Minimum alveolar concentration measures of central nervous system activation in cats anesthetized with isoflurane

Philip A. March, DVM, MS, and William W. Muir III, DVM, PhD

Objective—To compare the minimum alveolar concentration (MAC) of isoflurane required to prevent corticocerebral activation, autonomic responses, and purposeful movements after somatic or visceral stimulation in cats anesthetized with isoflurane.

Animals—17 healthy spayed female cats.

Procedure—Bispectral index (BIS), autonomic parameters, and purposeful movements were monitored before and after somatic or visceral stimuli in cats anesthetized with isoflurane. End-tidal (ET) isoflurane concentration was varied to determine MAC values for cortical arousal (MAC_{BIS}), autonomic responsiveness (MAC_{BAR}), and purposeful movement (MAC). Bispectral index values ≥ 60 were considered to represent corticocerebral activation.

Results—Minimum alveolar concentration for purposeful movement was significantly less than MAC_{BIS} and MAC_{BAR} for both somatic and visceral stimulation. Individual MAC values for somatic stimulation were not significantly different from respective MAC values for visceral stimulation. The percentage of cats that had a BIS response ≥ 60 was inversely related to the end-tidal isoflurane concentration.

Conclusions and Clinical Relevance—Corticocerebral arousal and subcortical autonomic reflexes occured at isoflurane anesthetic concentrations at which reflexive or purposeful movements were absent. These results suggested that isoflurane had a preferential effect on voluntary motor output at low end-tidal isoflurane concentrations, and that sensory pathways, subcortical sympathetic output, and cortical responsiveness are less susceptible to the anesthetic effects of isoflurane. Bispectral index values obtained after somatic or visceral stimulation were sensitive for the detection of early changes in cortical excitability. (*Am J Vet Res* 2003; 64:1528–1533)

A patient's responsiveness to a noxious stimulus serves as the basis for the determination of the **minimum alveolar concentration (MAC)** of an inhalant anesthetic agent. Merkel and Eger[1] first introduced the concept of MAC in 1963 during evaluation of gas anesthetic concentrations required to prevent gross movement in dogs following a noxious stimulus. The MAC_{50} or MAC 1.0 is defined as the MAC of an inhalant anesthetic at 1 atmosphere required to prevent purposeful movement in response to a standardized noxious stimulus in 50% of the population.[2,3] Final determination of the MAC of an anesthetic in humans is population-based and made by assessing movement in response to skin incision in different patients at different **end-tidal (ET)** inhalant anesthetic concentrations. Minimum alveolar concentration is determined in animals by delivering a noxious stimulus to an animal that is anesthetized at a preselected ET inhalant anesthetic concentration, recording the presence or absence of purposeful movement, and sequentially increasing or decreasing ET anesthestic concentration in a stepwise manner to determine the maximum anesthetic concentration at which movement is present and the minimum anesthetic concentration at which movement is absent after a noxious stimulus.[1,3,4] The mean is calculated from the individual MAC values from multiple animals to yield a population MAC.

Conventional MAC measurements provide general guidelines for minimizing patient movement; however, an optimal surgical plane of anesthesia occurs when unconsciousness is maintained, autonomic reflexes are minimized, and patient movements are absent. Motor and autonomic responses to noxious stimuli may be lost because of inhibition of sensory or motor transmission in the spinal cord and brain stem. The MAC_{BAR} is the minimum inhalant anesthetic concentration that prevents an autonomic response to a noxious stimulus.[5] The MAC_{BAR} is typically higher than the traditional MAC, which suggests that autonomic reflexes and responses are activated at a lower stimulus threshold than are movement responses.[6] Systematic MAC studies of autonomic responses to noxious stimuli in animals are sporadic despite the fact that autonomic parameters such as heart rate, blood pressure, and respiratory rate are routinely used as measures of adequate analgesia during surgical procedures in veterinary medicine.[2]

Patient perception of a noxious stimulus requires the functional integrity of nociceptive and mechanoreceptive pathways in the spinal cord, brain stem, and cerebral cortex. A true voluntary motor response would also require normal function of descending motor pathways. Consequently, loss of voluntary motor responsiveness may be caused by effects of the anesthetic on almost any region of the CNS. Furthermore, cortical processing and perception of the stimulus may occur in the absence of a motor response if subcortical motor pathways are preferentially inhibited by an anesthetic agent.[4,7]

The **bispectral index (BIS)** is a processed electroencephalographic parameter that assesses the magnitude

Received March 3, 2003.
Accepted May 2, 2003.
From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210.
Supported in part by a grant from the Fishbein Family Interstitial Cystitis Research Foundation of the Interstitial Cystitis Association.
The authors thank Dr. Tom Wittum for statistical analyses and Ms. Allison Lamb for technical assistance.
Address correspondence to Dr. March.

of corticocerebral depression induced by anesthetics and sedatives. The BIS is a number from 0 to 100 derived from an algorithm that relates 3 factors: the degree to which **electroencephalogram (EEG)** waveforms are in phase (bicoherence), the amount of EEG power in the Δ versus β range (power spectrum), and the proportion of the EEG that is isoelectric.[8-10] The degree of bicoherence or phase coupling between the sine wave components of the EEG increases with increasing anesthetic depth and is inversely related to the derived BIS number.[8]

The BIS has been used as a measure of patient consciousness, level of responsiveness, and hypnosis in humans.[8,11-15,a] Prestimulus BIS values ≥ 60 in humans are associated with conscious perception of various stimuli.[16-21,b] Although the BIS is not a direct measure of analgesia, it can be used as an indicator of a patient's responsiveness to a noxious stimulus under specific anesthetic conditions. An increase in the BIS number after noxious stimulation in humans has been used as a measure of adequate analgesia and sedation.[c-e]

The purpose of the study reported here was to compare the MAC required to prevent corticocerebral activation, autonomic responses, and purposeful movement after somatic or visceral stimulation in cats anesthetized with isoflurane. The BIS values, autonomic parameters, and movements of the cats were monitored before and after a noxious somatic or visceral stimulus. Visceral stimulation was incorporated into the study design to assess patterns of CNS activation that may accompany surgery on viscera. The ET concentration of isoflurane was varied to determine MAC values for cortical arousal (MAC_{BIS}), autonomic responsiveness (MAC_{BAR}), and purposeful movement (traditional MAC) for the 2 stimulus conditions. We hypothesized that MAC_{BIS} and MAC_{BAR} for isoflurane would be greater than traditional MAC values. We also hypothesized that ET isoflurane concentrations for MAC_{BIS}, MAC_{BAR}, and MAC after **somatic** ($_s$) stimulation would not differ from ET isoflurane concentrations for MAC_{BIS}, MAC_{BAR}, and MAC after **visceral** ($_v$) stimulation.

Materials and Methods

Animals and anesthetic monitoring—Seventeen healthy spayed female cats were evaluated. Complete blood counts, serum biochemical analyses, urinalysis, bacteriologic culture of the urine and susceptibility testing, and FeLV and FIV testing were performed in all cats to exclude any underlying abnormalities. All procedures were approved by the Institutional Animal Care and Use Committee of The Ohio State University, and all experimental protocols conformed to the guidelines for the care and use of animals issued by the American Physiological Society and the National Institutes of Health.

In all cats, anesthesia was induced by mask with isoflurane, and cats were mechanically ventilated[f] to an inspiratory pressure of 20 to 25 cm of water at a rate of 6 to 8 ventilations/min. Anesthesia was maintained with isoflurane in oxygen delivered by an out-of-circle, drug specific vaporizer and a semiclosed circle rebreathing system.[g] End-tidal carbon dioxide (CO_2), inspiratory and ET isoflurane concentrations, and **respiratory rate** (**RR**; breaths/min) were monitored by an infrared airway gas monitor[h] attached to an endotracheal tube. Arterial oxygen saturation of hemoglobin and **heart rate** (**HR**; beats/min) were monitored by use of a pulse oximeter.[i] **Arterial blood pressure** (**ABP**; mm Hg) was measured indirectly by oscillometry.[j] Body temperature was monitored with a rectal temperature probe and maintained between 36.6° and 38.3°C by use of a circulating water blanket and an infrared heat lamp.

Electroencephalogram signals and BIS measurements were acquired and recorded by use of an EEG-BIS monitor[k] with the high frequency filter set at 70 Hz and the low frequency filter set at 2 Hz. A BIS number was automatically calculated by the monitor's BIS algorithm software and displayed every 5 seconds. This number reflected the EEG activity during the previous 60 seconds. Amplified EEG and BIS signals were downloaded to a computer and digitized for eventual off-line analysis.[l] Platinum subdermal needle electrodes[m] were used to record EEG activity by use of a 2-channel referential montage. Recording electrodes were placed in a bifrontal configuration, and a reference electrode was placed at vertex (on midline at the level of a line bisecting the rostral margins of each ear pinna). A ground electrode was placed in the atlantooccipital region. Automatic impedance testing was performed by the monitor to ensure acceptable signal reception. Signals were excluded from analysis if contaminated by electromyographic activity (frequency > 70 Hz, amplitude > 70μV). The monitor also had an artifact detection system and calculated a signal quality index from the previous 60- second recording interval.[21]

Somatic stimulation and MAC determination—Somatic stimulation was evaluated in 17 cats during isoflurane anesthesia. Each cat was maintained at a stable ET isoflurane concentration for a minimum of 15 minutes before testing. An electrical stimulating device was secured to the ventral tail base with nonadhesive bandaging tape.[n] The electrical stimulus consisted of a 25 mA ramp signal[o] delivered during a period of 10 seconds. The electrical stimulus was stopped if purposeful movement was observed during the 10 second stimulation period. Respiratory rate, HR, ABP, BIS number, EEG characteristics, and body movements (motor responses, somatic reflexes) were monitored every 30 seconds after tail stimulation. Recordings of these parameters were obtained for a period of 5 minutes after stimulation. Bispectral index values ≥ 60 were considered to be representative of corticocerebral arousal.[16-20,b-e]

The MAC_{BISs} was defined as the mean of the highest isoflurane concentration at which the BIS was ≥ 60 and the lowest isoflurane concentration at which the BIS was < 60 after somatic stimulation. The MAC_{BARs} was defined as the mean of the highest isoflurane concentration at which a > 15% change from baseline occurred in RR, HR, and ABP and the lowest concentration at which the change from baseline was < 15% after somatic stimulation. Traditional MAC after somatic stimulation (MAC_s) was defined as the mean of the highest isoflurane concentration at which a purposeful motor response (eg, lifting or jerking of the head or repetitive limb movements) was observed and the lowest isoflurane concentration at which the stimulus did not cause purposeful movement. Coughing, rigidity, tail movement, swallowing, and chewing were not considered a purposeful movement response. The testing sequence began at high ET isoflurane concentrations (1.5× the reported MAC for tail-clamp studies[22,23]), followed by testing at sequentially lower concentrations. End tidal isoflurane concentrations were lowered by 0.2% until a response was observed, then increased in 0.1% increments until no response was observed. The testing sequence was continued until the MAC for each response was determined in each cat. The total number of stimuli and ET isoflurane concentrations tested varied slightly among cats because of individual differences in anesthetic effect and response thresholds.

Visceral stimulation and MAC determination—Visceral stimulation was induced by distension of the urinary bladder in 12 of the 17 cats used in the somatic stimulation studies.

Visceral studies were not performed in the remaining 5 cats because of an inability to place a urinary catheter in these cats. Cats were instrumented and anesthetized as described for the somatic stimulation studies. The order of somatic and visceral stimulation studies was randomized for each cat, and there were at least 2 weeks between studies. A double-lumen Foley catheter was placed transurethrally into the lumen of the urinary bladder to permit simultaneous fluid infusion and bladder pressure measurements. After removal of residual urine from the bladder, each cat was maintained at a stable ET isoflurane concentration for a minimum of 15 minutes before testing. The testing sequence was the same as that for the somatic stimulation studies. Initial ET isoflurane concentrations were 1.5X the MAC, as determined in tail-clamp studies.[22,23] Warmed (42°C) saline (0.9% NaCl) solution was infused[p] into the bladder at a rate of 10mL/m^2 body surface area per minute (approximately 2 to 2.5 mL/min). Simultaneous bladder pressure and volume measurements were recorded.[q] The maximum volume of saline solution infused into the bladder was ≤ 50 mL, and maximum pressure was ≤ 50 cm of water. Respiratory rate, HR, ABP, BIS value, EEG characteristics, and body movements (ie, voluntary motor responses) were monitored every 2 minutes during the infusion of saline solution into the bladder, then every minute after infusion. Recordings of these parameters were obtained for a maximum of 5 minutes after stimulation. The infusion was stopped if the BIS value was ≥ 60. The saline solution was withdrawn from the bladder, and the volume was recorded at the end of each infusion experiment. The MAC_{BISv}, MAC_{BARv}, and MAC_v values after visceral stimulation were determined similar to that for the somatic stimulation studies.

Statistical analyses—The MAC_{BIS}, MAC_{BAR}, and MAC values were analyzed by a 1-way ANOVA. Post-hoc tests were performed to identify differences between groups when indicated. The percentage of cats that had a significant BIS response (BIS value ≥ 60) to somatic or visceral stimulation at each ET isoflurane concentration was calculated. Linear regression analysis was performed to determine the correlation between percentage response and ET isoflurane concentration. A value of $P < 0.05$ was considered significant. All MAC values are expressed as mean ± SD.

Results

Mean ET isoflurane MAC_s for somatic stimulation (1.87% ± 0.14%) was significantly less than mean MAC_{BISs} and mean MAC_{BARs}. There was no significant difference between MAC_{BISs} (2.05% ± 0.11%) and MAC_{BARs} (2.07% ± 0.11%; **Fig 1**). The percentage of cats with a BIS response ≥ 60 was inversely related to the ET isoflurane concentration (R^2 = 0.94; **Fig 2**).

The mean ET isoflurane MAC_v for visceral stimulation (1.82% ± 0.10%) was significantly less than mean MAC_{BISv} and mean MAC_{BARv}. There was no significant difference between MAC_{BISv} (1.99 ± 0.12%) and MAC_{BARv} (1.98% ± 0.13%). The percentage of cats with a BIS response ≥ 60 was inversely related to the ET isoflurane concentration (R^2 = 0.83).

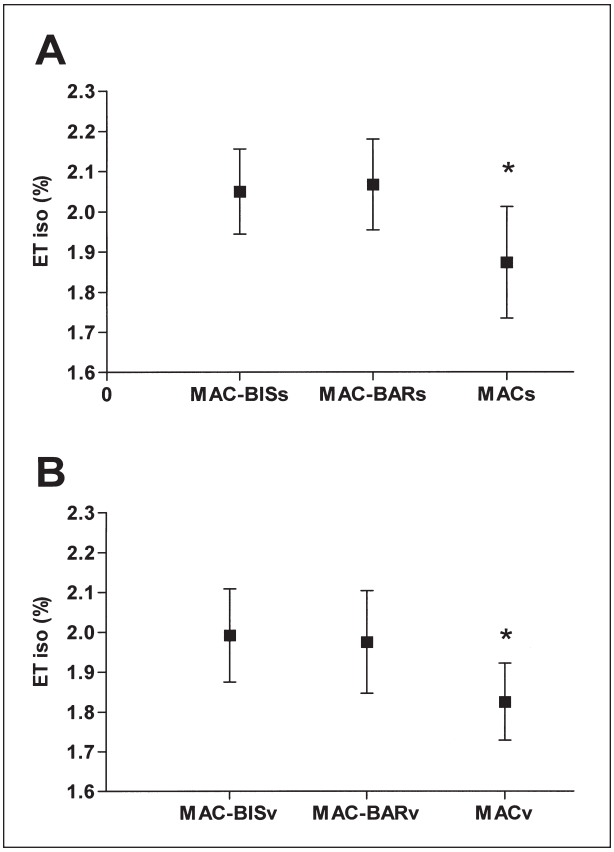

Figure 1—Mean ± SD end-tidal isoflurane (ET iso) concentrations for bispectral index (BIS), autonomic (BAR), and purposeful movement responses after somatic (A [n = 17]) and visceral (B [12]) stimulation in cats. MAC = Minimum alveolar concentration. S = Somatic. V = Visceral. The error bars represent 1 SD. *Significantly ($P < 0.05$) different from values for MAC_{BIS} and MAC_{BAR}.

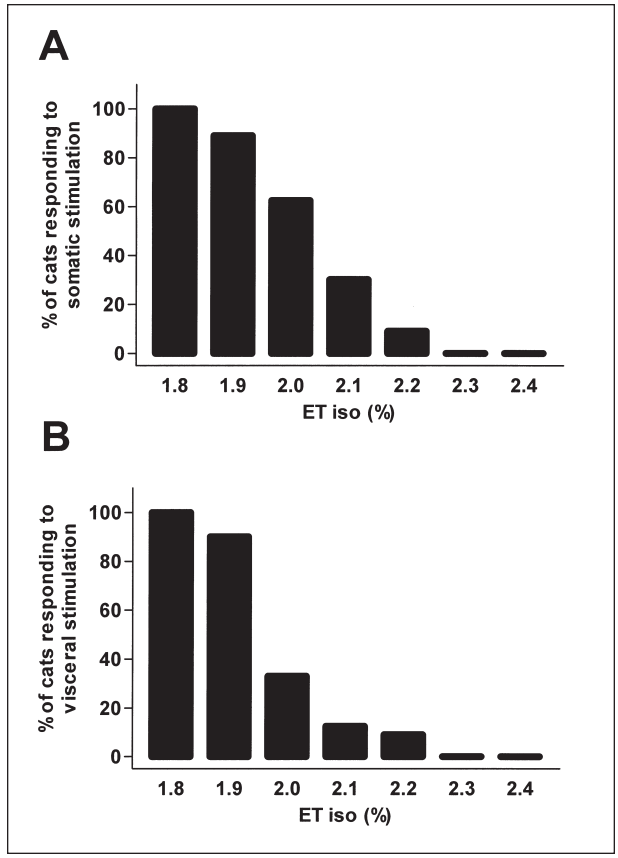

Figure 2—Percentage of cats that had a BIS value ≥ 60 after somatic (A [n = 17]) and visceral (B [12]) stimulation in cats. Notice that certain cats continued to have a BIS response ≥ 60 at ET iso concentrations of 2.0, 2.1, and 2.2%. *See* Figure 1 for key.

There was no significant difference between MAC_s and MAC_v. The MAC_{BISs} and MAC_{BARs} values were slightly greater than MAC_{BISv} and MAC_{BARv} values; however, those differences were not significant.

Discussion

Results of our study indicate that traditional MAC values for isoflurane in cats were significantly lower than MAC_{BIS} and MAC_{BAR} values, and that MAC_{BIS} and MAC_{BAR} values were not significantly different for somatic or visceral stimulation. The MAC, MAC_{BIS}, and MAC_{BAR} results indicate that corticocerebral arousal and subcortical autonomic reflexes occurred at isoflurane anesthetic concentrations at which reflexive or purposeful movements were absent. This finding supports the concept of differential effects of isoflurane on anatomically distinct areas of the CNS.[24-29] Most anesthetics induce loss of consciousness at concentrations below those required to suppress responses to noxious stimuli.[4,7] This gradient of effects was not apparent for isoflurane in our study and may not be characteristic of other volatile anesthetics. Results of our study indicate that there was a preferential effect of isoflurane on voluntary motor output at low ET concentrations.[24-31] At equivalent isoflurane concentrations, BIS and hemodynamic responses were preserved, which suggests that sensory input, corticocerebral activity, and autonomic function were spared.

Assessment of adequate anesthesia traditionally has relied on a patient's movement, hemodynamic response, or both to a surgical stimulus. Traditional MAC assessment is determined by the ET inhalant concentration that defines the threshold for movement after a noxious stimulus. Most MAC studies have assumed that the lack of movement is because of the direct effects of the inhalant anesthetic on the cerebral cortex.[4] However, this assumption has recently been challenged by results of studies[24,26-31] indicating that inhalant anesthetics suppress purposeful movements at the spinal cord or subcortical level. Depending on the type of anesthetic and severity of the noxious stimulus, suppression of purposeful movement may not coincide with suppression of conscious arousal or autonomic responsiveness.[32]

A recent study[33] in goats examined changes in the BIS in response to a noxious somatic stimulus. A toe pinch was applied to the dewclaw for 60 seconds, and changes in the BIS were recorded at various ET isoflurane concentrations. Increases in the BIS were observed at ET isoflurane concentrations that ranged from 0.8% to 1.5%, with BIS values > 60 in all goats tested after stimulation. The MAC_{50} of goats during the same conditions was 1.3% ET isoflurane.[33] This finding suggests that increases in the BIS and consciousness occur at isoflurane concentrations that exceed MAC_{50}. Similar findings in cats in our study support the conclusion that movement in response to noxious stimuli may be inhibited before changes in corticocerebral arousal. A preferential inhibitory effect of isoflurane on motor pathways in spinal cord, brain stem, or both at low ET concentrations likely explains the loss of movement responses.[24,26,27,31]

The ET isoflurane concentrations for autonomic responsiveness (MAC_{BAR}) were comparable with those for corticocerebral responsiveness (MAC_{BIS}) during the conditions of this study. Preservation of BIS responses and autonomic feedback at the same ET isoflurane concentrations suggests continued integrity of corticocerebral function, a functional sparing of ascending sensory pathways that activate brain stem and forebrain compartments, and preservation of sympathetic outputs that originate from subcortical sites. These findings of retained responsiveness to noxious stimuli are in agreement with those of Tsushima et al[34] who found poor suppression of cortical EEG response, brain stem activity, and hemodynamic changes after sciatic nerve stimulation in cats anesthetized with isoflurane at 1.3 and 2.0× MAC. Zbinden et al[35] found that increases in mean ABP and HR after different types of noxious stimuli were preserved during anesthesia with isoflurane. However, autonomic responses are mediated primarily by subcortical centers (hypothalamus, brain stem, and spinal cord) and do not require corticocerebral activation. Consequently, MAC_{BAR} is a useful measure of the effects of an anesthetic on autonomic pathways in the spinal cord and brain stem, but is not a reliable measure of anesthetic effects on cortical activity and arousal.[4]

The higher MAC values obtained in our study compared with results of those in tail-clamp studies may be a reflection of the type and intensity of the noxious stimulus that was used. The MAC values of 1.87% and 1.82% ET isoflurane concentrations for the somatic and visceral stimulation studies, respectively, exceeded the MAC value reported for isoflurane with the tail-clamp method (MAC, 1.6% ET isoflurane concentration).[22,23] Our MAC_s value closely approximated ET isoflurane concentrations that are considered as providing a surgical plane of anesthesia (1.2× MAC for tail-clamp studies).[2] The visceral stimulus was well defined, repeatable, and did not induce traumatic injury to tissues. In our study, inhibition of the micturition reflex by isoflurane in all cats permitted gradual distension of the urinary bladder and activation of sensory receptors without the confounding effects of detrusor muscle contractions. Hemodynamic and respiratory responses were pronounced after stimulation of the urinary bladder at isoflurane concentrations equivalent to MAC_v values of ≤ 1.0. The MAC_{BARv} and MAC_{BISv} were nearly identical, which indicates that ascending sensory signals were activating subcortical sites to induce a vesicosympathetic response and cortical sites to induce a BIS response.

Anesthetic depth and MAC are traditionally measured by use of somatic stimuli. Responses to different types of stimuli, including visceral stimuli, may be a more appropriate approach for determining surgical planes of anesthesia. Zbinden et al[36] examined the isoflurane concentration required to suppress motor responses to different stimuli in humans including verbal command, muscle squeeze, laryngoscopy, tetanic stimulation, skin incision, and endotracheal intubation. Depending on the stimulus, the isoflurane concentrations ranged from 0.84% to 1.76%. Endotracheal intubation required the greatest anesthetic concentration to suppress a motor response.[36] Various studies[37-43] in animals have evaluated changes in patterns of CNS

activation after noxious visceral stimuli. Stimulation of the rectum or urinary bladder activates a number of centrally mediated reflexes and responses including reflexive smooth muscle contractions, HR and blood pressure changes, respiratory changes, and purposeful motor responses.[38-41,44] A study[37] in cats evaluated conventional MAC values after airway occlusion but did not examine MAC_{BARv} and MAC_{BISv}. Results of our study indicate that distension of the urinary bladder caused patterns of CNS activation that closely paralleled those observed after somatic stimulation. The MAC_{BISv} and MAC_{BARv} values were slightly less than MAC_{BISs} and MAC_{BARs} values; however, the differences were not significant. This finding suggests that the visceral stimulus used in this study was comparable with a noxious somatic stimulus, and that the anesthetic sensitivities of neural networks responsible for urinary bladder and tail responses are similar even though the anatomic and physiologic properties of those networks are distinct.

The concept of MAC is useful for comparing the potency of volatile anesthetics. A MAC_{BIS} value that is predetermined for each gas anesthetic and noxious stimulus may have greater use than traditional MAC values in the prevention of overt patient arousal and movement during surgical procedures. However, multiple confounding factors can affect the MAC values of individual patients, including age, physiologic state, body temperature, concurrent drug administration, and the magnitude and duration of the noxious stimulus.[4] Furthermore, the MAC for a specific inhalant anesthetic is a population mean with certain variability of response around the mean. For this reason, the response of different individuals to the same delivered anesthetic concentration is variable. We observed a large percentage of cats that had a BIS response ≥ 60 at ET isoflurane concentrations greater than MAC_{BIS}. Another subgroup of cats did not have a BIS response at ET isoflurane concentrations less than MAC_{BIS}. Titration to MAC_{BIS} in these 2 subpopulations could cause under- or overdosing of a volatile anesthetic. Consequently, although MAC_{BIS} approximates the responsiveness of the majority of cats, its use in an individual cat, like that of MAC_{50}, has limitations. Furthermore, our selection of a threshold BIS value of 60 was determined by results of a series of studies[11-20,a-e] performed in humans in which consciousness was assessed according to responses to noxious and nonnoxious stimuli.[11-20, a-e] The magnitude of the change in the BIS value and not the actual BIS value obtained after stimulation may be more meaningful in assessing early nociceptive activation of cerebral somatosensory areas and early decreases in anesthetic depth in animals. Species-specific differences in the interpretation of the BIS are likely to emerge in the future as the physiologic importance of phase coherence and other factors that may affect the BIS are better understood.[24,45]

The MAC and MAC_{BAR} may provide an indirect assessment of the level of analgesia; however, they are not useful in the direct assessment of the level of cortical activation. Furthermore, use of neuromuscular blocking agents, narcotics, α_2-agonists, or combinations of these agents in a balanced anesthetic regimen may prevent meaningful assessment of motor and autonomic responses.[13,15,36,37] The BIS is a direct measure of corticocerebral responsiveness and, in our study, increased from baseline after a somatic or visceral noxious stimulus. We have found that BIS values obtained after stimulation provide a sensitive method of detecting early changes in cortical excitability. The MAC_{BIS} provides a direct measure of the efficacy of an anesthetic in the suppression of nociceptive transmission and arousal from the hypnotic state and, for certain anesthetics, may be a more reliable measure of anesthetic potency than the traditional MAC.

[a]Kearse L, Saini V, deBros F, et al. Bispectral analysis of EEG may predict anesthetic depth during narcotic induction (abstr). *Anesthesiology* 1991;75:A175.

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

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

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

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

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

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

[h]Datex capnomac ultima, Datex Medical Instruments Inc, Tewksbury, Mass.

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

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

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

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

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

[n]Vetrap, 3M Animal Care Products, St Paul, Minn.

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

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

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

References

1. Merkel G, Eger EI. A comparative study of halothane and halopropane anesthesia: including the method for determining equipotency. *Anesthesiology* 1963;24:346–357.

2. Haskins SC. Monitoring the anesthetized patient. In: Haskins SC, ed. *Veterinary anesthesia.* 3rd ed. Baltimore: The Williams & Wilkins Co, 1996;409–424.

3. Eger EL, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 1965;26:756–763.

4. Stanski DR. Monitoring depth of anesthesia. In: Miller RD, ed. *Anesthesia.* 5th ed. New York: Churchill Livingstone Inc, 2000; 1087–1116.

5. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision = MAC BAR. *Anesthesiology* 1981;54:390–398.

6. Schmeling WT, Ganjoo P, Staunton M, et al. Pretreatment with dexmedetomidine: altered indices of anesthetic depth for halothane in the neuraxis of cats. *Anesth Analg* 1999;88:625–632.

7. Prys-Roberts C. Anaesthesia: a practical or impossible construct? *Br J Anaesth* 1987;59:1341–1345.

8. Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 1994;10:393–404.

9. Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* 1998;88:642–650.

10. Detsch O, Schneider G, Kochs E, et al. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. *Br J Anaesth* 2000;84:33–37.

11. Berkenbosch JW, Fichter CR, Tobias JD. The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. *Anesth Analg* 2002;94:506–511.

12. Kearse LA, Rosow C, Zaslavsky A, et al. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. *Anesthesiology* 1998; 89:323–333.

13. Iselin-Chaves IA, Flaishon R, Sebel PS, et al. The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998;87:949–955.

14. Denman WT, Swanson EL, Rosow D, et al. Pediatric evaluation of the bispectral index (BIS) with end-tidal sevoflurane concentrations in infants and children. *Anesth Analg* 2000;90:872–877.

15. Singh H, Sakai T, Matsuki A. Movement response to skin incision: analgesia vs bispectral index and 95% spectral edge frequency. *Eur J Anaesth* 1999;16:610–614.

16. Glass PS, Bloom M, Kearse L, et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997;86:836–847.

17. Kearse LA, Manberg P, DeBros F, et al. Bispectral analysis of the electroencephalogram during induction of anesthesia may predict hemodynamic responses to laryngoscopy and intubation. *Electroencephalogr Clin Neurophysiol* 1994;90:194–200.

18. Kearse LA, Manberg P, Chamoun N, et al. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. *Anesthesiology* 1994;81:1365–1370.

19. Song D, Joshi GP, White PF. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. *Anesthesiology* 1997;87:842–848.

20. Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; 87:808–815.

21. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000; 93:1336–1344.

22. Steffey EP, Howland D Jr. Isoflurane potency in the dog and cat. *Am J Vet Res* 1977;38:1833–1836.

23. Drummond JC, Todd MM, Shapiro HM. Minimal alveolar concentrations for halothane, enflurane, and isoflurane in the cat. *J Am Vet Med Assoc* 1983;182:1099–1101.

24. Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; 78:707–712.

25. Rampil IJ. Anesthetic potency is not altered after hypothermic spinal cord transection in rats. *Anesthesiology* 1994; 80:606–610.

26. Rampil IJ, King BS. Volatile anesthetics depress spinal motor neurons. *Anesthesiology* 1996;85:129–134.

27. Antognini JF, Carstens E. Increasing isoflurane from 0.9 to 1.1 minimum alveolar concentration minimally affects dorsal horn cell responses to noxious stimulation. *Anesthesiology* 1999; 90:208–214.

28. Antognini JF, Carstens E. Isoflurane blunts electroencephalographic and thalamic-reticular responses to noxious stimulation in goats. *Anesthesiology* 1999;91:1770–1779.

29. Antognini JF, Schwartz K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. *Anesthesiology* 1993; 79:1244–1249.

30. Rampil IJ, Laster MJ. No correlation between quantitative electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. *Anesthesiology* 1992; 77:920–925.

31. Nicoll RA, Madison DV. General anesthetics hyperpolarize neurons in the vertebrate central nervous system. *Science* 1982; 217:1055–1057.

32. Kissin I. General anesthetic action: an obsolete notion? *Anesth Analg* 1993;76:215–218.

33. Antognini JF, Wang XW, Carstens E. Isoflurane anaesthetic depth in goats monitored using the bispectral index of the electroencephalogram. *Vet Res Commun* 2000;24:361–370.

34. Tsushima K, Shingu K, Ikeda S, et al. Suppressive actions of volatile anaesthetics on the response capability in cats. *Can J Anaesth* 1998; 45:240–245.

35. Zbinden AM, Petersen-Felix S, Thomson DA. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses. *Anesthesiology* 1994; 80:261–267.

36. Zbinden AM, Maggiorini M, Petersen-Felix S, et al. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. *Anesthesiology* 1994; 80:253–260.

37. Ide T, Sakurai Y, Aono M, et al. Minimum alveolar anesthetic concentrations for airway occlusion in cats: a new concept of minimum alveolar anesthetic concentration=airway occlusion response. *Anesth Analg* 1998;86:191–197.

38. Janig W, Habler H-J. Visceral-autonomic integration. In: Gebhart GF, ed. *Visceral pain*. Seattle: IASP Press, 1995;311–348.

39. DeGroat WC. Nervous control of the urinary bladder of the cat. *Brain Res* 1975;87:201–211.

40. Ness TJ, Geghart GF. Visceral pain: a review of experimental studies. *Pain* 1990;41:167–234.

41. Bahns E, Halsband U, Janig W. Responses of sacral visceral afferents from the lower urinary tract, colon, and anus to mechanical stimulation. *Pflugers Arch* 1987;410:296–303.

42. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibers by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol* 1990;425:545–562.

43. Page ME, Akaoka H, Aston-Jones G, et al. Bladder distention activates noradrenergic locus coeruleus neurons by an excitatory amino acid mechanism. *Neuroscience* 1992;51:555–563.

44. Schondorf R, Polosa C. Effects of urinary bladder afferents on respiration. *J Appl Physiol* 1980;48:826–832.

45. Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998;89:980–1002.