The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2008 VOL. 358 NO. 11

# Anesthesia Awareness and the Bispectral Index

Michael S. Avidan, M.B., B.Ch., Lini Zhang, M.D., Beth A. Burnside, B.A., Kevin J. Finkel, M.D., Adam C. Searleman, B.S., Jacqueline A. Selvidge, B.S., Leif Saager, M.D., Michelle S. Turner, B.S., Srikar Rao, B.A., Michael Bottros, M.D., Charles Hantler, M.D., Eric Jacobsohn, M.B., Ch.B., and Alex S. Evers, M.D.

## ABSTRACT

### BACKGROUND

Awareness during anesthesia is a serious complication with potential long-term psychological consequences. Use of the bispectral index (BIS), developed from a processed electroencephalogram, has been reported to decrease the incidence of anesthesia awareness when the BIS value is maintained below 60. In this trial, we sought to determine whether a BIS-based protocol is better than a protocol based on a measurement of end-tidal anesthetic gas (ETAG) for decreasing anesthesia awareness in patients at high risk for this complication.

### METHODS

We randomly assigned 2000 patients to BIS-guided anesthesia (target BIS range, 40 to 60) or ETAG-guided anesthesia (target ETAG range, 0.7 to 1.3 minimum alveolar concentration [MAC]). Postoperatively, patients were assessed for anesthesia awareness at three intervals (0 to 24 hours, 24 to 72 hours, and 30 days after extubation).

### RESULTS

We assessed 967 and 974 patients from the BIS and ETAG groups, respectively. Two cases of definite anesthesia awareness occurred in each group (absolute difference, 0%; 95% confidence interval [CI], −0.56 to 0.57%). The BIS value was greater than 60 in one case of definite anesthesia awareness, and the ETAG concentrations were less than 0.7 MAC in three cases. For all patients, the mean (±SD) time-averaged ETAG concentration was 0.81±0.25 MAC in the BIS group and 0.82±0.23 MAC in the ETAG group (P=0.10; 95% CI for the difference between the BIS and ETAG groups, −0.04 to 0.01 MAC).

### CONCLUSIONS

We did not reproduce the results of previous studies that reported a lower incidence of anesthesia awareness with BIS monitoring, and the use of the BIS protocol was not associated with reduced administration of volatile anesthetic gases. Anesthesia awareness occurred even when BIS values and ETAG concentrations were within the target ranges. Our findings do not support routine BIS monitoring as part of standard practice. (ClinicalTrials.gov number, NCT00281489.)

From the Department of Anesthesiology, Washington University School of Medicine, St. Louis. Address reprint requests to Dr. Avidan at Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8054, St. Louis, MO 63110, or at avidanm@wustl.edu.

N Engl J Med 2008;358:1097-108.

Anesthesia awareness, also known as unintended intraoperative awareness, is the explicit recall of sensory perceptions during general anesthesia. Anesthesia awareness is rare,[1,2] but the incidence may approach 1% in patients at high risk.[3-5] Anesthesia awareness can lead to anxiety and post-traumatic stress disorder.[6] The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has recommended that stringent efforts be made to prevent anesthesia awareness,[7] and the American Society of Anesthesiologists (ASA) has published guidelines on the subject.[8] According to a sentinel-event alert disseminated by the JCAHO, between 20,000 and 40,000 cases of anesthesia awareness may occur yearly in the United States.[7]

Of the 21 million patients who are given general anesthesia annually in the United States,[7] the vast majority inhale an anesthetic gas. It is routine to monitor the concentration of exhaled anesthetic gases by analyzing the absorption of infrared light, which provides accurate identification and quantification of the exhaled gases.[9] The minimum alveolar concentration (MAC) is the concentration of anesthetic gas required to prevent 50% of subjects from moving in response to a painful stimulus.[10] The standard metric for assessing and comparing the potency of anesthetic-gas concentrations is the MAC equivalent; when anesthetic gases are used in combination, their MAC equivalents are additive. When the end-tidal anesthetic gas (ETAG) concentration is approximately one third of the MAC, 50% of subjects are not awake.[10] Maintaining the ETAG concentration above 0.7 MAC may decrease the likelihood of anesthesia awareness.[11,12]

Several brain-function monitors based on the processed electroencephalogram or evoked potentials have been developed to assess anesthetic depth. The most widely used is the bispectral index (BIS) monitor (Aspect Medical Systems), which has been approved by the Food and Drug Administration. The BIS monitor processes a single frontal electroencephalographic signal to calculate a dimensionless number that provides a measure of the patient's level of consciousness. BIS values range from 100 to 0, reflecting the awake state and the absence of brain activity, respectively. Although the algorithm used to calculate the BIS number is proprietary, the electroencephalographic components of the algorithm have been identified: the frequency below which 95% of the power spectrum resides, the relative beta ratio, the relative synchrony of fast and slow waves, and the burst-suppression ratio.[13] BIS values between 40 and 60 purportedly indicate adequate general anesthesia for surgery, and values below 40 indicate a deep hypnotic state.[14] Targeting a range of BIS values between 40 and 60 is advocated to prevent anesthesia awareness while allowing a reduction in the administration of anesthetic agents.[15,16]

The B-Aware study showed an absolute risk reduction of 0.74% in anesthesia awareness among high-risk patients to whom anesthesia was administered according to a BIS-guided protocol, as compared with a control group who received no protocol-driven care.[3] In a large, multicenter cohort study, BIS monitoring was used in about 40% of the patients without a specified BIS-guided protocol, and there was no reduction in anesthesia awareness associated with BIS monitoring.[1] Despite the limited evidence, the BIS has been widely adopted, and many clinicians are administering anesthesia while aiming for BIS values below 60 in order to prevent anesthesia awareness.

We conducted the B-Unaware Trial to determine whether, in patients at high risk, the incidence of anesthesia awareness is reduced when clinicians follow a BIS-guided protocol rather than an ETAG-guided protocol.

## METHODS

### PATIENTS

The Washington University Human Research Protection Office approved the study. The Consolidated Standards of Reporting Trials guidelines were followed.[17] We evaluated patients who were older than 18 years of age who were undergoing surgery at Barnes–Jewish Hospital for eligibility on the day before or the day of their surgery on the basis of preoperative assessment records. Patients were required to be at high risk for anesthesia awareness, to have general anesthesia with isoflurane, sevoflurane, or desflurane, and supplemental nitrous oxide was permitted. The criteria for identifying patients at high risk for anesthesia awareness were based on previous studies, reviews, and guidelines.[3-5,7,8] The major criteria were preoperative long-term use of anticonvulsant agents, opiates, benzodiazepines, or cocaine; a cardiac ejection fraction less than 40%; a history of anesthesia awareness; a history of difficult intubation or anticipated difficult intubation; ASA physi-

cal status class 4 (those who have systemic disease that is a constant threat to life) or class 5 (those who are not expected to survive without the operation); aortic stenosis; end-stage lung disease; marginal exercise tolerance not resulting from musculoskeletal dysfunction; pulmonary hypertension; planned open-heart surgery; and daily alcohol consumption. The minor criteria were preoperative use of beta-blockers, chronic obstructive pulmonary disease, moderate exercise tolerance not resulting from musculoskeletal dysfunction, smoking two or more packs of cigarettes per day, and obesity, defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30. Patients at high risk were defined as those with at least one major criterion or two minor criteria. Patients were excluded if the surgical procedure or positioning of the patient prevented BIS monitoring or if the surgery required a wake-up test. Also excluded were patients who had dementia, who were unable to provide informed consent, or who had a history of stroke with residual neurologic deficits.

### STUDY DESIGN

The design was a single-center, prospective study, in which 2000 patients underwent prerandomization electronically in blocks of 100, with 50 patients assigned to a BIS-guided protocol and 50 to an ETAG-guided protocol. Eligible patients underwent randomization after providing written informed consent. The anesthesia practitioners were aware of the assignments of the patients, but the patients, the postoperative interviewers, the expert reviewers, and the statistician were not.

The manufacturer of the BIS monitor (Aspect Medical Systems) had no role in the study design, data collection, data analysis, or manuscript preparation. No study monitors or other means of support were provided by Aspect Medical Systems.

### PROCEDURES

A BIS Quatro Sensor (Aspect Medical Systems) was applied to the forehead of each patient. The anesthesia practitioners caring for the patients in the ETAG group used a monitor configuration that omitted the BIS number, so they were unaware of the BIS values. The practitioners in both groups could view the ETAG concentrations. In the BIS group, an audible alarm was set to indicate when the BIS value exceeded 60 or fell below 40; no ETAG alarms were set in the BIS group, and the practitioners were not instructed to maintain the ETAG concentration within any range.

In the ETAG group, an audible alarm was set to indicate when the ETAG concentration fell below 0.7 MAC or exceeded 1.3 MAC. Nitrous oxide was taken into account in the MAC calculations. During cardiopulmonary bypass, the anesthetic-gas concentration was measured from the effluent of the cardiopulmonary-bypass machine.[18] A sign was affixed to the anesthesia machines reminding the practitioners to check the BIS value or ETAG concentration and to consider whether the patient might have intraoperative awareness. BIS values and ETAG concentrations were collected at 1-second intervals and were downloaded to a computer for subsequent analysis with TrendFace Solo software (ixellence). Manual records of anesthesia and digital photographs of monitor trends were used as alternatives in the event that the computer data were incomplete.

Anesthesia awareness was assessed with the use of the Brice questionnaire.[19] The investigators were unaware of the patients' assignments and of previous assessments of their anesthesia awareness. Patients were contacted within 24 hours, between 24 and 72 hours, and at 30 days after extubation. Previous studies have shown that anesthesia awareness is not reliably detected with only a single interview.[3,20] While the study was ongoing, the quality-assurance coordinator in the anesthesiology department contacted the patients who had reported memories of the period between "going to sleep" and "waking up" at any interview and obtained further information about their experiences. The coordinator offered all patients who reported such memories referral for counseling.

After all patients had completed the study, three experts who were unaware of the assignments of the patients independently reviewed the questionnaire responses and decided whether each patient definitely had had anesthesia awareness, might have had anesthesia awareness, or did not have anesthesia awareness. In assessing whether anesthesia awareness occurred, the experts were instructed to focus on memories of events that could occur only in the operating room during the anesthetic and surgical periods. The outcome was determined when at least two of the experts were in agreement. If two experts held opposing views, a fourth expert was asked to review the questionnaires.

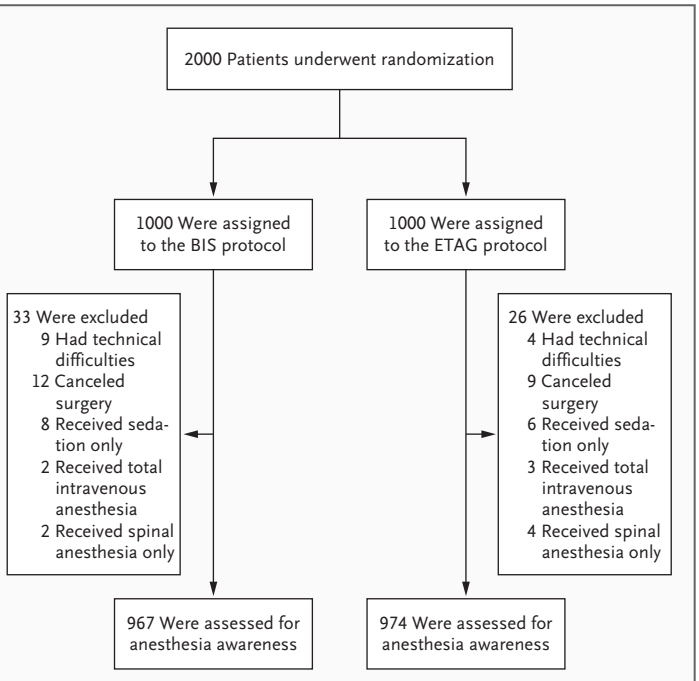



**Figure 1. Trial Enrollment.**
BIS denotes bispectral index, and ETAG end-tidal anesthetic gas.

On the basis of the accounts given by the patients and the information in the anesthesia records, an investigator who was unaware of the assignments identified a time window during which anesthesia awareness was likely to have occurred. When a specific time window could not be identified, the entire anesthetic period was considered.

To identify the maintenance period of anesthesia, researchers who were unaware of the treatment assignments systematically reviewed the BIS and ETAG traces from each patient who did not report anesthesia awareness. After the administration of the intravenous induction agent, there was a characteristic nadir in the BIS trace. The start of the maintenance period was defined as 3 minutes after the nadir unless the BIS rose above the upper bound of 60 during this time. Three minutes was predetermined to be adequate to account for the transition from an intravenous induction to a volatile gas-based general anesthetic. The end of the maintenance period and the start of emergence was defined as the beginning of a consistent and final decrease in the ETAG concentration to less than 0.2 MAC. If emergence did not occur in the operating room, the final data points were included in the maintenance period. Every trace was analyzed for sustained 30-second periods of BIS values above the threshold of 60 or ETAG concentrations below the threshold of 0.7 MAC during the maintenance period. Periods with missing data were excluded from the analysis.

### STATISTICAL ANALYSIS

The primary outcome of the study was a decrease in definite anesthesia awareness in the BIS group as compared with the ETAG group. The anticipated incidence of anesthesia awareness was 1% for the ETAG group, on the basis of the incidence rates reported for patients at high risk for anesthesia awareness,[3-5] and 0.1% for the BIS group, on the basis of previous studies.[3,21] A total of 940 patients would be required in each group to detect this 0.9% difference with a one-tailed alpha of 0.05 and a power of 80% with the use of Fisher's exact test. Confidence intervals for absolute risk reduction were calculated with the use of Newcombe's method without continuity correction.[22] There was no interim analysis. The chi-square test, Fisher's exact test, an unpaired t-test, and an unpaired Mann–Whitney test were used for other comparisons between groups. Intention-to-treat analysis was planned. Agreement among the experts who were assessing anesthesia awareness was quantified with the use of a two-way, random-effects, intraclass correlation coefficient for absolute agreement according to the following metric[23]: no=0, maybe=1, and yes=2. All reported P values are two-sided, and a P value less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with the R statistical environment (R Foundation for Statistical Computing).

## RESULTS

Of 2000 patients enrolled during a 14-month period (from September 2005 to October 2006), 1941 completed the study (Fig. 1). Patients were excluded as a result of changes in the planned anesthetic technique or canceled surgery. No patients who were assigned to the ETAG group were treated with the BIS protocol, and no patients assigned to BIS were treated with the ETAG protocol. A total of 1754 patients (90.4%) completed all three interviews, 133 patients (6.9%) completed only two interviews, and 18 patients (0.9%) completed only one interview. Table 1 shows the characteristics of

**Table 1. Patient Characteristics in the BIS-Guided and ETAG-Guided Groups.***

| Characteristic | BIS Group (N=967) | ETAG Group (N=974) | P Value† |
|---|---|---|---|
| Age — yr | 59.5±14.8 | 59.2±14.6 | 0.62 |
| Male sex — no. (%) | 516 (53.4) | 523 (53.7) | 0.88 |
| Weight — kg | 87.7±25.9 | 87.4±26.7 | 0.67 |
| ASA status — no./total no. (%) | | | 0.19 |
| 1 | 21/962 (2.2) | 15/972 (1.5) | |
| 2 | 265/962 (27.5) | 252/972 (25.9) | |
| 3 | 454/962 (47.2) | 503/972 (51.7) | |
| 4 | 222/962 (23.1) | 202/972 (20.8) | |
| Major inclusion criteria — no. (%)‡ | | | |
| Planned open-heart surgery | 270 (27.9) | 255 (26.2) | 0.39 |
| Aortic stenosis | 54 (5.6) | 42 (4.3) | 0.20 |
| Pulmonary hypertension | 24 (2.5) | 21 (2.2) | 0.63 |
| Opiate use | 290 (30.0) | 290 (29.8) | 0.92 |
| Benzodiazepine use | 148 (15.3) | 159 (16.3) | 0.54 |
| Anticonvulsant use | 83 (8.6) | 77 (7.9) | 0.59 |
| Daily alcohol consumption | 160 (16.5) | 185 (19.0) | 0.16 |
| ASA status 4 or 5 | 222 (23.0) | 202 (20.7) | 0.24 |
| End-stage lung disease | 11 (1.1) | 12 (1.2) | 0.85 |
| History of anesthesia awareness | 21 (2.2) | 20 (2.1) | 0.86 |
| History of or anticipated difficult intubation | 24 (2.5) | 20 (2.1) | 0.53 |
| Cardiac ejection fraction <40% | 73 (7.5) | 79 (8.1) | 0.65 |
| Marginal exercise tolerance | 387 (40.0) | 350 (35.9) | 0.06 |
| Minor inclusion criteria — no. (%)‡ | | | |
| Beta-blocker use | 429 (44.4) | 416 (42.7) | 0.46 |
| Chronic obstructive pulmonary disease | 105 (10.9) | 116 (11.9) | 0.47 |
| Moderate exercise tolerance | 486 (50.3) | 541 (55.5) | 0.02 |
| Smoking ≥2 packs of cigarettes/day | 74 (7.7) | 71 (7.3) | 0.76 |
| Obesity | 430 (44.5) | 411 (42.2) | 0.31 |
| Preexisting medical conditions — no. (%)§ | | | |
| Cardiovascular | 723 (74.8) | 762 (78.2) | 0.07 |
| Respiratory | 273 (28.2) | 263 (27.0) | 0.55 |
| Endocrine | 273 (28.2) | 269 (27.6) | 0.76 |
| Neurologic | 166 (17.2) | 214 (22.0) | 0.008 |
| Renal | 145 (15.0) | 139 (14.3) | 0.65 |
| Vascular | 125 (12.9) | 126 (12.9) | 0.99 |
| Hepatobiliary | 77 (8.0) | 80 (8.2) | 0.84 |

* Plus–minus values are means ±SD. ASA denotes American Society of Anesthesiologists, BIS bispectral index, and ETAG end-tidal anesthetic gas.
† The P values were calculated with the use of the chi-square test for all characteristics except age and weight, for which the P values were calculated with the use of the Mann–Whitney test.
‡ A patient could have more than one inclusion criterion.
§ A patient could have more than one preexisting medical condition.

**Table 2.** Patients Who Reported Memories of the Period between "Going to Sleep" and "Waking Up."

| Patient No. | Group* | Sex and Years of Age | Anesthetic Agent | Surgery | Reported Experience | Interview No. during which Memories Were Reported† | Determination of Anesthetic Awareness | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 3 Expert Reviewers | Overall Determination |
| 1 | ETAG | F, 37 | Isoflurane without nitrous oxide | Bilateral lung transplantation | Felt the incision but did not feel pain or pressure. Awoke during ventilation and fought as her wrists were restrained. Felt her wrists pulled into position and something wrapped around them. Felt unable to move and wanted to turn her head for comfort. | 2, 3 | Definite<br>Definite<br>Possible | Definite |
| 2 | ETAG | M, 65 | Isoflurane without nitrous oxide | Aortic-valve replacement | Heard and felt scissors cutting into his chest like the "feeling of cutting into a deer" but did not feel pain. Heard "bone-crunching noise like clipping limbs of a tree, but bones instead." | 1, 2, 3 | Definite<br>Definite<br>Definite | Definite |
| 3 | BIS | M, 51 | Desflurane without nitrous oxide | Drainage of pancreatic pseudocyst | Woke up during the surgery. Remembers someone saying "hairy" when his chest was shaved. Heard two or three female voices and one male voice, felt pain, and was unable to move. Remembers crying and thinking, "If someone can see me crying, then someone can help me." Felt constant "white-hot fire pain" in abdomen during surgery. Felt "organs and intestines moving around" and heard music playing. | 3 | Definite<br>Definite<br>Definite | Definite |
| 4 | BIS | M, 29 | Isoflurane without nitrous oxide | Percutaneous nephrolithotomy | Had a sense of a timeline, realized that he went to sleep, and was on his stomach at the time he became aware. At that time, heard nonspecific sounds and felt right-sided pain at the same location as his postoperative pain. Was upset and feared he would be awake the entire time. | 1, 2, 3 | Definite<br>Definite<br>Definite | Definite |
| 5 | BIS | M, 76 | Isoflurane without nitrous oxide | Off-pump coronary-artery bypass grafting | Experience lasted a few seconds. Woke up feeling cold on a board in the operating room. Does not remember whether he was intubated. Saw the anesthesiologist on the left. Was given a shot in his arm and heard "Here's more oxycontin." Then went "back out immediately." | 3 | Possible<br>No<br>Possible | Possible |
| 6 | BIS | F, 22 | Desflurane without nitrous oxide | Laparoscopic cholecystectomy | Remembers having something in her throat, wanting to gag, and feeling unable to move. Felt pain and felt as if she had "the chills," both "cold and hot." Heard doctors talking and a talkative Brazilian woman. Could not recall words. Was unable to move and was disturbed by this "because I had been sick." Remembers its being a very traumatic experience and feeling scared for her child. | 3 | Possible<br>Possible<br>Possible | Possible |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7 | BIS | M, 58 | Isoflurane without nitrous oxide | Aortic-valve replacement | It was a split-second but frightening experience. Was frightened and thought he was going to die because of the tube going in. Felt as if he "needed to fight for my life." Memory was triggered by a conversation with his wife in the intensive care unit. Does not remember pain, cold or hot sensations, or sounds. | 3 | Possible<br>Definite<br>Possible | Possible |
| 8 | BIS | M, 60 | Desflurane and sevoflurane without nitrous oxide | Placement of automatic implantable cardioverter–defibrillator | Remembers being unable to move. | 3 | No<br>Possible<br>Possible | Possible |
| 9 | ETAG | F, 76 | Isoflurane without nitrous oxide | On-pump coronary-artery bypass grafting | Heard a crack that she assumed was the cracking of her sternum and then drifted off again. Remembers being unable to move and felt as if she were floating. | 2 | Possible<br>Possible<br>No | Possible |
| 10 | BIS | F, 70 | Desflurane and sevoflurane without nitrous oxide | Fiberoptic bronchoscopy and lobectomy | Thinks she may have heard talking. Was unable to move. The last thing she remembered was asking if she could "see my doctor" and getting the response "Maybe yes, maybe no." The first thing she remembered on waking was her friend sitting at the side of the bed holding her hand. Remembers nothing in between. | 2 | No<br>Possible<br>No | No |
| 11 | ETAG | F, 72 | Desflurane and sevoflurane with nitrous oxide | Placement of subthalamic stimulator | Felt "pain in the front of my head." The last thing she remembered was how busy everyone was. The first thing she remembered on waking was hearing, "It's a sunny day." Thought, "Thank God I felt as good as I did." Remembers nothing in between. | 3 | No<br>No<br>Possible | No |
| 12 | ETAG | F, 55 | Isoflurane without nitrous oxide | Renal transplantation | Heard someone talking. The last thing she remembered was moving to the bed. Remembers "activity with arms and use of a chest catheter." Remembers the recovery area where she awoke. Remembers nothing in between. | 1 | No<br>No<br>No | No |
| 13 | ETAG | F, 82 | Isoflurane and desflurane without nitrous oxide | Fiberoptic bronchoscopy and wedge resection of the lung | People were "running around to try doing something." Remembers an "Asian woman doctor pushing this thing over my mouth" and thinking, "She is really rough." | 2 | Possible<br>No<br>No | No |
| 14 | BIS | F, 66 | Isoflurane with nitrous oxide | Anterior cervical diskectomy and fusion of L5 to L6 and L6 to L7 | "My neck got stiff and uncomfortable." Remembers nothing between going to sleep and waking up. | 1 | No<br>No<br>No | No |
| 15 | BIS | M, 53 | Sevoflurane without nitrous oxide | Resection of retroperitoneal tumor | Remembers hearing things but no specific words. Remembers nothing during the surgery. | 2 | No<br>Possible<br>No | No |
| 16 | BIS | F, 62 | Sevoflurane with nitrous oxide | Knee arthroscopy | Saw the surgeon opening up her knee, followed by a burst of blood. (Records note that her eyes were taped shut.) Remembers nothing between going to sleep and waking up. | 2 | No<br>No<br>No | No |

* BIS denotes bispectral index, and ETAG end-tidal anesthetic gas.
† Interview 1 occurred between 0 and 24 hours after extubation, interview 2 between 24 and 72 hours after extubation, and interview 3 at 30 days after extubation.

the patients. There were significantly more patients with underlying neurologic disease in the ETAG group than in the BIS group (22.0% vs. 17.2%, P=0.008). The groups were similar with respect to other baseline characteristics. Overall, 71.4% of patients had an ASA physical status class of 3 (severe systemic disease), 4, or 5; 27.0% underwent open-heart surgery; 74.6% had three or more inclusion criteria; and 61.6% had two or more preexisting medical conditions. Nitrous oxide was administered to 350 patients in the BIS group and 351 patients in the ETAG group.

Table 2 gives details for the 16 patients who, during at least one interview, reported memories of the period between "going to sleep" and "waking up" at the end of surgery. Experts who were unaware of the treatment assignments determined that four patients (Patients 1 through 4) had definite anesthesia awareness; two of these patients were in the BIS group and two were in the ETAG group (absolute risk reduction, 0%; 95% confidence interval [CI], −0.56 to 0.57). Two of these patients reported memories at all three interviews, one reported memories at only the last two interviews, and one reported memories at only the third interview. The overall incidence of definite anesthesia awareness was 0.21% (95% CI, 0.08 to 0.53).

Five other patients (Patients 5 through 9) had possible anesthesia awareness; four were in the BIS group and one was in the ETAG group. These patients reported memories at only one interview, and four reported memories at only the third interview. The incidence rates of definite or possible anesthesia awareness were 0.62% and 0.31% in the BIS and ETAG groups, respectively, with an absolute difference between the groups of 0.31% (95% CI, −0.36 to 1.07). The overall incidence of definite or possible anesthesia awareness was 0.46% (95% CI, 0.24 to 0.87). Table 2 shows the responses to interviews and the judgments of the expert reviewers, who had high agreement (intraclass correlation coefficient, 0.72; 95% CI, 0.49 to 0.88). There were no statistically significant differences between patients who had definite or possible anesthesia awareness and the rest of the patients in terms of the characteristics of the patients or the anesthetic drugs administered.

Figure 2 shows the BIS values and ETAG concentrations for the six patients in the BIS-guided group with definite (Patients 3 and 4) or possible (Patients 5 through 8) anesthesia awareness. Figure 3 shows the corresponding data for the three patients in the ETAG-guided group with definite (Patients 1 and 2) or possible (Patient 9) anesthesia awareness. The BIS value was above 60 in one of the four patients with definite anesthesia awareness and in three of the nine patients with possible or definite anesthesia awareness. The ETAG concentration was below 0.7 MAC in three of the four patients with definite anesthesia awareness and in seven of the nine with possible or definite anesthesia awareness.

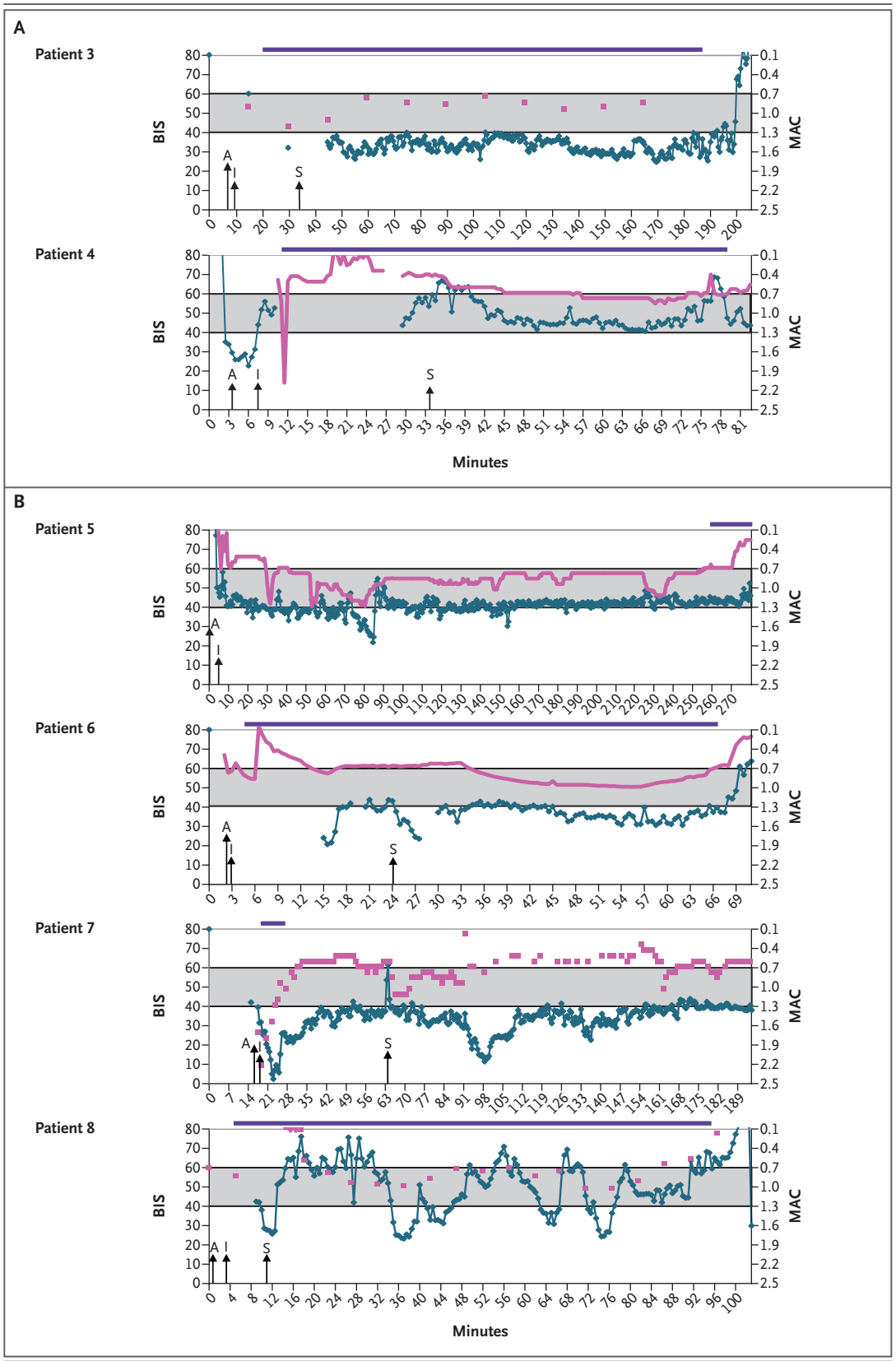
**Figure 2 (facing page). BIS Values and ETAG Concentrations over the Course of the Anesthesia in Patients with Definite or Possible Anesthesia Awareness in the BIS-Guided Group.**

Panel A shows records from Patients 3 and 4, with definite anesthesia awareness, and Panel B shows records from Patients 5 through 8, with possible anesthesia awareness. Purple bars show the period during which anesthesia awareness is likely to have occurred. Pink lines represent MAC equivalents of ETAG concentration, and blue lines with diamond-shaped markers represent BIS values. Gray shading shows the target ranges for BIS and MAC equivalents. The data points for all graphs are plotted as median values for 30-second intervals. Where continuous computer data are incomplete, interval data points are plotted. The initial BIS values for Patients 3, 6, and 7 were 90, 92, and 84, respectively. BIS denotes bispectral index, A induction of anesthesia, ETAG end-tidal anesthetic gas, I intubation, MAC minimum alveolar concentration, and S surgical incision. The patient numbers correspond to the patient numbers in Table 2.

During the maintenance phase of anesthesia, BIS values were continuously less than 60 in 825 of 1834 patients (45.0%), and ETAG concentrations were continuously greater than 0.7 MAC in 438 of 1717 patients (25.5%). The mean time-averaged BIS during the maintenance phase was 43.1±9.2 in the BIS group and 43.4±9.8 in the ETAG group (P=0.51; 95% CI for the difference between the BIS and ETAG groups, −1.2 to 0.6). The mean (±SD) time-averaged ETAG concentration during the maintenance phase was 0.81±0.25 MAC in the BIS group and 0.82±0.23 MAC in the ETAG group (P=0.10; 95% CI for the difference between the BIS and ETAG groups, −0.04 to 0.01 MAC).

## DISCUSSION

In the B-Unaware Trial, a structured protocol based on the BIS resulted in neither a lower incidence of anesthesia awareness nor a reduced administration of volatile anesthetic gas as compared with a structured protocol based on ETAG. It has been sug-



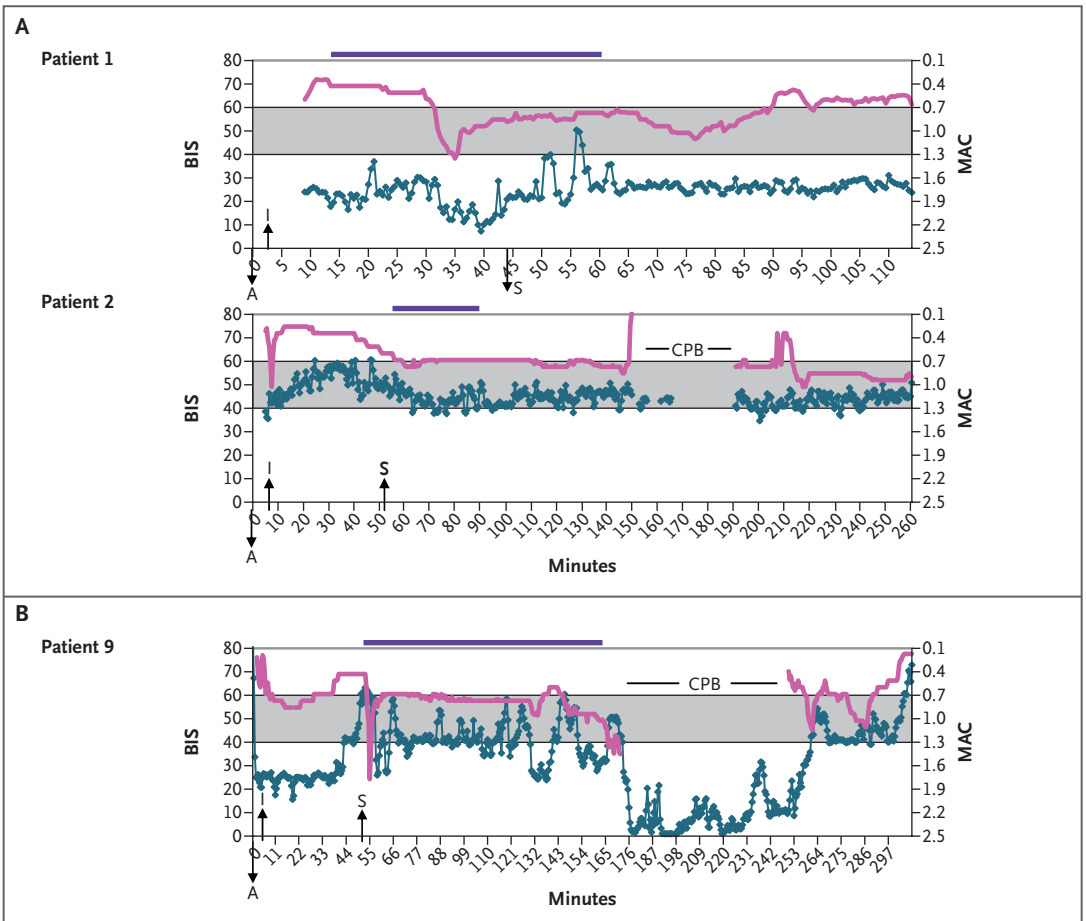



**Figure 3. BIS Values and ETAG Concentrations over the Course of the Anesthesia in Patients with Definite or Possible Anesthesia Awareness in the ETAG-Guided Group.**

Panel A shows records from Patients 1 and 2, with definite anesthesia awareness, and Panel B shows records from Patient 9, with possible anesthesia awareness. Purple bars show the period during which anesthesia awareness is likely to have occurred. Pink lines represent MAC equivalents of ETAG concentration, and blue lines with diamond-shaped markers represent BIS values. Gray shading shows the target ranges for BIS and MAC equivalents. The data points for all graphs are plotted as median values for 30-second intervals. Where continuous computer data are incomplete, interval data points are plotted. BIS denotes bispectral index, A induction of anesthesia, CPB cardiopulmonary bypass, ETAG end-tidal anesthetic gas, I intubation, MAC minimum alveolar concentration, and S surgical incision. The patient numbers correspond to the patient numbers in Table 2.

gested that when the BIS value is less than 60, anesthesia awareness is unlikely.[3,15,21] In the majority of cases of definite or possible anesthesia awareness, BIS values were persistently under 60 during the period when anesthesia awareness was likely to have occurred (Fig. 2 and 3).

There were sustained periods when BIS values were greater than 60 in 55.0% of patients and ETAG concentrations were under 0.7 MAC in 74.5% of patients who did not have anesthesia awareness. The low mean BIS values in the BIS group could reflect the unwillingness of the anesthesia practitioners to decrease anesthetic administration solely on the basis of the BIS. The mean BIS value of the BIS group in the B-Aware study was low and almost identical to that in the present study.[3] Both the BIS values and the ETAG concentrations were frequently outside the target ranges, possibly because of the difficulty of adhering to the prescribed protocols or reluctance on the part of the anesthesia practitioners to follow the protocols.

This trial has some important limitations. Although the trial did not demonstrate a reduction

in anesthesia awareness, with 95% confidence intervals for absolute risk reduction of definite anesthesia awareness of −0.56 to 0.57%, the results remain consistent with a clinically significant number needed to treat in order to benefit of 179 and a clinically significant number needed to treat in order to harm of 175 with the BIS protocol. This study is also subject to some concerns common to all studies of anesthesia awareness: the diagnosis of anesthesia awareness may be subjective, the awareness interview may be invalid because repeated questioning may induce false memories, and it may be difficult to distinguish between memories of events in the operating room and events in the intensive care unit. It is encouraging that there was good agreement among the three assessors, who were unaware of the treatment assignments, and it was unnecessary to refer any decision to a fourth assessor.

It is important to emphasize that the results of this trial should not be extrapolated to patients receiving total intravenous anesthesia, which is considered to be a risk factor for anesthesia awareness.[7] Indeed, BIS monitoring may be useful during total intravenous anesthesia, since it is not presently possible to monitor the blood concentrations of anesthetic agents continuously.

Anesthesia awareness cannot predictably be prevented in all patients with the BIS monitoring protocol used in this study. When a potent volatile anesthetic gas was administered, a structured protocol based on the BIS was not shown to be superior to a protocol based on ETAG concentrations for preventing anesthesia awareness. Reliance on BIS technology[24] may provide patients and health care practitioners with a false sense of security about the reduction in the risk of anesthesia awareness. If BIS monitoring were routinely applied to all patients in the United States receiving general anesthesia,[7] the cost of disposable electrodes alone would exceed $360 million annually. Our study was unable to demonstrate superiority of a BIS-guided protocol over an ETAG-guided protocol for preventing anesthesia awareness and does not provide support for the additional cost of BIS monitoring as part of standard practice.

Supported by a grant from the Barnes–Jewish Hospital Foundation (to Dr. Avidan).

No potential conflict of interest relevant to this article was reported.

We thank Jane Cueto, Dusica Stamenkovic, Elika Safarzadeh, Furqaan Sadiq, Barry Hong, Heiko Kaiser, Laura Veremakis, Brian Torres, Katy Dustman, Jeanine Riddle, Michael Rybak, Dia Tite, Nicholas Girdner, Bernadette Henrichs, and the many anesthesiologists, certified registered nurse anesthetists, and surgeons who facilitated the conduct of this study.

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