The effect of remifentanil on the minimum alveolar concentration (MAC) and MAC derivatives of sevoflurane in dogs

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ABSTRACT. Remifentanil is an ultra-short-acting \( \mu \)-opioid receptor agonist. The purpose of this study was to determine the relationship of the minimum alveolar concentration (MAC) of sevoflurane and other MAC derivatives, including the MAC for blocking adrenergic responses (MAC-BAR) and the MAC at which tracheal extubation is occurred (MAC-extubation), with or without remifentanil infusion. Six healthy adult beagle dogs were randomly anesthetized three times for determining the MAC-BAR (SEV MAC-BAR), MAC (SEVMAC), and MAC-extubation (SEV MAC-extubation) of sevoflurane under infusion of saline and remifentanil at rates of 0.15, 0.30, 0.60, 1.20, and 2.40 \( \mu \)g/kg/min. The ratio of the SEV MAC-BAR and SEVMAC and that of the SEV MAC-extubation and SEVMAC were not significantly different at baseline and during treatment. The MAC-BAR and MAC decreased in a dose-dependent manner until reaching 1.20 \( \mu \)g/kg/min, and the MAC-extubation decreased in a dose-dependent manner until reaching 0.60 \( \mu \)g/kg/min. The percentage reduction of SEV MAC-BAR, SEVMAC, and SEVMAC-extubation increased in a dose-dependent manner during remifentanil infusion. The heart rate significantly decreased in the MAC-BAR and MAC groups, and the systolic and mean arterial pressures increased after remifentanil infusion compared with the baseline values. Remifentanil infusion caused reduction of the SEV MAC-BAR, SEVMAC, and SEVMAC-extubation in a dose-dependent manner, and ceiling effects were observed in the dogs. Higher doses of remifentanil and sevoflurane were necessary for blocking the sympathetic response to the supramaximal stimulus to prevent movement and extubation in dogs.

KEY WORDS: dog, MAC derivative, minimum alveolar concentration (MAC), remifentanil, sevoflurane

There are several desired components of general anesthesia, including the lack of movement after exposure to a noxious stimulus, muscle relaxation, unconsciousness, and cardiovascular stability, particularly the suppression of the heart rate (HR) and blood pressure responses to noxious stimuli [2]. The minimum alveolar concentration (MAC), which is the alveolar concentration of an inhalation anesthetic preventing movement in 50% of subjects in response to a noxious stimulus, is the standard value used for comparing the potency of inhalation anesthetics [4, 22]. Recently, other MAC derivatives in animals were reported as the MAC for blocking adrenergic responses (MAC-BAR), which is defined as the MAC of volatile anesthetic that blocks autonomic responses to noxious stimulation in 50% of animals [12], and the MAC at which tracheal extubation is occurred (MAC-extubation) in 50% of animals [11]. MAC-extubation is substitute for MAC-awake in humans, which is defined as the MAC to prevent response to a verbal command in 50% of patients, because it is difficult to determine due to the impossibility of obtaining an appropriate response to a verbal command in animals [11].

The use of opioids in anesthetic practice is based on their ability to block sympathetic and somatic responses to noxious stimulation [14]. In previous human studies, the MAC and MAC-BAR were markedly reduced by low fentanyl concentrations [9], but the MAC-awake was not as steep as the MAC, and there was no pronounced ceiling effect of fentanyl [8].

Remifentanil is an ultra-short-acting \( \mu \)-opioid receptor agonist with a unique pharmacokinetic profile and is metabolized by nonspecific tissue and plasma esterases [3]. It has been reported to cause dose-dependent decreases in the MAC of enflurane [14] and isoflurane [16] in dogs. However, the effect of remifentanil on the MAC, MAC-BAR, and MAC-extubation of sevoflurane has not been determined in dogs.

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The purpose of the present study was to determine the relationship of the MAC, MAC-BAR, and MAC-extubation of sevoflurane with or without remifentanil infusion in dogs.

MATERIALS AND METHODS

Animals

Six healthy adult beagle dogs (3 neutered males and 3 neutered females), aged 2.2 ± 0.9 years (mean ± standard deviation [SD]; range, 1.0 to 3.0 years) and weighing 10.8 ± 1.1 kg (mean ± SD; range, 8.6 to 11.8 kg), were included in the study. Physical examinations performed prior to the experiments revealed that all dogs were healthy, and the hematological values were within respective reference limits. The study protocol was approved by the Animal Research Committee of Tottori University, Tottori, Japan.

Experimental design and drug administration

The dogs were randomly anesthetized on three separate occasions for determining the MAC-BAR (SEV\textsubscript{MAC-BAR}), MAC (SEV\textsubscript{MAC}), and MAC-extubation (SEV\textsubscript{MAC-extubation}) of sevoflurane during infusion of saline and remifentanil hydrochloride (Ultiva, Janssen Pharmaceutical K.K., Tokyo, Japan) at rates of 0.15, 0.30, 0.60, 1.20, and 2.40 µg/kg/min. The dogs were divided into the following three groups: MAC-BAR, MAC, and MAC-extubation. Each anesthetic event was separated by at least 4 weeks. Food was withheld for 12 hr prior to anesthesia, but access to water was allowed.

Anesthesia, instrumentation, and monitoring

Anesthesia was induced with sevoflurane (Sevoflo, DS Pharma Animal Health Co., Ltd., Osaka, Japan) delivered via a face mask and a pediatric, semi-closed circle circuit attached to an anesthesia machine (Aestiva 7900, GE Healthcare Japan Corp., Tokyo, Japan) in all dogs. During the induction phase, the vaporizer was adjusted to deliver 7% sevoflurane at an oxygen flow rate of 5 l/min until orotracheal intubation was achieved. Each dog was subsequently intubated with a cuffed endotracheal tube, which incorporated an 8F polyvinyl chloride catheter (Atom Multipurpose Tube, Atom Medical Corp., Tokyo, Japan) that passed to the distal end of the endotracheal tube, and the vaporizer was adjusted to deliver 3% sevoflurane at the oxygen flow rate decreased to 2 l/min. The dogs were positioned in lateral recumbency, and the synchronized intermittent mandatory ventilation, at a constant inspiration to expiration ratio (1:2), was adjusted to achieve a target end-tidal partial pressure of carbon dioxide (ETCO\textsubscript{2}) between 35 and 45 mm Hg. The esophageal temperature was continuously recorded and maintained from 37 to 38°C with a forced warm-air blanket (3M\textsuperscript{TM} Bair Hugger\textsuperscript{TM} Model 775 Patient Warming Unit, 3M Health Care Sales Limited, Tokyo, Japan).

The cephalic vein was catheterized with a 22-gauge catheter (Surflo F&F, Terumo Corp., Tokyo, Japan) for infusion of saline or remifentanil, the jugular vein was catheterized with an 18-gauge catheter (Introcan Safety\textsuperscript{®} 3, B. Braun Aesculap Japan Co., Ltd., Tokyo, Japan) for infusion of lactated Ringer solution (3 mEq/kg/hr), and the dorsal pedal artery was catheterized with a 24-gauge catheter (Surflo F&F, Terumo Corp.). The arterial blood pressure was directly measured with a pressure transducer (DTXPlus\textsuperscript{TM}, Argon Medical Devices Japan K.K., Tokyo, Japan) that was placed and zeroed at the level of the mid-sternum.

A lead II electrocardiogram, HR, systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), peripheral oxygen saturation (SpO\textsubscript{2}) (as measured by pulse oximetry), esophageal temperature, end-tidal sevoflurane concentration (ETSEV), and ETCO\textsubscript{2} were monitored continuously using a veterinary multiparameter monitor (BSM-5132, Nihon Kohden, Tokyo, Japan). The airway gas samples were collected from the distal end of the endotracheal tube at a rate of 200 ml/min. Prior to the experiment, the gas analyzer was calibrated with manufacturer-supplied calibration gases.

Determination of SEV\textsubscript{MAC-BAR}, SEV\textsubscript{MAC}, and SEV\textsubscript{MAC-extubation}

Approximately 60 min after anesthesia induction, the baseline SEV\textsubscript{MAC-BAR}, SEV\textsubscript{MAC}, and SEV\textsubscript{MAC-extubation} were measured. Physiologival saline solution was infused (1 ml/kg/hr) through the cephalic vein until the baseline values were determined. The dogs were allowed to equilibrate for at least 30 min at the ETSEV, 3.0% of MAC-BAR, 2.5% of MAC, or 2.0% of MAC-extubation.

The SEV\textsubscript{MAC-BAR} and SEV\textsubscript{MAC} were determined by judging the response to a noxious stimulus. A supramaximal noxious stimulus (50 V, 50 Hz, 10 msec) was applied by electrical stimulation (SEN-3401, Nihon Kohden, Tokyo, Japan) using two 25-gauge needles that were subcutaneously positioned 5 cm apart in the ulnar region of the forelimb. The stimulation protocol consisted of applying two single stimuli and two continuous stimuli for 3 sec with 5-sec intervals between all stimuli [12, 22]. When the dog showed a positive response before the cycle was completed, the electrical stimulation was stopped. A positive response to the electrical stimulation for determination of the SEV\textsubscript{MAC-BAR} was defined as the increase in the MAP or HR >15% above the value recorded at 1 min prior to applying the electrical stimulation [23]. A positive response to the electrical stimulation to determine the SEV\textsubscript{MAC} was defined as gross purposeful movements including head lifting and repeated limb movement, with the exception of the forelimb that underwent electrical stimulation. A negative response included the lack of head and limb movement, slight paw movement, back arching, chewing, swallowing, blinking, eye opening, and nystagmus [17]. One observer (Y.M.) classified the motor response on all occasions. When a positive response was not detected, the ETSEV was decreased by 20%, and the procedure was repeated after a 15-min period of equilibration until a positive response was achieved. When a positive response was detected, the ETSEV was increased by 10%, and the procedure was repeated after 15 min until the positive response was abolished. The SEV\textsubscript{MAC-BAR} and SEV\textsubscript{MAC} were defined as the mean of the ETSEV values that prevented and did not
prevent the positive response to the noxious stimulus in duplicates, respectively. The HR, SAP, MAP, DAP, ETCO₂, ETSEV, SpO₂, and esophageal temperature were recorded at 1 min prior to applying the electrical stimulation. The parametric variables were calculated as the mean of the values observed at the ETSEV used for determining the SEV counterpart.

The SEVMAC-extubation was determined by judging the response when the tracheal extubation was occurred. A positive response for SEVMAC-extubation was defined as the dog lifting its head or chewing on the endotracheal tube [6, 11]. When a positive response was not detected, the cardiovascular data (HR, SAP, MAP, and DAP), ETCO₂, ETSEV, SpO₂, and esophageal temperature were recorded, the ETSEV was decreased by 10% or 0.1%, and the procedure was repeated after a 15-min equilibration period until positive response was achieved. When a positive response was detected, the dog was manually retained, and the ETSEV was increased 2.0%. The SEVMAC-extubation was defined as the mean of the ETSEV before the positive response occurred and the ETSEV when a positive response was achieved. The parametric variables were calculated as the last values before the positive response occurred.

Remifentanil hydrochloride was infused at rates of 0.15, 0.30, 0.60, 1.20, and 2.40 µg/kg/min via a syringe pump (TOP-551VC, TOP Corp., Tokyo, Japan) through the catheter in the cephalic vein following the determination of the baseline SEVMAC-BAR, SEVMAC, and SEVMAC-extubation. Remifentanil was diluted with saline, and all infusions were delivered at a rate of 1 ml/kg/hr. A 30-min equilibration period was allowed before determining the SEVMAC-BAR, SEVMAC, and SEVMAC-extubation for each infusion rate [16]. The dogs were allowed to equilibrate for 30 min at the previous ETSEV when no positive response was detected. At the end of each experiment, all catheters were removed, 2 mg/kg robenacoxib (Onsior, Elanco Japan K.K., Tokyo, Japan) was administered subcutaneously, and the dogs were allowed to recover from anesthesia.

**Pharmacodynamic analysis**

Probit analysis was performed to estimate the effective dose (ED) of sevoflurane in 50% (ED₅₀) and 95% (ED₉₅) or 5% (ED₅) for blocking adrenergic responses (MAC-BAR₅₀ and MAC-BAR₉₅), for preventing purposeful movement (MAC₅₀ and MAC₉₅), and at which tracheal extubation is occurred (MAC-extubation₅₀ and MAC-extubation₉₅) prior to and during remifentanil infusion (IBM SPSS for Windows version 25.0, SPSS Inc., Chicago, IL, U.S.A.). The probability of 50% lack of response at the MAC-BAR, MAC, and MAC-extubation was defined as the mean of the ETSEV for all independent determinations of the SEV counterpart. Data were subjected to nonlinear least-squares regression analysis, which graphically demonstrated the relationship between the sevoflurane–remifentanil interaction for each ED of sevoflurane and remifentanil infusion.

Simple and sigmoid maximum inhibitory effect models [5] were fitted to the remifentanil infusion rate for the SEVMAC-BAR, SEVMAC, and SEVMAC-extubation data (Prism version 7.00, GraphPad Software, San Diego, CA, U.S.A.). Model equations were as follows:

\[ ED = E₀ - \frac{I_{max} \times D}{ID_{50} + D} \]

\[ ED = E₀ - \frac{I_{max} \times D^{\gamma}}{ID_{50} + D^{\gamma}} \]

for simple and sigmoid maximum inhibitory effect models, respectively. Parameters estimated by the model were \( I_{max} \) (decrease in maximum possible effect), \( ID_{50} \) (remifentanil infusion rate producing 50% of \( I_{max} \)), \( E₀ \) (baseline effect; the effect of sevoflurane alone), \( D \) (remifentanil infusion rate), and \( \gamma \) (sigmoidicity factor). The observation of the residual plot and use of corrected Akaike information criterion (AICc) were used to select the model that best fit the data [7]. The \( ID_{50} \) (remifentanil infusion rate producing 80% of \( I_{max} \)) and \( ID_{90} \) (remifentanil infusion rate producing 90% of \( I_{max} \)) were calculated by the selected models.

Each remifentanil infusion rate was plotted against its percentage reduction of the SEV counterpart. SEVMAC, and SEVMAC-extubation [16]. Simple and sigmoid \( E_{max} \) regression models were fitted to the data. Model equations were as follows:

\[ ED = E_{max} \times D \]

\[ ED = \frac{E_{max} \times D^{\gamma}}{ED_{50} + D^{\gamma}} \]

for simple and sigmoid \( E_{max} \) regression models, respectively. Parameters estimated by the model were \( E_{max} \) (maximum possible reduction), \( ED_{50} \) (remifentanil infusion rate producing 50% of \( E_{max} \)), \( D \) (remifentanil infusion rate), and \( \gamma \) (sigmoidicity factor). The observation of the residual plot and use of AICc were used to select the model that best fit the data [7]. The remifentanil infusion rate at 50% reduction of the SEV counterpart. SEVMAC, and SEVMAC-extubation was calculated by the selected models.

**Statistical analysis**

All data were analyzed using Prism statistical software. The normal distribution of data was verified using the Shapiro–Wilk test. The ETSEV and physiological data were reported as mean ± SD. Repeated one-way analysis of variance measures were used to examine the dose effect for each treatment; percentage reduction of the SEVMAC-BAR, SEVMAC, and SEVMAC-extubation; and the treatment effect at MAC-BAR, MAC, or MAC-extubation. The Bonferroni multiple comparison test was performed to identify
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Table 1. Minimum alveolar concentration of sevoflurane for blocking adrenergic responses (SEV_MAC-BAR), for preventing purposeful movement (SEV_MAC), and at which tracheal extubation is occurred (SEV_MAC-extubation), and the ratios of SEV_MAC-BAR to SEV_MAC and SEV_MAC-extubation to SEVMAC before remifentanil administration (baseline [BL]) and during remifentanil infusion (0.15, 0.30, 0.60, 1.20, and 2.40 µg/kg/min) in six dogs

|                    |                | Remifentanil infusion rate (µg/kg/min) |
|--------------------|----------------|----------------------------------------|
|                    |                | BL 0.15 0.30 0.60 1.20 2.40             |
| SEV_MAC-BAR (%)    |                | 4.48 ± 0.56<sup>a,b</sup> 3.66 ± 0.35<sup>b</sup> 3.16 ± 0.41<sup>b</sup> 2.55 ± 0.35<sup>b</sup> 1.95 ± 0.19<sup>b</sup> 1.48 ± 0.52<sup>b</sup> |
| SEV_MAC (%)        |                | 2.24 ± 0.37<sup>a</sup> 1.58 ± 0.42<sup>a</sup> 1.37 ± 0.30<sup>a</sup> 1.13 ± 0.28<sup>a</sup> 0.89 ± 0.16<sup>a</sup> 0.74 ± 0.22<sup>a</sup> |
| SEV_MAC-extubation (%) |        | 1.13 ± 0.13<sup>b</sup> 0.76 ± 0.09<sup>b</sup> 0.58 ± 0.16<sup>b</sup> 0.42 ± 0.20<sup>b</sup> 0.35 ± 0.18<sup>b</sup> 0.27 ± 0.23<sup>b</sup> |
| SEV_MAC-BAR-to-SEV_MAC ratio | | 2.05 ± 0.47 2.57 ± 0.94 2.46 ± 0.89 2.44 ± 0.87 2.25 ± 0.42 2.08 ± 0.76 |
| SEV_MAC-extubation-to-SEV_MAC ratio | | 0.51 ± 0.08 0.52 ± 0.13 0.45 ± 0.15 0.39 ± 0.18 0.42 ± 0.24 0.40 ± 0.39 |

Data are shown as the mean ± standard deviation. Within a each treatment, values differ significantly from the baseline value (a: P<0.05). Value differs significantly from the SEV_MAC (b: P<0.05). Value differs significantly from the SEV_MAC-extubation (c: P<0.05).

Table 2. Effective dose of sevoflurane in 50% (ED<sub>50</sub>) and 95% (ED<sub>95</sub>) or 5% (ED<sub>5</sub>) of the end tidal sevoflurane (ETSEV) for blocking adrenergic responses (MAC-BAR<sub>50</sub> and MAC-BAR<sub>95</sub>), for preventing purposeful movement (MAC<sub>50</sub> and MAC<sub>95</sub>), and at which tracheal extubation is occurred (MAC-extubation<sub>50</sub> and MAC-extubation<sub>95</sub>) with confidence intervals (CI) before remifentanil administration (baseline [BL]) and during remifentanil infusion (0.15, 0.30, 0.60, 1.20, and 2.40 µg/kg/min) in six dogs

|                    |                | Remifentanil infusion rate (µg/kg/min) |
|--------------------|----------------|----------------------------------------|
|                    |                | BL 0.15 0.30 0.60 1.20 2.40             |
| ETSEV (%) 95% CI   |                | MAC-BAR<sub>50</sub> 5.34 5.21–5.51 4.26 4.16–4.40 3.95 3.84–4.10 3.17 3.07–3.30 2.26 2.20–2.35 2.32 2.19–2.49 |
| ETSEV (%) 95% CI   |                | MAC-BAR<sub>95</sub> 4.48 4.41–4.55 3.66 3.61–3.72 3.16 3.09–3.23 2.56 2.50–2.62 1.95 1.91–1.99 1.47 1.40–1.54 |
| ETSEV (%) 95% CI   |                | MAC<sub>50</sub> 2.85 2.75–2.97 2.26 2.14–2.41 1.87 1.77–2.01 1.59 1.49–1.72 1.16 1.09–1.27 1.11 1.03–1.24 |
| ETSEV (%) 95% CI   |                | MAC<sub>95</sub> 2.25 2.18–2.30 1.58 1.51–1.64 1.37 1.32–1.43 1.14 1.08–1.19 0.89 0.85–0.93 0.73 0.67–0.78 |
| ETSEV (%) 95% CI   |                | MAC-extubation<sub>50</sub> 1.34 1.27–1.51 0.95 0.89–1.09 0.85 0.76–1.08 0.68 0.59–0.88 0.64 0.55–0.82 0.69 0.55–1.06 |
| ETSEV (%) 95% CI   |                | MAC-extubation<sub>95</sub> 1.13 1.07–1.18 0.78 0.73–0.83 0.59 0.53–0.65 0.38 0.32–0.45 0.35 0.28–0.41 0.26 0.16–0.34 |

The SEV_MAC-BAR, SEV_MAC, and SEV_MAC-extubation during remifentanil infusion decreased significantly compared with the baseline values (Table 1). The baseline SEV_MAC-BAR value was significantly higher than the baseline SEV_MAC value and the baseline SEV_MAC-extubation value, and the baseline SEV_MAC value was significantly higher than the baseline SEV_MAC-extubation value. Similar results were obtained for each treatment except during remifentanil infusion at 2.40 µg/kg/min. The ratio of the SEV_MAC-BAR and SEV_MAC and that of the SEV_MAC-extubation and SEVMAC were not significantly different at baseline and during treatment. According to probit analysis, the ED<sub>50</sub> and ED<sub>95</sub> or ED<sub>5</sub> of the ETSEV in the MAC-BAR, MAC, and MAC-extubation groups are presented in Table 2. The MAC-BAR<sub>50</sub> and MAC<sub>50</sub> decreased in a dose-dependent manner until reaching 1.20 µg/kg/min, whereas the MAC-extubation<sub>50</sub> decreased in a dose-dependent manner until reaching 0.60 µg/kg/min. The relationship between sevoflurane and remifentanil at the ED<sub>50</sub> and ED<sub>95</sub> or ED<sub>5</sub> of the ETSEV in the MAC-BAR, MAC, and MAC-extubation groups is shown in Fig. 1.

A simple inhibitory model was best fitted for the remifentanil dose with the SEV_MAC-BAR, SEV_MAC, and SEV_MAC-extubation data by AICc. The pharmacodynamic parameters are presented in Table 3.

The percentage reduction of SEV_MAC-BAR, SEV_MAC, and SEV_MAC-extubation increased in a dose-dependent manner during remifentanil infusion (Table 4). A simple E_max regression model was best fitted for remifentanil dose for SEV_MAC-BAR (Fig. 2A), SEV_MAC (Fig. 2B), and SEV_MAC-extubation (Fig. 2C) reduction data by AICc. The pharmacodynamic parameters are presented in Table 5.

The HR during remifentanil infusion in the MAC-BAR group significantly decreased compared with the baseline value. Also, the HR during remifentanil infusion at 1.20 and 2.40 µg/kg/min in the MAC group significantly decreased compared with the baseline value (Table 6). The HR during remifentanil infusion at 1.20 and 2.40 µg/kg/min in the MAC-BAR group were significantly higher than those in the MAC or MAC-extubation groups.

The SAP during remifentanil infusion at 1.20 and 2.40 µg/kg/min in the MAC-BAR and MAC groups and the value during remifentanil infusion at 2.40 µg/kg/min in the MAC-extubation group significantly increased compared with the baseline values.

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The baseline SAP in the MAC-BAR group was significantly lower than the baseline values in the MAC or MAC-extubation groups. Similar results were obtained for each treatment except during remifentanil infusion at 2.40 µg/kg/min. The MAP during remifentanil infusion at 2.40 µg/kg/min in the MAC-BAR and MAC groups significantly increased compared with the baseline values. The baseline MAP in the MAC-BAR group was significantly lower than the baseline values in the MAC and MAC-extubation groups. Similar results were obtained for each treatment except during remifentanil infusion at 2.40 µg/kg/min. The baseline DAP value in the MAC-BAR group was significantly lower than the baseline values in the MAC and MAC-extubation groups.

Fig. 1. Relationship of the effective dose (ED) of sevoflurane in 50% (ED50) and 95% (ED95) or 5% (ED5) of the end-tidal sevoflurane concentration for blocking adrenergic responses (MAC-BAR50 and MAC-BAR95), for preventing purposeful movement (MAC50 and MAC95), and at which tracheal extubation is occurred (MAC-extubation50 and MAC-extubation5) with or without remifentanil infusion in six dogs.

Table 3. Pharmacodynamic parameters for remifentanil infusion rate (Remi)-minimum alveolar concentration of sevoflurane for blocking adrenergic responses (SEV MAC-BAR), for preventing purposeful movement (SEV MAC), and at which tracheal extubation is occurred (SEV MAC-extubation) data with confidence intervals (CI) in six dogs

| Variable | SEV MAC-BAR | SEV MAC | SEV MAC-extubation |
|----------|-------------|----------|-------------------|
|          | ETSEV (%) | 95% CI   | ETSEV (%) | 95% CI   | ETSEV (%) | 95% CI   |
| E0       | 4.47       | 4.17–4.79 | 2.23      | 1.99–2.47 | 1.13      | 0.99–1.26 |
| Imax     | 3.66       | 3.10–4.34 | 1.62      | 1.28–1.98 | 0.94      | 0.75–1.13 |
| ID50     | 0.54       | 0.32–0.97 | 0.25      | 0.12–0.57 | 0.22      | 0.11–0.45 |
| ID80     | 2.14       | 1.27–3.88 | 1.01      | 0.47–2.29 | 0.88      | 0.43–1.79 |
| ID90     | 4.83       | 2.87–8.73 | 2.28      | 1.05–5.16 | 1.97      | 0.97–4.02 |

E0: baseline effect (the effect of sevoflurane alone), Imax: decrease in maximum possible effect, ID50: remifentanil infusion rate producing 50% of Imax, ID80: remifentanil infusion rate producing 80% of Imax, ID90: remifentanil infusion rate producing 90% of Imax.

Table 4. Percentage reduction of sevoflurane for blocking adrenergic responses (SEV MAC-BAR), for preventing purposeful movement (SEV MAC), and at which tracheal extubation is occurred (SEV MAC-extubation) during remifentanil infusion (0.15, 0.30, 0.60, 1.20, and 2.40 µg/kg/min) in six dogs

| Remifentanil infusion rate (µg/kg/min) | SEV MAC-BAR reduction (%) | SEV MAC reduction (%) | SEV MAC-extubation reduction (%) |
|----------------------------------------|---------------------------|-----------------------|----------------------------------|
| 0.15                                   | 18.0 ± 6.1 c)             | 28.5 ± 13.9           | 42.3 ± 10.8 c, d)                |
| 0.30                                   | 30.5 ± 8.9 c)             | 39.0 ± 8.9            | 49.9 ± 8.8 c, d)                 |
| 0.60                                   | 47.9 ± 14.5 c)            | 63.2 ± 16.4           | 69.1 ± 14.7 b, c)                |
| 1.20                                   | 55.8 ± 9.0 b)             | 65.5 ± 15.8 b, c)     | 76.0 ± 20.8 a)                   |
| 2.40                                   | 60.2 ± 5.9 b)             | 67.2 ± 6.3 b, c)      | 76.0 ± 20.8 a)                   |

Data are shown as the mean ± standard deviation. Within a each treatment, values differ significantly from the 0.15 (a: P<0.05), 0.30 (b: P<0.05), and 0.60 µg/kg/min (c: P<0.05) infusion of remifentanil. Value differs significantly from the SEV MAC-extubation reduction (d: P<0.05).

The baseline SAP in the MAC-BAR group was significantly lower than the baseline values in the MAC or MAC-extubation groups. Similar results were obtained for each treatment except during remifentanil infusion at 2.40 µg/kg/min. The MAP during remifentanil infusion at 2.40 µg/kg/min in the MAC-BAR and MAC groups significantly increased compared with the baseline values. The baseline MAP in the MAC-BAR group was significantly lower than the baseline values in the MAC and MAC-extubation groups. Similar results were obtained for each treatment except during remifentanil infusion at 2.40 µg/kg/min. The baseline DAP value in the MAC-BAR group was significantly lower than the baseline values in the MAC and MAC-extubation groups.
There were no significant differences between the baseline values of $\text{SpO}_2$, $\text{ETCO}_2$, and esophageal temperature in all three groups.

DISCUSSION

The results of the present study indicated that remifentanil caused a reduction in the SEV$_{\text{MAC-BAR}}$, SEV$_{\text{MAC}}$, and SEV$_{\text{MAC-extubation}}$ in healthy dogs. To the best of our knowledge, this is the first study to report the relationship of MAC-BAR, MAC, and MAC-extubation of sevoflurane during remifentanil infusion in dogs.

Our study revealed that the baseline SEV$_{\text{MAC-BAR}}$, SEV$_{\text{MAC}}$, and SEV$_{\text{MAC-extubation}}$ values were $4.48 \pm 0.56$, $2.24 \pm 0.37$, and $1.13 \pm 0.13\%$, respectively. The baseline SEV$_{\text{MAC}}$, SEV$_{\text{MAC-extubation}}$, and SEV$_{\text{MAC}}$ to SEV$_{\text{MAC-extubation}}$ ratio were approximately...
with fentanyl may have a more potent sedative effect. However, our data revealed that the ID50, ID80, and 50% reduction dose of remifentanil for the SEVMAC-BAR were higher than those for the SEVMAC and SEVMAC-extubation. Therefore, higher dose of remifentanil may be needed to decrease the MAC-BAR of sevoflurane compared with MAC and MAC-extubation in dogs, unlike humans.

Our results indicated that MAC-BAR50, MAC80, and MAC-extubation5 were 5.34, 2.85, and 1.34% under sevoflurane alone. The MAC-BAR50 and MAC80 decreased to 2.3 and 1.2% until reaching remifentanil infusion rates at 1.20 µg/kg/min, otherwise, the MAC-extubation5 decreased to 0.6% until reaching remifentanil infusion rates at 0.60 µg/kg/min. These results showed that higher

| HR (beats/min) | Remifentanil infusion rate (µg/kg/min) |
|---------------|--------------------------------------|
|               | BL 0.15 0.30 0.60 1.20 2.40           |
| MAC-BAR       | 115.0 ± 9.6 98.1 ± 12.3 94.9 ± 10.0 91.5 ± 10.9 89.0 ± 13.6 84.8 ± 15.0 |
| MAC           | 102.6 ± 19.8 82.2 ± 15.8 79.1 ± 16.6 75.4 ± 18.5 69.0 ± 13.4 65.0 ± 15.2 |
| MAC-extubation| 93.0 ± 21.9 84.8 ± 26.4 76.2 ± 23.8 68.2 ± 17.8 66.7 ± 13.5 62.0 ± 11.0 |
| SAP (mmHg)    | 82.7 ± 10.8 84.4 ± 9.3 89.5 ± 7.9 95.7 ± 12.7 103.4 ± 14.0 116.0 ± 12.0 |
| MAC           | 103.3 ± 7.4 105.3 ± 9.4 111.0 ± 9.5 116.9 ± 10.1 125.3 ± 15.2 132.7 ± 16.4 |
| MAC-extubation| 118.8 ± 16.8 113.5 ± 9.1 125.5 ± 13.7 131.3 ± 19.6 137.0 ± 17.2 145.8 ± 13.8 |
| MAP (mmHg)    | 62.7 ± 7.0 61.4 ± 6.2 64.8 ± 5.2 69.5 ± 9.1 74.5 ± 10.7 83.9 ± 9.7 |
| MAC           | 79.0 ± 7.3 78.4 ± 10.2 80.1 ± 11.7 85.5 ± 10.0 91.7 ± 13.6 95.7 ± 14.9 |
| MAC-extubation| 95.0 ± 11.2 84.2 ± 15.3 91.0 ± 17.1 95.5 ± 16.9 102.8 ± 16.3 107.3 ± 18.8 |
| DAP (mmHg)    | 53.5 ± 5.8 51.2 ± 4.9 53.8 ± 4.1 56.6 ± 8.4 60.3 ± 9.0 68.3 ± 9.4 |
| MAC           | 65.0 ± 6.9 63.0 ± 9.3 62.9 ± 8.8 66.7 ± 9.4 70.4 ± 10.9 74.0 ± 10.3 |
| MAC-extubation| 80.0 ± 9.1 68.6 ± 15.8 71.3 ± 16.6 73.8 ± 15.4 82.3 ± 14.2 84.0 ± 19.0 |
| SpO2 (%)      | 98.6 ± 0.4 98.9 ± 0.3 99.0 ± 0.5 99.3 ± 0.5 99.1 ± 0.4 99.3 ± 0.5 |
| MAC           | 99.0 ± 0.8 98.9 ± 0.9 99.3 ± 1.0 99.6 ± 0.6 99.5 ± 0.4 99.6 ± 0.4 |
| MAC-extubation| 98.7 ± 0.8 98.7 ± 0.8 98.7 ± 1.2 99.7 ± 0.5 99.7 ± 0.5 99.3 ± 0.8 |
| ETCO2 (mmHg)  | 41.0 ± 1.2 39.9 ± 2.0 39.9 ± 0.6 41.8 ± 1.0 41.5 ± 1.8 38.8 ± 2.0 |
| MAC           | 41.0 ± 1.6 41.0 ± 1.5 41.1 ± 1.9 40.8 ± 1.4 40.6 ± 1.1 40.0 ± 2.1 |
| MAC-extubation| 41.7 ± 3.3 41.0 ± 2.1 40.7 ± 2.0 40.7 ± 2.1 40.0 ± 2.1 40.8 ± 2.6 |
| Temperature (°C) | MAC-BAR 37.4 ± 0.3 37.5 ± 0.2 37.4 ± 0.3 37.5 ± 0.2 37.5 ± 0.3 37.7 ± 0.2 |
| MAC           | 37.3 ± 0.1 37.3 ± 0.1 37.4 ± 0.2 37.3 ± 0.2 37.4 ± 0.2 37.5 ± 0.2 |
| MAC-extubation| 37.6 ± 0.3 37.4 ± 0.2 37.6 ± 0.3 37.5 ± 0.2 37.6 ± 0.2 37.4 ± 0.3 |

Data are shown as the mean ± standard deviation. Within a each treatment, values differ significantly from the the baseline value (a: P<0.05). Value differs significantly from the MAC value (b: P<0.05). Value differs significantly from the MAC-extubation value (c: P<0.05).
dose of sevoflurane was necessary to block adrenergic responses to supramaximal stimulation to prevent movement and extubation. In the present study, the HR significantly decreased in the MAC-BAR and MAC groups, and the SAP and MAP increased after remifentanil infusion compared with the baseline values, which were consistent with previous reports on isoflurane–remifentanil anesthesia [15, 16]. In the MAC-BAR group, the HR was higher, and the SAP and MAP were lower than those in the MAC and MAC-extubation groups. Remifentanil produces bradycardia via its central vagotonic effect and by stimulating µ-opioid receptors presumably in the peripheral nervous and cardiovascular systems [19]. In addition, remifentanil has been reported to increase the plasma concentrations of vasopressin and the systemic vascular resistance index in dogs [15]. Vasopressin is known to cause vasoconstriction via the V1 receptor [21]. However, sevoflurane causes a dose-dependent vasodilator action and an increase in the HR via the baroreceptor reflex [18]. Therefore, in our study, the difference in the HR and blood pressure between the MAC-BAR and the MAC and MAC-extubation groups can be attributed to the sevoflurane requirement, vagal stimulation after remifentanil, and baroreceptor reflex.

In conclusion, remifentanil caused a reduction in the MAC-BAR, MAC, and MAC-extubation of sevoflurane in a dose-dependent manner, and ceiling effects were observed in the dogs. Higher doses of remifentanil and sevoflurane were required for blocking the sympathetic response to the supramaximal stimuli to prevent movement and extubation in dogs.

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