Assessment of the relationship of bispectral index values, hemodynamic changes, and recovery times associated with sevoflurane or propofol anesthesia in pigs

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Objective—To evaluate bispectral index (BIS) values in pigs during anesthesia maintained with sevoflurane-fentanyl or propofol-fentanyl as a predictor of changes in hemodynamic parameters and duration of recovery from anesthesia.

Animals—12 pigs.

Procedure—Pigs were randomly allocated to undergo 1 of 2 anesthetic regimens. Anesthesia was induced with propofol (2 mg/kg, IV); 6 pigs were administered sevoflurane via inhalation (1 minimum alveolar concentration [MAC] at a fresh gas flow rate of 3 L/min; group I), and 6 were administered propofol (11 mg/kg/h, IV; group II). All pigs received fentanyl (2.5 mg/kg, IV, q 30 min). After abdominal surgery, pigs were allowed to recover from anesthesia. Cardiovascular variables and BIS values were recorded at intervals throughout the procedure; duration of recovery from anesthesia was noted.

Results—No correlation was established between arterial blood pressure and BIS and between heart rate and BIS. Mean BIS at discontinuation of administration of the anesthetic agent was greater in group-II pigs (65.2 ± 10.6 minutes) than in group-I pigs (55.8 ± 2.9 minutes). However, recovery from anesthesia was significantly longer in group II (59.80 ± 2.52 minutes) than in group I (9.80 ± 2.35 minutes).

Conclusions and Clinical Relevance—In swine anesthetized with sevoflurane or propofol and undergoing abdominal surgery, the BIS value derived from an electroencephalogram at the end of anesthesia was not useful for predicting the speed of recovery from anesthesia. Moreover, BIS was not useful as a predictor of clinically important changes in arterial blood pressure and heart rate in those anesthetized pigs. (*Am J Vet Res* 2004;65:409–416)

The **bispectral index (BIS)** is a variable derived from an **electroencephalogram (EEG)** that has been reported to be a measure of the hypnotic component of the anesthetic state.[1-5,a] It is a dimensionless number from 0 to 100, and decreasing values indicate more sedation and hypnosis. The EEG (recorded from the skin of the head) provides measurement of the electrical activity in the cerebral cortex; changes in EEG recordings in association with variations of the depth of anesthesia have been identified in several species.[6-9] The BIS is calculated from an algorithm empirically derived from EEG studies in humans under anesthesia. The algorithm takes into account power spectral parameters, burst suppression, and the degree of phase coupling (assessed via bispectral analysis) and generates a BIS value from 0 to 100.[10]

Pigs are used extensively in biomedical research and may undergo extensive surgical procedures. The **minimum alveolar concentration (MAC)** cannot accurately indicate the depth of anesthesia because of individual responses to the anesthetic agents.[11] Because of this, development of an objective and reliable system to measure anesthetic depth in pigs would be useful.[12] During propofol anesthesia, an excessive depth of sedation may be associated with clinically relevant cardiovascular and respiratory depression, whereas less intense levels of sedation may be associated with intraoperative recall.[13] Similarly, sevoflurane depresses respiratory system function and causes dose-dependent myocardial depression and a decrease in sympathoadrenal activity.[14,15]

The BIS values in conscious animals change as a light plane of anesthesia is induced, and these values can be used to detect an excessively deep plane of anesthesia in pigs.[12] However, BIS values do not appear to change according to the anesthetic depth at clinically useful isoflurane concentrations,[12] nor do they indicate the extent of nociception in swine anesthetized with isoflurane.[16] Nevertheless, in our experience,[9] BIS has been useful for predicting changes in anesthetic depth with dosages of inhalant anesthetics (sevoflurane and isoflurane) that are commonly used clinically, although some variability was seen among individuals. Johnson and Taylor[17] demonstrated that isoflurane-mediated EEG depression in horses was of sudden onset and maximal at all concentrations of the anesthetic agent used in their study. Haga and Dolvik[18] reported that BIS cannot be used to measure CNS depression in isoflurane-anesthetized horses; BIS was measured in sedated and anesthetized horses, and no significant differences were detected between those groups.

The purpose of the study reported here was to evaluate BIS values in pigs during anesthesia maintained with sevoflurane-fentanyl or propofol-fentanyl as a predictor of changes in hemodynamic parameters and duration of recovery from anesthesia.

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Materials and Methods

Pigs—The experimental protocol was approved by the Centre Ethical Committee of Minimally Invasive Surgery Centre. Twelve healthy Large White × Landrace pigs (6 females and 6 males) were used in the study. Mean weight of the pigs was 29 ± 6 kg. Prior to inclusion in the study, pigs were determined to be clinically normal on the basis of findings of physical examination, serum biochemical analyses, and thoracic radiography.

During the study, pigs were housed indoors with free access to food and water; however, in the 24-hour period prior to anesthesia, pigs had access to water only. Animals were randomly assigned to 1 of 2 groups so that there were 3 females and 3 males/group. Pigs in group I were assigned to receive sevoflurane[b] via inhalation, and those in group II were assigned to receive propofol[c] via IV injection. Two days prior to the experimental anesthetic episode, each pig was anesthetized with sevoflurane and a 20-standard wire gauge catheter was placed in the external iliac artery through a femoral approach[19]; this catheter was flushed with heparinized physiologic saline (0.9% NaCl) solution and sutured to the skin.

Electroencephalographic monitoring—Before induction of anesthesia, the skin of each pig was shaved and defatted by use of diethyl ether. Gel-coated disposable silver-silver chloride electrodes[e] were applied to the skin to record the EEG: an electrode was placed 1 cm caudal to the lateral canthus of each eye, a central or reference electrode was placed on the midline on the frontal bone equidistant from each of the previously applied electrodes, and a ground electrode was placed 2 cm to the left or right edge of the central electrode, similar to the technique described for humans.[5] Before each recording, the impedance was checked and maintained below 10,000 Ω at 128 Hz. The electrodes were connected to an EEG monitor.[f] The low-frequency filter was set to 2 Hz, and the high-frequency setting was 70 Hz. Pigs were placed on a purpose-built stretcher consisting of a wooden frame and nylon straps. For each pig, BIS values were recorded during a 5-minute period of consciousness prior to induction of anesthesia.

The monitor used automatically detected only high-quality signals. Artifact-processing algorithms in the monitor automatically detected and corrected (or rejected) animal-associated artifacts in the EEG (eg, those attributable to eye-blinking, rolling of the eyes, and head shaking) prior to BIS calculation. Values of BIS were transferred to a computer for processing every 5 seconds. Bispectral index was recorded from a conscious state (awake) throughout induction and maintenance of and recovery from anesthesia. Values of BIS reported on the front panel of the monitor represent the mean value derived from the previous 60 seconds of useable data[20]; values were recorded every 60 seconds for the duration of the experiment.

Anesthesia—The 12 pigs were anesthetized in a randomized order. All of the animals were premedicated with simultaneous IM administration of atropine sulfate[g] (0.04 mg/kg), diazepam[h] (0.1 mg/kg), and ketamine[i] (10 mg/kg). After premedication, pigs were placed in a quiet area for 15 minutes and then provided with 100% oxygen via a facial mask at 5 L/min for 5 minutes.

For each pig, a 20-gauge catheter was placed in the marginal ear vein and anesthesia was induced with propofol (2 mg/kg) administered IV for 60 seconds. This dose was chosen because it had been previously used in swine with good results.[21] A cuffed endotracheal tube[j] was inserted in the trachea and then connected to a semiclosed circuit. In both groups, fentanyl (2.5 µg/kg)[22] was administered IV every 30 minutes; the first dose was administered immediately after endotracheal intubation. Two anesthetic protocols were employed for maintenance of anesthesia. In group I, a sevoflurane-fentanyl combination was used. The end-tidal concentration of sevoflurane was adjusted to 1 MAC (2.66%)[23] to maintain anesthesia with a fresh gas flow rate of 3 L/min in 100% oxygen. In group II, a propofol-fentanyl combination was used. Anesthesia was maintained with an IV infusion (via the catheter in the ear vein) of propofol at a rate of 11 mg/kg/h.[21] Intermittent positive-pressure ventilation was used during the procedure to maintain end-tidal CO_2 concentration below 6 kPa. The pigs were placed in dorsal recumbency on an electric blanket.

As soon as 1 MAC of sevoflurane was achieved in group I and 10 minutes after propofol infusion in group II, abdominal surgery was performed in all animals. The aorta was dissected through a midline laparotomy from the level of the renal arteries to the origin of the iliac arteries. During surgery, continuous infusion of physiologic saline solution via the 20-guage catheter previously placed in the ear vein at a rate of 10 mL/kg/h was performed. At the end of surgery, the vaporizer was switched off (group I) or propofol infusion was discontinued (group II) and the fresh gas flow rate was increased to 5 L/min in 100% oxygen. Pigs were extubated when they regained swallowing reflexes and were considered recovered from anesthesia when totally conscious and able to stand and walk.

Monitoring during anesthesia—All pigs were monitored during anesthesia. Electrocardiography (lead II[k]) with the electrodes placed in the interdigital spaces of all 4 limbs and pulse oxymetry (to measure oxygen saturation[Sp_{O_2}]by use of a probe[l] placed on the tongue were performed; also, rectal temperature (measured by use of a digital thermometer), tidal volume, end-tidal concentration of sevoflurane, end-tidal CO_2 concentration, and respiratory rate were monitored.[m] The probe used to sample exhaled gases was placed at the face mask in conscious pigs and at the oral end of the endotracheal tube in anesthetized pigs. Arterial blood pressure and heart rate were also measured by use of a blood pressure module[n] connected to a system for monitoring hemodynamic variables.[o] For each pig, tidal volume, end-tidal CO_2 concentration, and respiratory rate were monitored during anesthesia, but these data were not analyzed further.

Cardiovascular recordings were obtained by connecting the catheter previously inserted in an external iliac artery to the monitoring system via a transducer.[p] Heart rate was also measured by examination of the ECG tracing. Although the variables were continuously monitored during the experiment, cardiovascular values were recorded only at 5-minute intervals.

An anesthetist (JRL) who was unaware of the EEG signal assessed each pig for the type and strength of reflexes present. Reflexes evaluated included eyeball position and movement, photomotor reflexes and pupillary size, lacrimation, palpebral and corneal reflexes, laryngeal reflex, muscle tone, and digital (pedal) reflex. These evaluations were performed by the same investigator for each pig. These data were assessed in combination with the physiologic variables being monitored (heart rate and arterial blood pressure) to create a subjective judgement of the depth of anesthesia. This assessment of depth of anesthesia was made only for the purpose of performing the surgery.

Data processing—Values of BIS, heart rate, arterial blood pressure, and end-tidal concentration of sevoflurane were computerized, and means were calculated for the following times: baseline (awake), immediately before induction of anesthesia (after administration of premedication), immediately after induction, 30 seconds after intubation, 30 seconds before incision, 5 minutes after incision, 1 hour after

incision, 2 hours after incision, at the end of surgery (when administration of anesthetic agent was discontinued), and at extubation.

Statistical analyses—Results are reported as mean ± SD. Changes in variables with time were analyzed by use of an ANOVA for repeated measures, followed by the Tukey test to examine deviation from control values in each group. Differences between groups were analyzed by use of a 2-way ANOVA. Spearman rank-correlation was performed to evaluate the relationship between BIS values and arterial blood pressure and between BIS values and heart rate. Values of $P < 0.05$ were considered significant. Statistical analyses of data were performed by use of computerized software.[q]

Results

The mean ± SD age of pigs in groups I and II was 77 ± 3 days and 74 ± 4 days, respectively. Mean weight of pigs in groups I and II was 27.9 ± 2.8 kg and 27.2 ± 2.7 kg, respectively. There were no significant differences in age or weight between the 2 treatment groups. Baseline values of BIS, heart rate, and arterial blood pressure in the 2 groups were not significantly different.

Induction of anesthesia proceeded smoothly in all pigs, and no excitatory movements were observed. In all pigs, Spo_2 was > 97% throughout the study period; body temperature did not decrease at any point, compared with baseline values. No significant blood loss was caused by the surgical procedure in any of the pigs, and the surgical technique and stimulus were the same in both groups. Each of the 2 anesthetic regimens provided adequate anesthesia during long abdominal surgical procedures, as judged by the stability in blood pressure and heart rate measurements and BIS values. No movement by the pigs was observed during anesthesia. Recovery from anesthesia was similarly without complications. Mean duration of anesthesia was 280.8 ± 28.0 minutes and 297.5 ± 25.4 minutes in groups I and II, respectively; these values were not significantly different. Total mean time from baseline to extubation was 285.8 ± 28.6 minutes and 319.7 ± 23.6 minutes in groups I and II, respectively. The interval from baseline to incision was 72.5 ± 10.4 minutes and 74.8 ± 6.2 minutes in groups I and II, respectively.

Group I—Compared with the baseline value, **mean arterial blood pressure (MABP)** decreased in the latter stages of the anesthetic period in these pigs. Values of MABP at 2 hours after incision, at the end of surgery, and at extubation were significantly ($P < 0.05$) lower than the baseline value. Although MABP decreased from a value of 86.3 ± 8.9 mm Hg at baseline to 74.8 ± 11.9 mm Hg at the end of surgery (ie, at discontinuation of anesthesia), no significant changes in heart rate were noted during that interval (**Table 1**). After the vaporizer supplying sevoflurane was turned off, all pigs recovered from anesthesia (mean recovery time, 9.8 ± 2.3 minutes) and stood up at their first attempt (**Table 2**).

During the period of anesthesia, mean BIS values decreased significantly ($P < 0.001$) from the baseline value of 98.2 ± 0.4 (Table 1); a significant decrease in mean BIS was detected immediately after induction of anesthesia (54.5 ± 10.1). At 30 seconds after intubation, mean BIS value was 59.3 ± 6.3 (which was not significantly different from that detected immediately after induction of anesthesia), and this value decreased to 51.1 ± 4.1 at 1 hour after incision. Mean BIS at 5 minutes, 1 hour, and 2 hours after the incision did not differ significantly from the value at 30 seconds before the incision was made. During maintenance of anesthesia, there was a slight variation in mean end-tidal

Table 2—Mean ± SD time to extubation, detection of first movement, and attainment of sternal recumbency and standing position in anesthetized pigs from the point at which administration of sevoflurane via inhalation (group I; n = 6) or propofol via infusion (group II; 6) was discontinued, with corresponding BIS value calculated at discontinuation of administration of anesthetic agent

Variable	Group I	Group II
BIS value at discontinuation of administration of anesthetic agent	55.8 ± 2.9	65.2 ± 10.6*
Extubation (min)	5.0 ± 1.1	22.2 ± 1.2*
Detection of first movement (min)	4.6 ± 1.2	13.4 ± 1.1*
Attainment of sternal recumbency (min)	5.0 ± 1.1	28.0 ± 1.4*
Attainment of standing position (min)	9.8 ± 2.3	59.8 ± 2.5*

*Value for group II significantly ($P < 0.05$) greater than value for group I.

Table 1—Mean ± SD values of heart rate, invasive mean arterial blood pressure (MABP), bispectral index (BIS), and end-tidal concentration of sevoflurane (EtSVF) obtained from 6 pigs in which anesthesia was maintained with sevoflurane (group I) and 6 pigs in which anesthesia was maintained with propofol (group II) for the purpose of undergoing abdominal surgery

	EtSVF (%)	BIS value		Heart rate (beats/min)		MABP (mm Hg)	
Time points	Group I	Group I	Group II	Group I	Group II	Group I	Group II
Baseline (awake)	0.0 ± 0.0	98.2 ± 0.4	96.5 ± 0.8	93.0 ± 12.0	88.0 ± 3.0	86.3 ± 8.9	94.0 ± 10.4
Immediately before induction of anesthesia	0.0 ± 0.0	97.2 ± 0.4	95.5 ± 1.2	91.0 ± 11.0	91.0 ± 6.0	86.7 ± 8.9	93.3 ± 9.9
Immediately after induction	0.0 ± 0.0	54.5 ± 10.1*	69.3 ± 14.4*	89.0 ± 8.0	88.0 ± 6.0	88.0 ± 6.3	94.2 ± 9.3
30 seconds after intubation	0.0 ± 0.0	59.3 ± 6.3*	68.6 ± 6.7*	97.0 ± 15.0	126.0 ± 25.0*	88.5 ± 3.1	90.2 ± 10.9
30 seconds before incision was made	2.7 ± 0.4*	52.8 ± 3.1*	67.5 ± 6.7*†	81.0 ± 11.0	89.0 ± 14.0	80.3 ± 15.5	90.5 ± 17.2†
5 minutes after incision	2.8 ± 0.2*	53.3 ± 7.1*	65.0 ± 9.1*†	80.0 ± 12.0	94.0 ± 11.0	85.5 ± 19.3	103.3 ± 16.8†
1 hour after incision	2.9 ± 0.3*	51.1 ± 4.1*	63.7 ± 12.4*†	81.0 ± 12.0	95.0 ± 31.0	85.0 ± 12.2	97.5 ± 20.6†
2 hours after incision	2.9 ± 0.3*	53.5 ± 2.2*	60.2 ± 15.4*†	89.0 ± 18.0	107.0 ± 33.0	75.0 ± 14.8*	100.2 ± 20.9†
At the end of surgery and discontinuation of anesthesia	3.0 ± 0.3*	55.8 ± 2.9*	65.2 ± 10.6*†	90.0 ± 16.0	107.0 ± 31.0	74.8 ± 11.9*	100.8 ± 24.1†
Extubation	0.0 ± 0.0	97.2 ± 1.6	95.0 ± 1.1	107.0 ± 25.0	130.0 ± 16.0*	75.0 ± 11.5*	101.5 ± 23.7†

*Value significantly ($P < 0.05$) different from baseline.
†Value for group II significantly ($P < 0.05$) greater than value for group I at these times.

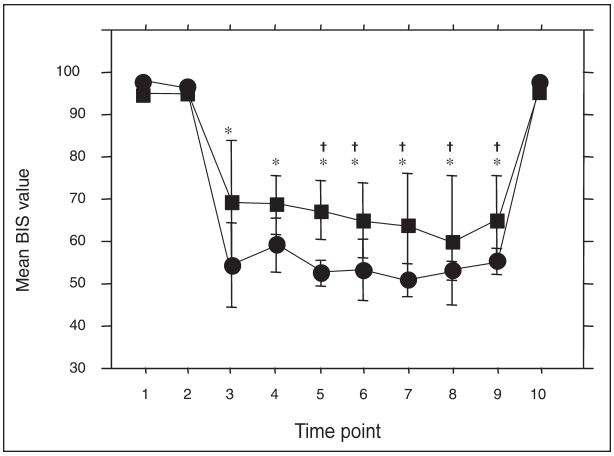

Figure 1—Mean ± SD values of bispectral index (BIS) derived from electroencephalograms obtained from 6 pigs in which anesthesia was maintained with sevoflurane (group I; circles) and 6 pigs in which anesthesia was maintained with propofol (group II; squares) for the purpose of undergoing abdominal surgery. Mean BIS values were calculated for the 2 groups at the following times: baseline (awake; time 1); immediately before induction (after administration of premedication; 2); immediately after induction (3); 30 seconds after intubation (4); 30 seconds before incision (5); 5 minutes after incision (6); 1 hour after incision (7); 2 hours after incision (8); at the end of surgery (when administration of anesthetic agent was discontinued; 9); and at extubation (10). *Value significantly ($P < 0.001$) different from baseline (time 1) in groups I and II. †Value for group II significantly ($P < 0.05$) greater than value for group I at these times.

concentration of sevoflurane (as measured at intervals between 30 seconds before incision and discontinuation of anesthesia; Table 1), but no changes in BIS values were associated with it.

Group II—At 30 seconds after endotracheal intubation, mean heart rate in group-II pigs was 126 ± 25 beats/min; this value was significantly ($P < 0.01$) increased, compared with the baseline value of 88 ± 6 beats/min. However, no significant changes in MABP values were detected during anesthesia, compared with the baseline value in this group (Table 1).

At baseline, mean BIS value was 96.5 ± 0.8; a significant ($P < 0.001$) decrease was detected immediately after induction of anesthesia (mean BIS, 69.3 ± 14.4). Mean BIS value decreased further at each data collection point and was 60.2 ± 15.4 at 2 hours after the incision was made. On discontinuation of anesthesia at the end of surgery, mean BIS was 65.2 ± 10.6 in this group. There was no significant change in BIS measured 30 seconds after intubation and 5 minutes after incision, compared with values immediately after induction and 30 seconds before incision.

After propofol infusion was discontinued, all pigs recovered from anesthesia (mean recovery time, 59.8 ± 2.5 minutes) and stood up at their third attempt in (Table 2).

Comparison between groups—In both groups, mean BIS values were significantly decreased immediately after propofol induction, compared with values obtained during consciousness at baseline. Anesthetic depth (evaluated by clinical observation) was similar in both groups; however, compared with group-I pigs, BIS values in group-II pigs were significantly ($P < 0.001$) greater from 30 seconds before incision to the moment anesthesia was discontinued (**Fig 1**). Also, MABP values from 30 seconds before incision to extubation were significantly ($P < 0.001$) higher in group II than in group I. In either group, there was no significant difference in BIS recorded 5 minutes after incision, compared with values obtained 30 seconds before incision. In group I, mean BIS increased slightly 30 seconds after endotracheal intubation, compared with the value immediately after induction of anesthesia; this change was not detected in group II.

A correlation between MABP and BIS values and between heart rate and BIS value was not detected in either group. On discontinuation of anesthesia, the mean BIS value associated with propofol anesthesia was significantly ($P < 0.001$) greater than that associated with sevoflurane anesthesia (65.2 ± 10.6 and 55.8 ± 2.9, respectively); however, mean recovery time was significantly ($P < 0.001$) longer in group II (59.8 ± 2.5 minutes) than it was in group I (9.8 ± 2.3 minutes; Table 2).

Discussion

Although the use of BIS assessments has been evaluated extensively in humans,[1,3,4,24-27,r] studies[9,12,16,18,28,29] evaluating its usefulness in veterinary practice are scarce; further investigation to provide a comprehensive evaluation of its usefulness in monitoring anesthesia in animals would be desirable.

At present, anesthesiologists lack a direct measure of anesthetic effects on the brain that is applicable to all anesthetics at the doses recommended for clinical use. The dose of an agent used to induce and maintain anesthesia is usually determined on the basis of a constellation of clinical signs. Because the main target site of action of general anesthetics is the brain, it would not be unreasonable to expect that a neurophysiologic measure of anesthetic effect could be found. However, the CNS is a complex system, and a full understanding of the mechanisms of action of anesthetic drugs is lacking. Results of recent experimental studies[30,31] in animals suggest that anesthetic agents may produce immobility via action on the spinal cord. To be of use, this neurophysiologic measure of anesthetic effect on the brain should be sensitive enough to detect insufficient levels of anesthesia and be used to predict recovery from anesthesia; it should also be independent of the anesthetic used and correlate with anesthetic concentration at the site of action.[2]

In clinical practice, it is very important to be able to predict and prevent increases in blood pressure during triggering events. In the study of this report, we analyzed the relationship between 2 hemodynamic variables and values of BIS. No correlation between arterial blood pressure and BIS and between heart rate and BIS was detected. In our study, BIS values after induction of anesthesia decreased significantly in both groups. However, compared with the baseline value, a significant increase in heart rate was detected in group II at 30 seconds after intubation, although this was not associated with a change in BIS values. We could not explain why this increase was evident only in group-II pigs; the same premedication and induction regimens

were used for both groups. Our finding was similar to that of another study,[32] which together suggest that BIS is not useful as an indicator of increases in heart rate associated with endotracheal intubation during induction of anesthesia with propofol. Despite the increase in heart rate after intubation in group II, no significant change in blood pressure was detected in this group. The first dose of fentanyl was administered immediately after endotracheal intubation to avoid drug-related effects on blood pressure, heart rate, or BIS assessments at 30 seconds after intubation because BIS values yielded by the monitor represent the electroencephalographic data obtained during the previous 60 seconds.[20]

The lack of correlation between BIS and arterial blood pressure values detected in our study contrasts with the data obtained by Masuda et al[32] and Heck et al,[33] who reported that BIS may be a useful indicator of increases in arterial blood pressure during anesthetic induction. These studies, however, were conducted in humans in whom the anesthetic agent was titrated to maintain a fixed BIS value of 40 before intubation; in our study, the dosage of propofol used in each pig was 2 mg/kg and this regimen yielded a great interindividual variability in BIS values. This may account for the different finding obtained in our study.

However, the lack of correlation between BIS and arterial blood pressure values detected in our study is in accordance with findings of studies by Lui et al[r] and Mi et al[34]; those investigators evaluated hemodynamic and EEG responses to intubation during induction with propofol and concluded that BIS is not a good predictor of hemodynamic responses to intubation after propofol induction. Similarly, White and Boyle[35] 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 with propofol and nitrous oxide. Marked increases in MABP and heart rate were detected without concomitant changes in spectral edge frequency in that study.

In other studies,[36-38] a similar lack of correlation between hemodynamic changes and BIS values derived from EEG analysis during important stages of anesthesia or triggering events has been determined. It has also been suggested that the increased MABP detected after CO_2 insufflation during laparoscopic surgery does not correlate with increased BIS values.[39] On the basis of findings in our study and those previously reported, we do not believe BIS assessment to be useful as an indicator of cardiovascular stability during intubation and surgery, particularly because great interindividual variability in BIS values has been identified.[9] It is also important to consider that neural reflexes leading to hemodynamic responses to laryngoscopic and nociceptive stimuli occur predominantly at the subcortical level, whereas BIS values indicate only cortical activity.[40]

Because of its low blood-gas partition coefficient, sevoflurane is eliminated rapidly from the body. Results of several studies[42,43,s] confirm short recovery times associated with its use as an anesthetic. In our study, pigs in which anesthesia was maintained with sevoflurane recovered more quickly than pigs in which anesthesia was maintained with propofol. Nonetheless, on discontinuation of anesthesia, BIS values were greater in the propofol group than those in the sevoflurane group. Humans sedated or anesthetized with propofol also have higher BIS values than when propofol is administered in conjunction with a nondepolarizing muscle relaxant; such higher values are attributed to **electromyographic (EMG)** activity that falsely increases BIS value.[43,44] Calculation of BIS requires the inclusion of frequencies above 40 Hz, which approach frequencies generated by muscle activity.[43] In the study reported here, a high-frequency filter setting of 70 Hz was used. A frequency of 70 Hz would likely include those frequencies generated by muscle activity, so EMG activity could be a confounding factor in BIS interpretation in our study. Although propofol is known to cause myoclonus, Greif et al[45] recently reported that BIS value and EMG tone are unaltered by administration of mivacurium during propofol anesthesia and that BIS can be used to estimate sedation in deeply unconscious humans who are paralyzed, partially paralyzed, or not paralyzed. In our study, it is possible that pigs in which anesthesia was maintained with propofol had higher BIS values than pigs in which anesthesia was maintained with sevoflurane as a result of greater EMG activity, but to confirm this, a neuromuscular blocking agent would have had to be administered.

In a study involving propofol for maintenance of anesthesia in women, Song et al[46] reported that targeting a high BIS value at the end of anesthesia leads to a faster emergence and shorter recovery from anesthesia. In that study, patients were transferred to the postanesthesia care unit after outpatient surgery sooner if BIS values were > 75 at the end of propofol anesthesia. In our study, mean BIS value at the discontinuation of anesthesia did not reach 75 in any of the pigs. Moreover, duration of anesthesia was considerably shorter in the study of Song et al,[46] compared with that in the study reported here. Thus, our data suggest that it is not possible to predict recovery times in swine solely on the basis of BIS values. In our study, the lack of correlation between BIS values at the discontinuation of anesthesia and recovery times could be attributed to the use of 2 different anesthetic agents (sevoflurane and propofol) that may have influenced BIS variability.[9,47]

Propofol has a large volume of distribution, which is not unexpected because of its lipophilic nature. Although there are no data available on pigs, recovery times in dogs may be prolonged after continuous infusion of propofol for more than 30 minutes.[48] It is not unreasonable to assume that the same effect could occur in swine because it has been reported that the pharmacokinetics of propofol in both species are similar.[49] In humans anesthetized with sevoflurane, no prolongation of recovery times after surgical operations of long duration has been reported,[50] although other data indicate that recovery times after sevoflurane anesthesia increase with the duration of anesthesia.[51] The reported differences between effects of anesthesia with sevoflurane or propofol support the postulate that the use of sevoflurane is associated with a more rapid

recovery from anesthesia than that achieved with propofol.[42,52]

Movement in response to skin incision during anesthesia represents a standard test of anesthetic effect.[53] In the study reported here, no significant increases were detected in BIS values, arterial blood pressure, or heart rate after skin incision. Similarly, movements were not observed in any pig during surgery, which suggested that each animal was in a surgical plane of anesthesia. However, evaluation of BIS values obtained from each animal suggested that BIS in itself is not enough to determine if the anesthetic depth is adequate because of great interindividual variability. Moreover, each anesthetic agent alters the EEG in a different fashion, making the establishment of precise correlations between EEG changes and anesthetic depth difficult. Although results of studies[1-3] have indicated that BIS could predict movement in response to skin incision, we detected differences in preincision BIS values (ie, range of values, 48 to 77) among the study pigs and higher BIS values did not correspond to movement in response to skin incision. Our finding is consistent with that of Katoh et al,[40] who did not find any difference in BIS values between anesthetized humans who moved or did not move in response to skin incision. These investigators concluded that BIS is a cortical function indicator that does not directly reflect the activity of subcortical structures (including the spinal cord) that primarily mediate motor response to a noxious stimulus. Thus, BIS values may not be reliable for predicting responsiveness to noxious stimuli.

Experimental evidence obtained from animal studies[30,31] strongly suggests that anesthetic agents produce immobility by an action on the spinal cord and that BIS reflects the level of consciousness, which is a process that occurs in the brain. This suggestion in combination with our data (ie, the range of preincision BIS values among individual pigs and the lack of movement response to incision in any study animal) leads us to believe that BIS monitoring cannot be used to predict movement occurring in response to nociceptive stimulation.

Assuming that motor responses to a noxious stimulus are primarily mediated by the activity of subcortical structures (including the spinal cord), appropriate analgesia is instrumental for avoiding movement in response to surgical stimuli (incision) and cannot be determined by calculation of BIS values. Reduction in the movement response induced by large doses of fentanyl may be associated with spinal rather than supraspinal inhibition.[54] In humans, addition of opioids to isoflurane or propofol anesthesia also decreases patient movement in response to incision.[55] The central effect of fentanyl on immobility during surgery remains to be elucidated.

Fentanyl has been reported to cause a progressive decrease in frequency and an increase in amplitude of delta waves detected via EEG.[56] In that study, the minimum dose that produced maximal slowing of the EEG within 1 to 2 minutes was 1.25 μg of fentanyl administered via bolus injection. Larger doses produced more rapid and extensive changes in spectral edge.[56] Slowing of the EEG waves should result in lower BIS values. Despite the results of a study by Scott et al,[56] we believe that IV administration of fentanyl boluses (2.5 μg/kg) does not affect BIS values. Although our study did not focus on the effects of fentanyl on BIS values, no significant difference between BIS values calculated before (ie, immediately after induction) and after (30 seconds before incision) fentanyl administration was detected in either group of pigs. It has been reported[57] that the relationship between the effect of propofol and BIS values is not influenced by opioid administration. Clinically, administration of an opioid increases propofol-induced hypnosis, but it is not associated with an increase in BIS values.

Duration of anesthesia did not have an effect on BIS values. In our study, MABP did not decrease significantly from the baseline value in group-II pigs during anesthesia maintained with propofol (administered at an infusion rate of 11 mg/kg/h), which has also been described in pigs by Tendillo et al.[21] However, a significant decrease in MABP from baseline value in group-I pigs was detected 2 hours after the incision was made (ie, after 3.2 hours of administration of sevoflurane). This decrease in MABP was attributed to the cardiovascular effects of sevoflurane because that agent induces dose-dependent hypotension. The decrease in blood pressure is usually associated with, at least, a decrease in stroke volume; in some instances, a decrease in peripheral vascular resistance may also play an important but lesser role.[58] In humans, propofol-induced hypotension develops immediately after drug administration, probably as a result of a decrease in systemic vascular resistance.[59] However, in pigs, no significant decrease in arterial blood pressure has been described in association with anesthesia maintained with propofol at an infusion rate of 11 mg/kg/h.[21] From our data, it appears that propofol is better than sevoflurane for anesthetic maintenance in pigs with regard to hemodynamic stability.

Results of 1 study[60] in newborn pigs indicated that the observed EEG remains stable until the MABP decreases to < 30 mm Hg. In the study reported here, MABP values were not so low as to have influenced the EEG recordings.

Despite the lack of correlation found between MABP and BIS values, both of these variables were higher during anesthesia (from 30 seconds before the incision was made to discontinuation of anesthesia) in group-II pigs (receiving propofol), compared with values in group-I pigs (receiving sevoflurane). The fact that BIS values were higher in the group of pigs in which anesthesia was maintained with propofol suggests that the relationship between BIS and sedation depth may not be independent of anesthetic agent. Ibrahim et al[47] reported that BIS was a better predictor of depth of sedation with propofol than depth of sedation with sevoflurane and that the relationship between BIS values and end-tidal sevoflurane concentration had large inter- and intraindividual variability. Our data differ from those of Ibrahim et al.[47] In our study, the range of BIS values recorded at each time point was wide in both groups but more so for the propofol group than the sevoflurane group. We believe

that BIS values may not be useful for predicting anesthetic depth in every individual.

In swine in which anesthesia was maintained with either sevoflurane or propofol, the BIS value derived from an EEG at the end of anesthesia was not useful for predicting the speed of recovery from anesthesia after abdominal surgery. Moreover, BIS was not useful as a predictor of clinically important changes in arterial blood pressure and heart rate in those anesthetized pigs. However, values of BIS appear to be useful for distinguishing between states of consciousness and unconsciousness in pigs during the induction and maintenance of anesthesia. Both anesthetic regimens used in the pigs of the study reported here provided adequate anesthesia during long abdominal surgical procedures.

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[a]Greenwald S, Chiang HH, Devlin P, et al. Bispectral index (BIS 2.0) as a hypnosis measure (abstr). *Anesthesiology* 1994;81:A477.
[b]Sevorane, Abbott Laboratories, Madrid, Spain.
[c]Recofol, Schering España SA, Madrid, Spain.
[d]Fentanest, Productos Roche SA, Madrid, Spain.
[e]Zipprep, Aspect Medical Systems Inc, Natick, Mass.
[f]A-1050TM, version 3.05.05, Aspect Medical Systems Inc, Natick, Mass.
[g]Atropina Braun, Braun Medical, Rubí, Barcelona, Spain.
[h]Valium, Roche, Madrid, Spain.
[i]Ketolar 50, Parke-Davis, Barcelona, Spain.
[j]Sims Portex Inc, Keene, NH.
[k]Hewlett-Packard model 86S, Hewlett-Packard, Geneva, Switzerland.
[l]Clip Tip sensor, Oximeter Sensor, Datex-Ohmeda, Louisville, Colo.
[m]Ohmeda RGM 5250, Ohmeda, Madrid, Spain.
[n]Hewlett-Packard Press M 1006B, Hewlett Packard, Geneva, Switzerland.
[o]Hewlett-Packard model 86S, Hewlett-Packard, Geneva, Switzerland.
[p]Ohmeda transducer DT-XX, Ohmeda, Madrid, Spain.
[q]SPSS 10.0 statistical package for Windows, SPSS Inc, Chicago, Ill.
[r]Lui PW, Wang H, Kearse LA. The bispectral index does not predict hemodynamic responses to laryngoscopy and intubation during propofol-induced EEG burst suppression (abstr). *Anesthesiology* 1996;85:A175.
[s]Davis PJ, Lerman J, Wellborn L, et al. Emergence and recovery from sevoflurane in pediatric ambulatory patients: a multicenter study(abstr). *Anesthesiology* 1993;79:A1165.

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