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Increases in mean arterial blood pressure during electrical stimulation are unreliable indicators of anesthetic depth measured with electroencephalogram in dogs anesthetized with sevoflurane

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OBJECTIVE
To evaluate the sparing effects of fentanyl and maropitant on sevoflurane minimum alveolar concentrations that block autonomic responses (MAC_{BAR}) and the hemodynamic and electroencephalographic responses to noxious stimuli in dogs.

METHODS
The sevoflurane MAC_{BAR} was determined in 5 healthy male Beagles with or without continuous infusions of fentanyl and maropitant. Then, intermittent noxious stimulation was applied at 1.3, 1.0, and 0.7 MAC_{BAR}. Heart rate (HR), mean arterial pressure (MAP), and Patient State Index (PSI) were measured for 6 minutes before and during 6 minutes of stimulation and analyzed with generalized linear mixed-effects models. Patient State Index occurrences above 50 during stimulation were noted. The effective dose for burst suppression was determined.

RESULTS
The baseline MAC_{BAR} was 2.26% (1.34, 3.19). No MAC_{BAR}-sparing effect of fentanyl and maropitant was observed. At 1.3 MAC_{BAR}, MAP, HR, and PSI were 50 (41, 91) mm Hg, 90 (64, 112) beats/min, and 2 (0, 44). Mean arterial pressure and PSI increased, but not HR, with lower MAC_{BAR} multiples ($P < .001$). Noxious stimulation did not alter HR or PSI but elevated MAP. No PSI above 50 occurred at 1.3 MAC_{BAR}; however, 2 and 3 dogs showed brief PSI increases at 1.0 and 0.7 MAC_{BAR}. The effective dose for burst suppression was 3.15% (2.75, 3.75).

CONCLUSIONS
Fentanyl and maropitant showed no MAC_{BAR}-sparing effect. At higher sevoflurane concentrations, noxious stimuli triggered an autonomic response; however, burst suppression was observed in the electroencephalogram.

CLINICAL RELEVANCE
Variations in HR and MAP are unreliable indicators of anesthetic depth measured by electroencephalogram.

Keywords: anesthesia safety, anesthetic depth monitoring, bispectral index, canine, sympathetic response

Assessing appropriate surgical anesthesia depth in animals is crucial to prevent inadvertent awareness during surgery. The traditional method of measuring anesthetic depth in veterinary medicine is based on the patterns described by Dr. Guedel in the early 20th century using ether.[1–2] One of the characteristics of the third plane of Guedel's stage III, which is the recommended anesthetic depth for surgical interventions, is the absence of a physiological response to noxious stimuli.[1]

The concentration of inhalant anesthetic required to prevent such changes in mean arterial blood pressure (MAP) and heart rate (HR) can be determined by conducting studies that establish the minimum alveolar concentration (MAC) that blocks autonomic response (MAC_{BAR}).[3,4] The MAC_{BAR} is defined as the concentration of inhalant anesthetic that prevents 50% of the studied population from experiencing a 15% increase in MAP or HR from its prenoxious stimulation values.[3,4] A significant limitation of using the third plane of stage III or MAC_{BAR} to determine

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adequate anesthetic depth for surgery is that these methods do not directly evaluate the patient's awareness status. Several factors, such as the use of sympathomimetic and anticholinergic drugs, can influence MAP and HR in anesthetized animals. In addition, high doses of inhalant anesthetic drugs are required to entirely prevent an autonomic response, which can lead to excessive anesthetic depth and several adverse effects, such as hypotension and burst suppression in the electroencephalogram (EEG).

The Patient State Index (PSI) can facilitate the interpretation of anesthetic depth based on real-time assessment of the EEG.[5] The PSI is a unitless number from 0 (electrical silence) to 100 (fully awake) obtained through a proprietary algorithm derived from the EEG recorded by surface electrodes placed on the dog's scalp.[5,6] In humans, the PSI-recommended range for surgical anesthesia is 25 to 50.[5,6] When the anesthetic plane is too deep, burst suppression occurs, which consists of periods of high EEG frequency followed by isoelectric activity.[7] The use of EEG-derived monitors helps prevent overly light anesthesia, which can result in awareness during surgery,[7] and overly deep anesthesia, which can increase morbidity.[8]

This study aimed to evaluate the sevoflurane MAC_{BAR}-sparing effect of fentanyl combined with maropitant as well as the EEG and hemodynamic responses to noxious stimuli at several sevoflurane MAC_{BAR} multiples.

The first hypothesis was that adding fentanyl, combined with maropitant, would decrease the MAC_{BAR} based on previous reports[9,10] in dogs when they were used individually. As MAC_{BAR} is higher than the dose that suppresses the response to verbal commands in people,[11,12] the authors hypothesized that no EEG response to noxious stimuli would be observed at 0.7, 1.0, and 1.3 MAC_{BAR}, whereas an increase in MAP and HR would be observed at 0.7 and 1.0 MAC_{BAR}.

Methods

This study was performed at the University of Georgia Veterinary Bioresources Facility under the approval of the University of Georgia IACUC (protocol A2022 02–018-Y1-A0). Data were collected from November 7 through November 22, 2022.

Animals

Based on a previous report[9,13] of the MAC-sparing effect of fentanyl, the authors expected a MAC_{BAR} reduction of at least 30% ± 15% when administering fentanyl to the animals. The estimated sample size required for this experiment was 5 animals after an a priori 1-tailed paired *t* test with an α of 5% and power of 95%. The number of enrolled animals had been increased to 6 to account for potential unexpected variability and data collection issues. Intact male Beagles aged 1 to 2 years weighing 9.7 to 12.3 kg and considered healthy based on physical examination, CBC, and serum biochemical analysis were enrolled in this study.

An animal was excluded from the experiment if it developed health issues or if data collection was impossible.

Instrumentation for experiments

Before each experiment, the sevoflurane concentration values from the fresh gas outlet were measured simultaneously using a gas analyzer and a standard refractometer (Riken Optical Gas Indicator; Riken Keiki Co). The end-tidal sevoflurane (ET_{SEVO}) concentrations were then corrected using linear regression.[14]

A 20-gauge catheter was inserted into the left cephalic vein to administer medications and fluids. Lactated Ringer solution was infused 3 mL/kg/h, IV. Oxygen was supplied for 3 to 5 minutes via a tight-fitting face mask connected to an adult anesthetic rebreathing system with a flow rate of 5 L/min. Anesthesia was induced by setting the calibrated vaporizer (Sigma Delta Sevoflurane Vaporizer; Penlon) to 8% until reaching an anesthetic depth suitable for endotracheal intubation with a cuffed endotracheal tube of 7.5 mm internal diameter. The animals were positioned in sternal recumbency with their pelvic limbs oriented toward the left side. The ET_{SEVO} was targeted to 2.2%, and fresh gas flow was set at 1 L/min. The anesthesia machine was connected to a mechanical ventilator (EMC Model 2000 Anesthesia Ventilator; Hallowell) with a respiratory rate of 8 to 12 breaths/min, aiming for an end-tidal partial pressure of carbon dioxide of 35 to 45 mm Hg. Blood pressure was continuously measured by inserting a 22-gauge catheter into the metatarsal artery, and the transducer was zeroed at the estimated level of the right atrium, the midpoint between the manubrium and thoracic column. The arterial blood pressure waveform was continuously recorded via software (LabChart Pro, version 8.1.13; ADInstruments). The software displayed a rolling average of 15 seconds for MAP and HR, which was used to determine the nociceptive threshold. The 6-minute averages for MAP and HR were calculated using the "average" function in LabChart. A circulating warm-water blanket and forced warmed air were applied for active warming to prevent hypothermia. Anesthesia standard monitoring also included pulse oximetry, ECG, oscillometric blood pressure, and esophageal temperature (Intellivue Reusable Temperature Probes Adult Esophageal/Rectal Probe; Philips)

The left peroneal nerve was stimulated using 2 needle electrodes positioned 2 cm apart at the level of the stifle, with the positive electrode located proximally. The acceleration sensor was taped over the metatarsal pad (Stimpod NMS450X Nerve Stimulator; Xavant Technologies). A Train-of-4 (TOF) stimulation consisting of 4 square electrical stimuli over 2 seconds at 40 mA was delivered every 15 seconds for 15 minutes before calibration to minimize the potentiation effect. Then, the peripheral nerve stimulator was calibrated for neuromuscular function monitoring, and TOF was applied every 15 seconds until the end of the experiment. The TOF ratio (peak acceleration of the fourth evoked twitch

divided by the peak acceleration of the first twitch) was recorded throughout the experiment. After administering a loading dose of 0.5 mg/kg of IV rocuronium (Zemuron; Merck & Co) to suppress neuromuscular function (TOF ratio, 0), a continuous rate infusion (CRI) at 0.2 to 0.4 mg/kg/h of IV rocuronium was started when initial signs of spontaneous recovery of the neuromuscular function appeared (the first twitch reappeared during TOF). The infusion was titrated to maintain no more than 2 twitches on TOF stimulation.

Minimum alveolar concentration that blocks autonomic response determination

The individual MAC_{BAR} was determined using the bracketing technique described by Eger et al.[15] Each nociceptive test was performed at least 20 minutes apart from the previous test, and the targeted ET_{SEVO} remained stable for at least 15 minutes before nociceptive stimulation. The determination of baseline MAC_{BAR} started with an ET_{SEVO} of 2.2%; the displayed MAP and HR immediately before the noxious stimulation were recorded, and the 15% upper limit threshold was calculated. For example, if prenoxious stimulation MAP was 100 mm Hg, the threshold would be 115 mm Hg. The noxious stimulus was provided by electrical stimulation applied through 2 electrodes, proximal and distal, to the lateral surface of the right antebrachium. The electrical stimulation pattern of the nociceptive test was previously described.[16] Four electrical stimuli of 50 V at 50 Hz with a 10-millisecond pulse duration were administered 5 seconds apart (S88 Square Pulse Stimulator; Grass Instruments). The first 2 stimuli were 10 milliseconds, and the last 2 were 5 seconds long. If the nociceptive test was negative (confirmed by MAP and HR below the established threshold), the targeted ET_{SEVO} was decreased by 0.15 to 0.20 vol%. If the nociceptive test was positive with MAP or HR reaching the threshold, the noxious stimulation delivery was promptly terminated once the threshold was reached, and the targeted ET_{SEVO} was increased by 0.15 to 0.20 vol%. A single MAC_{BAR} determination is the ET_{SEVO} average of a positive test result followed by a negative result or vice versa. After the initial determination of MAC_{BAR}, the ET_{SEVO} was adjusted based on the criteria for MAP and HR in further nociceptive testing until a duplicate MAC_{BAR} was calculated. If the duplicate MAC_{BAR} differed by more than 0.2% from the first one, a triplicate MAC_{BAR} was determined. The individual MAC_{BAR} was calculated as the average of all determined MAC_{BAR}. The values of MAP and HR before noxious stimulation on the tests that determined MAC_{BAR} were averaged for analysis.

After establishing the baseline MAC_{BAR}, the following drugs were administered: IV fentanyl (15 µg/kg over 20 minutes) and IV maropitant (1 mg/kg over 15 minutes), followed by constant rate infusions of IV fentanyl (6 µg/kg/h) and IV maropitant (30 µg/kg/h). Forty-five minutes after starting the fentanyl and maropitant infusions, MAC_{BAR} was determined with the bracketing technique described above. The duration to determine MAC_{BAR} without and with fentanyl and maropitant infusions was recorded.

The CRIs of fentanyl, maropitant, and rocuronium were discontinued after determining the treatment MAC_{BAR}. The recovery of the neuromuscular function was spontaneous or accelerated with IV sugammadex (2 mg/kg; Bridion; Merck). The allocation of spontaneous or accelerated recovery was part of another study performed simultaneously (Sakai DM, MV, University of Georgia, 2022, unpublished data). When the TOF ratio reached 0.9, the sevoflurane vaporizer and mechanical ventilator were turned off, and the animals were administered IV meloxicam (0.2 mg/kg) and allowed to recover. The endotracheal tube was removed once the animals regained their swallowing reflexes. The ET_{SEVO} immediately before extubation, the time from turning off the sevoflurane vaporizer to the time of tracheal extubation, and the total duration of anesthesia were recorded. After the animal could walk without assistance, the IV catheter was removed, and a small compression bandage was applied for at least 10 minutes before being returned to the housing facility.

Evaluation of hemodynamic and EEG responses

After a washout period of at least 7 days, the animals were anesthetized using the same dose regimen of the drugs, anesthesia monitoring, and noxious stimuli instrumentation used during MAC_{BAR} determination; however, catheters and electrodes were placed on the opposite forelimbs.

The EEG electrodes were placed on the forehead in the positions F3, F4, Fz, T3, T4, and Cz after clipping the hair, following previously described methods[7]; covered with a self-adherent bandage (2 Inch Vet Wrap; WildCow); and connected to the EEG-based monitoring device (SedLine Root Platform; Massimo).

After a minimum of 45 minutes of CRI of fentanyl and rocuronium, the ET_{SEVO} was adjusted to 1.3 MAC_{BAR} and kept stable for at least 15 minutes before data collection. The PSI was recorded every 15 seconds for 12 minutes. Electrical noxious stimuli were administered at 6, 8, and 10 minutes as described for MAC_{BAR} determination. Noxious stimuli were discontinued if there was a sustained increase in PSI, defined as values exceeding 60 for more than 30 seconds. Following the data collection at 1.3 MAC_{BAR}, the ET_{SEVO} was decreased to a target of 1.0 MAC_{BAR} to repeat 6 minutes without noxious stimulation and 6 minutes with noxious stimulation. It was then further reduced to 0.7 MAC_{BAR} for additional data collection using the same methodology. Each MAC_{BAR} data collection had to have at least 15 minutes of stable ET_{SEVO}, with a minimum interval of 15 minutes from the end of the previous data collection period. The MAP, HR, and PSI for the initial 6 minutes were averaged and compared with the average of the data collected at 6 to 12 minutes. The following episodes would be reported if they occurred: PSI briefly increased to over 50 or a paradoxical decrease in PSI occurring with noxious

stimulation. After data collection at 0.7 MAC_{BAR}, the animals were allowed to recover from anesthesia as described for MAC_{BAR} determination. During the recovery from general anesthesia, the ET_{SEVO} at which PSI reached 50 was recorded, along with the PSI values for 3 minutes after extubation (awake PSI).

Analysis of the raw EEG

The raw EEG was recorded continuously, and European Data Format files were exported for analysis using computer software (LabChart Pro, version 8.1.13; ADInstruments). Two excerpts (5-second and 1-minute durations) were extracted from each MAC_{BAR}'s data collection period at 30 seconds (without noxious stimulation), 10 minutes and 30 seconds (with noxious stimulation), and 5 to 10 minutes after endotracheal extubation. The 5-second segments were obtained to display raw EEG data during burst suppression, general anesthesia, and awake states. The 1-minute excerpt was processed to calculate the power spectral array at each MAC_{BAR} level and after recovery from general anesthesia. The EEG signal underwent filtering with a low-pass filter at 40 Hz. The density spectral array (DSA) was configured with the following settings: spectrogram color, "rainbow"; number of colors, 128; and PSD averaging, 1.

In cases of burst suppression, the periods of electrical silence of the 1-minute EEG excerpts were manually timed using software (LabChart Pro, version 8.1.13; ADInstruments) to calculate the burst suppression ratio (BSR; total time of electrical silence [in seconds]/60 seconds). The ET_{SEVO} at which burst suppression occurred was recorded.

Statistical analysis

Continuous data were assessed for normality using Shapiro-Wilk tests and presented as mean (95% CI). Paired *t* tests were used to analyze MAP, HR, duration to determine MAC_{BAR}, and ET_{SEVO} at baseline MAC_{BAR} and MAC_{BAR} with CRIs of fentanyl and maropitant. The effects of MAC_{BAR} multiples (1.3, 1.0, or 0.7) or ET_{SEVO}, the presence of noxious stimulation (yes or no), the presence of burst suppression (yes or no; only for EEG frequency bands), and the interaction between MAC_{BAR} multiple (or ET_{SEVO}) versus the presence of noxious stimulation were analyzed with a generalized linear mixed model (link function = identity; distribution = normal) for the responses MAP, HR, PSI, delta, theta, alpha, and beta-gamma. The individual dog was accounted for as a random effect. When awake EEG was included in the analysis, the effect of noxious stimulation and the interaction were removed along with data from dogs with burst suppression for delta, theta, alpha, and beta-gamma analysis. Tukey honest significant difference tests were used as post hoc analyses for multiple comparisons if necessary. Simple logistic regression was used to assess if there was a response of burst suppression (yes or no) with ET_{SEVO} as the predictor to calculate the mean effective dose (ED_{50}). Tests were performed via software (JMP Pro, version 17.2.0; SAS Institute Inc). Alpha was set at 5% for all tests.

Results

Five dogs completed the "MAC_{BAR} determination" and the "evaluation of hemodynamic and EEG responses" phases. One dog experienced injuries after the "MAC_{BAR} determination" phase due to accidental misuse of the electrical stimuli. This animal was removed from the study and did not participate in the "evaluation of hemodynamic and EEG responses" phase. The local veterinary research team provided medical care for the dog, which completely recovered from the incident. All animals were transferred to another experiment approved by the local ethics committee before being adopted to permanent private homes as companion animals.

Minimum alveolar concentration that blocks autonomic response determination

Baseline MAC_{BAR} was 2.26% (1.34, 3.19), and MACBAR with fentanyl and maropitant was 2.40% (1.65, 3.15; $P = .648$). At baseline MAC_{BAR}, the duration to determine the MAC_{BAR}, the MAP, and the HR were 1.8 (1.1, 2.4) hours, 100 (84, 116) mm Hg, and 125 (110, 140) beats/min, respectively. When fentanyl and maropitant CRI were administered, the duration to determine the MAC_{BAR}, the MAP, and the HR at MAC_{BAR} were 1.8 (0.9, 2.7) hours ($P = .740$), 65 (57, 73) mm Hg ($P = .002$), and 94 (76, 111) beats/min ($P = .001$), respectively.

Evaluation of hemodynamic and EEG responses

At 1.3 MAC_{BAR} without noxious stimulation, the MAP, HR, and PSI were 50 (41, 91) mm Hg, 90 (64, 112) beats/min, and 2 (0, 45), respectively; with noxious stimulation, the MAP, HR, and PSI were 65 (53, 93) mm Hg, 92 (76, 116) beats/min, and 2 (0, 44), respectively. Individual data points are presented in **Figure 1**.

The MAP, HR, and PSI were 65 (47, 91) mm Hg, 82 (68, 116) beats/min, and 40 (8,49), respectively, at 1.0 MAC_{BAR} without noxious stimulation. When noxious stimulation was applied at 1.0 MAC_{BAR}, the MAP, HR, and PSI were 79 (64, 93) mm Hg, 85 (81, 109) beats/min, and 41 (11,50), respectively. Individual data points are presented in Figure 1.

When the ET_{SEVO} decreased to 0.7 MAC_{BAR}, the MAP, HR, and PSI were 78 (70, 93) mm Hg, 84 (77, 113) beats/min, and 47 (38,55), respectively, without noxious stimulation. At 0.7 MAC_{BAR} with noxious stimulation, MAP, HR, and PSI were 97 (78, 98) mm Hg, 89 (74, 100) beats/min, and 46 (35, 60), respectively. Individual data points are presented in Figure 1.

The MAP at 1.3 MAC_{BAR} was lower than at 1.0 MAC_{BAR} ($P = .009$) and at 0.7 MAC_{BAR} ($P < .001$). The HRs at 1.3, 1.0, and 0.7 MAC_{BAR} were similar ($P = .379$). The PSI at 1.3 MAC_{BAR} was lower than 1.0 MAC_{BAR} ($P = .003$) and 0.7 MAC_{BAR} ($P < .001$). The PSIs at 1.0 and 0.7 MAC_{BAR} were similar ($P = .095$). Overall, noxious stimulation increased MAP ($P = .001$); however, it did not affect HR ($P = .379$) or PSI ($P = .918$). There was no interaction of MAC_{BAR} multiple with noxious stimulation on MAP, HR, and PSI ($P > .181$), showing that

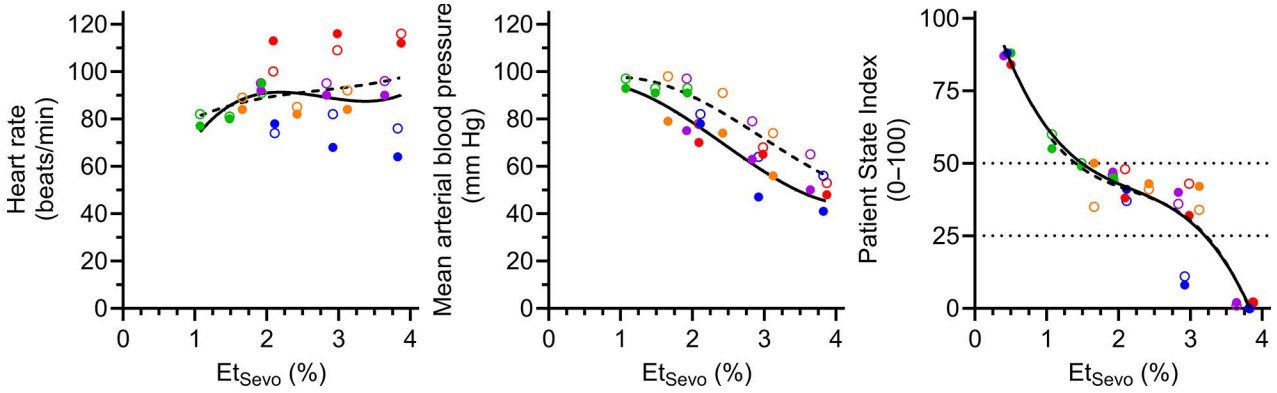

Figure 1—Heart rate, mean arterial blood pressure, and Patient State Index (PSI) variables at different end-tidal sevoflurane concentration (ET_{SEVO}) concentrations. Each color corresponds to a single individual. Open circles represent the variable without the influence of supranoxious stimulation. Closed circles represent the variable under the influence of supranoxious stimulation.

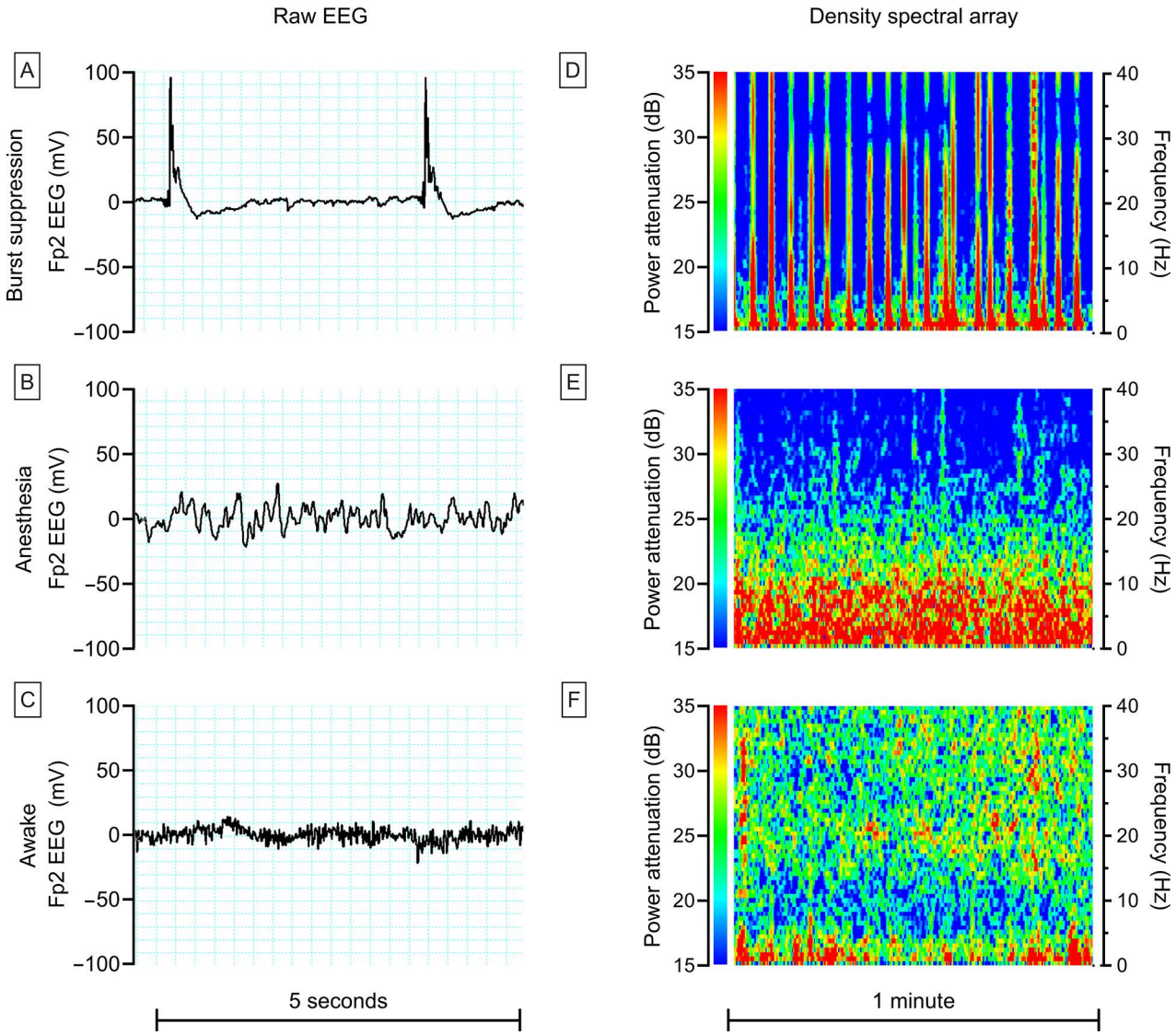

Figure 2—Raw electroencephalograph (EEG) data and its corresponding density spectral array (DSA) for 3 separate states: burst suppression, anesthesia, and awake. Density spectral array shows the direct relationship between power attenuation (dB) and frequency (Hz) though a spectrum of corresponding colors. Fp2 = frontopolar 2.

the effects of noxious stimulation were independent of sevoflurane concentration.

Brief increases in PSI above 50 were not observed at 1.3 MAC_{BAR}, but 2 and 3 dogs experienced short periods of increased PSI at 1.0 and 0.7 MAC_{BAR} **(Supplementary Figure S1)**. One dog had a paradoxical decrease in PSI during noxious stimulation at 0.7 MAC_{BAR} (Supplementary Figure S1).

Figure 2 shows examples of raw EEG and DSA at burst suppression, general anesthesia, and awake state.

In the absence of noxious stimulation, burst suppression was observed in 3 dogs (BRS ranging from 22.6% to 88.2%) at 1.3 MAC_{BAR}, in 1 dog (BSR of 36%) at 1.0 MAC_{BAR}, and in none of the dogs at 0.7 MAC_{BAR}. When there was noxious stimulation, burst suppression was observed in 4 dogs (BRS ranging from 23.5% to 85.6%) at 1.3 MAC_{BAR}, in 1 dog (BSR of 30.5%) at 1.0 MAC_{BAR}, and in none of the dogs at 0.7 MAC_{BAR}. The ET_{SEVO} ED_{50} for burst suppression was 3.15% (2.75, 3.75) as shown in **Figure 3**.

The dogs took 12.7 (9.8, 15.5) minutes from the end of anesthesia to endotracheal extubation with a PSI of 62 (27, 97) and ET_{SEVO} of 0.47% (0.39, 0.55). The PSI 3 minutes after extubation was 87 (85, 89).

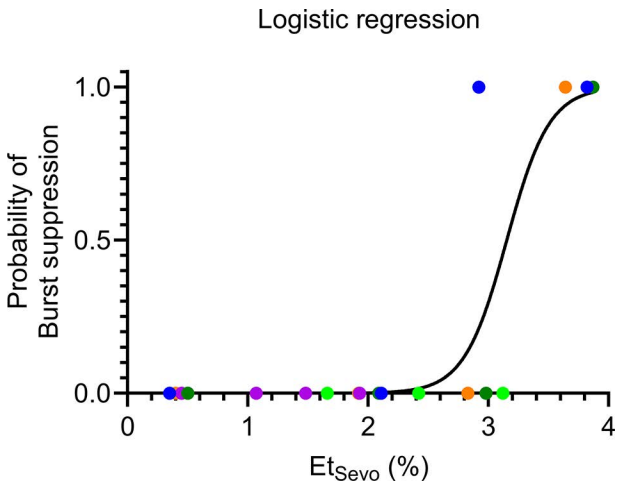

Figure 3—Logistic regression of burst suppression probability as it relates to individual ET_{SEVO}. Each filled-color circle corresponds to a single individual. The effective dose that has 50% probability of burst suppression is an ET_{SEVO} 3.15% ± 0.4% ($P < .001$).

Discussion

The study found that the combination of fentanyl and maropitant did not have a MAC_{BAR}-sparing effect. Additionally, sevoflurane at 1.3 MAC_{BAR} did not prevent the increase in MAP during the second phase of the study even though values above 1.0 MAC_{BAR} successfully blocked the autonomic response in the first phase. This increase occurred without an evident response in EEG variables, such as average PSI, power attenuation on beta-gamma, and increased "heat" on the DSA. The burst suppression seen at higher ET_{SEVO} concentrations was anticipated.

Both fentanyl and maropitant were reported to have a MAC-sparing effect,[9,10,17] contradicting our findings. The authors expected a synergistic MAC-sparing effect of fentanyl and maropitant, but it did not occur, likely due to the primary outcome measured being hemodynamic change versus motor movement. A 15% MAC_{BAR}-sparing effect is reported for maropitant[10] but not fentanyl. After administering fentanyl, the animals experienced lower MAP and HR, which may have influenced our results. The MAP and HR needed to rise by more than 15 mm Hg and 18 beats/min, respectively, to surpass the determined threshold when the animals were not treated with fentanyl and maropitant. However, an increase of just 10 mm Hg or 14 beats/min would suffice to exceed the threshold when the animals received fentanyl and maropitant.

The authors expected that sevoflurane at 1.3 MAC_{BAR} would prevent an autonomic response to noxious stimuli. However, increases in MAP occurred even with animals in burst suppression observed in the raw EEG and DSA. In this study, most dogs at 1.3 and 1.0 MAC_{BAR} were hypotensive (MAP < 60 mm Hg) without noxious stimulation in a dose-dependent manner, similar to what was previously reported.[18]

In this study, noxious stimulation in hypotensive dogs led to an increase in MAP toward normotensive levels (MAP between 60 and 85 mm Hg). Using a sympathetic response to surgical stimulation as a treatment for hypotension is controversial because there are concerns that this approach may increase the risk of intraoperative awareness. However, the average PSI remained below the cutoff of a PSI of 50. An increase in MAP, along with signs of adequate anesthetic depth as measured by EEG, was also observed in humans when propofol was administered for endotracheal intubation.[19] A spectral shift to delta oscillations, an EEG characteristic that indicates appropriate surgical anesthesia depth,[7] was observed in all 6 patients, but 3 had significant hemodynamic changes.[19] In pigs, changes in blood pressure did not predict a positive withdrawal response to a toe pinch.[20] Unfortunately, withdrawal responses were not feasible in this study. This is because a nondepolarizing neuromuscular block was induced with rocuronium administration, an agent that does not affect PSI readings in dogs anesthetized with propofol.[21] This was done to prevent motion artifacts and electromyographic signals from causing artifacts in the EEG readings. These observations raise the question of whether achieving a complete cessation of sympathetic response during clinical anesthesia is beneficial as it may lead to excessive depression of the CNS activity.

The noxious stimuli briefly increased HR, as shown in Supplementary Figure S1, but not enough to raise the average HR, unlike MAP. This suggests that changes in MAP are longer lasting than changes in HR. Additionally, the short increase in HR was not accompanied by similar changes in PSI (Supplementary Figure S1). Likewise, the change in HR did not have a significant predictive value for the motion response to toe pinch in pigs.[20]

The apparent dose-response curve of ET_{SEVO} predicting PSI shown in Figure 2 suggests that this EEG-based monitor can indicate the animal's current brain activity. However, hemodynamic responses occurred even with low PSI values. This differed from the evaluation of the bispectral index (BIS), an EEG-based monitor for anesthetic depth, where a higher BIS value strongly indicated the likelihood of a withdrawal reflex in pigs.[18] Antinociception was tested in dogs anesthetized with propofol and ketamine,[22] and this study showed that higher dosages resulted in lower PSI numbers, which is consistent with this research. However, unlike the study by Ko et al,[22] where lower PSI was linked to higher antinociception, this study did not demonstrate the same pattern. Instead, hemodynamic responses were observed during nociceptive stimulation at high ET_{SEVO} and low PSI. The differences could be due to variations in processing BIS and PSI and methodology for detecting nociception as well as in the antinociception mechanisms of fentanyl and sevoflurane versus propofol and ketamine.

The average PSI was not affected by noxious stimulation. However, brief increases in PSI were observed in some dogs at 1.0 and 0.7 MAC_{BAR} during noxious stimulation, which could indicate arousal. Nevertheless, there was no other evidence that awakening occurred in this study as no significant changes were observed in the DSA. The electrical noxious stimulation was administered within the gamma oscillation frequency band, specifically at 50 Hz, which is associated with an awakened state.[7] This may have caused artifacts during the stimulation, increasing PSI values. The cause for the paradoxical decrease in PSI in 1 dog is unclear. After reviewing the raw EEG, the researchers considered that the algorithm used to calculate the PSI might interpret a high-frequency, low-amplitude waveform as burst suppression. Further research using different pain stimuli can help determine if PSI can be used to prevent arousal during anesthesia.

Burst suppression was more likely to occur at high ET_{SEVO}. Similarly, other studies[23,24] observed burst suppression at 1.5 sevoflurane MAC or higher. The sevoflurane ED_{50} for burst suppression in this study was equivalent to 1.3 MAC_{BAR}. This finding supports avoiding higher ET_{SEVO} for clinical anesthesia as increasing ET_{SEVO} may not reduce the likelihood of hemodynamic response to noxious stimuli but could increase the chance of burst suppression. There are several complications associated with prolonged burst suppression in humans, such as increased mortality,[25,26] cognitive dysfunction,[26,27] and delirium during recovery from anesthesia.[8]

The average PSI was 62 at the time of extubation. Three minutes after extubation, the PSI increased to 87. This suggests progressive arousal, with the latter values being similar to the awake PSI in dogs reported previously, which ranged from 85 to 93.[21,22] The PSI values at extubation in this study were similar to the PSI of 61.5 reported in dogs recovering from IV anesthesia with propofol and ketamine.[22] The dogs were extubated within 16 minutes after the discontinuation of sevoflurane, which is similar to the time it takes for extubation in clinical conditions. At this time, the ET_{SEVO} decreased to 0.47%, similar to the sevoflurane MAC extubation reported when dogs received 36 µg/kg/h of remifentanil.[28]

In conclusion, it is challenging to suppress the autonomic response completely with this anesthetic protocol. At 1.3 and 1.0 MAC_{BAR}, burst suppression occurred. Nevertheless, there were still rises in MAP after noxious stimulation. Variations in HR and MAP were unreliable indicators of anesthetic depth measured by EEG variables.

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The authors have nothing to disclose.

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Supplementary Materials

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