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Relationship of Feline Bispectral Index to Multiples of Isoflurane Minimum Alveolar Concentration

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The study reported here was done to determine the relationship between bispectral index (BIS) values and minimum alveolar concentration (MAC) multiples of isoflurane in cats. Isoflurane MAC was determined using the tail-clamp method in eight domestic cats. Ten days later, the cats were anesthetized a second time with isoflurane at each of five MAC multiples administered in random order. Ventilation was controlled and, after a 20-min equilibration period at each MAC multiple of isoflurane, BIS data were collected for 5 min and the median BIS value calculated. Data from each isoflurane MAC multiple were compared using analysis of variance for repeated measures, and statistical significance was set at $P < 0.05$. The MAC of isoflurane (mean ± 1 standard deviation) was 1.8% ± 0.2%. BIS values at 0.5 MAC could not be recorded due to spontaneous movement in all eight cats. BIS values at 2.0 MAC were confounded by burst suppression in seven of the eight cats. Over the range of 0.8 to 1.5 MAC, BIS values decreased significantly with increasing end-tidal isoflurane concentrations. Mean (± 1 standard deviation) BIS measurements were 32 ± 3 at 0.8 MAC, 20 ± 4 at 1.0 MAC, and 5 ± 3 at 1.5 MAC. Therefore, BIS values are inversely and linearly related to end-tidal isoflurane concentrations in anesthetized cats. However, the consistently low BIS values recorded in this study suggest that clinical BIS endpoints used to titrate anesthetic agents in humans may not be applicable to cats.

Cats are commonly used subjects in the laboratory setting, most notably in neurophysiologic research (2, 20, 34). Many such investigations involve the use of volatile inhalant agents, such as isoflurane, to anesthetize animals to facilitate various invasive procedures. All anesthetic agents induce marked effects on central nervous system (CNS) function at the spinal cord, brainstem, and cerebral cortical levels (26), although these effects differ among various anesthetic agents and among species. These effects not only are relevant to the well-being of the animal undergoing anesthesia, but they also may notably affect data collected during neurophysiological experiments. Consequently, a thorough understanding of the components of general anesthesia is necessary to ensure the welfare of research animals and to avoid misinterpretation of data obtained in this setting.

It is now recognized that the phenomenon known as anesthesia is not a single graded effect, but it is rather a complex state characterized by hypnosis, analgesia, and areflexia (25, 35, 37, 38). 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 profound analgesia but are relatively poor hypnotics. Both classes of drugs may contribute to suppression of movement, although in many cases, analgesics are superior to hypnotics in obtunding intraoperative reflex activity (37). Traditionally, monitoring of anesthetic depth has involved titrating agents to analgesic endpoints, whereby doses are adjusted to control various somatic and autonomic responses. The clinical evaluation of the hypnotic component of anesthesia, in the absence of a system for objective graded measurement, is considerably more challenging.

For decades, monitoring CNS depression by using electroencephalography (EEG) during anesthesia has focused on achieving this goal (12, 36). However, examination of raw EEG data has not proven to be sufficiently reliable or time-responsive to have any sort of widespread clinical utility (36, 43). More recently, processed EEG monitoring has evolved as an effective means of providing the anesthetist with immediate feedback regarding the patient's level of hypnosis. Spectral edge frequency, total power, beta-to-delta ratios, and numerous other specific parameters derived from computer-processed EEGs have been evaluated with variable success. However, interpretation of the information generated can vary greatly depending on the anesthetic agents used (40, 41).

The bispectral index (BIS) is a relatively new approach to intraoperative EEG processing and constitutes a substantial improvement in reliability over historic techniques. The BIS is the first EEG-based technology approved by the Food and Drug Administration 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 which were found to be highly correlated with hypnosis were selected. Based on 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 (36, 37). Zero indicates an isoelectric EEG, whereas 100 represents the normal conscious state.

The bispectral index 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 anes-

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thetic agents (7, 10, 12, 28-30, 36). In light of these studies, it has been shown that maintaining an intraoperative BIS value between 40 and 60 represents an optimal level of hypnosis. In addition, titrating administration of anesthetic agents based on 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 postanesthesia patient care (4, 5, 7, 11, 17, 18, 23).

To date, there are relatively few reports on the use of BIS technology in anesthetized animals, and results seem to be mixed. In a recent study involving swine, BIS was not useful in distinguishing between moderate levels of isoflurane-induced CNS depression; however, it could be used to predict the point at which suppression of motor responses to noxious stimuli would occur in this species (15). Results of a study in unstimulated pigs did not indicate a reliable correlation between depth of isoflurane anesthesia and BIS (19), whereas those of another swine study indicated reliable correlation of BIS values to propofol-induced anesthetic depth during surgery (39). A recent study in pigs failed to demonstrate a correlation between BIS values and hemodynamic changes or recovery times associated with sevoflurane or propofol anesthesia (33).

In goats, the BIS has been shown to be inversely related to key points in the continuum of isoflurane-induced anesthetic depth, including time of recumbency, tracheal intubation, and loss of corneal or withdrawal reflexes (3). In dogs, an inverse relationship between BIS measurements and MAC multiples of sevoflurane and isoflurane has been reported (13, 14). In the same canine–isoflurane study, BIS measurements were significantly lower in dogs receiving medetomidine and isoflurane, compared with dogs receiving saline and isoflurane (14).

In our laboratory, BIS was found to be inversely related to end-tidal sevoflurane concentrations in anesthetized cats, although absolute values for BIS were considerably lower than those reported for other species (27). One other recent study has evaluated the utility of BIS, both prestimulation and after noxious stimulation, in assessing anesthetic depth is isoflurane-anesthetized cats. The investigators concluded that BIS, in the absence of noxious stimulation, is of limited value as an index of anesthetic depth in this species (32).

The varied results of the studies cited suggest that further investigation into the utility of BIS monitoring as a tool for quantifying the hypnotic component of anesthesia in animals is warranted. Clearly, agent- and species-specific data are required before any definitive conclusions can be made. BIS monitoring in the research laboratory has the potential to reduce animal morbidity and mortality by decreasing the incidence of excessive anesthetic depth; it also has the potential to improve animal welfare by decreasing the incidence of insufficient anesthetic depth during invasive procedures. Both of these possibilities may lead to generation of more accurate neurophysiologic data and legitimize data interpretation. The objective of the study reported here was to quantify the relationship between BIS and MAC multiples of isoflurane in cats. As has been demonstrated for sevoflurane (27), we hypothesized that BIS would be inversely and linearly related to isoflurane MAC multiples in the cat.

Materials and Methods

Animals. Eight colony-bred domestic cats (*Felis catus*; four male, four female; Harlan, Indianapolis, Ind.), with a mean age of 3.2 years and mean weight of 4.1 kg, were studied. Cats tested negative for feline leukemia virus and feline immunodeficiency virus. The university's institutional animal care and use committee approved the study, which was conducted in compliance with local and federal guidelines governing animal care and housing. All facilities were approved by the Association for the Assessment and Accreditation of Laboratory Animal Care, International. Animals were housed individually in indoor cages and fed a commercially prepared feline diet. The cats were examined thoroughly by a veterinarian and found to be healthy upon arrival at the housing facility. Blood and urine were collected prior to the study. A complete blood count, serum biochemistry values (total protein, albumin, electrolytes, urea nitrogen, creatinine, alanine aminotransferase, alkaline phosphatase, and total carbon dioxide), and results of urinalysis were found to be within respective reference ranges for each cat. A minimum of 2 weeks was allowed for acclimatization prior to commencing the study. Food, but not water, was withheld on the days of the study.

Procedure. Each cat was anesthetized twice. On the first occasion, each cat's MAC for isoflurane was determined by the use of the tail-clamp method as described below. On the second occasion, cats were instrumented for measurement of BIS, electrocardiogram (ECG), systolic arterial blood pressure, esophageal temperature, and end-tidal carbon dioxide (CO_2) and isoflurane concentrations. Cats were anesthetized at each of five isoflurane MAC multiples (0.5, 0.8, 1.0, 1.5, and 2.0 times MAC) according to each animal's individual predetermined isoflurane MAC value. The order of administration of MAC multiples was randomized for each trial. After 20 min of equilibration at each isoflurane MAC multiple, values for BIS and other physiologic parameters were recorded. BIS data were collected for 5 min, and the median BIS value determined for the recording period at each isoflurane MAC multiple.

Determination of MAC of isoflurane. The technique for determination of the MAC of volatile inhalant anesthetics used by our laboratory has been described previously (16). This same technique was adapted for use in cats in the present study. Each cat was placed in a purpose-made plexiglass induction chamber ($50 \times 40 \times 40$ cm) and oxygen delivered via a flow meter from an anesthetic machine (Narkovet 2, North American Drager, Telford, Pa.) at 5 liters/min for the first 5 min. Excess and waste gases were scavenged from the chamber by using an active disposal system. Isoflurane then was introduced into the chamber at a concentration of 5% by using a precision vaporizer (Isoflurane Vapor 19.1, North American Drager). Each cat was observed closely during the early stages of the induction and when signs of muscle relaxation were evident, the cats were removed from the chamber, and induction was completed using a clear plastic face mask and pediatric rebreathing circuit with an oxygen flow rate of 1 liter/min and an isoflurane concentration of 3%. When palpebral reflexes were diminished and jaw tone was sufficiently relaxed, lidocaine spray was applied topically to the arytenoids with the aid of a laryngoscope, and the trachea was intubated with a 4-mm or 5-mm diameter polyvinyl chloride cuffed endotracheal tube (Mallinckrodt, Hazelwood, Mo.). A catheter for sampling was introduced through the endotracheal tube adaptor, extending to the level of the carina.

Anesthesia was maintained for 20 min at 2% end-tidal isoflurane concentration and an oxygen flow rate of 1 liter/min, 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 sec, 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 isoflurane concentration then was increased (if a positive response had occurred) or decreased (negative response) by 10%. A 20-min equilibration period was allowed at each end-tidal isoflurane concentration before the stimulus was applied. 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 two determinations were averaged for each cat. After MAC was identified, butorphanol was administered at 0.2 mg/kg intramuscularly into the epaxial musculature. The vaporizer was turned off, and the cats continued to breathe 100% oxygen for 2 min or until return of an ear flick response or swallowing response was noted. At this time, the endotracheal tube was removed, and each cat was transferred to a clean dry cage with a circulating warm water system and warm blankets and where it was observed for a minimum of 2 h. A postanesthesia physical examination was completed for each cat prior to being returned to the animal holding facility.

Physiologic monitoring. On the day of the trial, cats were induced using exactly the same protocol and equipment described in the previous section . All cats were positioned in left lateral recumbency, and ventilation was controlled with a mechanical ventilator (Hallowell EMC, Pittsfield, Mass.) adjusted to maintain normocapnia (end-tidal CO_2 of 30 to 35 mm Hg [21]). A lead II ECG was monitored, and an esophageal stethoscope with temperature probe was placed (Datascope 3000A, Datascope Corporation, Paramus, N.J.). Heart rate was determined by auscultation by using the esophageal stethoscope. Systolic arterial blood pressure was measured indirectly by using a doppler system (Ultrasonic Doppler Flow Detector 811, Parks Medical Electronics Incorporated, Aloha, Oreg.). The piezoelectric crystal was placed over the left dorsal pedal artery of each cat, and a blood pressure cuff with a width measuring 40% the circumference of the hindlimb was placed immediately proximal to the tarsus and connected to a sphygmomanometer. End-tidal CO_2 and isoflurane concentrations were measured from samples taken at the tracheal carina by using a calibrated side-stream sampling anesthetic gas analyzer (Datascope Multinex 4100 Plus, Datascope Corporation).

Measurement of BIS. BIS was measured using a A-2000 BIS monitor with version 3.4 software (Aspect Medical Systems Incorporated, Natick, Mass.). BIS was recorded every 5 sec for 5 min after equilibration at each MAC multiple, and data were stored on a computer. 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 50/60 Hz filter was set to 60 Hz, and the high-frequency cutoff was set at 70 Hz. At startup, the monitor requires skin electrode impedance < 7.5 kΩ and thereafter provides for continuous impedance checking with 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 sec) used for BIS calculation. The percentage of epochs in the past 63 sec in which the EEG signal is suppressed is expressed as the suppression ratio (SR). Burst suppression is identified as isoelectric analog EEG for at least 1 sec and is detected by the monitor and indicated as an increased SR (i.e., SR > 1). Presence of burst suppression at deeper levels of isoflurane anesthesia readily was identified by spike activity followed by isoelectric EEG and by a concomitant increase in SR and the displayed BIS value. BIS values were not recorded if the SR was greater than 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. A previous study validated the use of needle electrodes in animal subjects as a feasible alternative to the proprietary adhesive one-piece patch electrodes recommended by the BIS manufacturer for use in humans (13). Therefore, we elected to use subdermal needle electrodes in the present study to avoid potential lead failure associated with poor skin contact and to allow each of the three leads to be placed individually. Hair removal or special skin preparation was not necessary with this approach. A modified ECG cable was connected to the BIS cable distal to the analog-to-digital converter, and three 1-cm 29-gauge platinum needle electrodes (E2-31 cm, Grass Instruments, Astro-Med Incorporated, West Warwick, R.I.) then were attached to this cable. The three needle electrodes were introduced through the skin into the subdermal space at the following locations, as described previously (13, 27): the primary lead was placed on the midline, approximately one 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; the secondary lead was placed 1 cm lateral and 0.5 cm caudal to the primary lead, over the right temple; and the ground lead was placed rostral to the tragus of the right ear.

Statistical analysis. Data are reported as mean ± 1 standard deviation (SD). Data from each MAC multiple of isoflurane were compared with an analysis of variance for repeated measures by using commercially available software (Sigma Stat Statistical Software Package, Version 2.0, SPSS Science, Chicago, Ill.). When indicated, specific treatment means were compared using the Tukey test. The level of significance was set at $P < 0.05$.

Results

The mean MAC of isoflurane was 1.8% ± 0.2% for this group of cats. Once animals were anesthetized, BIS values were readily obtained in all cats. Electromyographic activity was minimal and did not confound BIS interpretation at 0.8, 1.0, 1.5, and 2.0 MAC. As the end-tidal isoflurane concentrations approached 0.5 MAC, however, all eight cats exhibited spontaneous movement. In all cases, this movement was prefaced by spontaneous ventilatory efforts followed by movements of the head and limbs. Six of eight cats began to cough during this period. Because of the cats' head movements, it was not possible to maintain placement of the small needle electrodes. This inability, in addition to the confounding increase in EMG activity, meant that accurate BIS measurements could not be obtained at 0.5 MAC in any of the cats; we therefore removed this MAC multiple from analysis.

As end-tidal isoflurane concentrations approached 2.0 MAC, seven of eight cats began to exhibit burst suppression on the EEG, and this artifact was noted by the BIS monitor and regis-

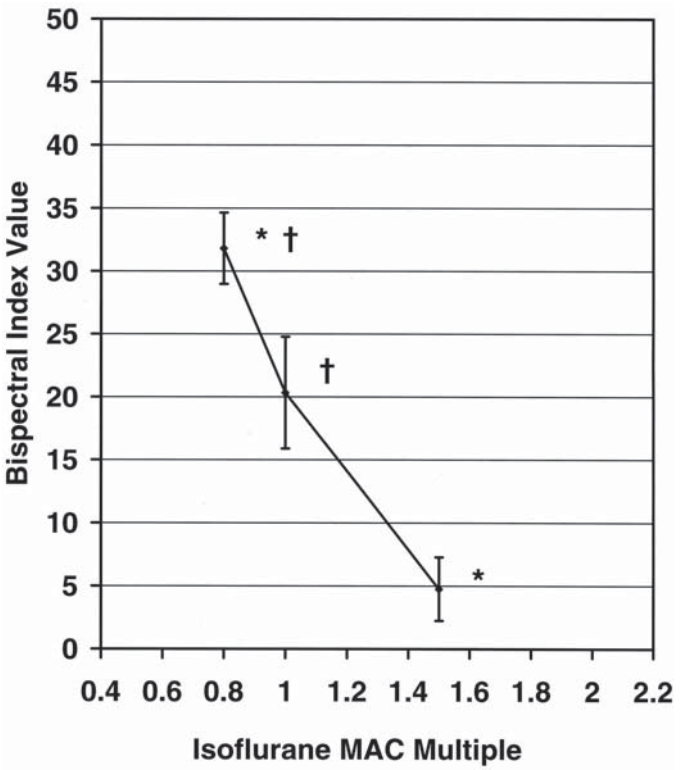

Figure 1. Mean bispectral index (BIS) measurements in eight cats at three minimum alveolar concentration (MAC) multiples of isoflurane. *, Significantly ($P < 0.05$) different from value for 1.0 MAC; †, significantly ($P < 0.05$) different from value for 1.5 MAC.

tered as an increased SR. The eighth cat, which did not exhibit burst suppression at 2.0 MAC, had an isoelectric EEG. Because BIS values in the face of burst suppression could not be interpreted, the 2.0-MAC multiple was eliminated from analysis.

In light of 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 noted that corresponded to doors opening and closing in the laboratory and conversation among investigators. Consequently, in an attempt to standardize data collection, we ensured that cats did not experience any tactile or auditory stimulation during the 5-min period of BIS measurement.

Mean BIS measurements at 0.8, 1.0, and 1.5 isoflurane MAC were 32 ± 3, 20 ± 4, and 5 ± 3, respectively (Fig. 1). BIS measurements were significantly greater at 0.8 MAC than at 1.0 and 1.5 MAC and were significantly greater at 1.0 MAC 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-min BIS collection period at 0.8, 1.0, and 1.5 isoflurane MAC (Table 1). Mean heart rate tended to increase with increasing end-tidal isoflurane concentration, but differences were not statistically significant. Mean systolic blood pressure was 87 ± 8, 81 ± 4, and 71 ± 8 mm Hg at 0.8, 1.0, and 1.5 MAC, respectively. Blood pressure measurements at 0.8 MAC and 1.0 MAC were significantly greater than those at 1.5 MAC. The difference between blood pressures at 0.8 and 1.0 MAC were not significant. End-tidal CO_2 concentration and esophageal temperature values did not differ significantly among MAC multiples.

Table 1. Mean (± 1 standard deviation) values of physiologic variables from eight cats during collection of bispectral index measurements at three minimum alveolar concentration (MAC) multiples of isoflurane

	0.8 MAC	1.0 MAC	1.5 MAC
Heart rate (beats/min)	112 ± 9	112 ± 13	119 ± 14
Systolic blood pressure (mm Hg)	87 ± 8[a]	81 ± 4[a]	71 ± 8
End-tidal CO_2 (mm Hg)	30 ± 1	32 ± 2	31 ± 1
Temperature (°C)	36.8 ± 0.3	37.1 ± 0.2	37.0 ± 0.2

[a]Significantly ($P < 0.05$) different from corresponding value at 1.5 MAC.

Discussion

The mean isoflurane MAC determined for these eight cats, 1.8%, was marginally higher than the standard reported feline value of 1.6% (9). However, the mean MAC we obtained is in line with that (1.87%) reported in a recent study that used an electrical stimulating device positioned at the ventral tail base in isoflurane-anesthetized cats (31). Various factors may influence laboratory MAC determinations, including the type of noxious stimulus used to elicit a response and the specific end-point established. To minimize variability in the application of the stimulus, the same clamp was used throughout the study.

The decision to predetermine isoflurane MAC values for each individual cat allowed us to compare BIS values to actual MAC multiples versus comparing BIS values to end-tidal isoflurane concentrations and making conclusions based on previously published isoflurane MAC values. Although MAC values typically are consistent within a given species, variability does exist, and there is potential for individual outliers. The extra experimental step incorporated into our protocol effectively eliminated this individual variation as a potential source of error and facilitated an essential validation of the relationship between BIS and isoflurane MAC multiples in cats.

As predicted, BIS values decreased as the isoflurane MAC multiple increased over the range of 0.8 to 1.5 MAC. This finding is consistent with those of a previous study done in our laboratory involving sevoflurane-anesthetized cats (27). Interference from EMG artifact was not problematic over this range, and BIS signal quality was good according to the displayed signal quality index. Burst suppression of the EEG has been reported at deep anesthetic planes for most anesthetic agents (36). During inhalant anesthesia, this EEG artifact causes a paradoxical increase in the BIS related to the monitor's interpretation of preburst EEG patterns as high-frequency activity (activation) (6, 8). Seven of the eight cats exhibited burst suppression at 2.0 MAC of isoflurane; this effect was readily apparent on the EEG tracing and was associated with increased SR and BIS values. Burst suppression at 2.0 MAC also was documented in the sevoflurane study cited (27) as well as in another recent study that reported burst suppression activity at end-tidal isoflurane concentrations between 2.3% and 3.2% (32). In our study, the one cat that did not exhibit burst suppression at 2.0 MAC isoflurane had an isoelectric EEG, and it is probable that, if the isoflurane concentration had been increased beyond 2.0 MAC, burst suppression would have been evident. Although the development of burst suppression precluded inclusion of the BIS values recorded at 2.0 MAC from analysis in this study, it would not adversely affect the clinical utility of this monitor, as long as the operator is aware of the significance of the SR when interpreting BIS values.

At 1.5 MAC isoflurane, the mean BIS value of 5 for our cats reflected a near-isoelectric EEG, and at 0.8 MAC, the mean BIS

value was only 32. These findings very closely parallel BIS values reported in sevoflurane-anesthetized cats, which were under identical experimental conditions (27). Only one other study in the literature reports BIS values and end-tidal isoflurane concentrations in cats (32). In that study by March and Muir, the mean BIS value at 1.8% (which corresponds to the 1.0 MAC multiple in our study) was approximately 20 in non-stimulated cats (32), a value that is in agreement with our findings. At 2.7% (which corresponds to the 1.5 MAC multiple in our study), the mean BIS value in nonstimulated cats was approximately 10 (32). Although this value is somewhat higher than our reported value of 5, the authors state that burst suppression was noted between end-tidal isoflurane concentrations of 2.3% and 3.2% and thus may explain the increased BIS values recorded in that study. The most pronounced difference between the cited study and ours was the BIS values reported at the 1.4% end-tidal isoflurane concentration (which corresponds to the 0.8 MAC multiple in our study). At this depth, the mean BIS in unstimulated cats in the March and Muir study was approximately 65 (32), whereas mean BIS in our study was only 32.

There are several possible reasons for the low BIS value we obtained at the 0.8-MAC isoflurane multiple. In pilot trials, considerable variability in BIS values was noted within individual cats at a given MAC multiple and appeared to be associated with changes in ambient noise levels 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 (24), so it is not entirely surprising that this BIS variability was observed in our cats. In an attempt to standardize data collection, we elected 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 eight cats were very consistent, with a low associated standard deviation. We recognize that this set-up is a somewhat artificial situation and that BIS values may have been higher, and probably more variable, had the environmental conditions been different. Therefore, differing experimental conditions constitute a logical explanation for the discrepancy in BIS values noted during "light" anesthesia between the March and Muir study and ours.

In a more general sense, though BIS decreased as predicted with increasing isoflurane MAC multiples the magnitude of individual BIS values, both in our study and in the March and Muir study, was considerably lower than those reported in other species. In a canine study done under similar experimental conditions, mean BIS values at 0.8, 1.0, 1.5, and 2.0 MAC isoflurane were 65, 60, 52, and 31, respectively (14). Similarly, in a swine study, mean BIS values from 0.8 to 2.0 MAC of isoflurane ranged from approximately 75 to 40, respectively (15).

Why cats would have considerably lower BIS values than other species at comparable depths of inhalant anesthesia is not entirely clear. 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 feline CNS depression, it is possible that the regression equation used to define the BIS scale is not directly applicable to cats. The distinct inverse, linear relationship between feline BIS and isoflurane MAC multiples that we documented here and in the sevoflurane study (27) seem to indicate that future studies are required to better characterize this association and determine optimal BIS ranges that could guide anesthetic titration in this species both during noxious stimulation and in the absence of such stimulation.

With regard to the other physiologic variables measured, only doppler assessment of systolic arterial blood pressure differed significantly among multiples of isoflurane, with decreasing pressures recorded at increasing end-tidal concentrations. We elected to measure blood pressure indirectly, using the doppler technique, to avoid the additional stimulation of arterial catheterization in our cats. The decrease in blood pressure at higher MAC multiples that we noted is in agreement with the sevoflurane study discussed previously (27) as well as other published data demonstrating the tendency for volatile inhalants to cause dose-dependent vasodilation and hypotension in cats (22).

Mean heart rate tended to be slightly higher at increased end-tidal isoflurane concentrations, although the difference was not significant. This trend may reflect reflex cardiac acceleration in response to isoflurane-induced hypotension (22). 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 (42), it is extremely unlikely that changes in CO_2 tension in the present study could have had any effect on our reported BIS values. Esophageal temperatures did not differ among MAC multiples, although mean values were less than 37.5°C, the lower limit typically accepted to define normothermia. Pronounced hypothermia generally will result in a corresponding decrease in BIS values as brain processes slow, and this association is reflected in the documented correlation between BIS and cerebral metabolic rate (1). However, the possibility that hypothermia contributed to the low BIS values reported in this study is unlikely, because body temperatures in human patients typically have to fall below 33°C before significant changes in EEG and BIS are noted (37).

In conclusion, BIS monitoring appears to have a predictive value in determining relative levels of CNS depression during isoflurane anesthesia in cats. However, the absolute values for BIS measured at various MAC multiples in unstimulated cats are not consistent with reported BIS ranges for other species under similar conditions. Further studies should be undertaken in an attempt to better clarify the relationship between BIS, MAC multiples of inhalant anesthetics and the effect of noxious stimulation on this relationship in anesthetized cats. It is possible that results from such investigations could result in the BIS monitor gaining widespread use in the research laboratory setting as a tool for standardizing anesthetic depth.

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