Hemodynamic effects of target-controlled infusion of propofol alone or in combination with a constant-rate infusion of remifentanil in dogs

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Abstract

The objective of this study was to evaluate the hemodynamic effects of target-controlled infusion (TCI) of propofol alone or in combination with a constant-rate infusion (CRI) of remifentanil. Six adult dogs were given 2 treatments in a randomized crossover study with a 7-day interval between treatments. Treatment 1 was propofol (P) and treatment 2 was propofol and remifentanil (P-Rem), without any premedication. Propofol was induced using a TCI system with a predicted plasma concentration (Cp) of 6.0 μg/mL. Anesthesia was maintained within the Cp range (0.65 to 3.0 μg/mL) for 120 min and remifentanil was administered at a rate of 0.3 μg/kg body weight (BW) per minute, CRI. Cardiopulmonary variables were recorded before (baseline), during, and 120 min after drug administration. Heart rate (HR) decreased significantly in the P-Rem group (46%) compared with baseline values. In the P-Rem group, the cardiac index (CI) decreased significantly (49% to 58%) and the stroke volume (SV) decreased compared with baseline values. The systemic vascular resistance index (SVRI) increased significantly in the P-Rem group compared with baseline values. There was no difference in mean arterial pressure (MAP) between the groups. Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) significantly increased in the P-Rem group compared with baseline values. In conclusion, the hemodynamic changes observed in this study indicate a compromise of the cardiovascular system, although the dogs in this study were healthy/euvolemic and there was no change in preload. More studies are required in order to evaluate the actual safety of the combination of propofol and remifentanil in patients with reduced cardiac reserve.

Résumé

L'objectif de la présente étude était d'évaluer les effets hémodynamiques d'une infusion à objectif de concentration (IOC) de propofol uniquement ou en combinaison avec une infusion à débit constant (IDC) de remifentanyl. Six chiens adultes reçurent deux traitements dans un essai aléatoire croisé avec un intervalle de sept jours entre les traitements. Le traitement 1 consistait en du propofol (P) et le traitement 2 était du propofol et du remifentanyl (P-Rem), sans aucune prémédication. Le propofol fut induit à l'aide d'un système d'IOC avec une concentration plasmatique prédéterminée (Cp) de 6,0 mg/mL. L'anesthésie fut maintenue à l'intérieur de l'écart de Cp (0,65 à 3,0 μg/mL) pendant 120 min et du remifentanyl administré à un taux de 0,3 μg/kg de poids corporel (PC) par minute, IDC. Les variables cardiopulmonaires furent enregistrées avant (valeurs de base), pendant, et 120 min après l'administration des médicaments. Le rythme cardiaque (RC) a diminué significativement dans le groupe P-Rem (46 %) comparativement aux valeurs de base. Dans le groupe P-Rem, l'index cardiaque (IC) a diminué significativement (49 % à 58 %) et le volume du débit systolique (VDS) a diminué comparativement aux valeurs de base. L'index de résistance vasculaire systémique (IRVS) a augmenté de manière significative dans le groupe P-Rem comparativement aux valeurs de base. Il n'y avait aucune différence entre les groupes pour la pression artérielle moyenne (PAM). La pression veineuse centrale (PVC) et la pression d'occlusion de l'artère pulmonaire (POAP) ont augmenté significativement dans le groupe P-Rem comparativement aux valeurs de base. En conclusion, les changements hémodynamiques observés dans cette étude indiquent un compromis du système cardio-vasculaire, bien que les chiens utilisés étaient en santé/euvolémiques et qu'il n'y avait pas de changement dans la précharge. Des études supplémentaires sont requises afin d'évaluer la sécurité de la combinaison de propofol et de remifentanyl chez des patients avec une réserve cardiaque diminuée.

(Traduit par Docteur Serge Messier)

Introduction

Target-controlled infusion (TCI) is an anesthetic delivery system widely used in human anesthesia (1). In veterinary medicine, some reports have been published using TCI in dogs during induction and maintenance of anesthesia (2,3). Using TCI allows the anesthetist to estimate the actual concentrations of plasma drug in the central compartment and to titrate the concentrations of the target drug according to patient requirements in the same manner that expired concentrations of inhaled anesthetic drugs are adjusted according to patient response (4). Maintaining a constant plasma concentration of an intravenous (IV) anesthetic requires continuous adjustment of the

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Received July 21, 2014. Accepted November 19, 2014.

infusion rate according to the pharmacokinetics of each drug. The anesthetist can select any target according to patient responses (5).

The cardiovascular effects of propofol have already been documented (6). Propofol administration by continuous infusion is associated with reduced hypotension compared with a bolus administration (7). In humans, continuous infusion of propofol using the TCI technique reduces the incidence of respiratory depression, improves hemodynamic stability, and provides faster recovery than constant-rate infusion (6).

Remifentanil is considered an ideal analgesic for continuous infusion when combined with propofol because its pharmacokinetic properties allow rapid equilibrium in plasma and a fast elimination half-life independent of infusion duration (8). The clinical use of total IV infusion of propofol and remifentanil has recently been reported in dogs and it was concluded that remifentanil is more appropriate in combination with propofol than with other short-acting opioids and the short recovery period after remifentanil administration is therefore clinically advantageous (9). While propofol TCI in combination with variable-rate infusion of remifentanil has been reported in dogs (10); the hemodynamic effects of this combination were not available.

The objective of this study was to evaluate the hemodynamic effects of the TCI method using propofol alone or in combination with a CRI (constant-rate infusion) of remifentanil.

Materials and methods

Animals

Six adult mongrel dogs 2 to 5 y old were used (3 castrated males and 3 spayed females), weighing 26.5 ± 3.6 kg [mean ± standard deviation (SD)]. Their health status was evaluated by clinical examination, complete blood count, biochemical examinations, and blood gas analysis. The dogs were kept in separate kennels and fed a balanced commercial dog food. The animals were submitted to a 12-h food and 2-h water fast before each experimental procedure. The study was approved by the Animal Care and Use Committee (protocol 382/2004 CEEA).

Study design and procedures

The dogs were given 2 treatments in this randomized crossover study with a 1-wk interval between experiments. Treatment 1 (P) consisted of propofol (Propovan 10 mg/mL; Cristália, Itapira, Brazil). Treatment 2 (P-Rem) consisted of propofol and remifentanil (Ultiva 5 mg/mL; Glaxo Wellcome, Rio de Janeiro, Brazil).

Instrumentation

Isoflurane was administered by a facemask connected to a circle breathing system with the vaporizer adjusted to deliver 5% isoflurane (Isoforine; Cristália) in 100% oxygen with a flow of 5 L/min. After orotracheal intubation was conducted, the vaporizer settings were adjusted to maintain a moderate depth of anesthesia on the basis of clinical assessment. Pressure-controlled ventilation (10 cm H_2O), an inspiratory/expiratory (I:E) ratio of 1:2 and respiratory rate was adjusted to maintain end-tidal carbon dioxide ($PECO_2$) of 35 to 45 mmHg (eucapnia). Body temperature was measured using an esophageal probe (AS/3 Monitor; Datex-Engstrom, Helsinki, Finland) placed at the level of the thoracic inlet; the dogs' body temperatures were maintained at 37.5°C to 38.5°C with the aid of a forced-air warming blanket (WarmTouch; Mallinckrodt Medical, St. Louis, Missouri, USA).

Dogs were positioned in dorsal recumbency and a 20-gauge, 5-cm-long catheter (BD Insyte; Becton Dickinson, São Paulo, Brazil) was aseptically placed into a cephalic vein and a dorsal pedal artery. After surgical preparation of the skin on the neck, an 8-French catheter introducer (Intro-Flex; Edwards Lifesciences, Irvine, California, USA) was placed into the jugular vein according to the Seldinger technique. A 7-French pulmonary artery catheter (Swan Ganz) (7-French Thermodilution Catheter; Baxter Healthcare, Irvine, California, USA) connected to a multiparameter monitor (AS/3 Monitor; Datex-Engstrom) was advanced by the introducer into the jugular vein until its distal lumen was positioned in the pulmonary artery. The correct location of the catheter in the pulmonary artery was based on observation of the characteristic pressure waveforms. The distal and proximal lumens of the catheter in the pulmonary artery were connected to pressure transducers for continuous measurements of mean pulmonary artery pressure (MPAP) and central venous pressure (CVP), respectively. Intermittent measurements of pulmonary artery occlusion pressure (PAOP) were obtained by insufflating the balloon located at the tip of the catheter in the pulmonary artery with 0.7 mL of air.

The pressure-sensing lumens of the catheter in the pulmonary artery and the catheters placed in the cephalic vein and in the dorsal pedal artery were filled with 0.9% sodium chloride (NaCl) solution containing heparin (5 IU/mL) and temporarily occluded until the start of baseline data recording. After the instrumentation phase was completed, isoflurane administration was discontinued and the orotracheal tube was removed when the swallowing reflux returned. After the dogs had completely recovered from anesthesia and displayed no ataxia and there were no isoflurane residues in the expired air as confirmed by gas analyzer (AS/3 Monitor; Datex-Engstrom) connected to the facemask, the dogs were placed in left lateral recumbency. Adhesive electrodes (3M, Ribeirão Preto, Brazil) (Lead II) were then attached to record the electrocardiogram (ECG) on the multiparameter monitor (AS/3 Monitor; Datex-Engstrom) in order to check heart rate (HR) and cardiac rhythm. The line of arterial pressure and the lumens of the Swan Ganz catheter were connected to the monitor by a pressure transducer (TruWave Disposable Pressure Transducer; Edwards Lifesciences).

Cardiac output (CO) (AS/3 Monitor; Datex-Engstrom) measurements were obtained by fast injection of 10 mL of a solution of 5% glucose (1°C to 4°C) through the proximal port of the pulmonary arterial catheter. Five measurements were taken, with the highest and lowest being discarded and the 3 remaining measurements used to calculate the mean CO value. If the remaining 3 measurements varied by more than 10%, a new series of 5 measurements was taken.

The dorsal pedal artery catheter was connected to a pressure transducer to measure systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure (DAP). The accuracy of the pressure transducer was verified with a mercury column before each experiment. The reference pressure (0 mmHg) was set at the level of the manubrium. The data were collected over time from the screen of the monitor.

Arterial blood samples were collected in previously heparinized syringes and immediately analyzed in a gas analyzer (Model 348 Blood Gas Analyzer; Chiron Diagnostics, Halstead, UK) for pH, carbon dioxide and oxygen partial pressures ($PaCO_2$ and PaO_2, respectively), and bicarbonate (HCO_3). The blood gas values determined were corrected for the body temperature recorded at each sampling time point.

The following hemodynamic variables were recorded using a monitor and calculated using previously reported equations (11): body surface area [BSA = weight (grams) $2/3 \times 10.1 \times 10^{-4}$] (11); cardiac output (L/min); cardiac index (L/min/m^2); stroke volume (mL/beats); stroke volume index (mL/beat/m^2); systemic vascular resistance index (dynes/s/cm^5/m^2); and pulmonary vascular resistance index (dynes/s/cm^5/m^2).

Study protocol

After the dogs had completely recovered from the isoflurane anesthesia, (50 ± 10 min after isoflurane was turned off), weight, age, gender, and the selected target concentration data were entered into the program. Propofol was administered using a TCI system (Pump 22 Syringe Pump; Harvard Apparatus, Holliston, Massachusetts, USA) using the Stanpump Program (Stanford University, Stanford, California, USA), and incorporating propofol pharmacokinetic parameters for dogs reported in a previous study (2). Remifentanil was administered using a continuous infusion pump (ST680; Samtronic, Socorro, Brazil) at a rate of 0.3 μg/kg body weight (BW) per minute.

Dogs in treatment 1 group (P) were given only TCI of propofol and those in treatment 2 group (P-Rem) were given a TCI of propofol combined with a constant rate of remifentanil (0.3 μg/kg BW per minute), which was initiated immediately after induction. The predicted plasma concentration (Cp) for propofol induction was 6.0 μg/mL in both groups, based on data determined in a previous study (12).

With the data from treatments 1 and 2 entered into the computer and the injection pump settings for remifentanil infusion calculated (treatment 2), propofol infusion was initiated at 6 μg/mL (induction). After loss of laryngeal reflexes, the dog was intubated and connected to a circle breathing system for oxygen (flow rate 2 L/min) and to control ventilation (7900 SmartVent; Datex/Ohmeda, Madison, Wisconsin, USA) at 10 cm H_2O, with an I:E ratio of 1:2 and the respiratory rate was adjusted to maintain end-tidal carbon dioxide at 35 to 45 mmHg. Anesthesia was maintained using individual predicted plasma concentrations (Cp) predetermined in a previous study (listed in Table I) that were input into the program immediately after induction. In this previous study (12), the anesthetic depth was monitored by electrical stimulus and the Cp used in this study was determined for each animal. Anesthesia was maintained for 120 min.

Body temperature was measured using an esophageal probe placed at the level of the thoracic inlet and was maintained at 37.5°C to 38.5°C throughout the study with the aid of a forced-air warm blanket.

Cardiopulmonary measurements

Hemodynamic variables, including cardiac index (CI), stroke volume (SV), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI), were calculated using standard equations determined in a previous study (11): body surface area [BSA = weight (grams) $2/3 \times 10.1 \times 10^{-4}$].

All hemodynamic variables including HR, CO, CVP, MAP, SAP, DAP, PAOP, MPAP, temperature, and blood gases were collected at the following time points: baseline (before induction), 15, 30, 60, 90, and 120 min after induction. At the end of infusion, the recovery from anesthesia was assessed by recording the time from when the orotracheal tube was removed (considered to be the point at which the swallowing reflex returned) until sternal recumbency and regaining a standing position.

Table I. Predicted individual propofol concentrations in 6 animals anesthetized by target-controlled infusion (TCI) of isolated propofol or TCI of propofol + constant-rate infusion (CRI) of remifentanil [0.3 μg/kg body weight (BW) per minute]

		Predicted concentration (μg/mL)	
Animals	Weight (kg)	Propofol	Propofol + remifentanil
1	27	1.75	0.80
2	29	2.25	0.65
3	22	1.62	0.90
4	29	1.75	0.37
5	30	1.60	0.85
6	22	3.00	1.65

Statistical analysis

A commercial software program was used to analyze data. For each group, cardiopulmonary variables were analyzed by a 1-way analysis of variance (ANOVA) for repeated measures, followed by Dunnett's test to compare all sample collection times with baseline data. The groups were compared by a 2-way ANOVA, followed by a paired *t*-test, to which a Bonferroni correction for multiple pairwise comparisons was applied. Differences were considered significant at values of $P < 0.05$.

Results

The baseline physiologic variables did not differ between the treatment groups. Compared with the baseline values, heart rate (HR) had a mean reduction of 14% to 35% in the P group, whereas in the P-Rem group, it reached 46% (at 90 min), which was significantly different from the propofol treatment value ($P < 0.001$). Cardiac index (CI) presented mean reductions of 32% to 42% and 49% to 58% in the P and P-Rem groups, respectively, compared with baseline values (Table II). This reduction was observed for all time points between groups.

In the P-Rem group, a significant difference in stroke volume (SV) was observed at 30, 60, 90, and 120 min compared with baseline values, with no difference between the treatment groups. Compared with baseline values, SVRI increased significantly in the P-Rem group (up to 100%) at 120 min ($P > 0.001$) and was significantly different than the propofol treatment at 60 min ($P > 0.001$). The CVP values in the P-Rem group increased significantly in relation to

Table 2. Hemodynamic variables from 6 dogs (mean ± standard deviation) after TCI infusion of isolated propofol or propofol + CRI of remifentanil (0.3 μg/kg BW per minute)

		Time after starting propofol or propofol + remifentanil infusion (min)					
Variables	Treatment	Baseline	15	30	60	90	120
HR (beats/min)	P	117 ± 24	100 ± 26	90 ± 24	88 ± 16*	82 ± 12	91 ± 14
	P-Rem	114 ± 13	63 ± 15*†	66 ± 11*†	64 ± 7*†	61 ± 5*†	64 ± 7*†
CO (L/min)	P	5.1 ± 1.2	3.5 ± 1.2*	3.2 ± 0.8*	3.3 ± 1.0*	2.9 ± 0.8*	3.0 ± 0.6*
	P-Rem	4.5 ± 0.4	2.3 ± 0.6*†	2.2 ± 0.4*	2.1 ± 0.5*†	1.9 ± 0.2*	1.9 ± 0.3*†
CI (L/min/m^2)	P	6.2 ± 1.2	4.2 ± 1.3*	4.0 ± 1.0*	4.0 ± 1.0*	3.6 ± 0.9*	3.6 ± 0.8*
	P-Rem	5.5 ± 0.6	2.8 ± 0.5*†	2.6 ± 0.3*†	2.5 ± 0.4*†	2.3 ± 0.2*†	2.3 ± 0.3*†
SV (mL/beat)	P	43.3 ± 6.6	34.4 ± 4.8	36.6 ± 5.8	37.1 ± 9.0	35.9 ± 8.0	33.1 ± 7.2
	P-Rem	40.9 ± 4.4	34.6 ± 7.9	30.9 ± 7.5*	29.8 ± 6.6*	28.8 ± 5.3*	27.9 ± 6.9*
SVI (mL/beat/m^2)	P	52.7 ± 4.5	42.1 ± 5.3	45.1 ± 9.2	44.9 ± 8.1	43.7 ± 8.0	40.5 ± 8.4*
	P-Rem	49.3 ± 8.2	46.1 ± 8.9	40.6 ± 6.4	39.3 ± 4.9	38.2 ± 6.0	37.0 ± 8.2*
SVRI	P	1190 ± 226	1459 ± 367	1580 ± 460	1682 ± 294	2005 ± 332	2104 ± 419*
(dynes/s/cm^5/m^2)	P-Rem	1370 ± 300	2119 ± 446*	2182 ± 303*	2475 ± 487*†	2716 ± 473*	2785 ± 696*
CVP (mmHg)	P	1.5 ± 1.0	1.7 ± 1.2	1.7 ± 1.2	2.2 ± 1.0	1.8 ± 1.2	1.8 ± 1.2
	P-Rem	2.0 ± 0.9	5.0 ± 0.9*†	5.5 ± 1.0*†	6.5 ± 2.0*†	6.3 ± 1.9*†	6.5 ± 2.0*†
MABP (mmHg)	P	91 ± 15	75 ± 17	76 ± 13	83 ± 11	90 ± 10	95 ± 14
	P-Rem	95 ± 11	78 ± 10	76 ± 4	82 ± 14	84 ± 12	85 ± 15
MPAP (mmHg)	P	15.0 ± 2.9	13.3 ± 3.2	12.3 ± 1.8	12.0 ± 1.7	11.5 ± 1.0*	11.8 ± 1.7
	P-Rem	15.8 ± 3.4	14.5 ± 3.4	13.5 ± 2.4	14.8 ± 3.1	14.5 ± 3.7	15.3 ± 3.7†
PAOP (mmHg)	P	5.7 ± 3.0	4.7 ± 2.0	4.2 ± 1.2	4.0 ± 1.3	3.7 ± 1.6	3.8 ± 1.0
	P-Rem	4.5 ± 2.4	7.0 ± 1.9	7.0 ± 1.1†	7.7 ± 2.5†	7.2 ± 2.8†	6.3 + 1.4†
PVRI	P	120 ± 17	170 ± 43	169 ± 27	166 ± 26	183 ± 48*	182 ± 40*
(dynes/s/cm^5/m^2)	P-Rem	164 ± 34	216 ± 67	199 ± 53	226 ± 59	258 ± 65	318 ± 99*†

* Significant ($P < 0.05$) difference in relation to baseline values.

† Significant ($P < 0.05$) difference between treatments.

HR — Heart rate; CI — cardiac index; SVI — stroke volume index; SVRI — systemic vascular resistance index; CVP — central venous pressure; MABP — mean arterial blood pressure; PAOP — pulmonary artery occlusion pressure; PVRI — pulmonary vascular resistance index.

baseline values at 15, 30, 60, 90, and 120 min and were significantly different than those of the propofol group. The PAOP values were significantly different between the groups at 30, 60, 90, and 120 min. The mean MPAP values in the P group were significantly different only at 90 min ($P < 0.05$) when compared with baseline values. Between groups, this difference occurred at 120 min ($P < 0.05$).

The pulmonary vascular resistance index (PVRI) increased in both groups with dogs in the P group presenting this increase at 90 ($P < 0.05$) and 120 min ($P < 0.05$) compared with baseline values. In the P-Rem group, this increase was significant only at 120 min ($P < 0.05$). Between groups, this difference occurred at 120 min ($P < 0.05$).

No significant differences were observed for pH, partial pressure of carbon dioxide ($PaCO_2$), HCO_3, and temperature and these parameters all remained within reference values during anesthesia. Only partial pressure of oxygen (PaO_2) displayed significant differences compared with baseline values: 89 + 7.0 mmHg (11.8 ± 0.9 kPa) and 88 ± 4.0 mmHg (11.7 ± 0.5 kPa), in the P and P-Rem groups, respectively. The PaO_2 increased to 437 ± 20 mmHg (58.2 ± 2.6 kPa) and 483 ± 16 mmHg (64.4 ± 2.1 kPa) at 15 min in the P and P-Rem groups, respectively and these values did not change.

For the recovery period, the extubation time was not significantly different between groups (4.3 ± 1.6 and 5.0 ± 1.5 min after the end of infusion for the P and P-Rem groups, respectively). There was a significant difference for sternal recumbency and standing position, [17.8 ± 6.8 and 12.2 ± 2.5 min for the P and P-Rem groups, respectively for sternal recumbency ($P = 0.048$) and 21 ± 6.2 and 15 ± 4.0 min for the P and P-Rem groups, respectively for standing position ($P < 0.05$)]. No dog vomited during induction of anesthesia or during recovery. Muscle tremors and opisthotonus were observed in 1 dog during recovery from anesthesia after both treatments. No long-term anesthetic complications were observed.

Discussion

The results of this study indicated that cardiovascular depression was more evident in dogs treated with a combination of propofol and remifentanil (P-Rem group) than in dogs treated with only

Table III. pH, blood gases, bicarbonate (HCO_3), and body temperature (BT) of 6 dogs (mean ± SD) after target-controlled infusion (TCI) of isolated propofol or propofol + controlled-rate infusion (CRI) of remifentanil [0.3 μg/kg body weight (BW) per minute]

Variables	Treatment	Time after starting propofol or propofol + remifentanil infusion (min)					
		Baseline	15	30	60	90	120
pH	P	7.37 ± 0.02	7.36 ± 0.02	7.35 ± 0.02	7.36 ± 0.03	7.37 ± 0.02	7.36 ± 0.03
	P-Rem	7.38 ± 0.01	7.37 ± 0.03	7.36 ± 0.03	7.36 ± 0.01	7.36 ± 0.01	7.36 ± 0.02
PaO_2 (mmHg)	P	89 ± 7.0	437 ± 20*	435 ± 21*	451 ± 24*	433 ± 32*	421 ± 36*
	P-Rem	88 ± 4.0	483 ± 16*	474 ± 27*	443 ± 20*	477 ± 34*	449 ± 33*
$PaCO_2$ (mmHg)	P	37 ± 2.0	40 ± 2.0	39 ± 2.0	40 ± 2.6	41 ± 2.6	41 ± 3.6
	P-Rem	36 ± 2.0	38 ± 2.4	40 ± 2.7	41 ± 2.7	40 ± 1.5	40 ± 0.6
HCO_3 (mmol/L)	P	20 ± 0.7	21 ± 0.7	21 ± 0.8	21 ± 1.0	21 ± 0.7	21 ± 0.8
	P-Rem	21 ± 0.6	22 ± 0.6	22 ± 0.7	22 ± 0.8	22 ± 0.7	22 ± 0.8
BT (°C)	P	38.0 ± 0.5	37.7 ± 0.6	37.8 ± 0.6	37.8 ± 0.6	38.1 ± 0.4	38.2 ± 0.3
	P-Rem	38.2 ± 0.7	37.8 ± 0.7	37.8 ± 0.7	37.8 ± 0.7	37.9 ± 0.7	37.9 ± 0.6

* Difference in relation to baseline values.

PaO_2 — partial pressure of arterial oxygen; $PaCO_2$ — partial pressure of arterial carbon dioxide.

propofol (P group). Heart rate (HR) was reduced significantly during anesthesia with both treatments compared with baseline values. In the P group, this reduction can be explained by the direct effects of propofol. The occurrence of bradycardia can be linked to an impairment of the baroreflex by the inhibition of sympathetic activity (13). The fact that this reduction in HR was more evident with P-Rem treatment at all time points compared with baseline and P treatment values can be explained by the addition of remifentanil (Table II). The opioids have a high affinity for μ-type receptors and significantly influence the cardiovascular system. Most opioids reduce HR through a central mechanism, with the opioid binding to receptors of the central vagal nuclei stimuli, which leads to bradycardia (14). These negative chronotropic effects are influenced by the dose and rate of administration (15). Like other opioids, remifentanil causes a dose-dependent reduction in HR (16). Despite the evident bradycardia in the P-Rem group, mean arterial blood pressure was not significantly compromised and always remained over 70 mmHg, which was most likely due to increased systemic vascular resistance.

The cardiac output (CO) and cardiac index (CI), however, decreased significantly in both treatment groups compared with baseline values. These reductions were significantly greater in the P-Rem group than in the P group. Propofol is known to promote dose-dependent reductions in CO due to its direct negative inotropic activity (17) resulting from preload reduction from the direct vasodilator effect and decreased HR (18). In the P-Rem group, the addition of remifentanil caused a more significant reduction in HR than in the P treatment group, which resulted in a larger reduction in CO and CI (19) (Table II). Another study on dogs anesthetized with fentanyl and enflurane demonstrated that CI was significantly higher when the bradycardia caused by fentanyl was prevented by administering atropine (20). Therefore, the CO/CI reduction in the P treatment group was most likely due to the reduction in stroke volume and, in the P-Rem group, to a reduction in HR.

A small reduction was observed in the stroke volume (SV) value compared with baseline values in both treatments, but was only significant in the P-Rem group. There was no significant difference between groups (Table II). The reduction in SV, which is a dose-dependent negative inotropic effect (21), is the main cause of reduction of the CI/CO in dogs anesthetized with propofol. In the P-Rem group, the reduction in SV could have been a negative inotropic effect caused by the opioid. In a previous study, remifentanil reduced the maximum elevation rate of left ventricular pressure, which suggests that the opioid inhibited myocardial contractility (15), despite another study stating that opioids have little influence on myocardial contraction force (22).

Many studies have shown that propofol reduces arterial blood pressure mainly because vascular system resistance is reduced due to the arterial and venous vasodilator effects (18). However, the mechanisms by which propofol decreases arterial pressure are still controversial. Although the arterial and venous vasodilator effects of propofol have been documented, vascular system resistance has been reported as reducing (18), increasing (23), or even not changing (24) during anesthesia with propofol. During propofol treatment in this study, we observed a significant increase in the systemic vascular resistance index (SVRI) from baseline values, which corroborates the results of other studies (23). These effects could explain why we did not observe a decrease in the arterial blood pressure (Table II).

Concomitant with the reductions in the HR, CO, and CI, remifentanil induced a significant increase of up to 100% in SVRI in the P-Rem group compared with propofol (observed increase of 75%). This increase could be caused by the increase in circulatory arginine vasopressin (AVP). An increase in this hormone, which is secondary to methadone, has been reported in conscious dogs (25,26). Another study demonstrated a strong positive correlation between plasma concentrations of AVP and systemic vascular resistance ($r = 0.81$), which suggests that vasoconstriction caused by liberation of vasopressin during remifentanil administration can be a determining factor in elevating systemic vascular resistance (27). Pure μ-opioid receptor agonists may cause the release of vasopressin, although the mechanism of vasopressin release under these circumstances is poorly understood. The increase in vasopressin concentrations could have been attributed to a direct action of remifentanil at μ-opioid

receptors located in the central nervous system (26) or it could have been a physiologic response to the decrease in arterial blood pressure (associated with the decrease in CO) induced by remifentanil (28). This was a limitation in our study, however, as we did not measure endogenous AVP.

The reduction in the MPAP in the P group coincided with moments of low cardiac output (CO). This could be caused by the direct inotropic activity of propofol (18), as this effect is dose-dependent and the propofol concentration in the P group was higher than in the P-Rem group. The results of a previous study indicate that propofol can reduce MPAP in a dose-dependent manner (18).

During remifentanil infusion (P-Rem), the systemic circulation preload (CVP) and pulmonary circulation preload (PAOP) indexes increased. The CVP and PAOP values were significantly higher in the P-Rem group. As these variables are measurements of cardiac preload (29), this could be due to a preload increase resulting from the increase in venous return secondary to the significant reduction in HR. The negative chronotropic effect mediated by remifentanil therefore appears to be the determining factor for the increases in the CVP and PAOP. A previous study demonstrated that the value of PAOP could be increased in bradycardia or when left ventricle performance is reduced (20). Despite the increase in CVP and PAOP in the P-Rem group, the values are still within the normal range. In addition, the vasoconstriction on the venous side with AVP released during remifentanil administration can increase the PAOP and CVP due to centralization of blood.

The up to 100% increase in the SVRI from baseline during anesthesia in the P-Rem group could lead to a negative impact on SV and, consequently, on CO and CI (30). Although these effects are tolerated in healthy dogs, substantial increases in the SVRI could cause cardiovascular compromise in dogs presenting with heart failure or in animals with reduced cardiovascular reserve. The increase in afterload because of vasoconstriction (increased SVRI) may result in greater depression of indexes of systolic function in animals with heart disease, as the failing heart can be more sensitive to the effects of increased afterload on myocardial performance (30).

Compared with anesthesia maintained with propofol alone, anesthesia maintained with a combination of propofol and remifentanil may decrease overall tissue perfusion as a result of decreases in CI and increases in SVRI. However, prevention or treatment of opioid-induced bradycardia by administering an anticholinergic agent, which has the potential for improving CI (20), was not investigated in this study. A study in humans, however, proposed the common use of TCI with propofol associated with remifentanil in heart surgery and demonstrated that the combination is safe even in patients with reduced left-ventricle function (31).

A case study in dogs demonstrated the use of TCI with propofol with a variable infusion rate of remifentanil (0.2 to 0.6 μg/kg BW per minute) for a patient with patent ductus arteriosus and concluded that this combination provided adequate reflex suppression and excellent intraoperative conditions (10). This study did not evaluate the systemic vascular resistance index (SVRI), however, despite it being the most important variable on SV and CO impact due to the increase in afterload. Although SVRI was increased in our study, the values were within the normal range up to 1 h after infusion.

At the end of drug infusion, spontaneous breathing immediately returned in all dogs, and they could be quickly extubated (up to 5 min), with no time difference between the treatments. In a previous study using total intravenous anesthesia (TIVA) with propofol during a 1-hour infusion, the total recovery time was approximately 30.7 min (32). In another study using continuous infusion of propofol, the time to standing position was 52 ± 22 min after 1 h of infusion time (33). A study on the cumulative effect of propofol found that this effect is dose-dependent and evident in infusions over 60 min as the drug accumulated in less vascularized peripheral tissues, thus prolonging the recovery period (32).

The addition of remifentanil resulted in faster recovery than treatment with propofol alone, as observed in other studies (34,35). This result is mainly due to the smaller predicted propofol concentrations in the P-Rem treatment than in treatment with propofol alone.

Target-controlled infusion (TCI) is the most recommended of the continuous-infusion methods as it allows the best estimates of drug concentrations in the blood and reaches the required target concentration more quickly and precisely than traditional methods, therefore preventing cumulative effects. The context-sensitive half-life for propofol increases with infusion duration (36), which is why TCI anesthesia has been suggested as an alternative to prevent these cumulative effects (37).

No incidence of apnea was observed after the induction. Side effects were observed in only 1 animal in both treatments, when muscle tremors, forelimb hyperextension with relaxed hind limbs, and opisthotonus developed. These effects were observed soon after induction and throughout infusion. Excitatory phenomena have been detected after propofol was administered in dogs (38,39). The signs include muscle twitching, paddling, and limb rigidity with opisthotonus, with some signs persisting into the recovery period (38).

In conclusion, the hemodynamic changes observed in this study indicate that the cardiovascular system is compromised, although the dogs were healthy/euvolemic and no change in preload was carried out. More studies are required in order to evaluate the actual safety of the combination of propofol and remifentanil in patients with reduced cardiac reserve.

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