

Use of bispectral index to monitor depth of anesthesia in isoflurane-anesthetized dogs

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Objective—To evaluate the correlation between the bispectral index (BIS) and end-tidal isoflurane (ET_{ISO}) concentration and compare the use of 3 BIS sensor positions in dogs.

Animals—6 adult dogs.

Procedures—Mechanically ventilated dogs received pancuronium, and depth of anesthesia was altered by increasing ET_{ISO} concentration from 1.5% to 2.3% and 3.0%. The BIS, suppression ratio (relative percentage of isoelectric electroencephalographic waveforms), and signal quality index (SQI) were recorded at each ET_{ISO} concentration for each of 3 BIS sensor positions (frontal-occipital, bifrontal, and frontal-temporal positions).

Results—The BIS and ET_{ISO} concentration were poorly correlated; regardless of sensor positioning, mean BIS values did not change significantly as ET_{ISO} was increased. At 3% isoflurane, regardless of sensor positioning, there was an increase in suppression ratio coincident with $BIS < 40$ in some dogs, whereas paradoxical increases in $BIS (> 60)$ were recorded in others. Furthermore, at 3.0% isoflurane, the SQI was significantly lower for the bifrontal sensor position (compared with values for the other positions), but low SQI values prevented recording of BIS values from the frontal-occipital sensor position in 2 dogs. Overall, BIS values derived from the 3 sensor positions did not differ.

Conclusions and Clinical Relevance—In dogs, BIS values may not reflect changes in depth of isoflurane anesthesia in the absence of noxious stimulation. Of the 3 sensor positions, frontal-temporal positioning provided better correlation with changes in depth of anesthesia induced via changes in isoflurane concentrations. However, the sensor placements yielded similar results at SQI values > 50 . (*Am J Vet Res* 2007;68:1300–1307)

Electroencephalography provides a graphic representation of the electrical activity of the cerebral cortex that is generated from the sum of excitatory and inhibitory postsynaptic potentials at the cortical gray matter.^{1,2} Anesthetic agents, neuroactive drugs, ischemia, hypothermia, and other physiologic alterations in brain function result in changes in the pattern of EEG signal.^{1,3} Although changes in depth of anesthesia are associated with changes in the EEG pattern, the use of this technique to monitor depth of anesthesia is not practical in clinical situations because it requires time and specialized personnel to analyze the unprocessed EEG signal.²

The BIS is derived from complex analysis of the EEG waveforms and was originally developed for assessment of the level of hypnosis in humans.¹⁻⁵ The BIS is a numeric variable that may range from 0 to 100,

Received February 1, 2007.

Accepted April 17, 2007.

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Supported by the Fundação de Amparo à Pesquisa de São Paulo (grant Nos. 05/56586-5 and 04/12951-0).

This manuscript represents a portion of the dissertation submitted by the first author to the Faculdade de Medicina, Universidade Estadual Paulista, for the MSc degree.

The authors thank Dr. José Eduardo Corrente for statistical assistance.

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ABBREVIATIONS

EEG	Electroencephalography
BIS	Bispectral index
MAC	Minimum alveolar concentration
SR	Suppression ratio
ET_{ISO}	End-tidal isoflurane
ET_{CO_2}	End-tidal carbon dioxide
SAP	Systolic arterial blood pressure
SQI	Signal quality index
TOF	Train-of-four
EMG	Electromyography

where 0 reflects cortical silence in the brain and 100 indicates a conscious and fully alert individual.^{2,4,5} In humans, BIS values ranging from 40 to 60 are consistent with surgical depth of anesthesia, in which the level of hypnosis may be enough to inhibit cardiovascular and motor responses to noxious stimuli.^{2,4,5} In various species of animals, BIS values consistent with surgical depth of anesthesia have not been established.

Progressively increasing end-tidal concentrations of inhaled anesthetic agents will result in isoelectric EEG waves (burst suppression) that are associated with a reduction in BIS values.^{2,4,5} In dogs anesthetized with isoflurane or sevoflurane, a previous version of the BIS algorithm was useful for assessing depth of anesthesia (level of hypnosis) because BIS values were inversely related to the MAC multiples of the volatile agent.^{6,7} However, in at least one of those studies,⁷ the BIS values

recorded during deep sevoflurane anesthesia ($2 \times \text{MAC}$) were not conclusive inasmuch as paradoxical increases in BIS values were associated with SR values > 0 ; because of this phenomenon, only dogs without burst suppression of the EEG (ie, SR = 0) were included in the results (2/8 dogs).

Although the algorithm for BIS calculation has not been published in detail, the recent updates of the proprietary algorithm are intended to improve manipulation and interpretation of EEG burst suppression.^{5,8} Together with the development and updates of the algorithm, the BIS sensor has also been developed into a single simplified strip comprising 4 adhesive electrodes for use in humans. Through these modifications, the objectives of the manufacturer were to guarantee adequate impedance between the electrodes and the skin and to reduce the influence of placement (distance among electrodes) on the amplitude of the registered EEG waves.⁹ In animals, however, this kind of sensor might not be adequate for the size and shape of the head if the electrodes are to be placed in accordance with the recommendations from the manufacturer for use in humans.

Thus, the primary purpose of the study reported here was to evaluate the correlation between the latest update of the proprietary BIS algorithm (version 4.1) and ET_{ISO} concentration in dogs. Because of the possible limitations associated with neurophysiologic and anatomic differences between dogs and humans and the fact that there is no standard configuration for placement of the electrodes supplied by the BIS manufacturer, we also intended to compare BIS values obtained from 3 BIS sensor positions in isoflurane-anesthetized dogs.

Materials and Methods

The study followed the guidelines of the Brazilian College of Animal Experimentation and the experimental procedure was approved by the Institutional Animal Care Committee (protocol No. 435/2004 CEEA).

Animals—Six mixed-breed dogs (4 males and 2 females) were used in the study; mean \pm SD weight of the dogs was 22.8 ± 6.0 kg. Dogs were considered clinically normal on the basis of findings of physical examination and clinicopathologic assessments (results of CBCs and serum biochemical analyses were within reference ranges).

Instrumentation—For each dog, the experiment was carried out during 1 single anesthetic procedure. On the study day, food but not water was withheld for 12 hours. Anesthesia was induced with 5% isoflurane^a in oxygen (4 to 5 L/min) delivered by means of a face mask. Following induction of anesthesia, each dog was intubated and the endotracheal tube was connected to a circle system with an oxygen flow rate of 2 to 3 L/min. The dog was positioned in sternal recumbency. Samples of airway gases were collected continuously at a constant rate (200 mL/min) into an infrared gas analyzer^b to monitor ET_{ISO} and ETCO_2 concentrations. The analyzer was previously calibrated with a standard calibration gas mixture.^c During instrumentation, the ET_{ISO} concentration was adjusted to maintain moder-

ate depth of anesthesia (assessed on the basis of clinical signs). Each dog was mechanically ventilated.^d To maintain ETCO_2 concentration at 35 to 45 mm Hg, peak inspiratory pressure and respiratory rate were adjusted from 9 to 15 cm H_2O and from 8 to 15 breaths/min, respectively, while the inspiration-to-expiration ratio was held constant (1:2). Following induction of anesthesia, each dog had a cephalic catheter^e placed percutaneously for fluid administration (lactated Ringer's solution, 3 mL/kg/h) via a peristaltic infusion pump.^f The SAP was monitored indirectly by means of a Doppler ultrasound flow probe^g placed over the palmar digital artery with a sphygmomanometer and cuff wrapped around the distal extremity of the radius (cuff width was approx 40% to 50% of the antibrachium circumference). To monitor heart rate, adhesive electrodes were placed on the skin for lead II ECG.^h Body temperature was monitored via an esophageal thermometer placed at the thoracic inlet^h; temperature was maintained at $> 37.0^\circ\text{C}$ by means of a forced warm air blanketⁱ and an electric heating pad.

BIS monitoring—Bispectral index was evaluated by use of a monitor^j connected to the manufacturer-designed BIS sensor.^k Each dog's skull was shaved and defatted with diethyl ether for sensor placement. Three positions of the sensor were assessed during a single anesthetic procedure, and the order in which sensor positions were evaluated was randomly assigned. Sensors were placed in frontal-occipital, bifrontal, and frontal-temporal positions. In the frontal-occipital position, all the electrodes were placed over the midline (Figure 1). Electrode 1 was placed 1 cm dorsal to an imaginary line connecting the medial canthi of the eyes, and electrode 3 was placed on the occipital crest. Because of the design of the sensor, electrodes 1, 2 (ground), and 4 (reference) were consequently placed at equidistant points (2-cm distance from each other). In the bifrontal position, electrodes 1 and 3 were placed 1 cm caudal to the lateral canthus of the right and left eye, respectively. Electrode 4 was placed on the midline, and electrode 2 was automatically placed between electrodes 1 and 4. Use of this configuration in dogs and in humans has been previously described.^{10,11} In the frontal-temporal position, electrode 1 was placed midline on the rostral third portion of an imaginary line connecting the zygomatic process of the frontal bone and the caudal portion of the frontal crest. Electrodes 2 and 4 were each placed at an angle of 15° to 30° to the transverse plane. As a result of this placement, electrode 2 remained dorsal to the eyelid, whereas electrode 4 was placed caudo-dorsal to the lateral canthus of the left eye. Electrode 3 was placed on the zygomatic process, cranial to the base of the left ear. This configuration is an adaptation of the placement recommended by the manufacturer of the BIS sensor for use in humans.¹²

The impedance of the electrodes was automatically checked by the BIS monitor and rejected if > 7.5 k Ω . Artifact detection was carried out by high- and low-frequency filters that were adjusted to 70 and 2 Hz, respectively. The SQI (a numeric variable calculated on basis of electrode impedance and artifacts that may interfere with the EEG signal) was recorded, and BIS values were rejected when the SQI was < 50 .

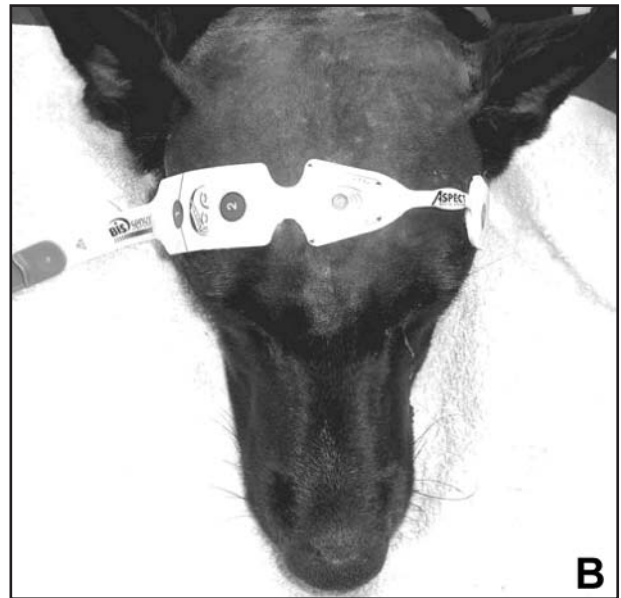
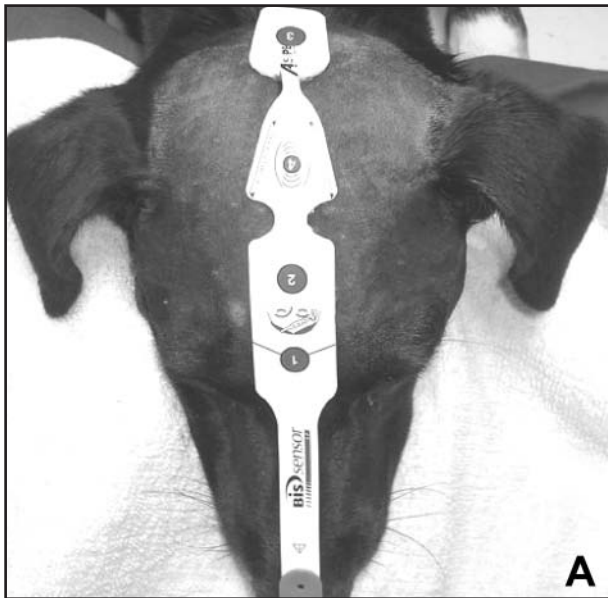


Figure 1—Photographs of a dog in which the BIS sensor has been applied in the frontal-occipital (A), bifrontal (B), and frontal-temporal position (C).

Experimental procedure and study design—Following instrumentation, the ET_{ISO} concentration was initially adjusted to 1.5%. Pancuronium bromide^l (0.06 mg/kg, IV) was administered to achieve neuromuscular blockade and minimize possible interference of electromyographic activity on BIS values.¹³⁻¹⁵ Neuromuscular function was evaluated by visual assessment of plantar contraction in response to a series of 4 supramaximal electrical stimulations administered at 0.5-second intervals (ie, a TOF stimulus) to the saphenous nerve.^m The intensity of the stimulus (30 to 60 mA) was evaluated before pancuronium administration and was considered supramaximal when further increases in intensity did not result in greater contractile response. Response to the TOF stimulus was monitored at 5-minute intervals, and additional doses of pancuronium (0.01 to 0.02 mg/kg, IV) were administered whenever return of the third plantar contraction associated with the TOF series was detected.

For each position of the BIS sensor, the vaporizer was adjusted to provide progressively increasing ET_{ISO}

concentrations (1.5%, 2.3%, and 3.0%). Each ET_{ISO} concentration was maintained for 10 minutes prior to starting BIS data collection. Subsequently, while still maintaining a constant ET_{ISO} concentration, the BIS, SQI, and SR (the relative percentage of isoelectric or low-voltage EEG waves registered during a 63-second period)¹² were recorded on a minute-by-minute basis for an additional 5-minute period. The BIS, SQI, and SR values representative of each ET_{ISO} concentration were averaged from data collected during the 5-minute period. The BIS and SR values were not included in the calculation if these variables were associated with an SQI < 50. Physiologic data (heart rate, esophageal temperature, SAP, and $ETCO_2$ concentration) corresponding to each ET_{ISO} concentration were recorded at the end of the 5-minute period used for BIS data sampling. After completion of data recording at the highest ET_{ISO} concentration (3%), the sensor was removed and repositioned according to 1 of the 3 previously described configurations before the changes in ET_{ISO} concentrations and the data sampling procedure were repeated. Thus, data were collected for each dog at 1.5%, 2.3%, and 3% ET_{ISO} concentrations for each of the 3 BIS sensor positions.

After BIS, SQI, SR, and physiologic variables were collected for all 3 placements of the BIS sensor, neostigmineⁿ (0.05 mg/kg) and atropine^o (0.03 mg/kg) were administered IV for reversal of neuromuscular blockade. Mechanical ventilation was interrupted once neuromuscular activity had returned, as indicated by visual evidence of all 4 plantar contractions in response to the TOF stimulation of the saphenous nerve, and isoflurane administration was discontinued to allow the dogs to recover from anesthesia.

Statistical analysis—Data are presented as mean \pm SD. Statistical analysis was performed with a commercial software program.^p For each BIS sensor position,

data obtained at 2.3% and 3.0% concentrations of isoflurane were compared with data obtained at 1.5% ET_{ISO} concentration by use of a 1-way ANOVA for repeated measures followed by a Dunnett test. Multiple comparisons among the 3 BIS sensor positions were carried out by an ANOVA followed by a Tukey test. A model of simple linear regression was adjusted to examine the correlation between BIS values obtained for each position of the sensor and the ET_{ISO} concentrations. Significance was set at a value of $P < 0.05$.

Results

The study was designed to collect 5 BIS values on a minute-by-minute basis during the 5-minute recording period at each ET_{ISO} concentration (1.5%, 2.3%, and 3.0%) in each dog; thus, 90 BIS values could have been recorded for each position of the BIS sensor from all 6 dogs. However, 69, 83, and 84 BIS values were recorded by use of the frontal-occipital, bifrontal, and frontal-temporal sensor configurations, respectively. The BIS values that were not included in the analysis because of low SQI (< 50) were recorded during the highest ET_{ISO} concentration (3.0%), with the exception of 2 BIS values that were recorded at the 2.3% isoflurane concentration. Despite the fact that low SQI values prevented BIS data collection in some instances, BIS values representing each ET_{ISO} concentration were successfully averaged for all dogs, with the exception of data collected from the frontal-occipital sensor position in 2 dogs during anesthesia with 3% isoflurane (low SQI throughout the 5-minute period prevented recording of BIS data). Therefore, BIS values from these 2 dogs were not included in the analysis for the frontal-occipital position of the sensor at the ET_{ISO} concentration of 3.0%. After reduction of the ET_{ISO} concentration from 3.0% to 1.5% while maintaining the same positioning of the sensor in those 2 dogs, SQI values increased (becoming > 50).

Mean \pm SD values of BIS and SQI values were recorded at progressively increasing concentrations of isoflurane for each one of the 3 configurations of the BIS sensor (Table 1). Regardless of the sensor position, mean BIS values obtained at ET_{ISO} concentrations of 2.3% and 3.0% did not differ from mean BIS values

recorded at the lowest isoflurane concentration (1.5%). At 3% isoflurane concentration, 1, 2, and 3 of the 6 dogs had BIS values < 40 in the frontal-occipital, bifrontal, and frontal-temporal BIS sensor positions, respectively. Greater variability in BIS was evident at the highest isoflurane concentration (3.0%). In the studied population, the highest and lowest BIS values for each sensor position at 3.0% isoflurane were 78 and 14 (frontal-occipital), 81 and 14 (bifrontal), and 70 and 7 (frontal-temporal), respectively. With the bifrontal sensor configuration, mean SQI at 3.0% isoflurane was lower than the value at 1.5% isoflurane. For the remaining configurations, SQI values did not differ among isoflurane concentrations.

When ET_{ISO} concentration was increased to 3.0%, some dogs had paradoxical increases in BIS, compared with values recorded previously at 1.5% and 2.3% isoflurane (1, 3, and 2 dogs with the frontal-occipital, bifrontal, and frontal-temporal sensor placements, respectively). At the highest isoflurane concentration, an increase in SR was always coincident with a decrease in BIS (compared with the previously recorded values). The SR was either low or 0 in all dogs with paradoxical increases in BIS during anesthesia with 3.0% isoflurane.

For all BIS sensor positions, SR values were higher at 3.0% isoflurane, compared with values at 1.5% isoflurane. During light isoflurane anesthesia (ET_{ISO} concentration, 1.5%), EEG burst suppression was not evident (ie, SR = 0) in any dog for any of the BIS sensor placements. After increasing the ET_{ISO} concentration to 2.3%, the SR was > 0 in 2 dogs via the frontal-temporal configuration (SR values, 1 and 3, respectively) and in 1 dog via the frontal-occipital configuration (SR value, 3). When the ET_{ISO} concentration was further increased to 3.0%, SR was > 0 in 4 of 6 dogs via the frontal-temporal configuration and in all dogs via the bifrontal and frontal-occipital configurations. The highest and lowest SR values for each sensor position obtained at the ET_{ISO} concentration of 3.0% were 68 and 0 (frontal-occipital), 66 and 0 (bifrontal), and 83 and 0 (frontal-temporal), respectively.

The mean values of BIS, SQI, and SR did not differ among the 3 positions of the BIS sensor. Heart rate, ETCO₂ concentration, and esophageal temperature did

Table 1—Mean \pm SD values of BIS, SQI, heart rate, SAP, ETCO₂ concentration, and esophageal temperature in 6 dogs fitted with a BIS sensor in each of 3 positions (frontal-occipital, bifrontal, and frontal-temporal) during anesthesia at ET_{ISO} concentrations of 1.5%, 2.3%, and 3.0%.

BIS sensor position	ET _{ISO} concentration (%)	BIS	SQI (%)	Heart rate (beats/min)	SAP (mm Hg)	ETCO ₂ concentration (mm Hg)	Esophageal temperature (°C)
Frontal-occipital	1.5	66 \pm 8	93 \pm 7	119 \pm 25	129 \pm 30	40 \pm 2	38.0 \pm 0.4
	2.3	63 \pm 5	78 \pm 17	125 \pm 21	115 \pm 35	40 \pm 1	38.0 \pm 0.6
	3.0	47 \pm 26	73 \pm 17	123 \pm 18	105 \pm 42*	39 \pm 1	38.0 \pm 0.6
Bifrontal	1.5	72 \pm 6	96 \pm 3	123 \pm 31	138 \pm 32	39 \pm 1	38.0 \pm 0.4
	2.3	64 \pm 3	88 \pm 1	129 \pm 22	123 \pm 30	39 \pm 1	37.8 \pm 0.4
	3.0	51 \pm 30	70 \pm 20*	117 \pm 15	100 \pm 40*	40 \pm 2	37.7 \pm 0.4
Frontal-temporal	1.5	66 \pm 6	94 \pm 6	125 \pm 32	140 \pm 18	40 \pm 2	38.1 \pm 0.5
	2.3	62 \pm 4	87 \pm 13	125 \pm 23	122 \pm 26	40 \pm 1	38.1 \pm 0.5
	3.0	47 \pm 25	76 \pm 17	120 \pm 17	104 \pm 45*	40 \pm 2	38.0 \pm 0.6

*For this sensor position, value of this variable is significantly ($P < 0.05$) different from value at the 1.5% ET_{ISO} concentration.

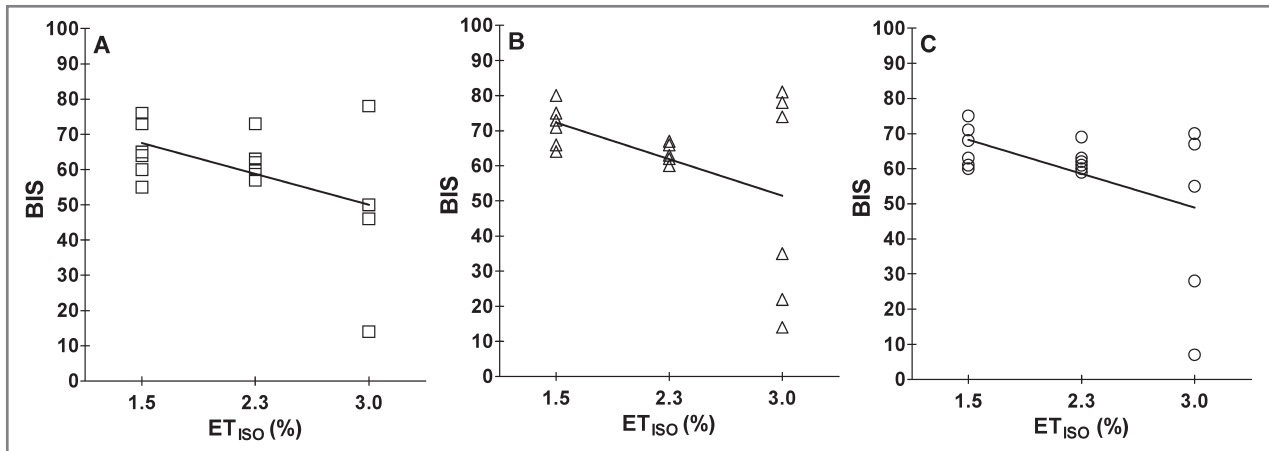


Figure 2—Scatter diagrams of BIS values in 6 dogs anesthetized with progressively increasing concentrations of isoflurane ($ET_{1.5O}$ concentration, 1.5%, 2.3%, and 3.0%) derived by use of a BIS sensor placed in the frontal-occipital (A), bifrontal (B), and frontal-temporal (C) positions. The line within each graph is the fitted regression line.

not differ significantly among the 3 BIS sensor placements nor within each sensor placement when the $ET_{1.5O}$ concentration was increased (Table 1). Mean SAP (indirect measurement) was lower at the 3.0% $ET_{1.5O}$ concentration, compared with the values at 1.5% $ET_{1.5O}$ concentration for all sensor positions. Systolic arterial pressure did not differ among the sensor positions.

Regression analysis of the scatter diagrams of BIS values and $ET_{1.5O}$ concentrations yielded a fitted regression line with negative slope for all 3 BIS sensor positions (Figure 2). Although the slopes of the fitted lines appeared to differ from 0 (negative slope) for the frontal-occipital and bifrontal sensor configuration data ($P = 0.07$ and $P = 0.05$, respectively), a significant ($P = 0.04$) finding was associated only with the frontal-temporal configuration data. The correlation coefficients for the equations were low regardless of the placement of the BIS sensor (-0.47 , -0.46 , and -0.50 in the frontal-occipital, bifrontal, and frontal-temporal configurations, respectively).

Discussion

The lowest $ET_{1.5O}$ concentration (1.5%) used in the present study approached the mean isoflurane MAC value in dogs determined in another investigation by our group,¹⁶ and the 2.3% and 3.0% $ET_{1.5O}$ concentrations corresponded to $1.5 \times$ MAC (moderate depth of anesthesia) and $2.0 \times$ MAC (deep level of anesthesia), respectively. However, there may be some variation in MAC values in individuals from a population or among different populations of dogs. In our study, the dynamic range of BIS values obtained while depth of anesthesia was progressively increased might have been limited by the use of the same $ET_{1.5O}$ concentrations for all dogs (1.5%, 2.3%, and 3.0%), instead of $ET_{1.5O}$ concentrations based on multiples of MAC determined for each animal.

In humans, BIS monitoring has been used as an ancillary method for adjusting the delivery of inhaled and injectable (IV) anesthetic agents.¹⁷⁻¹⁹ In 1 study,¹⁹ the isoflurane concentration was adjusted to maintain adequate levels of hypnosis as determined by BIS assessments (BIS values ranging from 40 to 60) and the con-

sumption of the volatile anesthetic agent was reduced by 12% to 25%, compared with a group of patients in which BIS monitoring was not used. As an indicator of the level of hypnosis during inhalant anesthesia in dogs, it is expected that BIS values will decrease as depth of anesthesia is increased.^{6,7} However, it has been reported that increased alveolar concentration of isoflurane may eventually result in a paradoxical increase in BIS values in humans and cats.^{5,8,20} In the present study, an increase in BIS was detected in some dogs during administration of the highest concentration of isoflurane, in contrast to the obvious reduction in BIS detected in other dogs under the same conditions. According to the BIS scale used to assess the level of hypnosis in humans, the highest BIS value recorded at 3.0% $ET_{1.5O}$ concentration in the present study (ie, 81) is suggestive of light to moderate sedation, whereas the lowest recorded BIS value (7) is suggestive of deep anesthesia or hypnosis.^{2,4,5} As reported previously for humans and cats,^{5,8,20} the results of the present investigation have suggested that in some dogs, the use of BIS as a guide for adjusting isoflurane concentrations may be misleading.

An EEG is based on 3 basic components: amplitude (voltage of the signal), frequency (number of times per second that voltage increases above 0), and phase angle (the expression used to describe the beginning of a wave).¹⁻⁵ In fully awake humans, the EEG is characterized by unsynchronized waves of high frequency and low amplitude.^{1,2} This EEG pattern is coincident with BIS values of approximately 100.² During light anesthesia, EEG wave amplitude increases and wave frequency decreases and EEG signals are typically synchronized.^{1,2} This change in EEG pattern is associated with decreases in BIS, compared with values recorded in awake individuals.² In people, BIS values in the range of 40 to 60 are consistent with moderate levels of hypnosis (surgical depth of anesthesia).^{2,4,5} In the dogs of the present study, mean BIS values ranged from 66 to 72 at the 1.5% $ET_{1.5O}$ concentration. This concentration is nearly $1 \times$ MAC of isoflurane in dogs, as determined in a study¹⁶ performed in our laboratory. In the present study, mean BIS values did not differ significantly when $ET_{1.5O}$ concentrations were increased by 50% (from 1.5%

to 2.3%). At this concentration, mean BIS values ranged from 62 to 64 for all BIS sensor positions. The mean BIS values obtained at 1.5% and 2.3% isoflurane concentrations were not consistent with surgical depth of anesthesia as defined from data obtained in humans, in whom surgical depth of anesthesia is associated with BIS values ranging from 40 to 60. However, interpretation of absolute BIS values may be difficult in animal species because to our knowledge, there are no large-scale studies in which the BIS values that are consistent with surgical depth of anesthesia in dogs have been established.

During deep anesthesia in humans, dogs, and cats, EEG burst suppression is evident. Burst suppression is characterized by periods of low-amplitude waves (isoelectric) intercalated by bursts of high-amplitude waves.^{1,2,4,5,7} It is apparent that previous versions of the BIS algorithm failed to properly manipulate EEG burst suppression in dogs and falsely high BIS values were associated with this EEG pattern.⁷ During deep anesthesia, the variable periods of isoelectric waves are detected concomitantly with BIS values < 40, indicative of profound hypnosis.^{2,4,5} In the present study, the highest concentration of isoflurane (3.0%) corresponded to approximately 2 × MAC, which is consistent with deep anesthesia. At this isoflurane concentration, only 1, 3, and 2 of 6 dogs had BIS values < 40 in the frontal-occipital, bifrontal, and frontal-temporal BIS sensor positions, respectively. Although mean BIS values recorded during the highest ET_{ISO} concentration (3.0%) were approximately 30% lower than mean BIS values recorded during the lowest ET_{ISO} concentration (1.5%), no significant difference in BIS values was detected among ET_{ISO} concentrations, probably because of the great variability in BIS values recorded during deep anesthesia.

The SR value generated by the BIS monitor used in the present study represents the relative percentage of isoelectric or low-voltage EEG waves registered during a 63-second period.¹² In humans, an increase in SR is expected during deep anesthesia.^{2,4} In our study, all dogs that had a reduction in BIS during anesthesia at 3.0% ET_{ISO} concentration also had a concomitant increase in the percentage of isoelectric waves in the EEG, expressed as an increase in the SR. Analysis of BIS and SR data for each dog individually revealed that decreases in BIS were more pronounced in dogs that had larger increases in SR. When the SR was 7, it was associated with a BIS value of 55, whereas the highest SR value (83) was associated with the lowest BIS value (7).

In all dogs that had a paradoxical increase of the BIS during deep anesthesia, periods of isoelectric waves were not detected (SR = 0) or were evident at a low percentage (SR = 3) in the EEG. In humans, increasing the ET_{ISO} concentration from 0.8% to 1.6% can result in decreases or increases of the BIS.⁸ The authors of that report suggested that the paradoxical increase of the BIS might be related to preburst suppression EEG patterns, which are characterized by continuous high-frequency waves that are not intercalated by periods of isoelectricity.

With the use of the bifrontal sensor configuration in 1 dog in the present study, BIS values (in the absence of burst suppression [SR = 0]) were 66 and 67 at ET_{ISO} concentrations of 1.5% and 2.3%, respectively. When

isoflurane concentration was increased to 3.0%, the BIS increased to 81, although the SR was low (3). However, when the frontal-occipital and frontal-temporal sensor configurations were assessed in that particular dog, BIS values progressively decreased as the ET_{ISO} concentration was increased. These results might suggest that, at least in that dog, the positions of the BIS sensor differed in performance; however, that interpretation may be misleading because the EEG is a complex and dynamic variable.¹ In the present study, the order of the sensor positioning was randomly assigned during each anesthetic procedure to avoid interference of possible temporal changes on the EEG tracing. One may hypothesize that for a more precise comparison among the BIS sensor placements, the 3 configurations would have to be evaluated simultaneously. However, because of anatomic limitations and the design of the sensor, simultaneous access to all 3 sites of sensor placement would not have been possible.

In another study⁷ in dogs, BIS decreased as end-tidal sevoflurane concentrations were increased from 0.8 to 2.0 × MAC. In that study, BIS values obtained in 6 of 8 dogs anesthetized with 2 × MAC of sevoflurane were excluded from the analysis because those dogs had paradoxical increases in BIS values associated with SR > 0.⁷ Paradoxically increased BIS values associated with burst suppression (SR > 0) may be related to limitations of the algorithm used in earlier versions of the BIS monitor.^{7,8} The latest versions of the proprietary BIS algorithm have attempted to avoid increases in BIS readings during burst suppression.⁵ In contrast to the data reported previously,⁷ increases in SR values were associated with a reduction in BIS in the dogs of the present study. We used the latest version of the BIS monitor (algorithm version 4.1), and this might explain the difference between the results of both studies.

One limitation of our study is the fact that BIS values were recorded only in the absence of supramaximal nociceptive stimulation, which is the most powerful stimulus for arousal from anesthesia.⁵ In cats anesthetized with isoflurane that did not receive noxious stimulation, there was little change in mean BIS values when isoflurane concentration was increased from 1.8% to 2.4%.²⁰ In the same study,²⁰ decreases in ET_{ISO} concentration to < 2.2% allowed BIS to significantly increase in response to noxious stimulation, whereas increases in ET_{ISO} concentration to values greater than this threshold inhibited significant BIS changes following noxious stimulation. Similar results were reported by Antognini et al²¹ in sheep; at 1 × MAC of isoflurane, the BIS increased markedly following mechanical noxious stimuli, but the magnitude of increase in BIS in response to nociceptive stimulation was progressively reduced as isoflurane concentrations were increased.²¹ The results of those studies^{5,20,21} suggest that the dynamic changes in BIS following noxious stimuli have greater correlation with the level of hypnosis and depth of anesthesia than BIS values recorded in the absence of noxious stimuli.

In humans, overlapping of the EEG and EMG frequency spectra may occur in the 30- to 50-Hz range.⁴ This frequency spectrum overlap cannot be removed by simple filtering, and the contamination of EEG signals

by EMG artifact may result in falsely high BIS values.^{4,13-15} Therefore, a neuromuscular blocking agent was administered to the dogs of the present study to minimize any possible influence of EMG artifact on BIS values.

Variations in sensor positioning may also interfere with BIS values because cortical electrical activity is topographically heterogeneous.^{1,9} To the authors' knowledge, no comparisons between placements of the BIS sensor in dogs have been published. In humans, it is controversial whether BIS measurements are influenced by topography. According to Manberg,⁹ incorrect placement of the electrodes might result in inadequate artifact processing. Another consequence of the improper positioning of the BIS sensor is potential error in recording the characteristics of the EEG (eg, false detection of EEG wave suppression). A short distance between the electrodes might result in lower amplitude of the signal, which could be mistakenly interpreted as EEG wave suppression.⁹ In humans, BIS values registered simultaneously from 2 BIS sensors placed over the frontal and occipital regions have proven to be similar.^{22,23} Conversely, other investigators have not identified good correlations among BIS values obtained from different configurations in humans.^{24,25}

In the present study, the BIS values derived from the 3 BIS sensor positions were similar. In general, all 3 sensor placements had a tendency to generate lower SQI values at the highest ET_{ISO} concentration (3.0%); however, the SQI at 3.0% ET_{ISO} concentration was significantly different from that at 1.5% ET_{ISO} concentration only in the bifrontal sensor configuration. Although SQI values were not significantly lower at 3.0% ET_{ISO} concentration (compared with the 1.5% ET_{ISO} concentration) in the frontal-occipital configuration, this sensor position may have been associated with reduced performance at 3.0% ET_{ISO} concentration because at that concentration, data from 2 of 6 dogs were excluded from statistical analysis because of SQI values < 50. According to the manufacturer, the variables involved in the calculation of SQI are electrode impedance and signal artifacts that may contaminate the EEG signal.¹² For the 2 dogs for which BIS values were not recorded because of SQI values < 50 at 3.0% ET_{ISO} concentration, we decreased the isoflurane concentration immediately after data collection and SQI increased progressively until values were considered acceptable (ie, > 50). On the basis of our findings, it appears that as depth of anesthesia is increased, SQI values typically decrease. However, we could not find a reasonable explanation for the influence of anesthetic depth on SQI values.

Although cardiovascular monitoring of the dogs during the study was limited, a reduction in SAP was detected at the highest concentration of isoflurane. These results corroborate findings of a previous study²⁶ in which dose-dependent cardiovascular depression was caused by inhalant anesthetics.

As the data collected in our study have illustrated, BIS may not reflect changes in depth of anesthesia in dogs in the absence of noxious stimulation because there was a poor correlation between the BIS values and changes in anesthetic depth induced by increasing ET_{ISO} concentrations. Further research is necessary to evaluate the influence of noxious stimuli on relative

changes in BIS as the depth of anesthesia is increased. Although the frontal-temporal configuration of the BIS sensor was superior to the other sensor placements in dogs; providing that SQI values were > 50, all 3 BIS sensor positions yielded similar results.

- a. Isoforine, Cristália, Itapira, Brazil.
- b. Gas analyzer module G-AO, Datex-Ohmeda, Helsinki, Finland.
- c. Quick Cal Calibration Gas, Datex-Ohmeda, Helsinki, Finland.
- d. Excel 7900 ventilator, Datex-Ohmeda, Madison, Wis.
- e. BD Insys, Becton Dickinson, São Paulo, Brazil.
- f. LF2001, Lifemed, São Paulo, Brazil.
- g. Doppler Flow Detector Model 811-B, Parks Medical Electronics, Aloha, Ore.
- h. A/S 3 monitor, Datex- Ohmeda, Helsinki, Finland.
- i. Warmtouch, Mallinkrodt Medical, Pleasanton, Calif.
- j. A-2000 XP, Aspect Medical Systems Inc, Natick, Mass.
- k. BIS Quatro Sensor, Aspect Medical Systems, Newton, Mass.
- l. Pancuron, Cristália, Itapira, Brazil.
- m. Estimulador de nervo periférico E2105, BGE Médica, São Paulo, Brazil.
- n. Prostigmine, Roche, Rio de Janeiro, Brazil.
- o. Atropion, Ariston, São Paulo, Brazil
- p. SAS for Windows, version 8.02, SAS Institute Inc, Cary, NC.

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