2.5$ (if American Society of Anesthesiologists physical status more than 3) $- 2.6$ (if deceased at 1 yr) $- 2.5$ (if N₂O was not used) $- 1.4$ (if midazolam dose more than 2 mg) $- 1.3$ (if opioid dose more than 50 morphine equivalents) $- 15.4 \times$ age-adjusted minimum alveolar concentration. Although a population relationship between ETAC and BIS was apparent, interindividual variability in the strength and reliability of this relationship was large. Decreases in BIS with increasing ETAC were not reliably observed. Individual-patient linear regression yielded a median slope of -8 BIS/1 age-adjusted minimum alveolar concentration (interquartile range

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–30, 0) and a median correlation coefficient of –0.16 (interquartile range –0.031, –0.50).

Conclusions: Independent of pharmacokinetic confounding, BIS frequently correlates poorly with ETAC, is often insensitive to clinically significant changes in ETAC, and is vulnerable to interindividual variability. BIS is therefore incapable of finely guiding volatile anesthetic titration during anesthetic maintenance.

INADEQUATE depth of anesthesia (DOA) can lead to intraoperative awareness with explicit recall. However, excessive anesthesia increases the incidence of nausea and vomiting, and is associated with delayed recovery and impaired lucidity postoperatively.^{1,2} Practitioners³ and regulatory groups⁴ have called for action in preventing awareness, promoting expansion of brain monitors intended to gauge anesthetic depth. DOA may be conceptualized as a continuum spanning from an anesthetized patient approaching consciousness (light anesthesia) to one with dramatically reduced brain activity (deep anesthesia). It is assumed that assessing DOA with brain monitors will prevent instances of awareness while allowing safe reduction in anesthetic administration.

Most brain monitors use data from the spontaneous electroencephalogram to assess DOA. γ -Aminobutyric acid agonists (including most common volatile anesthetic agents and several common intravenous anesthetics) cause predictable changes in the electroencephalogram waveform.⁵ Interpretation of the raw waveform requires training. Thus, algorithm-driven indices have been derived.⁶ Most algorithms simplify the waveform and its derivatives into a numeric index intended to reflect DOA.⁶ The most widely used brain monitor is the Bispectral Index (BIS) monitor[®] (Covidien, Boulder, CO). The BIS monitor processes a single frontal electroencephalograph signal to calculate a dimensionless number intended to reflect the patient's level of consciousness. BIS values range from 0 to 100, reflecting the absence of detectable brain electrical activity and brain electrical activity during the awake state, respectively. Targeting a BIS range between 40 and 60 has been advocated for awareness prevention and the avoidance of excessive anesthesia.^{7,8}

A DOA index potentially capable of finely guiding volatile anesthetic titration during the maintenance phase would necessarily approach fulfillment of a range of conditions. The most important conditions would include:

1. A high correlation coefficient would be observed between the DOA index and the anesthetic concentration in the brain.⁹
2. The DOA index would be sufficiently sensitive (the slope of the concentration-response curve would be sufficiently steep) in individual patients to allow reasonably accurate estimation of relative anesthetic concentration based on the index.
3. The DOA index would display a predictable value at which emergence from anesthesia occurs across a population of patients. Population differences in anesthetic sensitivity (modest right- or left-shift, or modest differences in slope) would be acceptable, provided that across the population the emergence DOA value was relatively consistent.

Criteria 1 and 2 can be estimated on the basis of a DOA-*versus*-effect-site concentration graph of data collected during the maintenance phase. Theoretic examples are shown in figure 1. Although perfect fulfillment of these criteria would be ideal, a DOA index may have practical utility even if it embodies these characteristics only to a moderate degree. One of the assumptions in this model is that there is no hysteresis in the concentration-response curves for induction and emergence with anesthetic drugs at steady state. Recent research suggests that there might well be such hysteresis,^{10,11} which would mean that the correlation coefficients, slopes, and functions describing the concentration-response curves could be different for induction and emergence.

This substudy of the B-Unaware trial¹² examines the population relationship between BIS values and end-tidal anesthetic concentrations (ETAC), and the effect of four patient characteristics on this relationship. Furthermore, we examine the intersubject variability of the BIS-ETAC relationship. We hypothesized that the BIS satisfies criteria 1 and 2 presented previously.

Materials and Methods

Subjects

Between September 2005 and October 2006, 1,941 patients age 18 yr or older undergoing surgery were screened and prospectively enrolled to the B-Unaware randomized clinical trial (NCT00281489), the details of which are described elsewhere.¹² This predetermined substudy was approved by the Washington University Human Research Protection Office (St. Louis, MO). Briefly, patients at high risk for awareness receiving isoflurane, sevoflurane, or desflurane for maintenance of general anesthesia were included. Supplemental N₂O was permitted. Criteria for identifying patients at high risk for intraoperative awareness were based on previous studies, reviews, and guidelines,^{3,4,8,13–15} and are described elsewhere.¹² Patients were excluded if the surgical procedure or positioning of the patient prevented BIS monitoring, if the surgery required a wake-up test, or if total intravenous anesthesia was required. Patients with dementia, those unable to provide informed consent, and those with a history of stroke with residual neurologic deficits were also excluded.

Procedure

After written informed consent was obtained, patients were randomly assigned to a BIS-guided protocol or to an ETAC-guided protocol, the details of which are described elsewhere.¹² Anesthesia practitioners were aware of the assignments of the patients, but the patients and the statistician

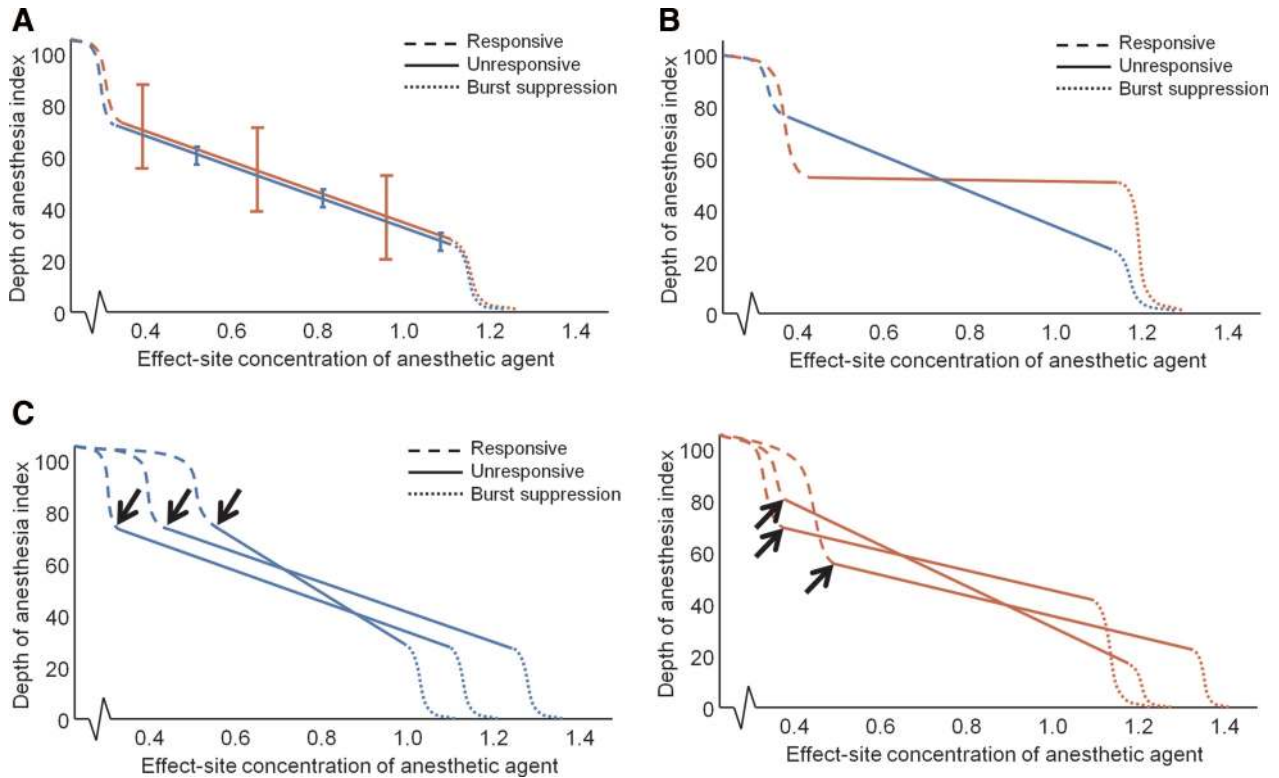


Fig. 1. Characteristics of a depth-of-anesthesia (DOA) monitor capable of finely titrating anesthetic dose during maintenance. (A) The monitor would have a high correlation coefficient between the DOA index and the effect-site (e.g., brain) anesthetic concentration within a single patient (blue line). Considerable within-patient variability at a single effect-site concentration is undesirable (red line). (B) The monitor would be sufficiently sensitive to reflect changes in relative effect-site concentration within a single patient (blue line). An index that is insensitive to clinically significant changes in relative effect-site concentration (red line) would be uninformative. (C) The monitor would display a predictable index value at which emergence from anesthesia occurs across a population of patients (blue lines). If the emergence DOA index value differs among patients (red lines), anesthetic emergence is unpredictable and the index cannot be used for safely titrating anesthesia while reducing the incidence of intraoperative awareness. Note that among-patient differences in anesthetic sensitivity (i.e., modest right- or left-shift, or modest differences in slope) are acceptable (blue lines); among-patient differences in DOA emergence threshold are not (red lines).

were not. The manufacturer of the BIS monitor® at the time the study was conducted (Aspect Medical Systems, Norwood, MA) had no role in the study design, data collection, data analysis and interpretation, manuscript preparation, or the decision to publish the study. No study monitors or other means of support were provided by Aspect Medical Systems.

A BIS Quatro® sensor (Covidien) was applied to the forehead of each patient and version XP® of the BIS software was used. In the BIS group, an audible alarm was set to indicate when the BIS value exceeded 60 or fell less than 40; no ETAC alarms were set in the BIS group, and the practitioners were not instructed to maintain the ETAC within any range. In the ETAC group, an audible alarm was set to indicate when the ETAC concentration fell less than 0.7 age-adjusted minimum alveolar concentration (aaMAC) or exceeded 1.3 aaMAC; practitioners were blinded to the BIS values. The practitioners in both groups could view the ETAC values.

Data Acquisition and Reduction

ETAC measurements were converted into aaMAC equivalents using existing formulae for both individual and multi-

ple anesthetics.¹⁶ (table 1) N₂O was taken into account in the aaMAC calculations, and was included as a variable in subsequent analysis because of the previously documented relative insensitivity of BIS to this agent.¹⁷ In the case of overlapping volatile anesthetics, the total aaMAC value was taken to be the sum of individual aaMAC equivalents. During cardiopulmonary bypass, the anesthetic concentration was

Table 1. Formulae for Age-adjusted Minimum Alveolar Concentration (MAC) Calculations for the Inhaled Anesthetic Agents

$$\begin{aligned}
 \text{aaMAC}_{\text{SEVO}} &= 1.8 \cdot 10^{((\text{Age}-40) \cdot (-0.00269))} \\
 \text{aaMAC}_{\text{ISO}} &= 1.17 \cdot 10^{((\text{Age}-40) \cdot (-0.00269))} \\
 \text{aaMAC}_{\text{DES}} &= 6.6 \cdot 10^{((\text{Age}-40) \cdot (-0.00269))} \\
 \text{aaMAC}_{\text{N}_2\text{O}} &= 104 \cdot 10^{((\text{Age}-40) \cdot (-0.00269))} \\
 \text{aaMAC}_{\text{Total}} &= \text{aaMAC}_{\text{SEVO}} + \text{aaMAC}_{\text{ISO}} + \text{aaMAC}_{\text{DES}} + \\
 &\quad \text{aaMAC}_{\text{N}_2\text{O}}
 \end{aligned}$$

aaMAC_{DES} = age-adjusted MAC equivalent of desflurane; aaMAC_{ISO} = age-adjusted MAC equivalent of isoflurane; aaMAC_{N₂O} = age-adjusted MAC equivalent of N₂O; aaMAC_{SEVO} = age-adjusted MAC equivalent of sevoflurane; aaMAC_{Total} = sum of age-adjusted MAC equivalents when concurrent agents are administered.

measured from the effluent of the cardiopulmonary-bypass machine.¹⁸ For all patients included in this substudy, BIS values and ETAC concentrations were digitally sampled at 1 Hz and were visualized, stored, and exported to.xls format using TrendFace Solo[®] software (ixellence GmbH, Wildau, Germany).

To avoid signal aliasing leading to inclusion of pharmacokinetically confounded data, only patients with ETAC data sampled at 1 Hz during the entire maintenance phase, including during cardiopulmonary bypass where applicable, were included. The analysis also only included periods where the anesthetic agent concentration had not increased or decreased by more than 0.05 aaMAC during the preceding 10 min. Once the stability criteria were met, all data points were included until the aaMAC again changed more than 0.05. This stipulation was set to decrease pharmacokinetic confounding on the relationship between anesthetic agent concentrations and BIS values.^{19,20} In order to fulfill the requirement for pharmacokinetic stability, a script m-file and multiple function m-files were written to implement these quality control criteria using MATLAB engineering software version 7.8 (The MathWorks Inc., Natick, MA).

Statistical Analysis

Continuous variables are presented as mean \pm SD or median (interquartile range), depending on normality of distribution. A three-dimensional bivariate joint probability distribution function was constructed to display the relative frequency of BIS values with respect to aaMAC level. A contour plot of this distribution function was also constructed to provide an unobstructed view of the entire probability space.

The primary outcome of this substudy was characterization of the relationship between the BIS values and ETAC values, expressed as aaMAC equivalents.^{16,21} The relationship between BIS values and ETAC was further contrasted between those with minimal or controlled systemic illnesses (American Society of Anesthesiologists physical status [ASAPS] 1 to 3) and those with severe, uncontrolled systemic disease (ASAPS 4); between men and women; between younger (<60 yr) and older patients (\geq 60 yr); between those alive and dead at 1 yr postoperatively; between those who did and did not receive N₂O; between those who received more than 2 mg and \leq 2 mg midazolam; between those who received more than 50 mg and \leq 50 mg morphine equivalents; and finally between patients allocated to the BIS-guided and ETAC-guided treatment groups. The standard way to model such (within-patient) repeated measurement data is through mixed-effect models. However, mixed-effect models require the normality assumption, which was shown not to hold true for the BIS data (fig. 2). These data are nonnormal with substantial excess kurtosis, and no simple transformation could remedy the nonnormality. Therefore, as a more conservative approach, a generalized estimating equation (GEE)²² was used, because this method does not require specifying the distribution of the response variable. Further-

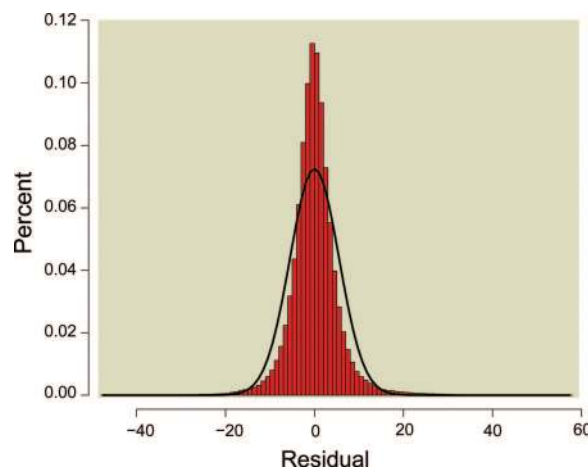


Fig. 2. Residual plot from a linear mixed effect model for bispectral index data, with a normal curve superimposed, demonstrating that the residuals are not normally distributed with substantial excess kurtosis.

more, consistent coefficient estimates can be obtained using a prespecified working correlation structure. Two different working correlation structures were considered: exchangeable and independent. The exchangeable structure assumes the correlation between any two observations (*e.g.*, two BIS values) from the same subject is a constant. The independent structure assumes that observations from the same subject are independent. Pan's proposed quasi-likelihood independence model criterion was used to determine which correlation structure better fit the data²³; the exchangeable working correlation structure produced a better fit. The next step in GEE is to find effects (predictor variables) that are statistically significant. The final analysis is given by GEE with main effects only with the exchangeable working correlation structure. *P* values less than 0.05 were considered significant. The model included all pharmacokinetically stable data within the dataset; more than 98% of the included ETAC values were between 0.42 and 1.51 aaMAC. All statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC).

The GEE presents a whole-population summary of the BIS-ETAC relationship; however, it provides no information on between-patient variability. To examine patterns in the BIS-ETAC relationship for individual patients, univariate linear regression was performed on pharmacokinetically censored data from each patient. Patients contributing BIS data over an ETAC range of less than 0.5 aaMAC were excluded from this analysis because linear regression is unreliable over restricted ranges. Nonparametric measures of central tendency and dispersion were obtained with SPSS Statistics version 18 (IBM Corporation, Somers, NY) providing a gross population estimate of the shape of individual BIS-ETAC relationships at pharmacokinetic stability. Representative BIS-ETAC relationships were graphed using Excel 2007 (Microsoft Corporation, Redmond, WA).

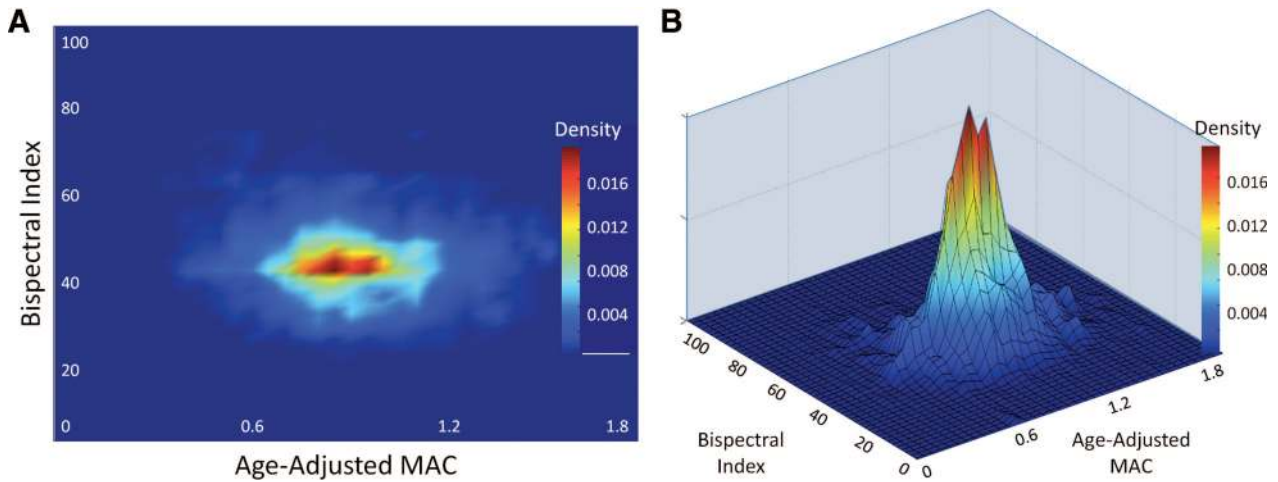


Fig. 3. A contour plot (A) and a three-dimensional bivariate joint probability distribution function (B) from 3,347,523 pharmacokinetically censored data points from 1,100 patients over an end tidal anesthetic concentration (ETAC) range from 0.42 to 1.51 age-adjusted minimum alveolar concentration (MAC) during anesthetic maintenance. The median was 1,883 data points from individual patients (range, 1 to 26,140). These plots demonstrate that for a given age-adjusted MAC, the response variable (*i.e.*, bispectral index value) displays its highest densities in the low 40s. The mode density of bispectral index values remains in the low 40s over the ETAC range from 0.42 to 1.51 age-adjusted MAC (more than 98% of the ETAC data).

Results

A total of 1,941 patients were considered for inclusion. Eight hundred and forty-one patients were excluded because of manually-recorded or undersampled ETAC recordings. With the methods described, 3,347,523 data points from a total of 1,100 patients were included in this study. Each data point represents a BIS-aaMAC sample pairing, for a total of 930 h of nonconsecutive, pharmacokinetically stable anesthetic data. The three-dimensional bivariate joint distribution and contour plots are shown in figure 3. For a given aaMAC concentration, the response variable (*i.e.*, BIS value) displays its highest densities at values in the low 40s (fig. 3A). The mode density of BIS values remains in the low 40s over the ETAC range from 0.42 to 1.51 aaMAC (fig. 3B).

Box plots of data showing the distributions of BIS values around six different aaMAC equivalent bands had similar medians and ranges (fig. 4). The GEE, using the exchangeable correlation structure, yielded the following equation as the best predictor over an ETAC range from 0.42 to 1.51 aaMAC: BIS value = 62.9–1.6 (if age younger than 60 yr) –1.6 (if female); –2.5 (if ASAPS more than 3; –2.6 (if deceased at 1 yr) –2.5 (if N₂O was not used); –1.4 (if midazolam dose more than 2 mg); –1.3 (if opioid dose more than 50 morphine equivalents); –15.4 × aaMAC. Allocation to BIS or ETAC group in the B-Unaware trial had a negligible effect on the relationship between BIS and ETAC. The estimates, standard errors, 95% CI, and *P* values for the GEE parameters are shown in table 2. Figure 5 depicts density plots of BIS values in the ETAC range from 0.8 to 0.99 aaMAC given one of the characteristics in the GEE. These graphs show how each parameter on average alters the relationship between BIS and ETAC.

The GEE demonstrates that, on average, for every 0.1 aaMAC increase in ETAC during the maintenance phase of

anesthesia, the BIS value will decrease by an estimated 1.5 units. According to this model, a doubling of ETAC from 0.6 to 1.2 aaMAC would on average be accompanied by a decrease of 9 BIS units. At equivalent aaMAC values, younger patients (younger than 60 yr) tend to have lower BIS values, women tend to have lower BIS values, sicker patients (ASAPS greater than 3) tend to have lower BIS values, and

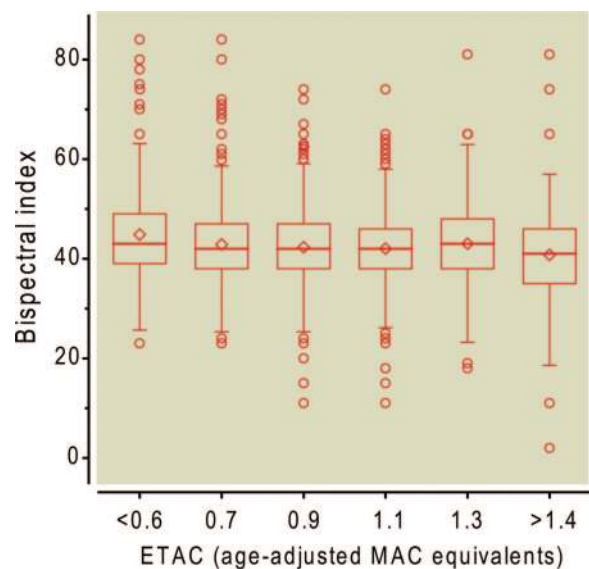


Fig. 4. Box and whisker plots of bispectral index ranges at six age-adjusted minimum alveolar concentration (MAC) ranges: <0.6, 0.6–0.79, 0.8–0.99, 1.0–1.19, 1.2–1.39, and ≥1.4. For each range, median bispectral index values were calculated for each patient using the pharmacokinetically stable end tidal anesthetic concentration (ETAC) data. The box and whisker plots were then constructed from these median values. The boxes depict the median values and the 25th and the 75th percentiles. The whiskers represent the two-fifth and ninety-seven-fifth percentiles.

Table 2. Estimates for the Generalized Estimating Equation Evaluating the Relationship between Bispectral Index and Age-adjusted Minimum Alveolar Concentration, Including Certain Modifying Parameters

Parameter	Estimate	Standard Error	95% CI	P Value
Age <60 yr	-1.9	0.55	-3.01 to -0.86	0.0004
Female	-1.6	0.54	-2.66 to -0.56	0.0026
ASAPS >3	-2.5	0.67	-3.80 to -1.19	0.0002
Dead at 1 yr	-2.6	0.88	-4.28 to -0.81	0.0040
N ₂ O not used	-2.5	0.76	-4.00 to -1.01	0.0010
Midazolam >2 mg	-1.4	0.57	-2.50 to -0.25	0.0164
Morphine equivalents >50 mg	-1.3	0.63	-2.53 to -0.08	0.0372
	—	—	—	—
The slope of the GEE equation (multiplied by ETAC in aaMAC equivalents)	-15.4	1.20	-17.78 to -13.06	<0.0001
	—	—	—	—
	—	—	—	—
BIS or ETAC group assignment in B-Unaware trial	Eliminated from GEE model because of nonsignificance			
	—	—	—	—
Extrapolated intercept of the GEE equation on the BIS (γ) axis	62.93	1.53	59.876–5.99	<0.0001

aaMAC = age-adjusted minimum alveolar concentration; ASAPS = American Society of Anesthesiologists physical status; BIS = bispectral index; ETAC = end-tidal anesthetic concentration; GEE = generalized estimating equation.

those who die 1 yr postoperatively tend to have lower intraoperative BIS values compared with those who were alive at 1 yr.

The GEE provides a whole-population estimate of the relationship between BIS and aaMAC. However, individual patients may differ in their BIS-aaMAC relationship in ways that are not reflected in the GEE. Limiting the patient population to those who were not subject to the problem of restricted range excluded 953 patients. Excluded patients tended to have more extreme values but similar measures of central tendency. Linear regression from the remaining 143 patients demonstrated a median BIS-aaMAC relationship slope of -8.56 BIS units per 1 aaMAC increase (interquartile range -30.4 to -0.68). The median correlation coefficient was -0.16 (interquartile range -0.031, -0.50), suggesting a generally weak relationship. A minority of patients received N₂O in addition to potent inhalational anesthetic agents, and the slopes and correlation coefficients were similar in these patients compared with those who did not receive N₂O. Representative BIS and aaMAC *versus* surgical time and BIS *versus* aaMAC relationships are shown in figure 6. Of note, although most patients have a negatively-sloping BIS-aaMAC relationship (fig. 6, A and B), approximately 1 in 4 have a slope of 0 \pm 5 BIS units per 1 aaMAC increase (fig. 6C), suggesting near-invariance of the BIS to clinically significant aaMAC increases.

Discussion

The two necessary criteria for a DOA monitor evaluated in this study were not reliably demonstrated in this population. First, the correlation between BIS value and pharmacokinetically stable aaMAC in most individual patients was weak.

Second, although some patients had a steep concentration-response relationship between aaMAC and BIS value, many patients displayed a near-invariant relationship with minimal change in the BIS value over a clinically relevant range of aaMAC, similar to the plateau that has previously been described.²³ The general estimating equation shows that the relationship between aaMAC and BIS is not independent of factors such as age, sex, and ASAPS. These effects on the relationship between BIS and aaMAC might reflect some average interpatient differences in anesthetic sensitivity.

The criteria for the utility of a DOA monitor during maintenance are not dichotomous; we demonstrate a modest negative correlation between BIS and pharmacokinetically stable ETAC across the population, and some patients did display a steep concentration-response relationship. Because of its lack of general precision, the BIS is probably not suitable for fine titration, although it may be helpful for gross anesthetic titration during the maintenance phase of anesthesia. However, gross titration of anesthetic administration is probably not consistent with the goal of safely decreasing DOA without increasing the risk of intraoperative awareness in all patients. A third criterion that we specified (a consistent value of the DOA index at return of responsiveness across patients) was examined in a recent study.²⁴ In this study, the BIS value at which responsiveness returned was not found to be consistent across individuals.²⁴

The high density of BIS values in the low 40s across the range of aaMAC equivalents seen in the probability density plots (fig. 3) reinforces the idea that BIS is insensitive to clinically significant changes in ETAC. BIS-guided titration of anesthesia might have increased the observed frequency of BIS values within the range of 40–60 at all aaMAC concen-

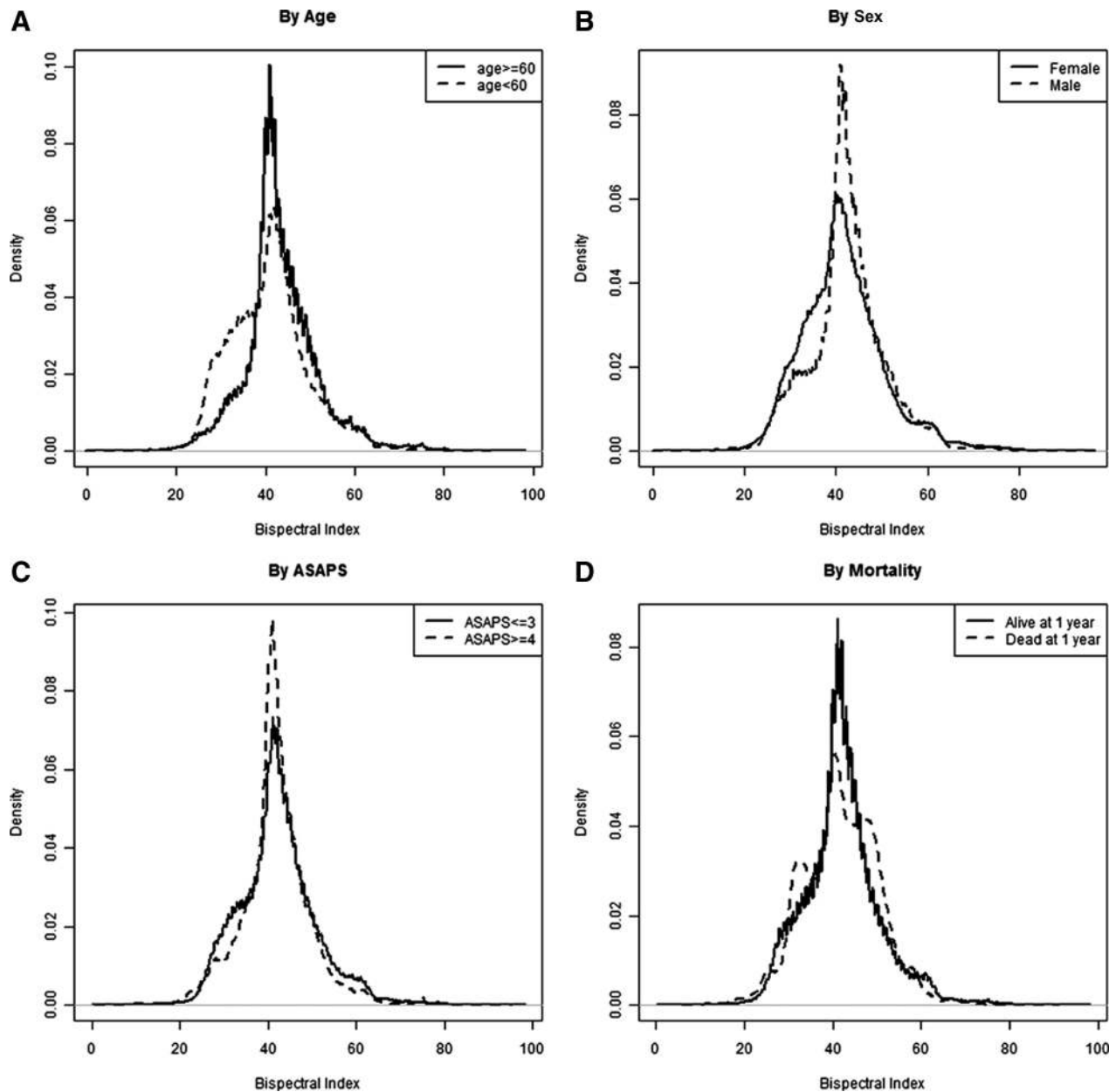


Fig. 5. Density plots of bispectral index values for 0.8 less than age-adjusted minimum alveolar concentration less than 0.99, stratified by patient characteristics entered into the generalized estimating equation. (A) Age. (B) Sex. (C) American Society of Anesthesiologists physical status (ASAPS). (D) Vital status at 1 yr postoperatively.

trations. However, similar distributions were apparent when the probability density plots were stratified based on group assignment (BIS or ETAC). Therefore, the high density of BIS values around 40 was apparent even when anesthesiologists were blinded to the BIS readings. On a cautionary note, both probability density plots (fig. 3) and the box plots (fig. 4) are not as robust statistically as a GEE model for datasets containing multiple repeated measures for each patient. Patients who contributed more data points might have biased the probability density plot.

Given the variability in the slopes of the individual aaMAC-BIS concentration-response curves, a patient-specific strategy would be needed to titrate anesthetic based on

the BIS. In patients with concentration-response curves of substantial slope (fig. 6A), also assuming a relatively high correlation coefficient, anesthetic titration to the upper portion of the recommended range of BIS values (*e.g.*, 50–60) might be appropriate and achievable. In patients with relatively invariant concentration response relationships (fig. 6C) or poor correlation coefficients of these relationships, the BIS would be of little use in guiding anesthetic titration during maintenance. Attempting in such patients to titrate anesthesia to achieve a particular BIS range (*e.g.*, 50–60) would probably be inappropriate and unachievable. An anesthesiologist approaching anesthetic titration for a particular patient usually would not have previous knowledge of the

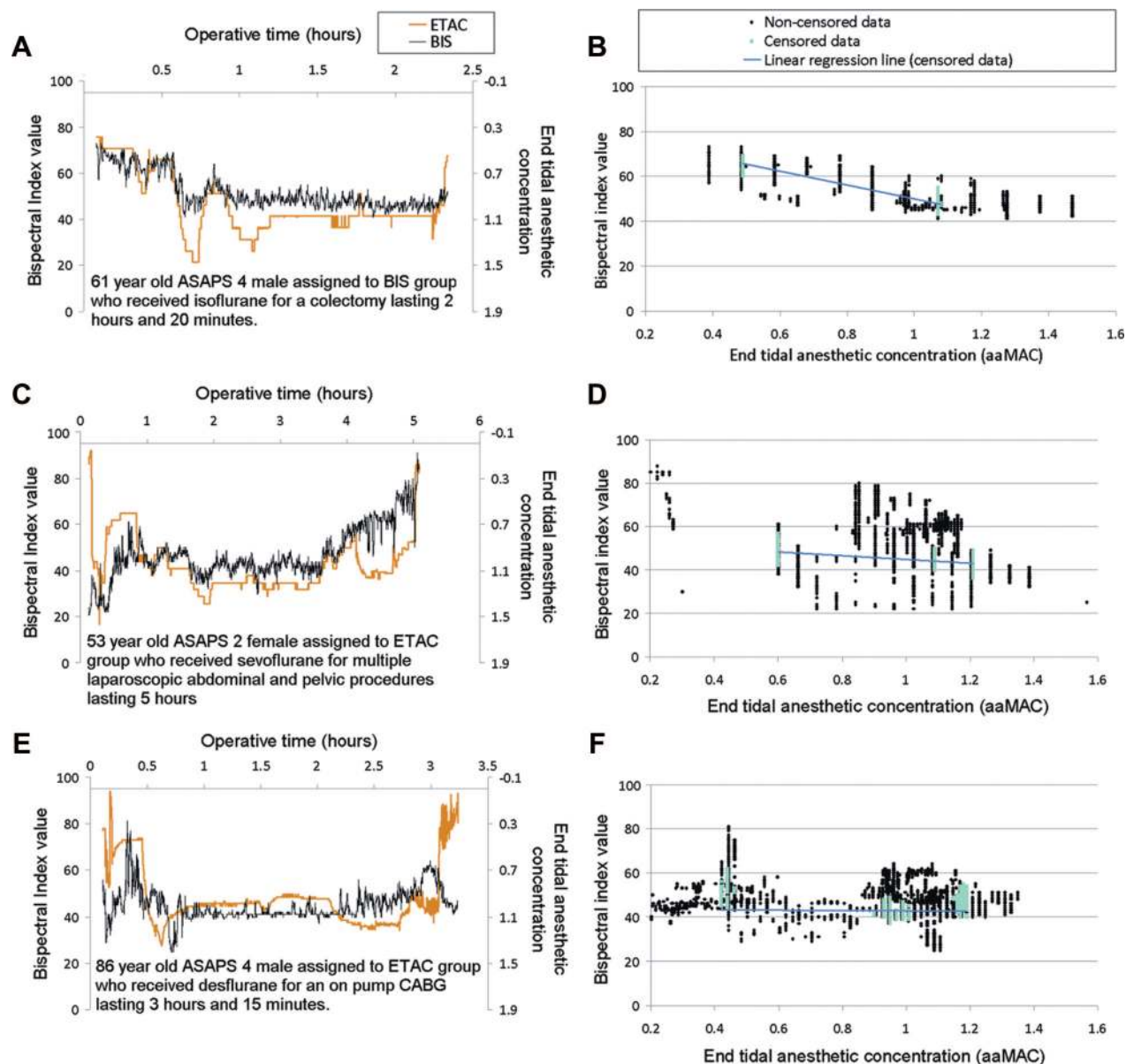


Fig. 6. Single-patient bispectral index (BIS) and end tidal anesthetic concentration (ETAC) in age-adjusted minimum alveolar concentration (aaMAC) equivalents over time (A, C, and E) and BIS-aaMAC relationship (B, D, and F). Patients were selected from those whose pharmacokinetically-censored data were over a more than 0.5 aaMAC range on the basis of their BIS-aaMAC slope in context of population characteristics. Patient A (A and B), -31 BIS units per 1 aaMAC increase (25th percentile for slope). Patient B (C and D), -9 BIS units per 1 aaMAC increase (median slope). Patient C (E and F), -0.3 BIS units per 1 aaMAC increase (75th percentile for slope). ASAPS = American Society of Anesthesiologists physical status; CABG = coronary artery bypass graft.

patient's aaMAC-BIS concentration-response curve. Therefore, the clinician would be unable to predict whether BIS use would prove beneficial in guiding anesthetic titration in the given patient.

The statistical significance of patient parameters such as sex and ASAPS in our GEE model does not imply clinical relevance. On a population basis, the average aaMAC-BIS relationship may be different between men and women. However, the effect of sex is not sufficiently reliable to allow prediction of how an individual man's BIS value will change

with increasing anesthetic compared with an individual woman's BIS value. In addition, although the GEE model demonstrates that BIS value has a significant negative relationship with the aaMAC, data from individual patients reveal the relationship to be unreliable. In practical terms, a statistically significant relationship between BIS, aaMAC, and several patient factors existing on a population level does not guarantee the clinical utility of the GEE in actually predicting an individual patient's BIS response to a given volatile anesthetic concentration.

It is worth pointing out that an association between intraoperative low BIS values and postoperative mortality has been demonstrated by our group²⁵ and others.^{7,26,27} The GEE from our analysis demonstrates on a population level that, at the same aaMAC, a patient who is dead in 1 yr will have a lower BIS value than a patient who is alive in 1 yr. This lends credence to the theory that low BIS value in some instances might be a marker of “anesthetic sensitivity” that in turn appears to be associated with increased postoperative mortality. Similarly, our finding that older age is associated with higher BIS values is consistent with the observation that older patients have higher processed frontal electroencephalography measures at loss of responsiveness.²⁸ However, the physiology underlying this association is currently unknown. As noted previously, N₂O does not decrease the BIS value comparably to potent volatile agents¹⁷; hence, the BIS *versus* ETAC curve is shifted up on the BIS axis when N₂O is factored in the aaMAC calculation. As expected, high midazolam and opioid dosages both shift the BIS *versus* ETAC curve down on the BIS axis.

As the BIS value is derived from a single frontal electroencephalogram channel, the results of this study could suggest that frontal electroencephalography is not always a reliable indicator of changes in volatile anesthetic concentrations over the range examined in this study, during anesthetic maintenance. Anesthetic-induced unconsciousness might lead to failure of information synthesis in the posterior parietal cortex and in parietal networks, whereas frontal networks are minimally affected.²⁹ Furthermore, single frontal electrode montages probably cannot be used to assess network relationships among brain regions, which have been shown to be altered with increasing anesthetic concentrations.³⁰ The BIS value itself also might not accurately reflect changes that occur in the frontal electroencephalogram with changes in anesthetic concentration. It might be possible to derive indices that are more discerning through greater precision of measurement; however, there is currently no means of calibrating such indices beyond the clinical endpoint of loss of responsiveness.

Limitations

First, the results of the current study might be subject to pharmacokinetic confounding; there is a delay between the equilibration of volatile anesthetic agent in the alveolus and at the effect site in central nervous system. However, we censored data where the ETAC had not been stable for the preceding 10 min; therefore, the number of data points with such a confounding would be substantially decreased.^{18,20} Furthermore, some patients did show a robust concentration-response relationship between BIS and aaMAC, whereas in some others, the BIS value was relatively invariant to clinically relevant changes in aaMAC. Second, the need to exclude considerable amounts of data on the basis of theoretic concerns about pharmacokinetic stability and the small population in which we were able to evaluate individual BIS-

aaMAC relationships is potentially a limitation of this study. Third, the B-Unaware trial enrolled surgical patients at high risk for intraoperative awareness; thus, the GEE model based on these patients might not be applicable to the general surgical population. Fourth, recent evidence shows that there might be a different concentration-response relationship during deepening of anesthesia with isoflurane or halothane compared with lightening of anesthesia.^{10,31} Our approach to data analysis did not take this hypothetical hysteresis into account. Fifth, we can make no conclusions about the responsiveness of BIS to propofol dosage during anesthesia maintenance, as all patients studied received inhaled anesthetic agents. Sixth, random fluctuation in BIS values could have worsened the regression fit and could have resulted in an overly pessimistic model. Seventh, it is important to emphasize that although the three criteria mentioned are necessary for a reliable DOA index, they are not sufficient. We did not examine other necessary attributes such as monitor response time, reliability with various anesthetic combinations, and resistance to artifact. Eighth, variable surgical stimulation is potentially an important confounder, which we could not factor into the GEE or the regression model. Ninth, opioid and midazolam doses were not incorporated in the regression model, although they would probably modify the regression relationships. Finally, and most importantly, the results of this study do not imply that monitors such as the BIS[®] have no utility for anesthetic depth assessment. Specifically, no inference can be drawn about usefulness during the periods of induction and emergence, because we could not assess the interpatient variability of the BIS value at emergence from anesthesia (*i.e.*, criterion 3). Furthermore, outcome studies strongly suggest that BIS-based protocols are efficacious in decreasing the incidence of intraoperative awareness.^{8,12,32}

A narrow interpretation of these results could be that BIS is limited as an aid to anesthetic titration during anesthetic maintenance. However, similar limitations probably apply to other current candidate DOA indices. Unless a particular patient's aaMAC-DOA index concentration-response curve has been previously characterized, the use of any current DOA index to achieve the goal of safely decreasing anesthetic depth without increasing the risk of intraoperative awareness is not recommended. This study identifies limitations to be overcome, and factors to be considered, in the development of future generations of candidate DOA monitors. The results of the GEE model could be viewed as a preliminary theoretical framework which attempts to incorporate interpatient anesthetic sensitivity into the scientific practice of anesthesia.

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