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Surgery

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 μ-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 ($SEV_{MAC\text{-}BAR}$), MAC (SEV_{MAC}), and MAC- extubation ($SEV_{MAC\text{-}extubation}$) of sevoflurane under infusion of saline and remifentanil at rates of 0.15, 0.30, 0.60, 1.20, and 2.40 μg/kg/min. The ratio of the $SEV_{MAC\text{-}BAR}$ and SEV_{MAC} and that of the $SEV_{MAC\text{-}extubation}$ and SEV_{MAC} were not significantly different at baseline and during treatment. The $MAC\text{-}BAR_{95}$ and MAC_{95} decreased in a dose-dependent manner until reaching 1.20 μg/kg/min, and the $MAC\text{-}extubation_5$ decreased in a dose-dependent manner until reaching 0.60 μg/kg/min. The percentage reduction of $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ 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

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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 μ-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 ($SEV_{MAC\text{-}BAR}$), MAC (SEV_{MAC}), and MAC-extubation ($SEV_{MAC\text{-}extubation}$) 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 reduced 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 ($ETCO_2$) 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™ Bair Hugger™ 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® 3, B. Braun Aesculap Japan Co., Ltd., Tokyo, Japan) for infusion of lactated Ringer solution (3 ml//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™, 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_2) (as measured by pulse oximetry), esophageal temperature, end-tidal sevoflurane concentration (ETSEV), and $ETCO_2$ 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 m*l*/min. Prior to the experiment, the gas analyzer was calibrated with manufacturer-supplied calibration gases.

Determination of $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$

Approximately 60 min after anesthesia induction, the baseline $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ were measured. Physiological saline solution was infused (1 m*l*/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 $SEV_{MAC\text{-}BAR}$ and SEV_{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 $SEV_{MAC\text{-}BAR}$ 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_{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 $SEV_{MAC\text{-}BAR}$ and SEV_{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, $ETCO_2$, ETSEV, SpO_2, 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 $SEV_{MAC\text{-}BAR}$ and SEV_{MAC}.

The $SEV_{MAC\text{-}extubation}$ was determined by judging the response when the tracheal extubation was occurred. A positive response for $SEV_{MAC\text{-}extubation}$ 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), $ETCO_2$, ETSEV, SpO_2, 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 $SEV_{MAC\text{-}extubation}$ 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$. Remifentanil was diluted with saline, and all infusions were delivered at a rate of 1 m*l*/kg/hr. A 30-min equilibration period was allowed before determining the $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ 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% (ED_{50}) and 95% (ED_{95}) or 5% (ED_5) for blocking adrenergic responses ($MAC\text{-}BAR_{50}$ and $MAC\text{-}BAR_{95}$), for preventing purposeful movement (MAC_{50} and MAC_{95}), and at which tracheal extubation is occurred ($MAC\text{-}extubation_{50}$ and $MAC\text{-}extubation_5$) 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$. 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ data (Prism version 7.00, GraphPad Software, San Diego, CA, U.S.A.). Model equations were as follows:

$$E_D = E_0 - \frac{I_{max} \times D}{ID_{50} + D}$$

$$E_D = E_0 - \frac{I_{max} \times D^{\gamma}}{ID_{50}^{\gamma} + D^{\gamma}}$$

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}), E_0 (baseline effect; the effect of sevoflurane alone), D (remifentanil infusion rate), and γ (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_{80} (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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ [16]. Simple and sigmoid E_{max} regression models were fitted to the data. Model equations were as follows:

$$E_D = \frac{E_{max} \times D}{ED_{50} + D}$$

$$E_D = \frac{E_{max} \times D^{\gamma}}{ED_{50}^{\gamma} + D^{\gamma}}$$

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 γ (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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$; and the treatment effect at MAC-BAR, MAC, or MAC-extubation. The Bonferroni multiple comparison test was performed to identify

Table 1. Minumum 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 SEV_{MAC} 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
$SEV_{MAC-BAR}$ (%)	$4.48 \pm 0.56^{b,c)}$	$3.66 \pm 0.35^{a, b, c)}$	$3.16 \pm 0.41^{a, b, c)}$	$2.55 \pm 0.35^{a, b, c)}$	$1.95 \pm 0.19^{a, b, c)}$	$1.48 \pm 0.52^{a, c)}$
SEV_{MAC} (%)	$2.24 \pm 0.37^{c)}$	$1.58 \pm 0.42^{a, c)}$	$1.37 \pm 0.30^{a, c)}$	$1.13 \pm 0.28^{a, c)}$	$0.89 \pm 0.16^{a, c)}$	$0.74 \pm 0.22^{a)}$
$SEV_{MAC-extubaion}$ (%)	$1.13 \pm 0.13^{b)}$	$0.76 \pm 0.09^{a, b)}$	$0.58 \pm 0.16^{a, b)}$	$0.42 \pm 0.20^{a, b)}$	$0.35 \pm 0.18^{a, b)}$	$0.27 \pm 0.23^{a)}$
$SEV_{MAC-BAR}$-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 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_{50}) and 95% (ED_{95}) or 5% (ED_5) of the end tidal sevoflurane (ETSEV) for blocking adrenergic responses ($MAC\text{-}BAR_{50}$ and $MAC\text{-}BAR_{95}$), for preventing purposeful movement (MAC_{50} and MAC_{95}), and at which tracheal extubation is occurred ($MAC\text{-}extubation_{50}$ and $MAC\text{-}extubation_5$) 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	ETSEV (%)	95% CI	ETSEV (%)	95% CI	ETSEV (%)	95% CI	ETSEV (%)	95% CI	ETSEV (%)	95% CI
$MAC\text{-}BAR_{95}$	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
$MAC\text{-}BAR_{50}$	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
MAC_{95}	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
MAC_{50}	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
$MAC\text{-}extuabion_5$	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
$MAC\text{-}extubation_{50}$	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

differences in the baseline values for each treatment and determine the overall comparison of percentage reduction and among groups. $P<0.05$ was considered statistically significant.

RESULTS

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 SEV_{MAC} were not significantly different at baseline and during treatment.

According to probit analysis, the ED_{50} and ED_{95} or ED_5 of the ETSEV in the MAC-BAR, MAC, and MAC-extubation groups are presented in Table 2. The $MAC\text{-}BAR_{95}$ and MAC_{95} decreased in a dose-dependent manner until reaching 1.20 μg/kg/min, whereas the $MAC\text{-}extubation_5$ decreased in a dose-dependent manner until reaching 0.60 μg/kg/min. The relationship between sevoflurane and remifentanil at the ED_{50} and ED_{95} or ED_5 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.

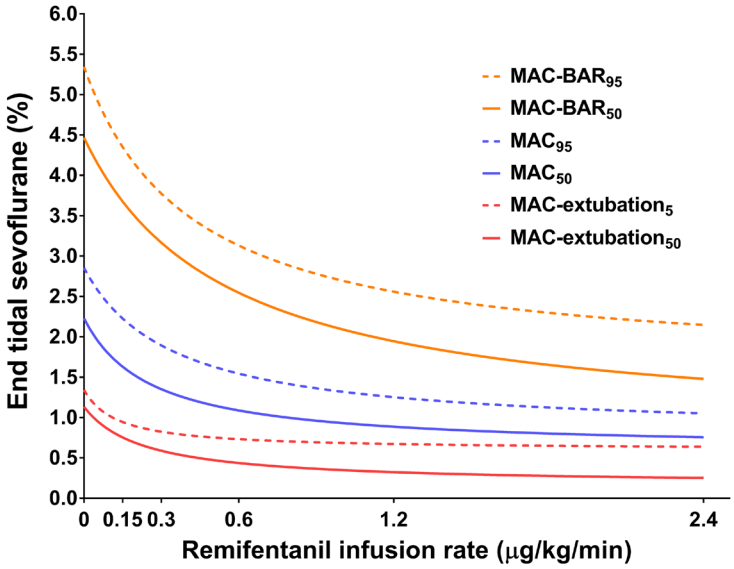

Fig. 1. Relationship of the effective dose (ED) of sevoflurane in 50% (ED_{50}) and 95% (ED_{95}) or 5% (ED_5) of the end-tidal sevoflurane concentration for blocking adrenergic responses ($MAC\text{-}BAR_{50}$ and $MAC\text{-}BAR_{95}$), for preventing purposeful movement (MAC_{50} and MAC_{95}), and at which tracheal extubation is occurred ($MAC\text{-}extubation_{50}$ and $MAC\text{-}extubation_5$) with or without remifentanil infusion in six dogs.

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

Variable	$SEV_{MAC\text{-}BAR}$		SEV_{MAC}		$SEV_{MAC\text{-}extubation}$	
	ETSEV (%)	95% CI	ETSEV (%)	95% CI	ETSEV (%)	95% CI
E_0	4.47	4.17–4.79	2.23	1.99–2.47	1.13	0.99–1.26
I_{max}	3.66	3.10–4.34	1.62	1.28–1.98	0.94	0.75–1.13
	Remi (μg/kg/min)	95% CI	Remi (μg/kg/min)	95% CI	Remi (μg/kg/min)	95% CI
ID_{50}	0.54	0.32–0.97	0.25	0.12–0.57	0.22	0.11–0.45
ID_{80}	2.14	1.27–3.88	1.01	0.47–2.29	0.88	0.43–1.79
ID_{90}	4.83	2.87–8.73	2.28	1.05–5.16	1.97	0.97–4.02

E_0: baseline effect (the effect of sevoflurane alone), I_{max}: decrease in maximum possible effect, ID_{50}: remifentanil infusion rate producing 50% of Imax, ID_{80}: remifentanil infusion rate producing 80% of I_{max}, ID_{90}: remifentanil infusion rate producing 90% of I_{max}.

Table 4. Percentage reduction of sevoflurane for blocking adrenergic responses ($SEV_{MAC\text{-}BAR}$), for preventing purposeful movement (SEV_{MAC}), and at which tracheal extubation is occurred ($SEV_{MAC\text{-}extubation}$) 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)				
	0.15	0.30	0.60	1.20	2.40
$SEV_{MAC\text{-}BAR}$ reduction (%)	18.0 ± 6.1[c)]	28.5 ± 13.9	42.3 ± 10.8[a, d)]	55.8 ± 9.0[a, b)]	65.5 ± 15.8[a, b, c)]
SEV_{MAC} reduction (%)	30.5 ± 8.9[c)]	39.0 ± 8.9	49.9 ± 8.8[a, d)]	60.2 ± 5.9[a, b)]	67.2 ± 6.3[a, b, c)]
$SEV_{MAC\text{-}extubation}$ reduction (%)	32.0 ± 9.1	47.9 ± 14.5[c)]	63.2 ± 16.4[b)]	69.1 ± 14.7[a, b)]	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 $SEV_{MAC\text{-}extubation}$ 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.

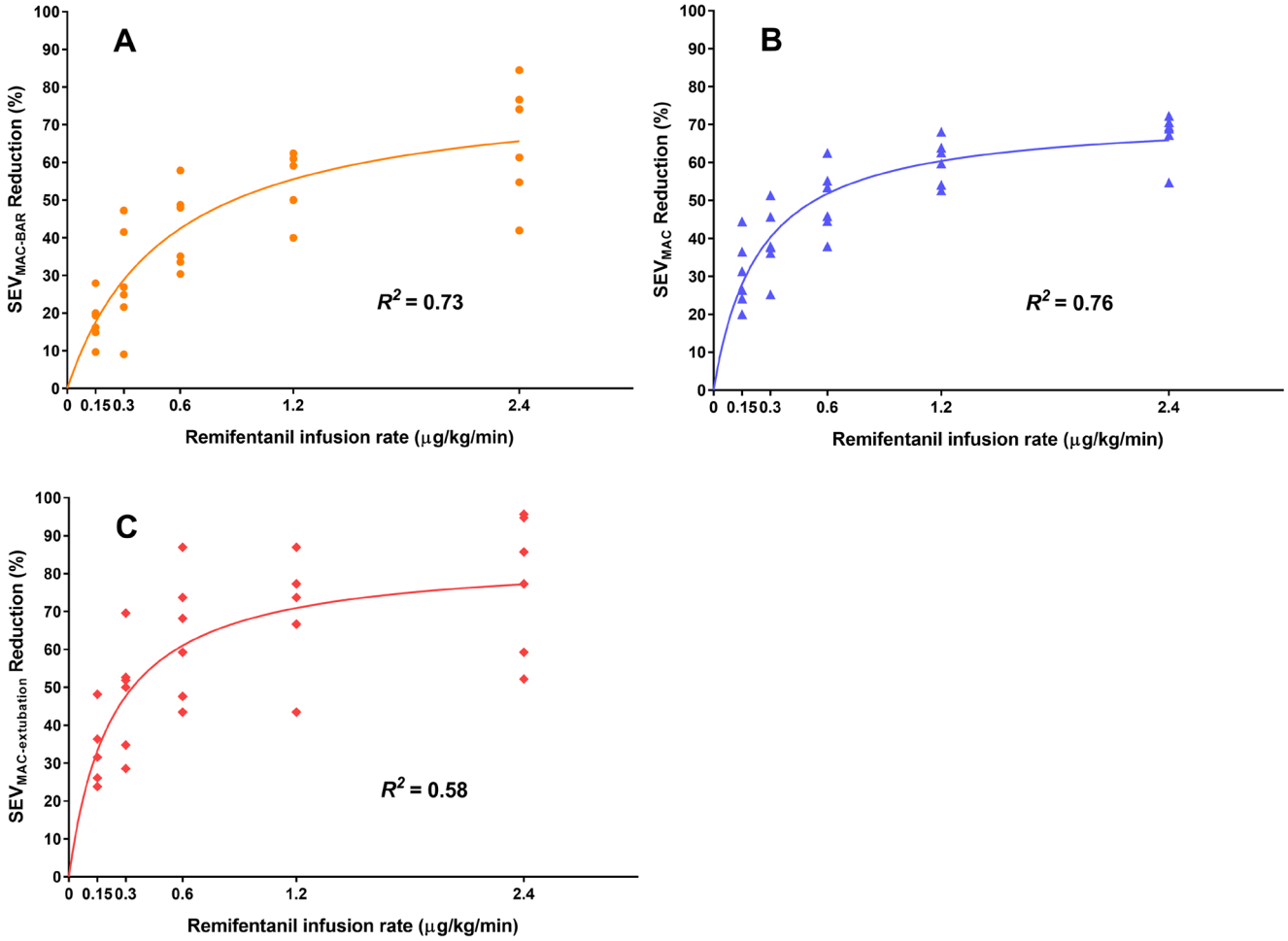

Fig. 2. Relationship between the remifentanil infusion rate and percentage reduction in the $SEV_{MAC\text{-}BAR}$ (A), SEV_{MAC} (B), and $SEV_{MAC\text{-}extubation}$ (C) data in six dogs.

Table 5. Pharmacodynamic parameters for remifentanil infusion rate (Remi)-minumum alveolar concentration of sevoflurane for blocking adrenergic responses ($SEV_{MAC\text{-}BAR}$), for preventing purposeful movement (SEV_{MAC}), and at which tracheal extubation is occurred ($SEV_{MAC\text{-}extubation}$) reduction data with confidence intervals (CI) in six dogs

Variable	$SEV_{MAC\text{-}BAR}$		SEV_{MAC}		$SEV_{MAC\text{-}extubation}$	
	$SEV_{MAC\text{-}BAR}$ reduction (%)	95% CI	SEV_{MAC} reduction (%)	95% CI	$SEV_{MAC\text{-}extubation}$ reduction (%)	95% CI
E_{max}	80.3	64.1–96.5	72.5	65.1–79.8	84.7	71.7–98.1
	Remi (μg/kg/min)	95% CI	Remi (μg/kg/min)	95% CI	Remi (μg/kg/min)	95% CI
ED_{50}	0.53	0.24–0.83	0.24	0.15–0.33	0.23	0.10–0.37
50% reduction	0.88	0.68–1.16	0.53	0.43–0.66	0.34	0.23–0.46

E_{max}: maximum possible reduction, ED_{50}: remifentanil infusion rate producing 50% of E_{max}, 50% reduction: remifentanil infusion rate producing 50% $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ reduction.

There were no significant differences between the baseline values of SpO_2, $ETCO_2$, and esophageal temperature in all three groups.

DISCUSSION

The results of the present study indicated that remifentanil caused a reduction in the $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ 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 $SEV_{MAC\text{-}BAR}$, SEV_{MAC}, and $SEV_{MAC\text{-}extubation}$ values were 4.48 ± 0.56, 2.24 ± 0.37, and 1.13 ± 0.13%, respectively. The baseline SEV_{MAC}, $SEV_{MAC\text{-}extubation}$, and SEV_{MAC} to $SEV_{MAC\text{-}extubation}$ ratio were approximately

Table 6. Heart rate (HR), systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DAP), peripheral oxygen saturation (SpO_2), end tidal partial pressure of carbon dioxide ($ETCO_2$), and esophageal temparature in minumum alveolar concentration for blocking adrenergic responses (MAC-BAR), for preventing purposeful movement (MAC), and at which tracheal extubation is occured (MAC-extubation) groups 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
HR (beats/min)						
MAC-BAR	115.0 ± 9.6	98.1 ± 12.3[a)]	94.9 ± 10.0[a)]	91.5 ± 10.9[a, c)]	89.0 ± 13.6[a, b, c)]	84.8 ± 15.0[a, c)]
MAC	102.6 ± 19.8	82.2 ± 15.8	79.1 ± 16.6	75.4 ± 18.5	69.0 ± 13.4[a)]	65.0 ± 15.2[a)]
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)						
MAC-BAR	82.7 ± 10.8[b, c)]	84.4 ± 9.3[b, c)]	89.5 ± 7.9[b, c)]	95.7 ± 12.7[b, c)]	103.4 ± 14.0[a, b, c)]	116.0 ± 12.0[a, c)]
MAC	103.3 ± 7.4	105.3 ± 9.4	111.0 ± 9.5	116.9 ± 10.1	125.3 ± 15.2[a)]	132.7 ± 16.6[a)]
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[a)]
MAP (mmHg)						
MAC-BAR	62.7 ± 7.0[b, c)]	61.4 ± 6.2[b, c)]	64.8 ± 5.2[b, c)]	69.5 ± 9.1[b, c)]	74.5 ± 10.7[b, c)]	83.9 ± 9.7[a)]
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[a)]
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)						
MAC-BAR	53.5 ± 5.8[b, c)]	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	66.8 ± 15.8	71.3 ± 16.6	73.8 ± 15.4	82.3 ± 14.2	84.0 ± 19.0
SpO_2 (%)						
MAC-BAR	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
$ETCO_2$ (mmHg)						
MAC-BAR	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
Esophageal 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: $P<0.05$).

consistent with those reported in previously canine studies [6, 10, 12, 23]. However, the baseline $SEV_{MAC\text{-}BAR}$, which was approximately 2 MAC in the present study, was higher than that reported previously in dogs [12, 20, 23]. This disagreement may be due to the difference of the experimental conditions.

The results of the present study indicated that a constant rate of remifentanil infusions decreased the MAC-BAR, MAC, and MAC-extubation of sevoflurane in dogs in a dose-dependent manner, and ceiling effects were observed by a simple inhibitory model and E_{max} model. The decrease of SEV_{MAC} and the predicted a maximum percentage reduction in the SEV_{MAC} during remifentanil infusion were in agreement with previous reports that remifentanil caused reductions in the MAC of enflurane [14] and isoflurane [16] in dogs. To the best of our knowledge, this is the first study to report that remifentanil decreases the MAC-BAR and MAC-extubation of sevoflurane in a dose-dependent manner in dogs, and our results are consistent with those of previous humans studies, which report that remifentanil decreased the MAC-BAR of sevoflurane [1] and the Observer's Assessment of Alertness/Sedation score [13]. Plasma fentanyl concentrations of 0.78, 1.8, and 7.3 *n*g/m*l* caused a 50% reduction in the MAC-BAR, MAC, and MAC-awake of sevoflurane, respectively, in human patients [8, 9]. Additionally, remifentanil markedly decreased the MAC-BAR of sevoflurane, with a mixture of nitrous oxide [1], and the Observer's Assessment of Alertness/Sedation score [13], suggesting that low fentanyl and remifentanil concentrations markedly reduced the MAC-BAR, and remifentanil compared with fentanyl may have a more potent sedative effect. However, our data revealed that the ID_{50}, ID_{80}, ID_{90}, and 50% reduction dose of remifentanil for the $SEV_{MAC\text{-}BAR}$ were higher than those for the SEV_{MAC} and $SEV_{MAC\text{-}extubation}$. 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 $MAC\text{-}BAR_{95}$, MAC_{95}, and $MAC\text{-}extubation_5$ were 5.34, 2.85, and 1.34% under sevoflurane alone. The $MAC\text{-}BAR_{95}$ and MAC_{95} decreased to 2.3 and 1.2% until reaching remifentanil infusion rates at 1.20 μg/kg/min, otherwise, the $MAC\text{-}extubation_5$ decreased to 0.6% until reaching remifentanil infusion rates at 0.60 μg/kg/min. These results showed that higher

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 V_1 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 stimulus to prevent movement and extubation in dogs.

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