Use of the bispectral index as a monitor of anesthetic depth in cats anesthetized with isoflurane

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Objective—To determine whether the prestimulation bispectral index (BIS) value or relative change in BIS after noxious stimulation can be used to assess the depth of isoflurane anesthesia in cats.

Animals—17 healthy female cats.

Procedure—Electroencephalogram (EEG) patterns and BIS values were examined in cats that received increasing end-tidal (ET) isoflurane concentrations. Subsequently, BIS values were determined before and after either a noxious somatic or visceral stimulus in cats that received ET isoflurane concentrations ranging from 1.8% to 2.4%. Electrical stimuli of the tail base and bladder distension to 50 cm of water were the somatic and visceral stimuli, respectively.

Results—The resting BIS at ET isoflurane concentrations from 1.4% to 1.9% steadily decreased concurrently with increasing degrees of EEG suppression. Prestimulation BIS values, however, were not related to 1.8% to 2.4% ET isoflurane concentrations and not useful for prediction of BIS values or hemodynamic and movement responses after a noxious stimulus. The poststimulation BIS value and the difference between mean BIS values before and after stimulation were inversely correlated with increasing ET isoflurane concentrations. Poststimulation BIS values > 60 were observed at ET isoflurane concentrations greater than those associated with a movement response after a stimulus.

Conclusions and Clinical Relevance—The prestimulation BIS value has limited use in assessing anesthetic depth in cats during isoflurane anesthesia. The change in BIS values after a noxious somatic or visceral stimulus was a reliable measure of anesthetic depth and may be a useful measure of early arousal from the hypnotic state. (*Am J Vet Res* 2003; 64:1534–1541)

Anesthesia is subjectively evaluated on the basis of the degree of hypnosis, analgesia, and muscle relaxation produced by an anesthetic regimen. Movements in response to noxious stimuli are lost as a result of the effects of anesthetics on the peripheral nervous system and CNS. Lack of responsiveness to noxious stimuli may be caused by inhibition of sensory and motor transmission at the spinal cord and brain stem levels or attributable to a direct effect of the anesthetic on corticocerebral processing.[1-5] Consequently, anesthetic agents may selectively inhibit voluntary movements independent of effects on corticocerebral activity. Arousal from anesthesia-induced hypnosis is a dynamic process that is dependent upon the degree of corticocerebral depression and nociceptive inhibition (analgesia).[1] Inadequate analgesia in the presence of a sufficiently intense surgical stimulus may lead to activation of CNS areas that mediate arousal. Changes in hemodynamic parameters are frequently used as measures of analgesia,[6-9] but these CNS responses are subcortically mediated and do not require corticocerebral activation.[1] A direct measure of cortical activity in response to a noxious stimulus could provide a means of differentiating hypnosis from analgesia during anesthesia.

The **bispectral index (BIS)** is a number from 0 to 100 derived from an algorithm that relates the following 3 factors: 1) the degree to which waveforms of the **electroencephalogram (EEG)** are in phase (ie, bicoherence); 2) the amount of EEG power in the delta versus beta range (ie, power spectrum); and 3) the proportion of the EEG that is isoelectric. The degree of bicoherence or phase coupling between the sine wave components of the EEG increases with increasing anesthetic depth and is inversely related to the derived BIS.[10-12] The BIS value is typically > 90 in unmedicated, awake humans and steadily decreases with increasing amounts of sedation and hypnosis.[1,10,13] A BIS value of 0 signifies an isoelectric EEG and the complete absence of cortical activity. Consequently, the BIS number is inversely related to the depth of anesthesia and currently used clinically as a measure of patient hypnosis and responsiveness in humans undergoing anesthetic procedures.[10,13-19] The relationship of the BIS to clinical indicators of anesthesia has been investigated in humans and veterinary species.[18,20,21,a] Prestimulation BIS values ≥ 60 in humans are reported to be associated with conscious perception of somatic and visceral stimuli,[17,18,20,22,b] and BIS values in animals have been correlated with the loss of reflexive and purposeful movements, **minimum alveolar concentration (MAC)**, and MAC multiples during inhalant anesthesia.[23-26] Although the BIS is not a direct measure of analgesia, it is an indirect indicator of a patient's responsiveness to noxious stimuli under specific anesthetic conditions. An increase in the BIS after noxious stimulation has been used as a measure of adequate analgesia and sedation in humans.[c,d] Similarly, recent studies[24,26] in goats and horses have evaluated BIS changes in response to noxious somatic and visceral stimuli. Findings in these studies suggest that the magnitude of change in the BIS after a noxious stimulus is a more accurate predictor of analgesia and anesthesia than the prestimulation BIS value.

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The purpose of the study presented here was to determine whether the prestimulation BIS value or relative change in BIS after noxious stimulation could be used to assess the depth of isoflurane anesthesia in cats. Initially, we examined the effect of increasing **end-tidal (ET)** isoflurane concentrations on the EEG and BIS in nonstimulated cats. Subsequently, we evaluated BIS values, autonomic variables, and patient movements before and after a somatic or visceral stimulus in isoflurane-anesthetized cats. We hypothesized that the change in BIS was more predictive of anesthetic depth than the prestimulation BIS value.

Materials and Methods

Measurement of the baseline EEG and BIS at increasing ET concentrations of isoflurane—Resting BIS values were determined in 17 healthy spayed female cats by use of isoflurane as a single anesthetic agent. Complete blood count determination, serum biochemical analysis, urinalysis, bacteriologic culture of urine samples followed by susceptibility testing, and FeLV and FIV testing were performed in all cats to exclude any underlying abnormalities. All procedures were approved by the Institutional Animal Care and Use Committee of The Ohio State University, and all experimental protocols conformed to the guidelines for the care and use of animals issued by the American Physiologic Society and the National Institutes of Health.

After mask induction with isoflurane, all cats were mechanically ventilated[e] to maintain a constant ET isoflurane concentration. The ventilator was set to an inspiratory pressure of 20 to 25 cm of water at a rate of 6 to 8 ventilations/min. Anesthesia was maintained with isoflurane in oxygen delivered by an out-of-circle, drug-specific vaporizer and a semi-closed circle rebreathing system.[f] End-tidal carbon dioxide, inspiratory and ET isoflurane concentrations, and respiratory rate (breaths/min) were monitored by use of an infrared airway gas monitor[g] attached to the endotracheal tube. Arterial oxygen saturation of hemoglobin and heart rate (beats/min) were monitored by use of a pulse oximeter.[h] Arterial blood pressure was indirectly measured by oscillometry.[i] Body temperature was monitored with a rectal temperature probe and maintained between 36.6° and 38.3°C by use of a circulating water blanket and an infrared heat lamp.

The EEG and BIS were acquired and recorded by use of an EEG-BIS monitor.[j] The high-frequency filter was set at 70 Hz and the low-frequency filter at 2 Hz. A BIS number was automatically calculated by the monitor's BIS algorithm software and displayed every 5 seconds. This number reflected the EEG activity during the previous 60 seconds. Amplified EEG and BIS signals were downloaded to a computer and digitized for eventual off-line analysis.[k] Platinum subdermal needle electrodes[l] were used to record EEG activity by use of a 2-channel referential montage. Recording electrodes were placed in a bifrontal configuration, and a reference electrode was placed at vertex (ie, on midline at the level of an imaginary line connecting the rostral margins of each ear pinna). A ground electrode was placed in the atlanto-occipital region. Automatic impedance testing was done by use of the monitor to ensure acceptable signal reception. Each cat was maintained at a stable ET isoflurane concentration for a minimum of 15 minutes before EEG and BIS measurements were recorded. The EEG activity was analyzed for 5 minutes and characterized as continuous burst suppression with a burst suppression ratio of < 8:1, isoelectric with a burst suppression ratio of > 8:1, or isoelectric with intermittent single spikes. Burst suppression was defined as periods of normal to high voltage activity alternating with periods of low voltage (< 5 μV) or isoelectricity. The burst suppression ratio was defined as the time of EEG activity during which voltages did not exceed 5 μV divided by the time of burst activity within a 48-second epoch. The burst suppression ratio was calculated only if individual periods of suppression exceeded 0.5 seconds.[27] Data were excluded from analysis if contaminated by electromyographic activity (frequency > 70 Hz; amplitude > 70 μV). The range of ET isoflurane concentrations at which specific EEG features were observed was recorded. A minimum of 8 BIS measurements were obtained from each cat over a period of 5 minutes and used to calculate a mean BIS value for each ET isoflurane concentration. Electroencephalographic and BIS evaluations were performed at ET isoflurane concentrations ranging from 1.4 to 3.2%.

The BIS was recorded from 6 cats during induction, while testing palpebral and pedal (flexor) reflexes at different ET isoflurane concentrations, and during recovery. Clinical markers of recovery, such as purposeful limb, head, or tail movement and an increase in jaw tone, swallowing or coughing, vocalization, and eye opening, were recorded in conjunction with the BIS measurements. Induction and recovery BIS values were recorded simultaneously with the onset of each event. A minimum of 6 BIS measurements was obtained after each event's onset.

Somatic stimulation and monitoring variables—Somatic stimulation was evaluated in 17 cats during isoflurane anesthesia. Each cat was maintained at a stable ET isoflurane concentration for a minimum of 15 minutes before testing. An electrical stimulating device was secured to the ventral surface of the tail base.[m] The electrical stimulus consisted of a 25 mA ramp signal delivered over a period of 10 seconds. Patient respiratory rate, heart rate, arterial blood pressure, BIS number, raw EEG waveforms, and body movements (motor responses and somatic reflexes) were monitored every 30 seconds after tail stimulation. Recordings of these variables were obtained for a period of 5 minutes after stimulation. A BIS value > 60 is associated with conscious perception of various noxious stimuli in humans[17,18,20,22,28,b] and was identified as the threshold at which early clinical markers of arousal were observed in our initial experiments. Consequently, we chose a BIS value > 60 to be representative of corticocerebral activation. The testing sequence began at high ET isoflurane concentrations (1.5 times the reported MAC for tail clamp studies[29,30]), followed by testing at sequentially lower isoflurane concentrations. The total number of stimuli and ET isoflurane concentrations tested varied slightly among cats as a result of individual differences in anesthetic effect and response thresholds.

Visceral stimulation and monitoring variables—Visceral stimulation by means of bladder distension was assessed in 12 of the 17 cats used in the somatic stimulation studies. Cats were instrumented and anesthetized as described for the somatic stimulation studies. The order of somatic and visceral stimulation was randomized, and at least 2 weeks were allowed between studies. A double-lumen Foley catheter was placed transurethrally into the bladder lumen to permit simultaneous fluid infusion and bladder pressure measurements. After removal of residual urine from the bladder, each cat was maintained at a stable ET isoflurane concentration for a minimum of 15 minutes before testing. The testing sequence was the same as for the tail stimulation studies. Starting ET isoflurane concentrations were 1.5 times the MAC for tail clamp studies.[29,30] Warmed (42°C) saline (0.9% NaCl) solution was infused[n] into the bladder at 10 mL/m^2 body surface area/min (approx 2 to 2.5 mL/min). Simultaneous bladder pressure and volume were recorded.[o] Maximum volume infused did not exceed 50 mL, and max-

imum pressure was not allowed to exceed 50 cm of water. Patient respiratory rate, heart rate, arterial blood pressure, BIS number, EEG waveforms, and body movements (ie, voluntary motor responses) were monitored every 2 minutes during bladder infusion, then every minute after infusion. Recordings of these variables were obtained for a maximum of 5 minutes after stimulation. Bladder infusion was stopped if the BIS number exceeded 60. Saline solution was withdrawn from the bladder, and the volume was recorded at the termination of each infusion experiment.

Statistical analysies—The BIS values for the baseline studies were compared by use of Kruskal-Wallis 1-way ANOVA and Dunn multiple comparison tests. Linear regression analysis was performed to determine the correlation between BIS values and isoflurane concentration. Mean BIS values before and after stimulation at each ET isoflurane concentration were compared by use of a Student *t* test. A value of $P < 0.05$ was considered significant. All values are expressed as means (± SD).

Results

Effect of varying ET isoflurane concentrations on EEG and BIS measures—The range of threshold ET isoflurane concentrations at which specific EEG features were observed was characterized by considerable overlap among cats. Generally, increasing ET isoflurane concentrations correlated with loss of continuous EEG activity and progressively longer periods of isoelectric activity. At low ET isoflurane concentrations (1.3 to 1.6 %), the EEG pattern was characterized by continuous waveforms of moderate to high amplitude and moderate to low frequency. Mean BIS values were inversely correlated ($r^2 = 0.95$) with ET isoflurane concentrations between 1.4% and 1.9% (**Fig 1**). The steep decline in BIS measurements between 1.4% and 1.9% ET isoflurane concentrations was associated with increasing EEG suppression. An EEG burst suppression ratio of < 8:1 was observed at ET isoflurane concentrations ranging from 1.5% to 2.1%. Induction of isoelectric activity was present at ET isoflurane concentrations as low as 1.8% and as high as 2.5%. The isoelectric pattern was present in most cats at concentrations between 2.1% and 2.4%.

An isoelectric EEG was associated with BIS values between 0 and 14 that were significantly lower than BIS values for the other EEG patterns (**Fig 1** and **2**). The EEG at high ET isoflurane concentrations (between 2.3 and 3.2%) was characterized by isoelectric periods interrupted by discrete, high amplitude spikes. Intermittent spiking on an isoelectric background was associated with an increase in the BIS value (mean BIS, 23).

The BIS correlates of the induction phase of isoflurane anesthesia, the presence of motor reflexes, and markers of patient recovery were evaluated in 6 cats. After mask induction and just prior to intubation, the mean BIS value was 52. The palpebral reflex was present at a mean BIS value of 67 and an initial mean ET isoflurane concentration of 1.5%. The pedal reflex was elicited at BIS values of ≥ 66 and at a threshold ET isoflurane concentration of 1.6%. Increased jaw tone, purposeful limb or head movement, swallowing or coughing, vocalization, and eye opening during recov-

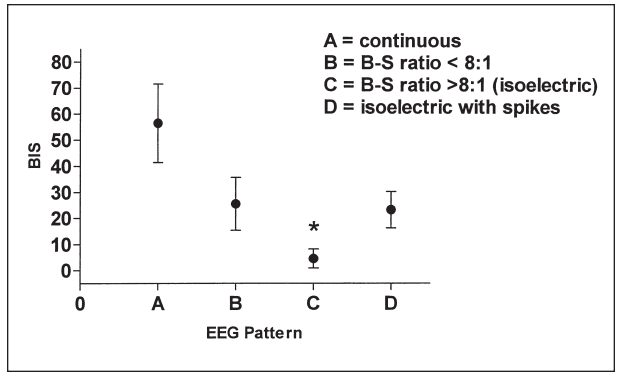

Figure 2—Mean (± SD) BIS values (closed circles) associated with electroencephalogram (EEG) patterns in isoflurane-anesthetized cats. A burst suppression (B-S) ratio of 8:1 indicates 8 periods to 1 period of isoelectric activity to bursting activity, respectively. The isoelectric with a spike pattern signifies predominant isoelectric activity with intermittent single spikes. Mean BIS values of patterns A, B, and D are not significantly ($P < 0.05$) different from each other. *Significantly ($P < 0.05$) different mean BIS value of pattern C, compared with mean BIS values of all other patterns.

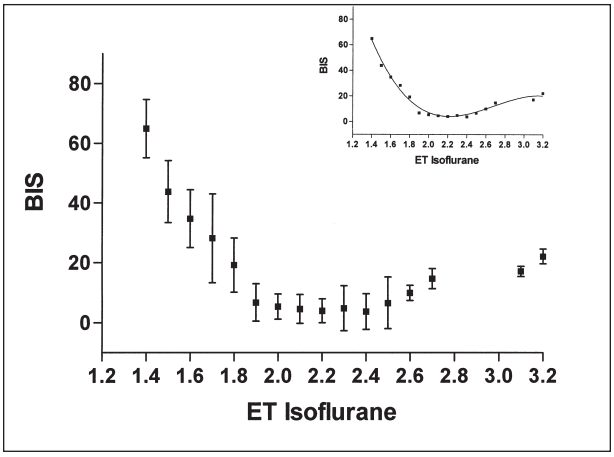

Figure 1—Mean (± SD) baseline bispectral index (BIS) values (closed squares) at different end-tidal (ET) isoflurane concentrations (%). Notice that the BIS mean values decline in a linear fashion with increasing ET isoflurane concentrations between 1.4 and 2.0%. Nonlinear regression of the best fit as described by a polynomial equation of the third order was determined (insert).

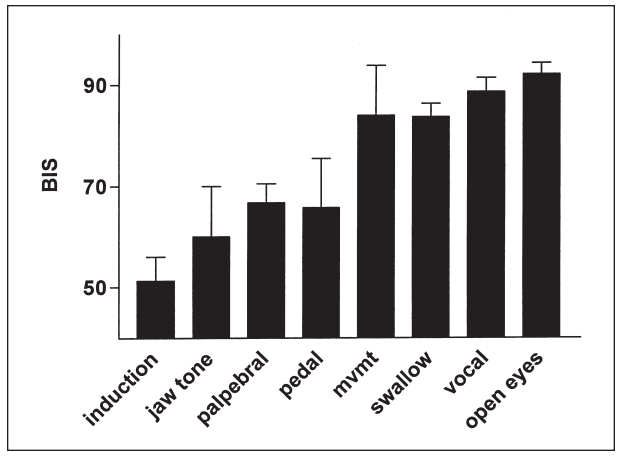

Figure 3—Mean (± SD) BIS values associated with induction, presence of motor reflexes, and markers of recovery. Notice that with the exception of the mean BIS value at induction, BIS values are thresholds above and below which the reflex or movement was regained and lost, respectively. Mvmt = Purposeful movement.

ery were associated with threshold mean BIS values of 60, 83, 84, 89, and 90, respectively (**Fig 3**).

BIS values before and after somatic stimulation—Prestimulation mean BIS values recorded from cats that received ET isoflurane concentrations ranging from 1.8% to 2.4% were not significantly different from each other, and the slope of mean BIS values versus ET isoflurane concentration was not significantly different from zero (**Fig 4**). Before and after stimulation, the **differences between mean BIS values (dBIS)** were greatest at 1.9% ET isoflurane concentration, but these differences steadily decreased with increasing ET isoflurane concentrations (Fig 4). The mean threshold ET isoflurane concentration for voluntary movement after stimulation (ie, MAC_{50}) was 1.87%. Significant differences between BIS values before and after stimulation were found at ET isoflurane concentrations of 1.8%, 1.9%, 2.0%, 2.1%, and 2.2%; however, mean poststimu-

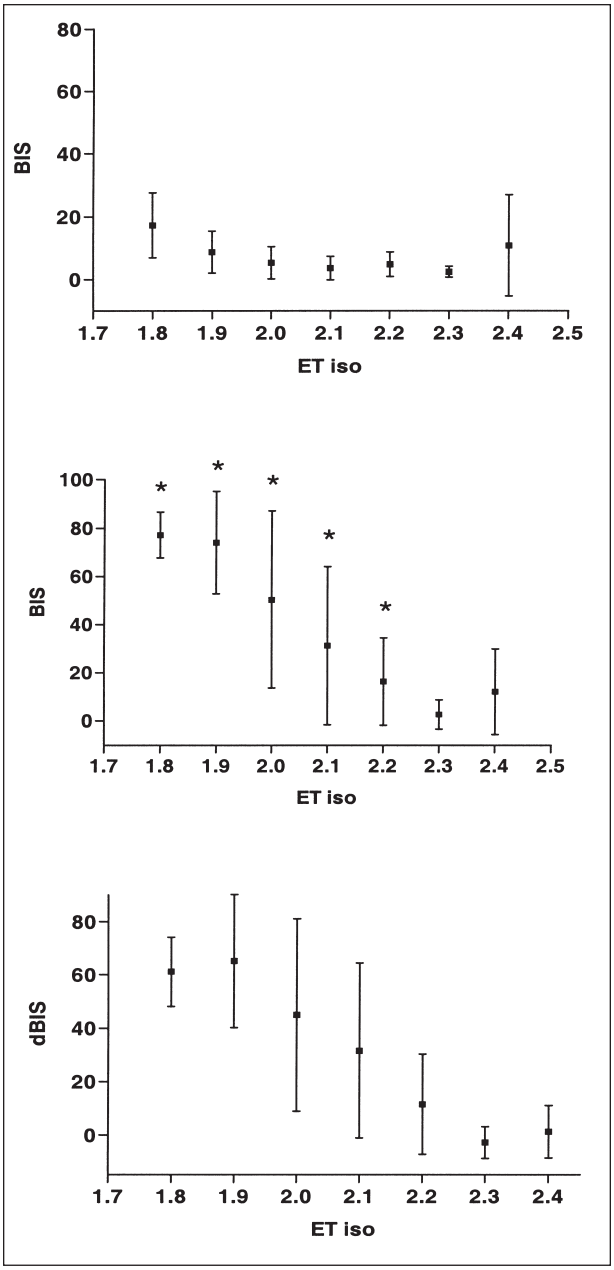

Figure 4—Top panel—Mean (± SD) BIS values before somatic stimulation at increasing ET isoflurane concentrations. Middle panel—Mean BIS values after somatic stimulation at increasing ET isoflurane concentrations. *Significant ($P < 0.05$) difference between poststimulation mean BIS values and prestimulation mean BIS values. Bottom panel—Differences between mean BIS values (dBIS) before and after somatic stimulation at increasing ET isoflurane concentrations.

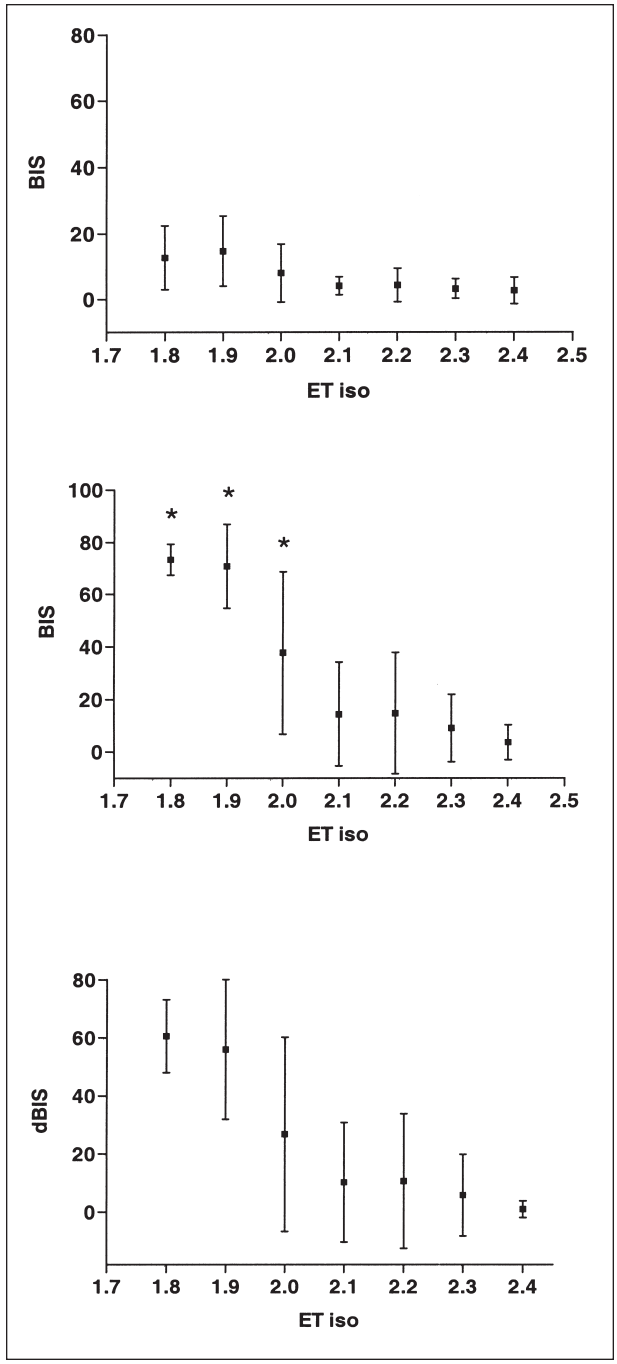

Figure 5—Top panel—Mean (± SD) BIS values before visceral stimulation at increasing ET isoflurane concentrations(%). Middle panel—Mean BIS values after visceral stimulation at increasing ET isoflurane concentrations. *Significant ($P < 0.05$) difference between poststimulation mean BIS values and prestimulation mean BIS values. Bottom panel—The dBIS before and after visceral stimulation at increasing ET isoflurane concentrations.

lation BIS values exceeded 60 at only 1.8% and 1.9% ET isoflurane concentration. Poststimulation mean BIS values were not significantly different from prestimulation mean BIS values at ET isoflurane concentrations > 2.2%.

Mean dBIS was inversely correlated with ET isoflurane concentration (r^2 = 0.93). The mean dBIS at 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, and 2.4% ET isoflurane concentrations were 65, 45, 32, 11.5, 3, and 1, respectively (Fig 4). Responses of BIS that were < 60 were observed. For example, at 2.1% ET isoflurane, 5 of 17 cats had a dBIS between 20 and 60 while 3 of 17 cats had a dBIS > 60. Examination of cats that had a dBIS response between 10 and 40 at any isoflurane concentration revealed that 7 of 17 cats subsequently had a dBIS of > 60 at the next lowest isoflurane concentration.

BIS values before and after visceral stimulation—Prestimulation mean BIS values recorded from cats that received ET isoflurane concentrations ranging from 1.8% to 2.4% were not significantly different from each other **(Fig 5)**. Differences between mean BIS values before and after stimulation were greatest at the lowest ET isoflurane concentration tested (1.8%), but these differences steadily decreased with increasing ET isoflurane concentrations. The mean threshold ET isoflurane concentration for voluntary movement after stimulation (ie, MAC_{50}) was 1.82%. Significant differences between mean BIS values before and after stimulation were found at ET isoflurane concentrations of 1.8%, 1.9%, and 2.0%; however, mean poststimulation BIS values were > 60 at only the 1.8% and 1.9% ET isoflurane concentrations. Poststimulation mean BIS values were not significantly different from prestimulation mean BIS values at ET isoflurane concentrations > 2.0%.

The mean dBIS was inversely correlated with ET isoflurane concentration (r^2 = 0.87). The mean dBIS values at 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, and 2.4% ET isoflurane concentration were 56, 27, 10, 11, 6, and 1, respectively (Fig 5). Changes in BIS that were < 60 were observed. For example, at 2.0% ET isoflurane concentration, 3 of 12 cats had a dBIS between 20 and 60, whereas 4 of 12 cats had a dBIS > 60. Examination of individual cats that had a dBIS response between 10 and 40 at any isoflurane concentration revealed that 7 of 12 cats subsequently had a dBIS of > 60 at the next lowest isoflurane concentration.

Discussion

In our study, increasing ET isoflurane concentrations were correlated with loss of a continuous EEG and progressively longer periods of isoelectric activity. Greater suppression of the EEG often coincided with a progressive decrease in the BIS. The transition from continuous activity to isoelectricity in individual cats was rapid and frequently occurred over a restricted range of ET isoflurane concentrations (0.2% to 0.4%). Increasing concentrations of inhalant anesthetics initially produce a progressive increase in amplitude and a decrease in frequency of the EEG waveform.[31] At progressively greater concentrations of inhalation anesthetic, the EEG may display burst suppression or become isoelectric. Burst suppression is anesthetic- and species-dependent but is usually apparent at ET anesthetic concentrations that represent MAC values of 1.5 or higher.[2,25,31] An isoelectric pattern is continuous and uninterrupted by burst activity and indicates electrical silence of the brain as a result of reduced cerebral oxygen consumption.[31] Onset of burst suppression has historically been associated with surgical depths of anesthesia (ie, Stage III and planes 2 and 3).[6] Burst suppression and isoelectric EEG patterns occurred at moderate ET isoflurane concentrations in the cats of our study. Burst suppression was observed at ET isoflurane concentrations that were equivalent to or less than ET isoflurane concentrations that represent a MAC value of 1.0 in cats.[29,30] Consequently, EEG suppression occurs at ET isoflurane concentrations that would not be considered a surgical plane of anesthesia in cats.

The EEG at high ET isoflurane concentrations was characterized by isoelectric periods intermittently interrupted by discrete, high-amplitude spikes. This EEG pattern has been described in cats and other species that received high concentrations of inhalant anesthetics[30,32-34] and is associated with phasic activation of the reticular formation in the brain stem.[33] Spiking characteristics of the EEG result in an increase in the BIS value (range, 15 to 35) and may interfere with the correct interpretation of the BIS at high ET isoflurane concentrations.

Our data indicated variability among cats with respect to the ET isoflurane concentrations at which specific EEG features were observed. This resulted in overlap of the ET concentration ranges for patterns of continuous EEG, burst suppression, and isoelectric signal with intermittent spikes. The range of ET isoflurane concentrations associated with BIS values also had considerable variability. A study[9] investigating the effect of halothane on EEG variables in cats produced similar results. In that study, the variability of ET halothane concentrations at which burst suppression and isoelectric patterns predominated was considerable, resulting in overlap between ET concentrations associated with each EEG feature.[9] Taken together, these findings indicate that there are differences in anesthetic sensitivity among individual cats.

Mean BIS values had a significantly inverse correlation with ET isoflurane concentrations ranging between 1.4% and 1.9%. Frequency slowing and, as already discussed, greater EEG suppression accompanied the decline in BIS values with increasing anesthetic depth. Increased phase coherence and greater EEG power in the delta range may have also contributed to the lower BIS measurements.[10,13,27] The BIS algorithm takes into account the degree of burst suppression and isoelectricity by incorporating 2 separate calculations, the burst suppression ratio and the QUAZI suppression index.[11] Consequently, unlike other processed EEG parameters, the BIS is sensitive to and not invalidated by EEG burst suppression.[11,13]

The relationship of the resting BIS to various depths of inhalant anesthesia has been investigated in dogs, pigs, and goats.[23-25] In a study by Greene et al,[23] the MAC_{50} was initially determined in isoflurane-anesthetized dogs by use of the tail-clamp method. Subsequently, resting BIS measures were obtained at

ET isoflurane concentrations that corresponded to MAC multiples of 0.8%, 1.0%, 1.5%, and 2.0%. Results from these studies revealed an inverse relationship between BIS and MAC values.[23] Bispectral analysis was performed in pigs at different ET isoflurane concentrations, and measured values were compared with a clinical visual analogue scale.[25] In that study, a correlation between the BIS and clinical visual analogue scale was not found, although a nonlinear decrease in BIS was observed with increasing ET isoflurane concentrations. End-tidal isoflurane concentrations of 2.5% (considered a surgical degree of anesthesia in pigs) were associated with a large BIS decrease as a result of the development of EEG burst suppression.[25]

The threshold BIS value at which pedal and palpebral reflexes were lost or regained in cats of our study was approximately the same (BIS of 66 to 67). This indicates that motor reflexes are lost at anesthetic planes that would not be sufficient to suppress cortical activity in most cats that received isoflurane anesthesia. Similar findings were reported in goats in which corneal and flexor withdrawal reflexes were lost at BIS values ≤ 65 and ≤ 64, respectively.[24] Other clinical end points of anesthesia associated with induction and recovery were associated with specific BIS values in our study. Induction with 5% isoflurane reduced the BIS to a mean of 52. Markers of recovery, such as an increase in jaw tone, voluntary movements, swallowing, vocalization, and eye opening, occurred at BIS values ranging between 60 and 90. The BIS has been used as a predictor of anesthetic emergence and recovery in humans.[10,13,16,19,35] Bispectral analysis was performed in children before induction (awake state), within 10 minutes after induction (nadir), during maintenance anesthesia, and during emergence from sevoflurane anesthesia. Mean BIS values were 94 in awake children and ranged from 6 to 36 during the nadir period. The mean BIS was 42 during maintenance sevoflurane anesthesia. The mean BIS associated with eye opening, spontaneous movement, and vocalization during the initial recovery period was 83.[16]

We observed that prestimulation mean BIS values at ET isoflurane concentrations ranging between 1.8% to 2.4% were consistently between 0 and 20 and did not significantly differ from each other. Isoflurane induced EEG suppression in the nonstimulated state at relatively low ET isoflurane concentrations. Surprisingly, isoelectric features of the EEG and the low BIS values before stimulation did not necessarily predict loss of responsiveness (BIS, hemodynamic activity, or movement) after stimulation. In humans and other animals anesthetized with isoflurane or propofol, baseline prestimulation BIS values in subjects that had purposeful movement after a stimulus are usually > 55 to 65.[17,20,22-24,26,28,b] This range has been considered the threshold range above which conscious perception of noxious stimuli is present and below which it is absent.[13] The effect of isoflurane on the baseline BIS underscores the fact that resting or prestimulation BIS values are strongly influenced by the anesthetic or combination of anesthetic drugs administered and that the magnitude of the prestimulation BIS reduction may not predict a patient's ability to respond to a noxious stimulus. Retained responsiveness to stimuli at low BIS values and during EEG burst suppression in cats in our study suggests that burst suppression may not be associated with surgical depths of anesthesia in isoflurane-anesthetized cats.[6] The concurrent use of other drugs and anesthetics with isoflurane may reduce the isoflurane requirement and thus circumvent this unusual drug effect.

Prestimulation BIS values in humans have been successfully used to predict movement in response to surgical incision in some studies but not others.[18,21,32,a,b,p] Singh et al[21] demonstrated that prestimulation BIS values in patients that did not move in response to skin incision were significantly lower than prestimulation BIS values in patients that did move. Patients in that study[21] received various doses of injectable anesthetics with or without analgesics. In a study of anesthetized horses by Haga and Dolvik,[26] the absolute BIS number calculated prior to stimulation had little value for predicting movement during surgery. Results of other studies[12,21] suggest that the use of the prestimulation BIS value predicts movement to skin incision less reliably when different combinations of hypnotic and analgesic agents are used.

Results of our study indicate that the poststimulation BIS value and relative BIS change are more reliable indicators of anesthetic depth than the prestimulation BIS value. For example, at ET isoflurane concentrations of 1.8% and 1.9% (the mean baseline), prestimulation BIS measurement was < 20. However, mean BIS values after either somatic or visceral stimulation exceeded 60 at both isoflurane concentrations in 14 of 17 cats tested (Fig 4 and 5). These findings of retained responsiveness to noxious stimuli are in agreement with those of Tsushima et al[34] who found poor suppression of response capability to sciatic nerve stimulation in isoflurane-anesthetized cats.

An increase in the BIS has been used to predict movement in response to skin incision in human studies.[c,d,q] Poststimulation BIS values have been examined in human patients undergoing isoflurane anesthesia with and without concurrent opioid analgesia.[d] The change in the BIS from prestimulation values proved to be significantly greater in those patients receiving isoflurane alone, compared with those receiving both isoflurane and an opioid. The authors concluded that the presence of opioid analgesia reduces the degree of hypnotic arousal as measured by changes in the BIS. The relative change in the BIS value, instead of the prestimulation baseline BIS value, may thus be a better measure of inadequate analgesia.[d] This concept is reinforced by a study conducted by Bloom et al.[c] Humans who responded to a noxious stimulus had a greater increase in the BIS than patients who did not respond. Moreover, increases in the BIS were associated with a lightening of the anesthetic plane, even in those subjects who did not overtly respond to the noxious stimulus. A decrease in the change in BIS values and the arousal response were found in those patients receiving analgesics.[c] Results of similar studies in humans, goats, and horses also suggest that the change in the BIS after a stimulus is more reliable than the prestimulation BIS value when evaluating anesthetic depth.[12,24,26,a,c,q]

In our study, increasing ET isoflurane concentra-

tions were associated with prestimulation and poststimulation BIS values that failed to exceed 60; however, closer examination of BIS changes revealed a graded BIS response to increasing isoflurane concentrations (Fig 4 and 5). The graded character of the overall BIS response was, in part, attributable to between cat variability in responsiveness. However, intermediate BIS responses between 10 and 60 were observed in many cats at ET isoflurane concentrations of 2.0% and 2.1%, and 8 of 17 cats that had a submaximal response had a BIS > 60 at slightly lower isoflurane concentrations. Furthermore, significant differences were detected between mean BIS values before and after stimulation at ET isoflurane concentrations as high as 2.2%. The presence of a detectable BIS change between 10 and 60 at moderate depths of isoflurane anesthesia may signify early changes in corticocerebral activity as a result of early nociceptive activation of cortical somatosensory areas.

Poststimulation BIS values in our study exceeded 60 in 8 of 17 cats when ET isoflurane concentrations were close to 2.0%. However, movements after noxious stimulation were not observed until ET isoflurane concentrations were decreased to approximately 1.85% and below. This finding indicates that purposeful movements are inhibited at ET isoflurane concentrations that are associated with retained corticocerebral responsiveness to a noxious stimulus. Further evidence for this anesthetic effect was found in a recent study[24] in goats. Blunting of the BIS response was observed at ET isoflurane concentrations ranging from 0.8% to 1.5%, but the poststimulation BIS value consistently exceeded 60. Movement responses after noxious stimulation were lost at ET isoflurane concentrations of 1.3% or higher in this study and both pedal and palpebral reflexes were lost at BIS values that were greater than those associated with corticocerebral responsiveness.[24] These findings indicate that movements in response to noxious stimuli are inhibited by isoflurane prior to changes in corticocerebral arousal. Isoflurane, at moderate concentrations, appears to have a more potent inhibitory effect on motor systems in the spinal cord or brain stem than on sensory systems that transmit nociceptive signals to the cerebral cortex.[5,36-39]

Results of our study and studies in other species[26,26,c,d,q] indicate that the relative change in the BIS after a noxious stimulus and not the prestimulation BIS value itself may be more important in assessing the adequacy of analgesia and nonresponsiveness. The anatomic integration, processing efficiency, and subjective analysis of nociceptive signals in different species may differ, and more studies are needed to clarify the physiologic importance of BIS changes in cats. Nevertheless, poststimulation BIS values > 60 likely signify corticocerebral arousal and were observed at ET isoflurane concentrations greater than those associated with movement responses in our study. The graded feature of the BIS response at subarousal anesthetic depths may be an important predictor of early cortical activation after a noxious surgical stimulus. Early deviations in the BIS from baseline may precede the all-or-none responses typically associated with other anesthetic monitoring methods. Recognition of real-time BIS changes in animals intraoperatively could be used to titrate anesthesia to a more precise surgical plane where noxious stimuli fail to induce patient arousal.

[a]Lang E, Sebel P, Manberg P. Bispectral EEG analysis, analgesia, and movement at incision during propofol/alfentanil/N_2O anesthesia (abstr). *Anesthesiology* 1994;81:A476.

[b]Vernon J, Bowles S, Sebel PS, et al. EEG bispectrum predicts movement at incision during isoflurane or propofol anesthesia (abstr). *Anesthesiology* 1992;77:A502.

[c]Bloom M, Greenwald S, Day R. Analgesics decrease arousal response to stimulation as measured by changes in bispectral index (BIS) (abstr). *Anesthesiology* 1996;85:A481.

[d]Jopling M, Cork R, Greenwald S. Changes in the bispectral index (BIS) in the presence of surgical stimulation reflect the level of analgesia (abstr). *Anesthesiology* 1996;85:A478.

[e]Ohio anesthesia ventilator, Airco Inc, Madison, Wis.

[f]MDS Matrx VMC anesthesia machine, Matrx Medical Inc, Orchard Park, NY.

[g]Datex Capnomac Ultima, Datex Medical Instruments Inc, Tewksbury, Mass.

[h]VetOx, model 4402, SDI Sensor Devices Inc, Fort Collins, Colo.

[i]Surgivet, BCI International, Waukesha, Wis.

[j]A-1000 EEG monitor, Aspect Medical Systems, Natick, Mass.

[k]Hyperterminal software, Hilgraeve Inc, Monroe, Mich.

[l]Model Grass E-2, Grass Instrument Co, Quincy, Mass.

[m]Shockscan analgesiometer, Acuscan Instruments Inc, Columbus, Ohio.

[n]Syringe infusion pump 2010, Medfusion Inc, Duluth, Ga.

[o]Ponemah physiology platform, Gould Instrument Systems Inc, Valley View, Ohio.

[p]Sebel PS, Bowles S, Saini V, et al. Accuracy of EEG in predicting movement at incision during isoflurane anesthesia (abstr). *Anesthesiology* 1991;75:A446.

[q]Bloom M, Kearse L, Rosow C, et al. Bispectral index measures EEG changes during response to stimulus (abstr). *Anesthesiology* 1995;83:A516.

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