

Effects of Lidocaine, Dexmedetomidine or Their Combination on the Minimum Alveolar Concentration of Sevoflurane in Dogs

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ABSTRACT. The aim of this study was to determine the effects of lidocaine (LIDO) and dexmedetomidine (DEX) or their combination (LIDO-DEX), administered by constant-rate infusion (CRI), on the minimum alveolar concentration (MAC) of sevoflurane in dogs. Seven healthy mongrel dogs were used with a 2-week washout interval between treatments in this study. Anesthesia was induced with propofol and maintained with sevoflurane in oxygen, and MAC of sevoflurane was determined after 90 min equilibration period in the dogs (SEV-MAC_{BASAL}). Then, sevoflurane MAC was determined again in the dogs after 45 min equilibration period of one of the following treatments: an intravenous loading dose of lidocaine 2 mg/kg followed by 6 mg/kg/hr CRI (SEV-MAC_{LIDO}); an intravenous loading dose of dexmedetomidine 2 µg/kg followed by 2 µg/kg/hr CRI (SEV-MAC_{DEX}); or their combination (SEV-MAC_{LIDO-DEX}). These SEV-MACs were determined in duplicate. Data were analyzed using ANOVA and *post hoc* Tuckey test when appropriate. The SEV-MAC_{BASAL} was 1.82 ± 0.06%, SEV-MAC_{LIDO} was 1.38 ± 0.08%, SEV-MAC_{DEX} was 1.22 ± 0.10%, and SEV-MAC_{LIDO-DEX} was 0.78 ± 0.06%. The CRI administration of lidocaine, dexmedetomidine and their combination produced a significant reduction in the MAC of sevoflurane by 26.1 ± 9.0% ($P < 0.0001$), 43.7 ± 11.8% ($P < 0.0002$) and 54.4 ± 9.8% ($P < 0.0001$), respectively. The MAC reduction was significantly greater after the CRI combination of lidocaine and dexmedetomidine when compared with lidocaine CRI ($P < 0.0001$) or dexmedetomidine CRI treatments ($P < 0.025$).

KEY WORDS: canine, dexmedetomidine, lidocaine, minimum alveolar concentration (MAC), sevoflurane.

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Sevoflurane is a volatile anesthetic with a low blood–gas partition coefficient and produces a rapid induction and recovery of anesthesia [16]. During last decade, clinical use of sevoflurane has been spreading in veterinary practice. Sevoflurane is minimally metabolized and easily cleared in animals, however, it should be remembered that sevoflurane has a dose-dependent depressant effect on cardiorespiratory function in dogs [22]. Because of these side effects, sevoflurane must be carefully titrated, and vigilant monitoring should be employed to avoid excessive anesthetic depth. The term of balanced anesthesia usually refers to the use of different drugs in combination to provide hypnosis, analgesia and muscle relaxation [25]. Administration of analgesic drugs as a part of the balanced anesthesia is sparing with requirements of anesthetic drugs, including sevoflurane, thereby reducing their depressant effects on the cardiovascular system and improving the quality of anesthesia [24].

Minimum alveolar concentration (MAC) is defined as the partial pressure of a gas that produces immobility in 50% of individuals exposed to a supramaximal noxious stimulation [12]. The MAC is the standard measure to evaluate inhaled anesthetic potency [27]. Lidocaine is a sodium channel blocker, and its intravenous infusion can be spared with anesthetic requirements in dogs undergoing surgery [9, 19, 31]. It is also reported that the intravenous infusion of lidocaine decreases the MAC of isoflurane [21, 36] and sevoflurane [7, 11, 20] in a dose-dependent manner in dogs. Studies in humans and in dogs suggest that low doses of alpha₂-adrenergic agonists may produce the sparing effects of anesthetic requirements and analgesia with minimal impact on cardiovascular function [1–3, 24]. In dogs, dexmedetomidine has been shown to reduce the anesthetic requirement for induction and maintenance of general anesthesia [2, 8, 24, 34]. Therefore, it is expected that the balanced anesthesia using a combination of lidocaine and dexmedetomidine infusion may decrease sevoflurane requirement and therefore may reduce the incidence of its side effects.

The aim of the present study was to evaluate the effects of constant rate infusion (CRI) of a combination of lidocaine and dexmedetomidine on the MAC of sevoflurane in dogs. The authors suggest the hypothesis that the combination of lidocaine with dexmedetomidine significantly reduces the MAC of sevoflurane in dogs.

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MATERIALS AND METHODS

Animals and experimental protocol: Seven adult mixed-breed neutered dogs, age 1–2 years, three males and four females and body weight (mean \pm SD) 18.1 ± 9 kg, were included in a prospective randomized cross-over experiment with a 2-week washout period between treatments. Dogs were considered to be healthy on the basis of medical history, physical examination, complete blood count (CBC) and serum biochemical analysis. Food but not water was withheld 8 hr prior to each anesthetic procedure. This study was planned as a randomized crossover trial. Each dog was anesthetized three times and received one of the following three treatments: 1) an intravenous (IV) loading dose (LD) of 2 mg/kg lidocaine (Lidocaína 2% Inyectable: Pisa, México) followed by lidocaine 6 mg/kg/hr CRI (LIDO), 2) LD of 2 μ g/kg IV dexmedetomidine (Dexdomitor, Orion Corporation, Espoo, Finland, 0.5 mg/ml) followed by dexmedetomidine 2 μ g/kg/hr CRI (DEX) and 3) LDs of lidocaine 2 mg/kg IV and dexmedetomidine 2 μ g/kg IV followed by lidocaine 6 mg/kg/hr and dexmedetomidine 2 μ g/kg/hr CRI (LIDO-DEX). Loading doses were diluted up to a final volume of 3 ml with sterile water and administered IV over 1 min. Treatments were diluted up to 60 ml with saline 0.9% and delivered as a CRI accordingly. All CRIs were started immediately after bolus administration using a syringe infusion device (Colleague, Baxter Healthcare Corporation Medication Delivery, Deerfield, IL, U.S.A.). The sevoflurane MAC was determined before (SEV-MAC_{BASAL}) and during one of the three CRI treatments (SEV-MAC_{LID}, SEV-MAC_{DEX} and SEV-MAC_{LID-DEX}) in each dog. This study was approved by the animal research ethics committee of the Universidad Autonoma de Mexico with protocol number 2267/2010.

Anesthetic procedure and instrumentation: A 20-gauge catheter was aseptically placed into the cephalic vein. Anesthesia was induced with an intravenous administration of propofol (Fresofol 1%, Fresenius Kabi, Pimble, Australia) at a dose of 6 mg/kg. Orotracheal intubation was performed in all dogs with an appropriately sized, cuffed endotracheal tube that was attached to a circle anesthetic rebreathing system (Fabius Dragër Medical GmbH 23542, Lübeck, Germany). Anesthesia was maintained with sevoflurane (Sevorane Abbott Laboratories, Bogota, Colombia) vaporized in 100% oxygen with a flow rate of 2 l/min (Dragër medical, AG&CO, KGaA, Lubeck, Germany, Dragër Vapor 2000). All dogs were administered lactate Ringer's solution at a flow rate of 3 ml/kg/hr through the catheter by the use of an infusion pump (Colleague, Baxter Healthcare Corporation Medication Delivery) and mechanically ventilated with intermittent positive-pressure ventilation (IPPV) (Fabius Dragër Medical GmbH Lübeck) to maintain eucapnia (35–40 mmHg of end-tidal CO₂) during the anesthesia. End-tidal concentration of sevoflurane SEVO (ET_{SEV}) and ET_{CO₂} was continuously monitored by a side-stream infrared gas analyzer (Dräger Vamos, Dräger Medical GmbH). Dogs were placed in lateral recumbency, and a 22-gauge catheter was aseptically placed in the dorsal metatarsal artery and attached to an electrical transducer (DTX Plus DT-4812, Becton Dickinson Critical

Care Systems Pte Ltd., Singapore) connected to a multi-parameter monitor (WL Surgivet V9212SR 2009-01, Smith Medical PM Inc., Waukesha, WI, U.S.A.). Systolic, diastolic and mean arterial blood pressures (SAP, DAP and MAP, respectively) were continuously monitored via a blood-pressure transducer system connected to the dorsal pedal artery (DTX plus[®] DT 4812, Becton Dickinson Critical Care Systems Pte Singapore Ltd.). The zero reference point of the pressure transducer was set at the level of the heart. Heart rate and rhythm (EGG lead II) and pulse oximetry were also continuously monitored by placing the electrodes at the level of the elbows and left patella and an infrared sensor attached to the dog's tongue, respectively (WL Surgivet V9212SR 2009-01, Smith Medical PM Inc.). A circulating warm-water blanket was used to maintain the esophageal temperature between 37.5 and 38.5°C.

MAC determination: Following the propofol induction, the dogs had been anesthetized for at least 90 min as an initial equilibration period at an ET_{SEV} of 2.7% to minimize the effects of propofol. The determination of SEV-MAC_{BASAL} for each dog was started after the initial equilibration period. Once the SEV-MAC_{BASAL} was determined, dogs were received the CRI treatment of lidocaine, dexmedetomidine or combination. The SEV-MAC_{LID}, SEV-MAC_{DEX} and SEV-MAC_{LID-DEX} were determined after 45 min equilibration period of the CRI treatments [15, 36]. Cardiovascular parameters and other variables were recorded immediately before the determination of minimum alveolar concentration (MAC) of sevoflurane.

MAC was determined by use of a previously described technique. Noxious stimulation was applied by clamping a paw of the third or fourth digits. The clamping technique was performed with 24-cm sponge forceps (with protective plastic tubing on each jaw) clamped to the first notch until gross purposeful movement was detected or a period of 60 sec elapsed [35]. A negative response included the lack of movement of head and limbs, muscle rigidity, shivering, tail movement, coughing, swallowing or an increase in spontaneous respiratory efforts during controlled ventilation. When a positive response was elicited, the ET_{SEV} was increased by 0.1% and maintained at this concentration for at least 20 min, and the noxious stimulus procedure was repeated. When a negative response was detected, the ET_{SEV} was decreased by 0.1% and maintained at this concentration for at least 20 min, and the noxious stimulus procedure was repeated. The procedure was continued until purposeful movement ceased (increase in anesthetic concentration) or returned (decrease in anesthetic concentration). The sevoflurane MAC was calculated as a mean value between the highest ET_{SEV} at which the purposeful movement was detected and the lowest ET_{SEV} at which the purposeful movement was not detected. In each dog, the sevoflurane MAC was evaluated in duplicate.

The sevoflurane MAC values were corrected to sea level by use of the formula (barometric pressure of location/760 mmHg) \times obtained MAC value. The mean barometric pressure was obtained from the official city meteorological station for the altitude at which the experiment was performed (2,680 m above sea level) and was 556 mmHg. Once the ex-

periment had been finalized, the dogs were recovered from anesthesia and administered 4 mg/kg carprofen (Rimadyl, Pfizer Animal Health BV, Capelle a/d I Jssel, The Netherlands) subcutaneously every 24 hr for 2 days.

Statistical analysis: Statistical analysis was performed using computer software (SigmaStat 3.5 program, Systat Software Inc., Point Richmond, CA, U.S.A.). The Shapiro-Wilk test was used for assessment of data normality. Data are reported as means \pm standard deviations (SD). A repeated-measures ANOVA was used to evaluate percentage change in sevoflurane MAC before and after the CRI treatments, time to MAC determination and extubation time. A post-hoc Tukey test was used where appropriate. Values were considered significantly different when $P < 0.05$.

The interaction of lidocaine and dexmedetomidine was used to evaluate whether change in cardiorespiratory data and MAC values departed from an additive model. The changes observed in dogs treated with lidocaine and dexmedetomidine ($SEV-MAC_{LIDO-DEX}$) were compared with those observed in groups ($SEV-MAC_{LIDO}$ and $SEV-MAC_{DEX}$) by use of two-way repeated-measures ANOVA, if a significant difference was obtained with a significant interaction, the drug interaction between $SEV-MAC_{LIDO-DEX}$ and $SEV-MAC_{LIDO}$, $SEV-MAC_{DEX}$ was judged to be synergistic. If the interaction term was not significant, the main effects of lidocaine and dexmedetomidine was judged to be additive. For all analyses, values of $P < 0.05$ were considered significant [18, 39]. Values are expressed as mean \pm SD.

RESULTS

Times to $SEV-MAC_{BASAL}$ determination were 174 ± 24 min, 196 ± 18 min and 181 ± 19 min for dogs receiving the LIDO, DEX and LIDO-DEX CRI treatments, respectively. Times to $SEV-MAC_{LIDO}$, $SEV-MAC_{DEX}$ and $SEV-MAC_{LIDO-DEX}$ was 172 ± 24 min, 194 ± 17 min and 181 ± 18 min, respectively. These times were not significantly different when groups were compared.

The LIDO, DEX and LIDO-DEX CRI treatments significantly decreased the sevoflurane MAC (Table 1). The $SEV-MAC_{BASAL}$ of all treatments was $1.82 \pm 0.06\%$. The $SEV-MAC_{LIDO}$ was $1.38 \pm 0.08\%$, $SEV-MAC_{DEX}$ was $1.22 \pm 0.10\%$, and $SEV-MAC_{LIDO-DEX}$ was $0.78 \pm 0.06\%$. The $SEV-MAC_{LIDO-DEX}$ was significantly lower compared with the $SEV-MAC_{LIDO}$ or $SEV-MAC_{DEX}$ ($P < 0.05$). The LIDO, DEX and LIDO-DEX CRI treatments significantly decreased the sevoflurane MAC by $27.3 \pm 8.0\%$, $41.0 \pm 12.0\%$ and $54.14 \pm 8.0\%$ for all treatments, when compared with $SEV-MAC_{BASAL}$ ($P < 0.05$). Therefore, it indicates that sparing effects of the combination lidocaine with dexmedetomidine were additive.

All dogs recovered smoothly from anesthesia and were extubated within 10 min after the discontinuation of sevoflurane anesthesia. Extubation time was 361 ± 17 min, 384 ± 20 min and 372 ± 19 min for LIDO, DEX and LIDO-DEX, respectively. These values were not significantly different when groups were compared.

The statistical interaction of change in heart rate between LIDO+DEX and LIDO, DEX groups was significant

($P < 0.0001$) (Table 2). Therefore, it indicates that effects of the combination of lidocaine with dexmedetomidine were additive. The statistical interaction of the % change in MAC was significant between LIDO-DEX and LIDO, DEX groups. Therefore, it indicates that sparing effects of the combination with lidocaine and dexmedetomidine on MAC were additive.

DISCUSSION

In this study, the CRI treatments using lidocaine (2 mg/kg IV followed by 6 mg/kg/hr CRI) or dexmedetomidine (2 μ g/kg IV followed by 2 μ g/kg/hr) produced significant and clinically meaningful reductions in the sevoflurane MAC. In particular, the CRI combination of lidocaine and dexmedetomidine was synergistic and reduced the sevoflurane MAC by half in dogs. In addition, the recovery from anesthesia was smooth and uneventful in all dogs. Therefore, the combination of lidocaine and dexmedetomidine infusions is expected to provide a clinically useful balanced anesthesia in dogs anesthetized with sevoflurane. However, the combination of lidocaine and dexmedetomidine infusions coincidentally produced significant cardiovascular changes, such as a decrease in heart rate and an increase in blood pressure. A further study will be necessary to clarify the cardiovascular effects in dogs receiving the CRI combination of lidocaine and dexmedetomidine.

The sevoflurane MAC in dogs is reported at a range from 2.1% to 2.4% in most previous studies [13–15, 17, 20, 38]. The baseline MAC of sevoflurane in our study was 1.82% (i.e. $SEV-MAC_{BASAL}$), which is approximately 14–20% less than that reported in these previous studies, but very similar to that reported by Seddighi *et al.* [30] (1.78% of the sevoflurane MAC) and Wilson *et al.* [38] (1.9% of the sevoflurane MAC). However, the MAC of an inhalational anesthetic can differ substantially among animals of the same species [34]. Factors affecting variability in MAC include the type of noxious stimulus, subjectivity in interpretation of purposeful movement, differences in the anatomical site of stimulation and differences in physiological variables, such as $PaCO_2$, body temperature, arterial blood pressure and age of the test subjects [26, 39, 40]. Variation within this study was minimized by using a one observer (MRS) and maintaining temperature, $ETCO_2$ and arterial blood pressure within the physiological range.

In dogs, continuous infusion of lidocaine has been shown to reduce the MAC of inhalational anesthetics, such as isoflurane and sevoflurane, in a dose related fashion [20, 36]. Valverde *et al.* [36] reported that lidocaine infusion reduced the isoflurane MAC by 18.7% at an infusion rate of 3 mg/kg/hr CRI and 43.3% at an infusion rate of 12 mg/kg/hr CRI. Matsubara *et al.* [20] reported that lidocaine infusion reduced the sevoflurane MAC by 15% at an infusion rate of 3 mg/kg/hr CRI and 37% at an infusion rate of 12 mg/kg/hr CRI. In the present study, the lidocaine infusion at 6 mg/kg/hr CRI reduced the sevoflurane MAC by 26.1%. This is similar to a previous study reported by Wilson *et al.* [38] where lidocaine infusion at 6 mg/kg/hr CRI reduced the sevoflurane

Table 1. Mean \pm standard deviations of the minimum alveolar concentration (MAC) of sevoflurane and percentage of MAC reduction recorded in dogs after a constant-rate infusion (CRI) of lidocaine or dexmedetomidine or their combination

The CRI treatment	SEV-MAC _{BASAL} (%)	SEV-MAC during the CRI treatment (%)	MAC reduction (%)
LIDO	1.90 \pm 0.2%	1.38 \pm 0.08*	27.3 \pm 8.0*
DEX	1.82 \pm 0.17%	1.10 \pm 0.23*	40.5 \pm 12.0*
LIDO-DEX	1.82 \pm 0.17%	0.78 \pm 0.14* [‡]	54.1 \pm 8.0* [‡]

MAC of sevoflurane was determined after 90 min equilibration period in the dogs (SEV-MAC_{BASAL}). Then, sevoflurane MAC was determined again in the dogs after 45 min equilibration period of one of the following treatments: an intravenous loading dose of lidocaine 2 mg/kg followed by 6 mg/kg/hr CRI (LID); an intravenous loading dose of dexmedetomidine 2 μ g/kg followed by 2 μ g/kg/hr CRI (DEX); or their combination (LID-DEX). The % reduction in the sevoflurane MAC after treatments was calculated from (SEV-MAC during the CRI treatment – MAC_{BASAL} \times 100). *Significantly different from MAC_{BASAL} ($P < 0.05$). [‡]Significantly different from LIDO and DEX treatments ($P < 0.05$). Sparing effect of these combination (LIDO-DEX) on sevoflurane MAC was additive.

Table 2. Cardiorespiratory parameters observed during the determination of minimum alveolar concentration (MAC) of sevoflurane in dogs

Variables	MAC _B	MAC _{T1}	MAC _{T2}	MAC _{T3}
Heart rate (beats/min)	118 \pm 5	110 \pm 5*	83 \pm 9**	76 \pm 22**
Systolic blood pressure (mmHg)	99 \pm 8	106 \pm 3	99 \pm 8	104 \pm 7
Diastolic blood pressure (mmHg)	68 \pm 5	71 \pm 4	73 \pm 3	79 \pm 3**
Mean arterial pressure (mmHg)	78 \pm 4	83 \pm 2	82 \pm 3	87 \pm 4**
Oxygen saturation (SpO ₂ , %)	97.4 \pm 1	97 \pm 2	97.5 \pm 1	95.5 \pm 0.2
Esophageal temperature ($^{\circ}$ C)	38.1 \pm 0.5	37.8 \pm 0.5	38.4 \pm 0.5	38.2 \pm 0.2
End-tidal CO ₂ (mmHg)	36.2 \pm 2	35.8 \pm 1.0	36.5 \pm 1	36.0 \pm 1

Data are expressed as mean \pm standard deviation for n=7 dogs. Cardiovascular parameters and other variables were recorded immediately before the determination of minimum alveolar concentration (MAC) of sevoflurane. The time determination for the MAC basal (MAC_B) was 174 \pm 24 min, 196 \pm 18 min and 181 \pm 19 min, respectively, for lidocaine, dexmedetomidine or the combination. The time determination for the MAC treatments groups (MAC_T) was 172 \pm 24 min, 194 \pm 17 min and 181 \pm 18 min, respectively. Treatment 1 (T₁) lidocaine, treatment 2 (T₂) dexmedetomidine and treatment 3 (T₃) lidocaine and dexmedetomidine combination. The MAC_{T1} was 1.38 \pm 0.08%, the MAC_{T2} 1.10 \pm 0.23% and the MAC_{T3} 0.78 \pm 0.14%. *Significant differences compared to baseline. +Significantly differences compared to LIDO group. **Significantly differences compared to DEX group. Statistical significance ($P < 0.05$).

MAC by 29%. While the mechanisms of MAC reduction by lidocaine infusion are still not well known, there are some possibilities. Analgesia produced by lidocaine infusion may be due to a mechanism at the level of the supraspinal or spinal cord [4], which may be expected to cause a decline in the MAC with inhalant anesthetics. Another serious theory is that the mechanism acts at the level of the voltage-dependent sodium channels in the central nervous system [26, 27]. In addition, there are some reports of inhibition of potential action on the excitability of the cells in the nervous system [6], which may explain both the analgesic properties and the ability of lidocaine to reduce the MAC [6]. The mechanism for MAC reduction with lidocaine is unclear. Whether it is associated with the analgesic or sedative effects of lidocaine is unknown. While lidocaine's analgesic effects may be responsible for the sparing effect on volatile anesthetic MAC, it is also possible that the MAC reduction resulted from the sedative effects of lidocaine as drugs with sedating actions, such as acepromazine, also reduce MAC [10, 27].

Dexmedetomidine infusion reduces the MAC of isoflurane in dogs [11, 24]. Pascoe *et al.* [24] reported that dexmedeto-

midine infusion reduced the isoflurane MAC by 18% at an infusion rate of 0.5 μ g/kg/hr CRI following a loading dose of 0.5 μ g/kg IV and 59% at an infusion rate of 3 μ g/kg/hr CRI following a loading dose of 3 μ g/kg IV. Ebner *et al.* [11] reported that dexmedetomidine infusion reduced the isoflurane MAC by 30% at an infusion rate of 0.5 μ g/kg/hr CRI without loading dose. As so far the authors know, there is no study investigating the effects of dexmedetomidine infusion on the sevoflurane MAC in dogs. In our study, dexmedetomidine infusion at 2 μ g/kg/hr CRI following a loading dose of 2 μ g/kg IV produced 43.6% of reduction in the MAC of sevoflurane in dogs. This is similar to the results of a previous study reported by Pascoe *et al.* [24] that investigated the effects of dexmedetomidine infusion on isoflurane MAC in dogs. The possible central mechanism that explains the reduction of MAC inhaled anesthetic induced by α 2 agonists is the reduction in the releasing of nor- epinephrine in the CNS caused by presynapsis stimulated by α 2-adrenergic receptors and neural hyperpolarization induced by post-synaptic activation of α 2-adrenergic receptors [28, 29, 32, 33].

Lidocaine is a sodium channel blocker that produces an-

algnesia by inhibition of potential action on the excitability of the cells in the nervous system [6]. Dexmedetomidine is an α_2 -adrenergic agonist that produces analgesia by activation of dorsal horn α_2 -receptors [1, 2]. Because of the different mechanisms of analgesic properties, it is expected that the combination of lidocaine and dexmedetomidine may produce an additive analgesic effect. In the present study, the combination of lidocaine (2 mg/kg IV followed by 6 mg/kg/hr CRI) and dexmedetomidine (0.5 μ g/kg IV followed by 2 μ g/kg/hr CRI) infusions provided a significant reduction in the sevoflurane MAC by 54.4% in the dogs. As mentioned above, we also observed that the lidocaine infusion alone (2 mg/kg IV followed by 6 mg/kg/hr CRI) reduced the MAC by 26.1% and the dexmedetomidine infusion alone (0.5 μ g/kg IV followed by 2 μ g/kg/hr CRI) reduced the MAC by 43.6% in the same dogs [18]. The interaction between lidocaine and dexmedetomidine infusions on the sevoflurane MAC reduction was judged to be additive in dogs. It is considered that the combination of lidocaine and dexmedetomidine infusions produces an additive interaction on the anesthetic requirements in dogs.

The cardiovascular effects observed in our dogs were similar to those in previous reports in dogs [5, 26, 37]. Valverde *et al.* [36] reported that lidocaine infusions (3 and 12 mg/kg/hr CRI following 2 mg/kg IV) did not induce clinically significant changes in heart rate and arterial blood pressure in dogs anesthetized with isoflurane. Nunes de Moraes *et al.* [23] reported there were not any detrimental cardiovascular effects related to an infusion of lidocaine at 7.2 mg/kg/hr during isoflurane anesthesia in healthy dogs or dogs with aortic stenosis. Matsubara *et al.* [20] reported that lidocaine infusions (3 and 12 mg/kg/hr CRI following 2 mg/kg IV) did not induce clinically significant changes in heart rate and arterial blood pressure in dogs anesthetized with sevoflurane. In the present study, minimal effects were observed on heart rate and blood pressure in dogs receiving the lidocaine infusion alone. Therefore, it is considered that the lidocaine infusion has minimal side-effects on cardiovascular function of dogs anesthetized with isoflurane or sevoflurane.

On the other hand, an administration of dexmedetomidine resulted in a decrease in heart rate and cardiac output and an increase in systemic vascular resistance in dogs [37]. Pascoe *et al.* [24] reported that heart rate decreased with increasing doses of dexmedetomidine infusion, while blood pressure increased in dogs anesthetized with isoflurane. Ebner *et al.* [11] also reported that dexmedetomidine infusion (0.5 μ g/kg/hr CRI) induced decreases in heart rate and cardiac output and increases in arterial blood pressure and systemic vascular resistance in dogs anesthetized with isoflurane. In the present study, it was also observed that the dexmedetomidine infusion induced a decrease in heart rate; however, the increase in arterial blood pressure was only observed in the LIDO-DEX group. A decrease of heart rate is commonly observed after the administration of dexmedetomidine due to an increased systemic vascular resistance induced by α_2 -adrenergic receptor. Pypendop & Verstegen (1998) [25], investigating the dose dependency of these effects in dogs, found that medetomidine caused qualitatively similar

hemodynamic changes, irrespective of dose between 1 and 20 μ g kg⁻¹ IV, although these changes were less at doses of 1 and 2 μ g/kg. This could explain, because, in our study not observed a significant increase in blood pressure.

As so far the authors know, the interaction between systemic lidocaine and dexmedetomidine on cardiovascular function has not been clarified in dogs. In the present study, the combination of lidocaine and dexmedetomidine infusions produced cardiovascular changes, such as a decrease in heart rate and an increase in arterial blood pressure, compared to the CRI administration of lidocaine alone. Sevoflurane has a dose-dependent depressant effect on cardiovascular function, such as a decrease in cardiac output in dogs [20]. We speculate that these cardiovascular changes induced by a preservation of cardiac output as a benefit from the additive sparing effect on the sevoflurane MAC were produced by the combination of lidocaine and dexmedetomidine infusions. The preserved cardiac output might cause a significant increase in arterial blood pressure and a baroreflex followed by a significant decrease in heart rate. However, we did not measure cardiac output in the present study. A further study will be necessary to clarify the cardiovascular effects in dogs receiving the CRI combination of lidocaine and dexmedetomidine.

In conclusion, the combination of lidocaine and dexmedetomidine infusions is expected to provide a clinically useful balanced anesthesia in dogs anesthetized with sevoflurane.

The sparing effects of lidocaine with dexmedetomidine on sevoflurane MAC reduction in dogs were additive.

However, significant cardiovascular changes were coincidentally observed in our dogs receiving the CRI combination. A further study will be necessary to clarify the cardiovascular effects in dogs receiving the CRI combination of lidocaine and dexmedetomidine.

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