Relationships between a proprietary index, bispectral index, and hemodynamic variables as a means for evaluating depth of anesthesia in dogs anesthetized with sevoflurane

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Objective—To evaluate relationships among various techniques for monitoring anesthetic depth in sevoflurane-anesthetized dogs undergoing orthopedic surgery.

Animals—10 dogs.

Procedure—Dogs were medicated with acepromazine (0.05 mg/kg, IM), buprenorphine (0.01 mg/kg, IM), and atropine (0.04 mg/kg, IM). Anesthesia was induced and maintained with sevoflurane. Cardiovascular and respiratory responses were monitored. Anesthetic depth was monitored by use of the bispectral index (BIS), and a proprietary index was used to monitor activity of the autonomic nervous system.

Results—A significant decrease in BIS was seen after induction but concurrent changes were not observed for the other techniques. The proprietary index increased significantly after intubation, but no changes were seen for the other techniques. No significant changes were detected during incision or when higher nociceptive stimuli were applied. We did not identify a correlation between BIS and the proprietary index, the proprietary index and hemodynamic variables, or the BIS and hemodynamic variables during induction and maintenance. A significant increase in the proprietary index and BIS was detected at the time of resumption of reflexes. During anesthetic recovery, a correlation was found between the proprietary index and BIS but not between hemodynamic variables and the other techniques.

Conclusions and Clinical Relevance—A significant increase in the proprietary index, but not the BIS or hemodynamic variables, was detected during intubation. Anesthetic induction with sevoflurane did not prevent the sympathetic stimulus attributable to tracheal intubation. Monitoring of hemodynamic variables does not provide sufficient information to allow clinicians to evaluate stress during anesthetic recovery. (*Am J Vet Res* 2004;65:1128–1135)

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Depth of anesthesia is difficult to define. Without objective monitoring, depth of anesthesia is a dimensionless concept, and the subjective descriptors of too light, too deep, or enough are not helpful for rigorous assessment of a patient's actual degree of anaesthesia.[1] A means of objectively measuring anesthetic depth would be of considerable value. The dose of inhalation drug delivered (expressed in terms of the **minimum alveolar concentration [MAC]**) is not a reliable indicator of anesthetic depth because the response of individuals to the concentration of anesthetic varies.[2] Evaluation of anesthetic depth relies on a subject's physiologic responses to surgery (eg, **heart rate [HR]** and blood pressure) considered against a subjective assessment of general reflex activity and combined with the knowledge of the drugs administered and their dosages. Stressful effects of anesthesia and surgery on patients have been described.[3,4] Similarly, stressful effects of anesthesia and surgery on morbidity in patients are also known. However, we are not aware of any way to monitor anesthetic or surgical stress in real time in anesthetized patients because intraoperative data could not be collected that would enable clinicians to pharmacologically modulate these anesthetic effects.

An **electroencephalogram (EEG)** recorded from the body surface indicates cortical electrical activity. Patterns of the EEG change in accordance with anesthetic depth in a number of species.[5-7]

The **bispectral index (BIS)** is a variable derived from the EEG that reportedly[8-13] has the ability to measure the hypnotic component of the anesthetic state. The BIS is calculated from an algorithm empirically derived from EEG studies in anesthetized humans.[14] This algorithm takes into account power-spectral variables, burst suppression, and the degree of phase coupling assessed through BIS analysis and generates a value from 0 to 100, with lower values indicating a higher degree of sedation and hypnosis. During anesthesia, an excessive depth of hypnosis may be associated with clinically important cardiovascular and respiratory depression, whereas a less intense degree of hypnosis may be associated with intraoperative recall in humans.[15]

Volatile anesthetics commonly used to anesthetize patients depress the autonomic nervous system. Use of these drugs contributes to the safe management of anesthesia because they help to mitigate excessive sympathetic nervous system responses to surgical stress

and also contribute to suppression of parasympathetic reactions to operative procedures.

General anesthetics decrease baroreflex arterial control of HR in domestic animals and humans.[16] However, surgical nociceptive stimuli can increase adrenergic activity and may thus interact with the depressive effects of general anesthetics on baroreflex-induced cardiovascular modulation. It has been hypothesized[16] that baroreflex sensitivity may be increased by surgical nociceptive stimuli and that even high isoflurane concentrations during surgery will not modify this sensitivity.

In practice situations, attenuation of sympathetic nerve activity during anesthesia is usually assessed by monitoring cardiovascular reactions, such as variations in blood pressure or HR. Beat-to-beat fluctuation in HR is closely linked to activity of autonomic nerves. In the past 2 decades, spectral analysis of HR variability has enabled continuous, noninvasive quantification of cardiac autonomic function. Variability in HR can be portioned into 2 components. The **high-frequency (HF)** component (0.15 to 0.4 Hz) is mediated solely by the parasympathetic nervous system, whereas the **low-frequency (LF)** component (0.04 to 0.15 Hz) reflects the effects of sympathetic and parasympathetic nerve activity.[17,18]

In another study,[19] it was reported that HR variability is a valuable physiologic indicator for stress in conscious calves and cows. Linear variables of HR variability are supposedly useful for qualitatively separating various degrees of stress, whereas nonlinear components of HR variability distinguish quantitative differences.

Cardiac pulsations are generated by the heart and regulated by the autonomic nervous system. There are a number of variables specifically associated with this regulation. The number of variables is directly linked to the fractal dimension of a digital series of R–R intervals. Administering 1 or more types of anesthetic agents to a patient modifies the number of variables that can be used to monitor regulation of cardiac function and, consequently, the fractal dimension of the series of R–R intervals corresponding to a patient's heartbeat. Therefore, calculation of the fractal dimension provides a measurement of the depth of anesthesia.

Monitoring equipment[a] has been developed to measure **HR variability (HRV)** and its interaction with the sympathetic and parasympathetic nervous systems. This system can assess reactivity of the autonomic nervous system in real time through fractal analysis of HRV. The system yields a proprietary index that is qualitative and easy to interpret. The proprietary index ranges from 0 to 200 and can be used to assess the degree of protection conferred to the patient during surgical manipulations.[1,20] Substantial increases in the proprietary index reflect an increase in sympathetic activity. Thus, monitoring by use of the proprietary index allows for better anesthetic management of patients.[b]

Even a seemingly stable HR, as measured by conventional ECG monitoring equipment, can have substantial fluctuations (a few milliseconds) in accurately measured R–R intervals.[21] A correct anesthetic balance with good analgesic protection from surgical stimuli is reflected in a stable value for the proprietary index. When the amount of surgical stimulation increases above anesthetic protection, the proprietary index rapidly increases minutes before clinical changes (eg, variations in HR and arterial blood pressure) are evident.[20,c]

Heart rate variability is widely used in cardiology. However, its application during anesthesia is still limited. In the study reported here, we evaluated usefulness of HRV, assessing the relationship between the determination of the amount of stress by means of clinical observation (neuromuscular signs, hemodynamic response, and ventilatory state) or by use of the proprietary index during anesthesia induced by administration of sevoflurane.

Hypnosis, analgesia, response of the sympathetic nervous system, and hypomyotonia are useful variables for anesthetic monitoring. The relationship among these variables and their usefulness in anesthetic monitoring is still unclear. In the study reported here, we investigated the relationship between BIS (which is considered a clinical variable for hypnosis), a proprietary index (which is considered a reflection of activity of the autonomic nervous system), and hemodynamic variables to determine a subject's physiologic responses to surgery. Our objective was to determine whether BIS and the proprietary index are useful indicators of anesthetic depth and whether they can be used to predict increases of HR and blood pressure during triggering events, which would assist anesthesiologists in preventing such increases.

Materials and Methods

Animals—Ten adult mixed-breed dogs (5 males and 5 females) were used in the study. Mean ± SD weight of the dogs was 28.3 ± 6.8 kg. Dogs had been referred to the Veterinary Teaching Hospital of the Extremadura University for various conditions that required major orthopedic surgery (5 dogs had ruptured a cranial cruciate ligament and were treated by use of the 3-in-1 technique, and the other 5 dogs had a coxofemoral luxation that was corrected by use of open reduction). Complete physical examination, serum biochemical analyses, and thoracic radiography were completed for all dogs prior to inclusion in the study. Food, but not water, was withheld for 12 hours prior to surgery in all dogs. The experimental protocol was approved by the Ethical Committee of the Minimally Invasive Surgery Centre.

BIS monitoring—The skin surface was shaved, and diethyl ether was used to remove sebaceous material. Gel-coated disposable silver-silver chloride electrodes[d] were then applied to record the EEG. Two electrodes were placed 1 cm caudal to the lateral canthus of each eye, a central (ie, reference) electrode was placed on the midline of the frontal bone (equidistant from the aforementioned electrodes), and a ground electrode was placed 2 cm to the left or right edge of the central electrode, as has been described for humans.[12] Before each recording, impedance was assessed and maintained below 10,000 ohms at 128 Hz. Electrodes were connected to an EEG monitor.[e] The LF filter was set at 2 Hz, and the LF setting was 70 Hz. Dogs were placed in a quiet place, and the EEG was recorded for 5 minutes with dogs in a conscious state. The system automatically detected only high-quality signals. Artifact-processing algorithms in the monitor automatically detected and corrected (or rejected) patient-induced artifacts in the EEG (eg, eye blinking, eye rolling,

and head shaking) before BIS calculation. The BIS values were transferred at 5-second intervals to a computer for processing.

Proprietary index monitoring—The proprietary system[a] had a single 3-lead ECG. Electrodes for the ECG module were placed on each dog in accordance with a standard (ie, lead II) configuration. The proprietary index was recorded continuously beginning during the conscious state and continuing through induction, maintenance, and recovery from anesthesia. Proprietary index values were transferred at 5-second intervals to a computer for processing.

Anesthesia—Dogs were medicated with acepromazine maleate (0.05 mg/kg, IM), buprenorphine (0.01 mg/kg, IM), and atropine sulfate (0.04 mg/kg, IM). Dogs were administered 100% oxygen at a rate of 5 L/min for 5 minutes by use of a facemask. Anesthesia was induced with sevoflurane (5%) in oxygen (5 L of oxygen/min). To determine when to intubate each dog, several factors were monitored. When lack of jaw tone, loss of swallowing, lack of head shaking, loss of palpebral and pain reflexes, and ventromedial rotation of the eyes were all detected, an endotracheal tube was inserted; the tube was then connected to a semiclosed circular anesthetic circuit connected to a ventilator.[f] Beginning sevoflurane[g] concentration was 5%, which enabled us to rapidly achieve 1.25 MAC (2.36%)[22] with an oxygen flow rate of 5 L/min. Once 1.25 MAC was reached, the vaporizer setting was adjusted as needed to maintain that concentration. Intermittent positive-pressure ventilation was established to maintain **partial pressure of end-tidal carbon dioxide (P_{ETCO_2})** at < 45 mm Hg.

After completion of surgery, anesthetic administration was discontinued, and oxygen flow rate was increased to 10 L/min. Dogs were deemed to have recovered from anesthesia when they were completely conscious and capable of standing and walking.

Monitoring of other variables—A lead II ECG was monitored[h] continuously; **oxygen saturation measured by pulse oximetry (S_{PO_2})** was determined by use of a pulse oximeter probe[i] placed on the tongue of each dog. A 10.5-cm pressure cuff was placed over the median artery for noninvasive measurement of arterial blood pressure.[h] Body temperature was measured with an esophageal probe. Expired sevoflurane concentrations and P_{ETCO_2} were measured[j] continuously at the proximal end of the endotracheal tube, and values were recorded every 5 minutes. During recovery from anesthesia, the ECG, S_{PO_2}, arterial pressure, expired sevoflurane concentration, P_{ETCO_2}, and respiratory rate were measured continuously and recorded every minute.

An anesthesiologist who was not aware of the results for the EEG and proprietary index assessed each dog to determine the type and strength of reflexes. This information was considered in conjunction with values for physiologic variables and used to create a subjective judgment of the depth of anesthesia. Anesthetic recovery time was determined by recording the interval until extubation, first movement, sternal recumbency, and standing.

Data processing—All the recorded data, including BIS and proprietary index values, were manually entered into a computer, and mean values were calculated for several time points, including baseline (conscious state); immediately after induction; immediately after intubation; 30 seconds before skin incision; during skin incision; 15, 30, 45, and 60 minutes after skin incision (ie, during surgery); maximal nociceptive stimulus; and end of surgery and cessation of anesthetic administration.

All data recorded during anesthetic recovery were entered into a computer, and mean values were calculated for several time points, including vaporizer shut off, resumption of palpebral reflex, resumption of swallowing reflex, trembling, extubation, and first purposeful movement.

Statistical analysis—Results were calculated as mean ± SD. A Kolmogorov Smirnov test[23] was used to determine that data were normally distributed. Changes in the BIS, proprietary index, hemodynamic variables, and ventilatory variables at each time point were analyzed by use of a 1-way ANOVA for repeated measures, followed by use of the Tukey test to examine deviation from control values. A Bonferroni procedure for multiple comparisons was conducted to minimize the possibility of finding significant results by chance. Spearman rank-correlation analysis was performed to evaluate the relationship between BIS and hemodynamic variables, the proprietary index and hemodynamic variables, and the proprietary index and BIS. Values of $P < 0.05$ were considered significant. All statistical analyses were performed by use of commercially available statistical software.[k]

Results

Anesthesia was smoothly induced in all dogs, and excitement was minimal, with no signs of hypertonia, myoclonia, or involuntary movement. Excessive salivation or vomiting was not observed during induction. All dogs were intubated without difficulty, and none of them developed apnea during induction of anesthesia. Heart rate did not increase significantly after anesthetic induction.

Duration of anesthesia was determined by the amount of time needed to complete each surgical procedure. Mean ± SD duration of sevoflurane-induced anesthesia was 145 ± 73 minutes. Ventilation was controlled by use of intermittent positive-pressure ventilation to maintain P_{ETCO_2} at < 45 mm Hg. The S_{PO_2} was > 97% in all dogs.

The anesthetic regimen used provided adequate anesthesia during long surgical procedures, as judged by stability in blood pressure, HR, BIS, and the proprietary index. Although a significant ($P < 0.001$) decrease in mean BIS values was evident after anesthetic induction, examination of changes in BIS values throughout the recording time revealed variability among dogs for the other time points (**Figure 1**).

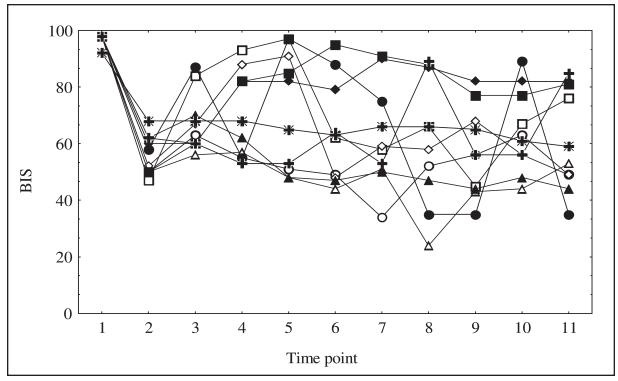

Figure 1—Bispectral index (BIS) obtained for 10 dogs at various time points during sevoflurane-induced anesthesia and orthopedic surgery. Each dog is indicated by a unique symbol. Time points were as follows: 1, conscious and unmedicated (baseline); 2, immediately after induction; 3, immediately after intubation; 4, 30 seconds before the skin incision; 5, during the skin incision; 6, 15 minutes after the skin incision; 7, 30 minutes after the skin incision; 8, 45 minutes after the skin incision; 9, 60 minutes after the skin incision; 10, maximal nociceptive stimulus; and 10, end of surgery and cessation of anesthetic administration.

Similarly, variability among the dogs at the various time points was evident in the proprietary index values recorded during the study (**Figure 2**).

A significant ($P < 0.001$) decrease in BIS was detected after anesthetic induction; there were no additional significant changes detected during maintenance of anesthesia (**Table 1**). The proprietary index increased significantly ($P < 0.001$) after intubation, but BIS or hemodynamic variables did not change significantly. Significant changes were not detected for the proprietary index, BIS, or hemodynamic variables during the skin incision or during maximal nociceptive stimulus throughout the surgical procedures.

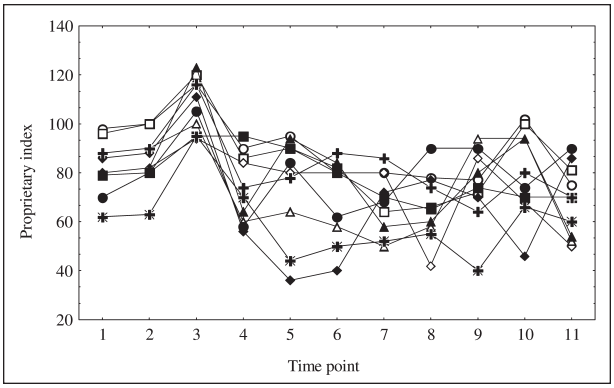

Figure 2—Proprietary index score obtained for all 10 dogs at various time points during sevoflurane-induced anesthesia. *See* Figure 1 for key.

Anesthesia with sevoflurane caused a mild but significant decrease in mean arterial pressure at the time of the skin incision and 15 and 30 minutes during surgery (Table 1). However, concurrent significant changes were not detected in systolic or diastolic blood pressures. Heart rate did not vary significantly during anesthesia.

During anesthesia, none of the dogs responded to external stimuli, good muscular relaxation was observed, and analgesia appeared to be appropriate. Similarly, we did not observe movement of the dogs during anesthesia.

The first signs of recovery from anesthesia were movement of the tail and lifting of the head. Mean ± SD interval from the end of sevoflurane administration until the palpebral reflex was regained was 10 ± 4 minutes, whereas mean interval until first movement and extubation (14 ± 5 and 14 ± 4 minutes, respectively) were slightly longer. Mean interval until sternal recumbency was 16 ± 4 minutes, and all dogs were able to stand at 17 ± 4 minutes after cessation of sevoflurane administration. We did not observe signs of excitement or other complications during the recovery period. All dogs appeared friendly, curious, and interested in their

Table 1—Mean ± SD values for the bispectral index (BIS), a proprietary index, heart rate, and arterial blood pressures in 10 dogs anesthetized with sevoflurane and undergoing orthopedic surgery.

			Arterial Blood Pressure			
Time point	BIS	Proprietary index	Heart rate (beats/min)	Systolic (mm Hg)	Diastolic (mm Hg)	Mean (mm Hg)
Conscious (baseline)	97.4 ± 1.9	82.7 ± 11.0	110 ± 18	102 ± 6	54 ± 4	73 ± 5
Immediately after induction	55.9 ± 7.0*	82.5 ± 10.8	112 ± 18	104 ± 7	58 ± 5	75 ± 6
Immediately after intubation	67.5 ± 10.4*	107.5 ± 11.1*	134 ± 20	102 ± 6	53 ± 4	71 ± 5
30 seconds before skin incision	69.5 ± 15.3*	73.7 ± 14.3	120 ± 11	96 ± 15	48 ± 9	63 ± 13
During skin incision	71.7 ± 20.8*	75.5 ± 20.9	123 ± 13	89 ± 10	48 ± 9	59 ± 11*
15 minutes after skin incision	63.9 ± 18.1*	70.4 ± 16.6	122 ± 29	89 ± 10	50 ± 8	62 ± 12
30 minutes after skin incision	62.7 ± 18.1*	68.0 ± 12.1	114 ± 24	84 ± 12	48 ± 7	60 ± 8*
45 minutes after skin incision	61.2 ± 22.5*	66.5 ± 13.7	118 ± 25	95 ± 25	51 ± 18	66 ± 20
60 minutes after skin incision	57.1 ± 15.6*	74.7 ± 15.3	117 ± 20	96 ± 28	51 ± 11	66 ± 14
Maximal nociceptive stimulus	64.3 ± 14.6*	79.4 ± 18.0	126 ± 33	94 ± 11	52 ± 7	65 ± 10
End of surgery and cessation of anesthetic	61.3 ± 18.1*	68.8 ± 14.4	115 ± 24	93 ± 21	52 ± 11	65 ± 15

*Within a column, value differs significantly ($P < 0.05$) from baseline value.

Table 2—Mean ± SD values for the BIS, proprietary index, heart rate, and mean arterial blood pressure during recovery from anesthesia in 10 dogs anesthetized with sevoflurane and undergoing orthopedic surgery.

Time point	BIS	Proprietary index	Heart rate (beats/min)	Mean arterial blood pressure (mm Hg)
Vaporizer shut off	61.3 ± 18.1	68.8 ± 14.4	115 ± 24	65 ± 15
Resuption of palpebral reflex	83.0 ± 10.4*	83.4 ± 14.7	113 ± 21	73 ± 3
Resumption of swallowing reflex	85.7 ± 9.8*	92.3 ± 20.2*	116 ± 25	74 ± 4*
Trembling	91.8 ± 5.2*	98.6 ± 15.4*	113 ± 21	75 ± 5*
Extubation	93.4 ± 5.4*	100.4 ± 15.1*	110 ± 20	73 ± 4
First purposeful movement	94.1 ± 5.7*	98.6 ± 10.3*	110 ± 15	72 ± 4

See Table 1 for key.

surroundings. The BIS was significantly ($P < 0.001$) increased at the time of resumption of the palpebral reflex and swallowing reflex (**Table 2**). The BIS was also significantly ($P < 0.001$) increased at the time of resumption of the swallowing reflex. We did not detect significant changes in HR during recovery from anesthesia, although mean arterial blood pressure increased significantly after resumption of the swallowing reflex.

During sevoflurane-induced anesthesia in the study, we did not detect a correlation between the proprietary index and BIS or the proprietary index and hemodynamic variables (HR and mean arterial blood pressure). We did detect a significant ($P < 0.001$) correlation between the proprietary index and BIS during anesthetic recovery, but no correlation was evident during recovery from anesthesia between the proprietary index and hemodynamic variables or the BIS and hemodynamic variables.

Discussion

Sevoflurane is an inhalant anesthetic agent with a low blood-gas partition coefficient (0.68),[24] which allows for rapid changes in depth of anesthesia. The MAC of sevoflurane in dogs is reported to be 2.36%.[22] In the study reported here, we used a sevoflurane concentration of 1.25 MAC because it was stated in another study[25] that the degree of hypnosis achieved with 1.25 MAC is sufficient for surgical procedures. Moreover, high BIS values were obtained by use of 1 MAC of sevoflurane in 2 other studies,[13,26] which indicates that hypnosis achieved at 1 MAC is not adequate for surgery. The anesthetic dose used in our study was the same in all dogs to avoid the influence that changes in concentrations of sevoflurane may have had on the results. Sevoflurane was chosen for the study because it is not associated with increases in sympathetic nerve activity or plasma norepinephrine concentrations.[27] Thus, we attempted to minimize the influence that the anesthetic agent may have exerted on the proprietary index.

Usefulness of the BIS in humans has been evaluated.[8,10] Its usefulness for anesthesia in other species, including dogs, has also been evaluated.[13,26,28-30] Currently, a direct measure of anesthetic effects on the brain that spans all anesthetics and is applicable at clinically used ranges of anesthetics is lacking. Anesthetic doses are generally determined on the basis of a combination of clinical signs. Because the main site of action of general anesthetics is the brain, it would be reasonable to expect a neurophysiologic measure of anesthetic effect to exist. However, the CNS is a complex system, and a full understanding of the mechanisms of action of anesthetic drugs is lacking. Studies[31,32] in animals have suggested that anesthetic agents may cause immobility by actions on the spinal cord. This measure of anesthetic effect on the brain should be sufficiently sensitive to detect an inadequate plane of anesthesia and be useful in predicting recovery from anesthesia. It should also be independent of the anesthetic agent used and should correlate with the anesthetic concentration at the site of action. Movement in response to skin incision during anesthesia represents a standard test of anesthetic effect,[33] but skin incision may underestimate the MAC in dogs and rabbits.[34] In other studies,[8,10] BIS was found valuable for use in predicting a response to skin incision.

Cardiac sympathetic and parasympathetic nervous system are attractors that modify the fractal complexity of the ECG signal. Changes in reactivity of the autonomic nervous system can be determined by fractal analysis of the R–R interval of the ECG signal by use of the proprietary monitor.[20,c,l] In the study reported here, atropine was administered as a preanesthetic medication. It is a parasympathetic antagonist that inhibits the parasympathetic system, thus decreasing the variability of R–R intervals. Theoretically, administration of atropine should have caused a decrease in the proprietary index. However, we did not detect a significant decrease in the proprietary index between baseline (conscious and before any preanesthetic medications) and immediately after anesthetic induction (ie, after administration of atropine).

Depth of anesthesia can be estimated on the basis of a combination of objective measurements (eg, HR and mean arterial blood pressure) and subjective measurements (eg, degree of the response to stimuli). We did not detect a correlation between the BIS and hemodynamic variables. This lack of correlation between the BIS and arterial blood pressure contrasts with data obtained in other studies[35,36] in which investigators found that the BIS may help clinicians prevent substantial increases in arterial blood pressure during anesthetic induction. However, those studies were conducted on patients in whom the anesthetic agent was titrated to maintain a fixed BIS value of 40 before intubation, whereas our dose of sevoflurane was fixed at 1.25 MAC; thus, our regimen yielded greater variability in BIS values among dogs and may have accounted for the results obtained in our study.

Hemodynamic and electroencephalographic responses to intubation during induction were examined in 2 other studies.[11,37] Conclusions of those studies support our results (ie, BIS is not a good predictor of hemodynamic responses to intubation). Similarly, investigators in another study[38] found no consistent relationship between hemodynamic responsiveness to stimulation (laryngoscopy, intubation, and surgical manipulations) and changes in the EEG spectral edge frequency during general anesthesia induced by use of propofol and nitrous oxide. Marked increases in mean arterial blood pressure and HR were evident without concomitant changes in spectral edge frequency.

Results of other studies[39,40,m] also support our findings. In those studies, a disparity was observed between hemodynamic changes and bispectral EEG analysis during important stages of anesthesia or triggering events. It has also been suggested that the increase in mean arterial blood pressure after insufflation with carbon dioxide during laparoscopic surgery does not correlate with increased BIS values.[41] On the basis of those reported data and results of the study reported here, we do not consider BIS to be useful as an indicator of cardiovascular stability during intubation and surgery because great variability among patients has been observed. It is also important to consider that neural reflexes leading to hemodynamic responses to

laryngoscopy and nociceptive stimuli are predominantly at the subcortical level, whereas BIS measures only cortical activity.[42]

Our study did not reveal a correlation between the proprietary index and hemodynamic variables. This lack of correlation suggests that monitoring hemodynamic variables during anesthesia may not be useful in helping anesthesiologists ensure areflexia and stability of the autonomic nervous system. It was stated in another study[20] that the proprietary index could be a marker of hemodynamic responses to a nociceptive or stressful stimulus that would be evident sooner than would changes in HR or arterial pressure. The period that elapses between changes in the proprietary index and hemodynamic variables may account for the lack of correlation in our study. This difference in the time frame between changes in the proprietary index and hemodynamic changes makes the proprietary index a valuable therapeutic tool.

We did not detect significant changes in the proprietary index and hemodynamic variables after anesthetic induction with sevoflurane. In a study[l] conducted in humans, a significant increase in the proprietary index was recorded a few seconds before the patients lost consciousness; there also was an increase in HR during anesthetic induction. Those investigators attributed their results to the psychologic stress that humans have immediately before losing consciousness. Taking these observations and our own results into account, it may be hypothesized that domestic animals do not have the same psychologic stress that affects humans immediately before loss of consciousness.

One of our objectives was to evaluate the relationship between anesthetic depth, as measured by the BIS, and the rate of decrease in responses of the autonomic nervous system to stress or an external nociceptive stimulus. However, we did not detect a correlation between the proprietary index (as an indicator of activity of the autonomic nervous system) and BIS values (which reflect the degree of hypnosis) during anesthetic induction and maintenance. Reduction in the LF component of HRV during anesthesia may result from a decrease in adrenergic activity, including nonspecific decreases attributable to loss of consciousness and specific decreases attributable to modification of activity of the autonomic nervous system induced by anesthetic agents.[43]

In another study,[42] it was reported that variables derived from the EEG (eg, BIS values) are reliable guides to the depth of sedation but not to the adequacy of anesthesia for preventing neurovegetative responses to nociceptive stimuli during sevoflurane administration. In goats, a noxious mechanical stimulus (ie, application of a hemostat for 10 to 20 seconds) markedly increases the BIS value when the isoflurane concentration is ≤ 1 MAC.[30] However, the influence of noxious stimuli on BIS in that study was less at higher isoflurane concentrations. These data are consistent with the results reported here because a correlation between the BIS and proprietary index was evident during recovery, a period when sevoflurane concentration decreased to < 1 MAC. A significant increase in BIS and the proprietary index was seen during this period. These data are consistent with results of another study[n] conducted by our laboratory group.

It has been proposed[44] that HRV modifications be used as an indicator of postoperative recovery. The increase in BIS and the proprietary index during this phase was related to recovery of consciousness, and it was accompanied by a substantial activation of the autonomic nervous system secondary to a stress response or to discomfort of the patient, which is recognized as a reflection of invasive stimulus against the body. Values for the proprietary index obtained at that time reflect the fact that the anesthetic protocol we used was not successful in minimizing stress responses of the autonomic nervous system to the recovery of consciousness. Despite the fact investigators in another study[45] reported that this anesthetic regimen was suitable for providing postoperative analgesia after elective arthrotomy in dogs, we detected significant activation of the autonomic nervous system during anesthetic recovery. However, this increase in the proprietary index was not followed by clinical signs suggestive of stress or pain during recovery from anesthesia, nor did we detect hemodynamic changes. This supports the assumption that HR and clinical signs are not good indicators of stimulation of the autonomic nervous system during anesthetic recovery, and these data are not sufficient to determine the degree of stress in patients at this stage of anesthesia.

Tracheal intubation is a stressful event during anesthesia. In the study reported here, tracheal intubation caused a significant increase in the proprietary index, which was accompanied by a nonsignificant increase in HR. This increase in the proprietary index suggests that intubation may represent a stressful event during anesthesia,[o] although additional studies are needed to validate the use of the proprietary index. Anesthetic induction with sevoflurane does not prevent the sympathetic stimulus caused by tracheal intubation in dogs, as indicated by the increase in the proprietary index.

We used intermittent positive-pressure ventilation in all dogs to avoid chemoreflex activation secondary to hypoventilation-induced hypercapnia and hypoxemia. Moreover, variables were measured as soon as possible after induction (ie, a time when capnic changes are minimal). Variables of mechanical ventilation (tidal volume and respiratory rate) were set near those observed for conscious dogs. In fact, in conscious subjects, reduction of tidal volume is associated with a reduction in HF spectral energy and, through a complex dynamic interaction, causes an increase in the LF components.[46] This implies that changes in spectral variability of HR during induction of anesthesia depend on drug-induced modifications of activity of the autonomic nervous as well as their effects on respiration. Nevertheless, the analyses of changes in the proprietary index recorded during anesthetic induction did not reveal variations in activity of the autonomic nervous system; thus, it is our opinion that ventilation did not substantially influence the proprietary index.

One limitation of the study reported here was the fact that the autonomic balance in dogs differs from that

observed in humans. Whereas vagal activity predominates in the control of HR in dogs, the sympathetic nervous system in humans makes a larger contribution than vagal activity.[47] The equipment we used to conduct our study was designed to be used in humans, and additional studies will be needed to validate its use in dogs. However, our results, in addition to results reported for swine,[p] are encouraging and support the usefulness of this monitoring equipment in dogs and pigs.

In the study reported here, we did not observe burst suppression, so this variable did not affect EEG measurements. On the other hand, electromyographic activity increases BIS values.[48] We did not record electromyographic activity, but a low amount of muscular activity was consistently seen in all dogs, so it is our opinion that our results were not affected by it. However, to validate this conclusion, electromyographic activity should have been recorded, although neuromuscular blockade is not a prerequisite to meaningful interpretation of the BIS.[26]

In the study reported here, the BIS was a good indicator for predicting the depth of anesthesia in dogs, and the proprietary index was useful in reflecting activity of the autonomic nervous system during tracheal intubation and recovery from anesthesia. However, we did not detect a correlation between the BIS and proprietary index during anesthetic induction and maintenance. Variability among patients must be taken into account when monitoring depth of anesthesia by use of BIS values in a clinical setting; therefore, we believe that the BIS may not always be useful for predicting anesthetic depth in every patient. Similarly, high variability of the proprietary index among patients influences clinical application of this technique. Tracheal intubation caused a significant increase in the proprietary index. This suggests that intubation may represent a stressful event during anesthesia, although additional studies are needed to validate the use of the proprietary index. Anesthetic induction by administration of sevoflurane does not prevent the sympathetic stimulus caused by tracheal intubation in dogs, as indicated by the increase in values for the proprietary index.

[a]Anemon I, version 4.20, Medical Control SA, Geneva, Switzerland.

[b]Ohse K, Kadota Y, Kanmura Y. Changes in Anemon-I index during anesthetic induction: comparison with bispectral index (abstr). *Anesthesiology* 2001;95:A570.

[c]Marenco ML, Carrasco-Jiménez MS, Rodríguez-Agea E, et al. Monitoring of autonomic nervous system response to gynaecological procedures under TIVA (abstr), in *Proceedings*. Eur Acad Anesthesiol 2001;57.

[d]Zipprep, Aspect Medical Systems Inc, Natick, Mass.

[e]A-1050TM, version 3.05.05, Aspect Medical Systems Inc, Natick, Mass.

[f]Ventilador 7800, Ohmeda, Madrid, Spain.

[g]Sevorane, Abbott Laboratories, Madrid, Spain.

[h]Hewlett Packard model 86S, Hewlett Packard, Geneva, Switzerland.

[i]Clip Tip sensor, Oximeter Sensor, Datex-Ohmeda, Louisville, Colo.

[j]Ohmeda RGM 5250, Ohmeda, Madrid, Spain.

[k]SPSS 10.0 statistical package for Windows, SPSS Inc, Chicago, Ill.

[l]Vibe K, Courvoisier J, Cohen-Laroque ES, et al. Decreased reactivity of the autonomic nervous system during induction of general anesthesia (abstr). *Schweiz Med Wochenschr* 1999;129(suppl 112):9S.

[m]Baumgartner A, Voit-Augustin H, Schwarz G, et al. Bispectral EEG analysis (BIS) and hemodynamic parameters during sevoflurane anesthesia (abstr). *Anesth Analg* 1998;86:S198.

[n]Moruno M, Martín MF, Ezquerra LJ, et al. Evaluation of the anaesthetic recovery after sevoflurane anaesthesia in dogs during orthopaedic surgery or soft tissue surgery (abstr), in *Proceedings*. 27th Cong World Small Anim Vet Assoc 2002;153.

[o]Martín MF, Moruno M, Lima JR, et al. Use of bispectral index and Anemon index to evaluate the quality of sevoflurane anaesthesia in dogs (abstr), in *Proceedings*. 27th Cong World Small Anim Vet Assoc 2002;24–25.

[p]Martín MF, Lima JR, Luis L, et al. Use of the Anemon index to evaluate the quality of analgesia during fentanyl and sevoflurane anesthesia in pigs (abstr). *Vet Anesth Analg* 2003;30:97–98.

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