Relationship of bispectral index to minimum alveolar concentration multiples of sevoflurane in cats

Leigh A. Lamont, DVM, MS; Stephen A. Greene, DVM, MS; Kurt A. Grimm, DVM, PhD; William J. Tranquilli, DVM, MS

Objective—To determine the relationship between bispectral index (BIS) and minimum alveolar concentration (MAC) multiples of sevoflurane in cats.

Animals—8 domestic cats.

Procedure—Each cat was anesthetized twice with sevoflurane. First, the MAC of sevoflurane for each cat was determined by use of the tail clamp method. Second, cats were anesthetized with sevoflurane at each of 5 MAC multiples administered in random order. Ventilation was controlled, and after a 15-minute equilibration period at each MAC multiple of sevoflurane, BIS data were collected for 5 minutes and the median value of BIS calculated.

Results—The mean (± SD) MAC of sevoflurane was 3.3 ± 0.2%. The BIS values at 0.5 MAC could not be recorded as a result of spontaneous movement in all 8 cats. The BIS values at 2.0 MAC were confounded by burst suppression in all 8 cats. Over the range of 0.8 to 1.5 MAC, BIS values decreased significantly with increasing end-tidal sevoflurane concentrations. Mean (± SD) BIS measurements were 30 ± 3, 21 ± 3, and 5 ± 2 at 0.8, 1.0, and 1.5 MAC, respectively.

Conclusions and Clinical Relevance—Values of BIS are inversely and linearly related to end-tidal sevoflurane concentrations in anesthetized cats, and BIS may be a useful predictor of CNS depression in this species. The consistently low BIS values recorded in this study suggest that clinical BIS end points used to titrate anesthetic agents in humans may not be applicable to cats. (*Am J Vet Res* 2004;65:93–98)

The search for an objective, accurate, and reliable means of measuring the effects of anesthetic agents at their target site, the CNS, has been a focal point in the field of anesthesiology for more than 2 decades. It is now recognized that general anesthesia is not a single graded effect but rather a complex state characterized by hypnosis, analgesia, and areflexia.[1-4] The actions of agents such as barbiturates, propofol, and volatile inhalant anesthetics are primarily hypnotic and as such have little effect on autonomic and hormonal responses to noxious stimulation. Conversely, opioids produce substantial analgesia but are relatively poor hypnotics. Both classes of drugs may contribute to suppression of movement, although in many instances analgesics are superior to hypnotics in obtunding intraoperative reflex activity.[2] Traditional approaches to monitoring anesthetic depth have involved titrating agents to analgesic endpoints, whereby doses are adjusted to control various somatic and autonomic responses. Clinical evaluation of the hypnotic component of anesthesia, without a system for objective graded measurement, is considerably more challenging. It is accepted that most human patients probably have more hypnotic effect than they need, whereas only a select few have inadequate CNS depression.[2] Although data for veterinary patients are lacking, the reliance on anesthetic protocols based predominantly on administration of hypnotic agents (such as volatile inhalant anesthetics) suggests that excessive hypnosis is likely a common phenomenon among veterinary patients as well.

The **bispectral index (BIS)** is the first **electroencephalographic (EEG)**-based technology approved by the FDA specifically for the measurement of the hypnotic effects of anesthetic agents in human patients. It is an empirical, statistically derived measurement based on analysis of EEG bicoherence patterns. The BIS was derived by applying stepwise regression analysis to EEGs from anesthetized human subjects in known awake and asleep states. A set of various EEG features that were found to be highly correlated with hypnosis was selected. On the basis of this large database of EEG features, multivariate statistical models were used to ascertain the optimum combination of these features, and the resulting regression equation was transformed into a linear, dimensionless scale from 0 to 100.[2,5] Zero indicates an isoelectric EEG, whereas 100 represents the normal conscious state.

The BIS has been validated in a series of human volunteer trials and has proven to be an extraordinarily good predictor of the hypnotic state produced by a variety of anesthetic agents.[5-11] On the basis of the findings in these studies, it has been shown that maintaining an intraoperative BIS value between 40 and 60 represents an optimal degree of hypnosis. In addition, titrating administration of anesthetic agents on the basis of this objective measure of CNS depression has been shown to result in more rapid emergence from anesthesia, with decreased costs associated with anesthetic use and postanesthetic patient care.[6,12-17]

Despite the fact that, to date, more than 5,000,000 anesthetics have been administered to human patients by use of BIS monitoring,[1] there are few reports on the use of BIS technology in anesthetized animals. In pigs undergoing surgery, BIS measurements during 1.0 times

Received March 10, 2003.
Accepted June 2, 2003.
From the Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802. Dr. Lamont's present address is Department of Companion Animals, Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, PEI C1A 4P3, Canada.
Address correspondence to Dr. Lamont.

the **minimum alveolar concentration (MAC)** of halothane or xenon were comparable to those during total IV anesthesia with azaperone, atropine, and buprenorphine combined with continuous infusion of pentobarbital.[18] In another study[19] where pigs were maintained at surgical depths of anesthesia with isoflurane, the BIS did not correlate with the perceived depth of anesthesia as assessed by a visual analogue scale. In a study[20] on horses, the BIS also failed to correlate with end-tidal isoflurane concentrations in horses that received detomidine, butorphanol, ketamine, diazepam, and isoflurane. In goats, the BIS has been shown to be inversely related to critical points in the continuum of isoflurane-induced anesthetic depth, including time of recumbency, tracheal intubation, and loss of corneal or withdrawal reflexes.[21] In dogs, an inverse relationship between BIS measurements and multiples of the MAC for sevoflurane and isoflurane has been reported.[22,23] In the same isoflurane study[23] on dogs, BIS measurements were significantly lower in dogs receiving medetomidine and isoflurane, compared with dogs receiving saline (0.9% NaCl) solution and isoflurane. To our knowledge, there have been no published reports of BIS monitoring in anesthetized cats.

Bispectral index monitoring is a novel tool that offers unparalleled insight into the hypnotic component of anesthesia. Whether this technology will prove useful in clinical management of anesthetized animals remains to be seen. The objective of the study reported here was to determine the relationship between BIS and multiples of the MAC for sevoflurane in cats. The authors hypothesized that BIS would be inversely and linearly related to multiples of the MAC for sevoflurane in this species.

Materials and Methods

Eight domestic cats (4 males and 4 females; mean age and weight, 3.2 years and 4.1 kg, respectively) were studied. The university's institutional animal care and use committee approved the study. It was conducted in compliance with local and federal guidelines governing animal care and housing. Food was withheld on the days of the study.

Procedure—Each cat was anesthetized twice. On the first occasion, each cat's MAC for sevoflurane was determined by the use of the tail clamp method. On the second occasion, cats were instrumented for measurement of BIS, ECG, systolic arterial blood pressure, esophageal temperature, and end-tidal **carbon dioxide (CO_2)** and sevoflurane concentrations. Cats were anesthetized at each of 5 multiples of the MAC (0.5, 0.8, 1.0, 1.5, and 2.0 times MAC) for sevoflurane on the basis of each cat's individual predetermined MAC of sevoflurane. The order of administration of MAC multiples was randomized for each trial. After 15 minutes of equilibration at each MAC multiple for sevoflurane, values for BIS and other physiologic variables were recorded. The BIS was collected for 5 minutes and the median BIS value determined for the recording period at each MAC multiple for sevoflurane.

Determination of the MAC for sevoflurane—The technique for determination of the MAC of volatile inhalant anesthetics in dogs used by our laboratory has been described previously.[24] This same technique was adapted for use in cats in the present study. Briefly, each cat was induced with sevoflurane in oxygen, and the trachea was intubated. Anesthesia was maintained for 15 minutes at a constant end-tidal sevoflurane concentration, at which time a padded sponge clamp was placed on the base of the tail at a point measuring 5 cm in circumference. The clamp was closed to full ratchet and held in place for 60 seconds, and the cat's response was recorded. The stimulus was discontinued if a positive response was observed before the minute elapsed. Gross purposeful muscular movement of the head or extremities was considered a positive response, whereas coughing or swallowing did not constitute a positive response. The end-tidal sevoflurane concentration was then increased (if a positive response) or decreased (if a negative response) by 10%. A 15-minute equilibration period was allowed at each end-tidal sevoflurane concentration before the stimulus was applied. Each individual MAC was determined as the average of the lowest concentration preventing a positive response and the highest concentration allowing a positive response. A minimum of 2 determinations was averaged for each cat. After the MAC was identified, anesthesia was discontinued, butorphanol was administered IM at 0.2 mg/kg, and cats were allowed to recover.

Physiologic monitoring—On the day of the trial, cats were mask induced with sevoflurane[a] and positioned in left lateral recumbency. The trachea was intubated, and a catheter for sample collection was introduced through the endotracheal tube adaptor, extending to the level of the carina. Anesthesia was maintained with sevoflurane in oxygen by use of a precision vaporizer[b] and a pediatric rebreathing circuit on an anesthesia machine.[c] Ventilation was controlled with a mechanical ventilator[d] and adjusted to maintain normocapnia (end-tidal CO_2 of 30 to 35 mm Hg[25]). A lead II ECG was monitored, and an esophageal stethoscope with temperature probe was placed.[e] Heart rate was determined by auscultation with an esophageal stethoscope. Systolic arterial blood pressure was measured indirectly by use of a Doppler system.[f] End-tidal CO_2 and sevoflurane concentrations were measured from samples taken at the tracheal carina by use of a calibrated side-stream sample collection anesthetic gas analyzer.[g]

Measurement of the BIS—The BIS was measured by use of a BIS monitor with software.[h] The BIS was recorded every 5 seconds for 5 minutes after equilibration at each MAC multiple. Data were stored on a computer. The BIS is reported as a unitless whole number between 0 and 100. Filters for elimination of electrical noise were set as follows: the low-frequency cutoff was set at 2 Hz, the 50- to 60-Hz filter was set to 60 Hz, and the high-frequency cutoff was set at 70 Hz. At startup, the monitor requires a skin-electrode impedance of < 7.5 kΩ and thereafter provides for continuous impedance checking with an impedance < 2 kΩ at 16 Hz. High-frequency activity (70 to 110 Hz) is identified as **electromyographic (EMG)** activity measured in decibels with respect to 0.0001 μV^2 and is graphed in real time with the BIS. Increases in BIS coincident with increases in EMG activity confound interpretation of BIS measurements. The monitor has automatic artifact detection and displays a signal quality index as a function of good epochs and suppressed epochs over the previous 120 epochs (61.5 seconds) used for BIS calculation. The percentage of epochs in the past 63 seconds in which the EEG signal is suppressed is expressed as the **suppression ratio (SR)**. Burst suppression is identified as an isoelectric analog EEG for at least 1 second and is detected by the monitor and indicated as an increased SR (ie, SR > 1). Presence of burst suppression at deeper degrees of sevoflurane anesthesia was readily identified by spike activity followed by an isoelectric EEG and a concomitant increase in SR and the displayed BIS value. The BIS values were not

recorded if the SR was > 0 or if EMG activity was present. Measurements of BIS in the presence of burst suppression or EMG activity were treated as missing values and not included in the analysis.

Electrodes—The primary lead was placed on the midline approximately a third of the distance from a line connecting the zygomatic processes of the frontal bone and the most caudal portion of the external frontal crest that was palpable. A secondary lead was placed 1 cm lateral and 0.5 cm caudal to the primary lead over the right temple. A ground lead was placed rostral to the tragus of the right ear. A modified ECG cable was connected to the BIS cable distal to the analog-to-digital converter. Three 29-gauge platinum needle electrodes[i] were connected to the modified cable and placed subdermally on the locations, as previously described.[22]

Statistical analysis—Data are reported as the mean (± SD). Data from each MAC multiple for sevoflurane were compared with an ANOVA for repeated measures by use of commercially available software.[j] When indicated, specific treatment means were compared by use of the Tukey test. The level of significance was set at $P < 0.05$.

Results

The mean MAC of sevoflurane was 3.3 ± 0.2% for this group of cats. Once cats were anesthetized, BIS values were readily obtained in all cats. The EMG activity was minimal and did not confound BIS interpretation at 0.8, 1.0, 1.5, and 2.0 MAC. As the end-tidal sevoflurane concentrations approached 0.5 MAC, however, all 8 cats had spontaneous movement. Spontaneous ventilatory efforts were observed first, and this was followed by movements of the head and limbs. Five of 8 cats began to cough during this period. As a result of an inability to maintain placement of the electrodes and the confounding increase in EMG activity, accurate BIS measurements could not be obtained at 0.5 MAC in any cats, and this MAC multiple was removed from the analysis.

As end-tidal sevoflurane concentrations approached 2.0 MAC, all 8 cats began to have burst suppression on the EEG, and this was detected by the BIS monitor and registered as an increased SR. Because BIS values in the face of burst suppression could not be interpreted, the 2.0 MAC multiple was also eliminated from the analysis.

On the basis of findings in pilot investigations, it was apparent that any benign tactile or auditory stimulation had an obvious effect on BIS measurements in the cats especially at 0.8 and 1.0 MAC. Transient and variable increases in BIS values were observed that corresponded to doors opening and closing in the laboratory and conversation among investigators. Consequently, in an attempt to standardize data collection, it was assured that cats were not subjected to any tactile or auditory stimulation during the 5-minute period of BIS measurement.

Mean BIS measurements at 0.8, 1.0, and 1.5 MAC multiples for sevoflurane were 30 ± 3, 21 ± 3, and 5 ± 2, respectively (**Fig 1**). Bispectral index measurements at 0.8 MAC were significantly greater than at 1.0 and 1.5 MAC, and BIS measurements at 1.0 MAC were significantly greater than at 1.5 MAC.

Heart rate, systolic arterial blood pressure, end-tidal CO_2 concentration, and esophageal temperature were recorded immediately after the 5-minute BIS collection period at 0.8, 1.0, and 1.5 MAC multiples for sevoflurane (**Table 1**). Mean heart rate increased with increasing end-tidal sevoflurane concentration; however, differences were not significant. Mean systolic blood pressure was 87 ± 11, 77 ± 7, and 70 ± 8 mm Hg at 0.8, 1.0, and 1.5 MAC, respectively. Blood pressure measurements at 0.8 MAC were significantly greater than those at 1.0 and 1.5 MAC, and blood pressure measurements at 1.0 MAC were significantly greater than those at 1.5 MAC. End-tidal CO_2 concentration and esophageal temperature values did not differ significantly among MAC multiples.

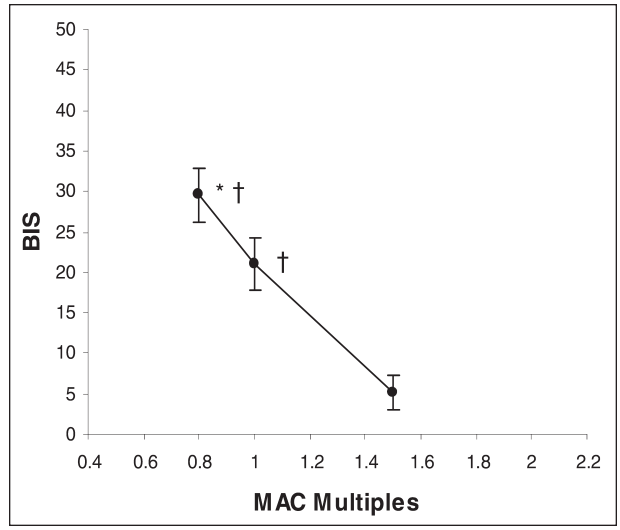

Figure 1—Mean (± SD) bispectral index (BIS) measurements versus 3 minimum alveolar concentration (MAC) multiples of sevoflurane in 8 cats. *Significantly ($P < 0.05$) different from 1.0 MAC. †Significantly ($P < 0.05$) different from 1.5 MAC.

Table 1—Mean (± SD) values of physiologic variables from 8 cats during collection of bispectral index measurements at 3 minimum alveolar concentration (MAC) multiples of sevoflurane

	Multiples of MAC		
Variables	**0.8 MAC**	**1.0 MAC**	**1.5 MAC**
Heart rate (beats/min)	112 ± 19	115 ± 15	121 ± 16
Systolic blood pressure (mm Hg)	87 ± 11*†	77 ± 7†	70 ± 8
End-tidal CO_2 (mm Hg)	31 ± 1	32 ± 2	31 ± 1
Temperature (°C)	36.8 ± 0.2	36.8 ± 0.3	36.9 ± 0.2

*Significantly ($P < 0.05$) different from 1.0 MAC. †Significantly ($P < 0.05$) different from 1.5 MAC.

Discussion

Ideally, the evaluation of BIS monitoring as an objective measure of the hypnotic component of anesthesia would require comparison to some sort of gold standard. Unfortunately, no such standard exists in veterinary patients, and it is well recognized that traditional end points thought to reflect hypnosis, such as palpebral reflexes, eyeball position, and corneal reflexes, often fail to discriminate between degrees of hypnosis in a clinical setting. Lack of a movement response to a noxious stimulus is the customary way to define anesthetic potency for the volatile agents and is also thought to predict the level of unconsciousness pro-

duced by these drugs.[2] Thus, multiples of MAC for sevoflurane were chosen as the most appropriate independent variable for objective BIS assessment in our study. Although MAC values are typically consistent among individuals within a given species, variability does exist, and there is potential for individual outliers. Therefore, in our study, MAC values were initially determined for each individual cat, with subsequent BIS measurements made during titration of sevoflurane to an end-tidal concentration expressed as a multiple of each cat's MAC. This extra experimental step effectively eliminated individual variability as a potential source of error and facilitated an essential validation of the relationship between BIS and MAC multiples for sevoflurane in these cats.

The mean MAC for sevoflurane determined for these 8 cats, 3.3%, was considerably higher than the standard reported value of 2.6% for cats.[26] In a more recent study,[27] the mean MAC for sevoflurane in 24 cats was 3.1% on the basis of results of a toe-pinch stimulus, which compares much more favorably to our own findings. It is likely that differing stimuli, end point determinations, or both are responsible for the variation in MAC values obtained from these studies. The validity of the higher MAC values determined in our study was supported by the observation that 8 out of 8 cats had spontaneous movement in the complete absence of stimulation at 0.5 MAC. Similar findings were reported in another study[28] on cats where 5 of 5 cats had spontaneous coughing, followed by running behavior, eye opening, and ultimately extubation when end-tidal sevoflurane concentrations reached 1.7%, which corresponds to our 0.5 MAC multiple.

As predicted, BIS values decreased as MAC multiples for sevoflurane increased over the range of 0.8 to 1.5 MAC. Interference from an EMG artifact was not substantial over this range, and BIS signal quality was good. Burst suppression of the EEG has been reported at deep anesthetic planes for most anesthetic agents.[5] During inhalant anesthesia, this EEG artifact causes a paradoxic increase in the BIS related to the monitor's interpretation of preburst EEG patterns as high-frequency activity (activation).[29,30] All 8 cats had burst suppression at 2.0 MAC of sevoflurane, which was readily apparent on the EEG tracing and was associated with an increased SR and BIS value. Burst suppression has similarly been reported in dogs anesthetized with isoflurane[22] and sevoflurane[23] at 2.0 MAC. Although burst suppression precluded inclusion of the BIS values recorded at 2.0 MAC from analysis in our study, it would not adversely affect the clinical use of this monitor, as long as the operator is aware of the importance of the SR when interpreting BIS values.

Although BIS decreased as predicted with increasing MAC multiples for sevoflurane, the magnitude of individual BIS values was surprising. At all MAC multiples, mean BIS values were far below the targeted upper limit commonly used in surgical patients. On the basis of the results of studies[8,31] in human volunteers, BIS values < 60 are thought to represent an optimal degree of CNS depression and have been shown to correlate with a low probability of intraoperative recall. Bispectral index values at or below 40 indicate substantial CNS depression in humans and correlate with an extremely low probability of any responsiveness whatsoever.[8] At the 1.5 MAC of sevoflurane, the mean BIS value of 5 in our cats reflected a near isoelectric EEG, and at 0.8 MAC, the mean BIS value was only 30. By comparison, in a study[22] on dogs done under similar experimental conditions, mean BIS values at 0.8, 1.0, 1.5, and 2.0 MAC of sevoflurane were 80, 72, 56, and 50, respectively. There are a number of potential reasons for this discrepancy.

First, it is possible that the degree of CNS depression produced in these cats by sevoflurane at 0.8 to 1.5 MAC was, in fact, excessive in light of the conditions they were subjected to. One key observation that argues against this hypothesis is the fact that all 8 cats had movement when the vaporizer was decreased to 0.5 MAC in the complete absence of any stimulation. Although movement in this setting probably did not imply consciousness per se, it presumably indicated a nominal degree of CNS depression, suggestive of light anesthesia.

Nonetheless, some consideration must be given to the experimental conditions under which BIS was measured. In pilot trials, substantial variability in BIS values was observed within individual cats at a given MAC multiple and appeared to be associated with changes in the degree of ambient noise or benign tactile stimulation, such as reattachment of ECG leads. Environmental auditory stimulation has been shown to increase BIS values in human patients given propofol,[32] so it is not entirely surprising that this BIS variability was observed in our cats. In an attempt to standardize data collection, we chose to make all BIS measurements under identical conditions, in a dark, quiet room without interventions on the part of the investigators. Under these circumstances, BIS values in all 8 cats were consistent with a low associated SD. We recognize that this is a somewhat artificial situation and that BIS values may have been higher, and probably more variable, had the environmental conditions been different. The next logical step required to better characterize the degree of CNS depression induced by sevoflurane, and its relationship to BIS values, must be to evaluate the effects of auditory, benign tactile, and noxious stimulation on the BIS of cats.

There is a second potential explanation for the extremely low BIS values recorded at clinically useful MAC multiples for sevoflurane in our study. The derivation of BIS is based on statistical analyses designed to specifically predict the hypnotic component of anesthesia in human patients. The scale is empirical and truly represents a state of the human brain. Although it seems likely that the set of EEG features incorporated into the BIS (including power, frequency, bicoherence, β activation, and burst suppression) are probably also relevant descriptors of CNS depression in cats, it is possible that the regression equation used to define the BIS scale is not directly applicable to cats that are patients. The distinct inverse linear relationship between the BIS of cats and MAC multiples for sevoflurane documented in our study would seem to indicate that future investigations should endeavor to better characterize this association

and determine optimal BIS ranges that could guide anesthetic titration in this species.

With regard to the other physiologic variables measured, only Doppler assessment of systolic arterial blood pressure differed significantly among MAC multiples for sevoflurane, with decreasing pressures recorded at increasing end-tidal concentrations. We elected to measure blood pressure indirectly, by use of the Doppler technique, to avoid the additional stimulation of arterial catheterization in our cats. Consequently, it is difficult to directly compare our results with those of other studies on cats where blood pressure was measured invasively. Nonetheless, the observed decrease in blood pressure observed at higher MAC multiples in our study appears to be in agreement with previously published data that demonstrate the tendency for volatile inhalants to cause dose-dependent vasodilation and hypotension in cats.[33]

Mean heart rate was slightly higher at increased end-tidal sevoflurane concentrations, although the difference was not significant. This finding may reflect reflex cardiac acceleration in response to sevoflurane-induced hypotension.[33] End-tidal CO_2 measurements were consistent among MAC multiples once initial ventilator settings were established. Although large changes in CO_2 tension have been shown to alter quantitative EEG data in dogs anesthetized with halothane,[34] it is extremely unlikely that changes in CO_2 tension in our study could have had any effect on our reported BIS values. Esophageal temperatures did not differ among MAC multiples, although mean values were < 37.5°C, the lower limit that is typically accepted to define normothermia. Substantial hypothermia will generally result in a corresponding decrease in BIS values as brain processes slow, and this is reflected in the documented correlation between BIS and cerebral metabolic rate.[k] However, the possibility that hypothermia contributed to the low BIS values reported in our study is unlikely because body temperatures in human patients typically have to decrease below 33°C before significant changes in EEG and BIS are observed.[2]

[a]Sevoflo, Abbott Laboratories, North Chicago, Ill.
[b]Sevoflurane Vapor 19.1, North American Drager, Telford, Pa.
[c]Narkovet 2, North American Drager, Telford, Pa.
[d]Hallowell EMC, Pittsfield, Mass.
[e]Datascope 3000A, Datascope Corp, Paramus, NJ.
[f]Ultrasonic Doppler Flow Detector 811, Parks Medical Electronics Inc, Aloha, Ore.
[g]Datascope Multinex 4100 Plus, Datascope Corp, Paramus, NJ.
[h]A-2000 BIS monitor with version 3.4 software, Aspect Medical Systems Inc, Natick, Mass.
[i]E2-31 cm, Grass Instruments, Astro-Med Inc, West Warwick, RI.
[j]SigmaStat statistical software package, version 2.0, SPSS Science, Chicago, Ill.
[k]Alkire MT, Pomfrett C. Toward the fundamental unit of anesthetic depth: positron emission tomography evidence suggests bispectral index (BIS) monitors are an important component of anesthetic depth (abstr). *Anesthesiology* 1996;85:A174.

References

1. Rosow CE. Can we measure depth of anesthesia?, in *Proceedings*. Annu Meet Am Soc Anesthesiol 1999;44–50.
2. Rosow C, Manberg PJ. Bispectral index monitoring. *Anesthesiol Clin North Am* 2001;19:947–966.
3. Kissin I. General anesthetic action: an obsolete notion? *Anesth Analg* 1993;76:215–218.
4. Prys-Roberts C. Anaesthesia: a practical or impractical construct? *Br J Anaesth* 1987;59:1341–1345.
5. Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998;89:980–1002.
6. Denman WT, Swanson EL, Rosow D, et al. Pediatric evaluation of the bispectral index (BIS) monitor and correlation of BIS with end-tidal sevoflurane concentration in infants and children. *Anesth Analg* 2000;90:872–877.
7. Gale T, Leslie K, Kluger M. Propofol anaesthesia via target controlled infusion or manually controlled infusion: effects on the bispectral index as a measure of anaesthetic depth. *Anaesth Intensive Care* 2001;29:579–584.
8. Glass PS, Bloom M, Kearse L, et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; 86:836–847.
9. Leslie K, Sessler DI, Schroeder M, et al. Propofol blood concentration and the bispectral index predict suppression of learning during propofol/epidural anesthesia in volunteers. *Anesth Analg* 1995; 81:1269–1274.
10. Liu J, Singh H, White PF. Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. *Anesthesiology* 1996;84:64–69.
11. Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997;84:185–189.
12. Bannister CF, Brosius KK, Sigl JC, et al. The effect of bispectral index monitoring on anesthetic use and recovery in children anesthetized with sevoflurane in nitrous oxide. *Anesth Analg* 2001; 92:877–881.
13. Burrow B, McKenzie B, Case C. Do anaesthetized patients recover better after bispectral index monitoring? *Anaesth Intensive Care* 2001;29:239–245.
14. Guignard B, Coste C, Menigaux C, et al. Reduced isoflurane consumption with bispectral index monitoring. *Acta Anaesthesiol Scand* 2001;45:308–314.
15. Hachero A, Alamo F, Caba F, et al. Influence of bispectral index monitoring on fentanyl requirements during total intravenous anesthesia for major gynecological surgery. *Rev Esp Anestesiol Reanim* 2001; 48:364–369.
16. Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* 1998;88:642–650.
17. Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997;87:808–815.
18. Schmidt M, Papp-Jambor C, Marx T, et al. Evaluation of bispectral index (BIS) for anaesthetic depth monitoring in pigs. *Appl Cardiopulm Pathophysiol* 2000;9:83–86.
19. Haga HA, Tevik A, Moerch H. Bispectral index as an indicator of anaesthetic depth during isoflurane anaesthesia in the pig. *J Vet Anaesth* 1999;26:3–7.
20. Haga HA, Dolvik NI. Evaluation of the bispectral index as an indicator of degree of central nervous system depression in isoflurane-anesthetized horses. *Am J Vet Res* 2002;63:438–442.
21. Antognini JF, Wang XW, Carstens E. Isoflurane anaesthetic depth in goats monitored using the bispectral index of the electroencephalogram. *Vet Res Commun* 2000;24:361–370.
22. Greene SA, Benson GJ, Tranquilli WJ, et al. Relationship of canine bispectral index to multiples of sevoflurane minimal alveolar concentration, using patch or subdermal electrodes. *Comp Med* 2002; 52:424–428.
23. Greene SA, Tranquilli WJ, Benson GJ, et al. Effect of medetomidine administration on bispectral index measurements in dogs during anesthesia with isoflurane. *Am J Vet Res* 2003;64:316–320.
24. Grimm KA, Tranquilli WJ, Thurmon JC, et al. Duration of nonresponse to noxious stimulation after intramuscular administration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. *Am J Vet Res* 2000; 61:42–47.
25. Haskins SC. Blood gases and acid-base balance: clinical inter-

pretation and therapeutic implications. In: Kirk RW, ed. *Current veterinary therapy VIII*. Philadelphia: WB Saunders Co, 1983;201–215.

26. Doi M, Yunoki H, Ikeda K. The minimum alveolar concentration of sevoflurane in cats. *J Anesth* 1988;2:113–114.

27. Ide T, Sakurai Y, Aono M, et al. Minimum alveolar anesthetic concentrations for airway occlusion in cats: a new concept of minimum alveolar anesthetic concentration-airway occlusion response. *Anesth Analg* 1998;86:191–197.

28. Osawa M, Shingu K, Murakawa M, et al. Effects of sevoflurane on central nervous system electrical activity in cats. *Anesth Analg* 1994;79:52–57.

29. Detsch O, Schneider G, Kochs E, et al. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. *Br J Anaesth* 2000;84:33–37.

30. Conreux F, Best O, Preckel MP, et al. Electroencephalographic effects of sevoflurane in pediatric anesthesia: a prospective study of 20 cases. *Ann Fr Anesth Reanim* 2001;20:438–445.

31. Sebel PS, Lang E, Rampil IJ, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997;84:891–899.

32. Kim DW, Kil HY, White PF. The effect of noise on the bispectral index during propofol sedation. *Anesth Analg* 2001;93:1170–1173.

33. Hikasa Y, Ohe N, Takase K, et al. Cardiopulmonary effects of sevoflurane in cats: comparison with isoflurane, halothane, and enflurane. *Res Vet Sci* 1997;63:205–210.

34. Smith LJ, Greene SA, Moore MP, et al. Effects of altered arterial carbon dioxide tension on quantitative electroencephalography in halothane-anesthetized dogs. *Am J Vet Res* 1994;55:467–471.