

Effects of ketamine, propofol and isoflurane on electrocardiographic variables in clinically healthy dogs premedicated with medetomidine and midazolam

Masoud Khaleghi¹, Ali Asghar Sarchahi^{2*}, Hossein Kazemi Mehrjerdi², Mehdi Rasekh³, Dariush Saadati⁴

¹ DVM Graduate, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran; ² Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran; ³ Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran; ⁴ Department of Food Hygiene, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran.

Article Info	Abstract
Article history: Received: 29 July 2023 Accepted: 08 January 2024 Available online: 15 April 2024	<p>The purpose of this study was to investigate the effects of three anesthetic agents, with premedication of medetomidine and midazolam, on electrocardiographic variables in dogs. Ten adult mixed breed dogs were used in a crossover design study, where they received ketamine, propofol and isoflurane treatments with a one-week washout period between them. In all three groups, medetomidine was administered first followed by midazolam after 15 min. Then, after 20 min, group 1 received ketamine intravenously (IV), group 2 received propofol (IV), and group 3 received isoflurane (inhalation). In all dogs, electrocardiographs were taken before and after premedication's, as well as every 15 min during anesthesia. Medetomidine significantly decreased heart rate and P wave amplitude and increased PR interval, R wave amplitude, QT interval, and T wave amplitude. Midazolam increased the amplitude of the R and T waves. Ketamine increased the heart rate and PR interval. Propofol increased the heart rate for up to 15 min, decreased the PR interval for up to 30 min, and the QT interval for up to 45 min. Isoflurane increased the heart rate and decreased the amplitude of R and T waves. The results showed that the drugs used in this study did not have many side effects on electrocardiographic variables and could be used without serious concern. The most important side effects observed were a severe reduction in heart rate and 1st degree atrioventricular (AV) block and, to a lesser extent, 2nd degree AV block caused by medetomidine and midazolam which were masked by the anesthetics.</p>
Keywords: Electrocardiographic variables Isoflurane Ketamine Medetomidine Propofol	

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Introduction

One method of investigating the side effects of drugs is to record and evaluate electrocardiograms. Electrocardiography (ECG) is one of the best methods for diagnosing drug poisoning and cardiac arrhythmias.¹ In a clinical setting, tranquilizers and sedatives are usually used to examine restless animals and also as pre-anesthesia to reduce the dosage of anesthetic drugs and prevent their adverse effects.² Currently, different anesthesia methods employing different pre-anesthesia agents are used in small animals. Some of the most important pre-anesthetic and anesthetic drugs used include medetomidine, midazolam, ketamine, propofol and isoflurane.

Medetomidine, as an alpha-2 agonist, is a sedative-hypnotic drug that acts centrally on alpha-2 adrenergic

receptors, primarily in the brainstem and locus coeruleus. It reduces sympathetic tone and peripherally causes vasoconstriction by activating sympathetic postsynaptic receptors. Therefore, its most important side effects include: (after an initial and short-lasting increase) a decrease in blood pressure and body temperature, respiratory depression, bradycardia, and diuresis.³⁻⁵

Midazolam, as a benzodiazepine receptor agonist, facilitates the action of gamma-aminobutyric acid (GABA) and increases the influx of chloride ions into cells. With the entry of chloride ions, the cell becomes hyperpolarized and the inhibitory effect of GABA is strengthened. By reducing the excitability of neurons, benzodiazepines reduce brain activity and cause muscle relaxation.⁶

Ketamine, a derivative of phencyclidine, is a selective and non-competitive antagonist of N-methyl-d-aspartate (NMDA) receptor which is used to induce and maintain

*Correspondence:

Ali Asghar Sarchahi. DVM, PhD

Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran

E-mail: sarchahi@um.ac.ir



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anesthesia. Ketamine can also be used as a pain reliever in low doses. In high doses, it may cause a series of side effects including increased heart rate, elevated arterial blood pressure and hallucinations.⁷⁻⁹

Propofol is an alkyl phenol derivative that reduces the metabolic activity of the brain by affecting on the inhibitory neurotransmitter GABA. Propofol also slows the release of GABA from its receptors, therefore, it increases the opening time of chloride channels. This drug is used for short-term sedation, long-term sedation, induction of general anesthesia, maintenance of anesthesia and epilepsy treatment.¹⁰

Isoflurane is an inhaled general anesthetic that is used to induce and maintain general anesthesia. It acts on the central nervous system by inhibiting the GABA, glycine and NMDA receptors. One of its most important side effects is lowering blood pressure.¹¹

These anesthetics may have side effects on the heart that restrict their use in certain situations. Some of the side effects of these drugs on the cardiovascular system have been identified,¹²⁻¹⁷ but their combined effects are still not fully understood. Thus, in this study, the effects of three anesthesia methods (ketamine, propofol, and isoflurane) with two premedication (medetomidine and midazolam) on electrocardiographic variables were investigated.

Materials and Methods

This study was approved by the Research Ethics Committee of University of Zabol, Zabol, Iran (Approval ID: IR.UOZ.REC.1401.005). This study was conducted on 10 intact adult mixed breed dogs of both sexes (four males and six females) aged between 16 and 36 months (mean \pm SD: 24.40 \pm 6.60 months) and weighting between 13.00 and 28.00 kg (mean \pm SD: 22.20 \pm 4.60 kg). All dogs included in the study were clinically healthy. All ten dogs were included in each of the following three treatment groups in a crossover design, with at least a 1-week washout period between treatments. Dogs were randomly selected to start in each group:

Group 1: The 15.00 $\mu\text{g kg}^{-1}$ medetomidine (Syva Laboratories S.A., Leon, Spain), intramuscularly (IM),¹⁸ 0.25 mg kg^{-1} midazolam (Exir Pharmaceutical Company, Boroujerd, Iran, IM),¹⁹ ketamine hydrochloride (6.00 mg kg^{-1} ; Bremer Pharma GmbH, Warburg, Germany, administered intravenously (IV) for induction and 3.00 mg kg^{-1} administered once every 15 min for maintenance).²⁰

Group 2: The 15.00 $\mu\text{g kg}^{-1}$ medetomidine (IM), 0.25 mg kg^{-1} midazolam (IM), and propofol (B. Braun Melsungen AG, Melsungen, Germany). Propofol was administered IV at a dose of 6.50 mg kg^{-1} for induction and at a rate of 0.25 mg kg^{-1} per min for maintenance of anesthesia.²¹ The maintenance dose of propofol was prescribed using a syringe infusion pump (SP-510; JMS Co. Ltd., Hiroshima, Japan).

Group 3: The 15.00 $\mu\text{g kg}^{-1}$ medetomidine (IM), 0.25 mg kg^{-1} midazolam (IM), and isoflurane (Piramal Critical Care Ltd., West Drayton, UK). In this group, the anesthesia was initially induced using 5.00% isoflurane in 100% oxygen administered through a mask. Tracheal intubation was then performed immediately and connected to the anesthesia machine. When the desired level of anesthesia was reached, it was maintained using 2.00% isoflurane in 100% oxygen.²²

The method and timing of drug administration were as follows: In all treatments, an intravenous line was placed in the cephalic vein and Ringer's solution was administered at a rate of 10.00 mL kg^{-1} per hr. additionally, an electrocardiogram was taken before drug injection to establish a baseline. Then, medetomidine was injected and another ECG was taken 15 min later at the time when the drug maximum effect was observed. Then, midazolam was injected immediately and an electrocardiogram was taken 20 min later when the maximum effect of the drug seemed to be present. Then, in each group, the desired anesthetic was administered immediately and maintained for 60 min with appropriate maintenance doses of each drug. During anesthesia an ECG was taken every 15 min. Only the dogs in the isoflurane group were intubated while all the dogs in the three groups were breathing spontaneously.

ECG recording. During the ECG recordings, the dogs were placed on their right lateral position and three standard bipolar limb leads I, II and III, and three augmented unipolar leads aVR, aVL and aVF were recorded on electrocardiograph papers (BCM-600; Bionics, Hongcheon-gun, South Korea). The sensitivity and speed of the device were set at 10.00 mm mV^{-1} and 50.00 mm per sec, respectively. Then, the heart rates, P wave duration and amplitude, QRS duration, R wave amplitude, PR interval, QT interval, T wave amplitude, T wave deviations from the baseline and mean electrical axis were calculated in lead II.

Statistical analysis. The normality of the data was checked using the Kolmogorov-Smirnov test. The variables measured at three timepoints, before drug injection (baseline values), after medetomidine and after midazolam injections in dogs of three treatment groups (30 measurements) were pooled. The measured data at these three timepoints were compared using repeated measures analysis of variance (ANOVA) and Dunnett's test. Also, for the data collected after the induction of anesthesia, the timepoint at which midazolam injected was considered as a reference. The data from the timepoints after anesthesia induction in each group were compared to the midazolam timepoint using repeated measures analysis of variance (ANOVA) and with Tukey's test. Data analysis was performed using statistical software SPSS Software (version 25.0; IBM Corp., Armonk, USA) and GraphPad Prism (version 9.0; GraphPad Software Inc., San Diego, USA). A significant level of $p < 0.05$ was considered significant.

Results

The results of the Kolmogorov-Smirnov test confirmed the normality of the data for all parameters. Table 1 shows the measured parameters in the timepoints before the drug injections (baseline values), after medetomidine and after midazolam injections.

As shown in the Table 1, after medetomidine injection compared to baseline values, the heart rate and P wave amplitude were decreased significantly ($p < 0.01$), however, the decrease in P wave duration was not significant. The PR interval, R wave amplitude, the QT interval and T wave amplitude were increased significantly ($p < 0.01$). However, there were no significant increase in QRS duration, the ST segment and the mean electrical axis.

After the injection of midazolam compared to medetomidine, there was a significant increase in R wave and T-wave amplitudes ($p < 0.01$). However, there were no significant changes observed in P wave duration, P wave amplitude, PR interval, QRS duration, QT interval and ST Segment. The heart rate and mean electrical axis were decreased, but these decreases were not statistically significant.

Table 2 shows the measured parameters after midazolam injection until 60 min later in three treatment groups of ketamine, isoflurane and propofol. For each parameter, the timepoint of midazolam injection was considered as a reference and the values of the variables at the subsequent timepoints were compared to the timepoint of midazolam injection.

In the ketamine treatment group (group 1), heart rate was increased after the induction of anesthesia and was significantly higher than the value measured after midazolam injection at all timepoints ($p < 0.01$). P wave duration and amplitude showed slight changes during the anesthesia period, but these changes were not significant. The PR interval began to decrease after the administration of anesthesia and by 60th min it was significantly lower

than the measurement taken after the injection of midazolam ($p < 0.05$). The R wave amplitude was gradually decreased until 30th min and then gradually increased but these changes were not statistically significant. However, at all timepoints, it was lower than the value measured after the injection of midazolam. Partial changes of QRS duration, Q-T interval, T wave amplitude and ST segment and mean electrical axis were not significantly different from the values measured after midazolam injection.

In propofol treatment group (group 2), after induction of anesthesia, the heart rate was increased so that it was significantly ($p < 0.01$) different in 15th min with the value measured after midazolam injection. After induction of anesthesia with propofol the P wave duration and amplitude were increased up to 45 min, then they started to decrease, but these changes were not significantly different from the values measured after midazolam injection. The PR interval started to decrease after induction of anesthesia with propofol, so that at 30 min after induction, it had a significant difference with the value measured after midazolam injection ($p < 0.05$). Then it started to increase until the end of anesthesia. The R wave amplitude began to decrease after the administration of anesthesia, so that, at 15 and 45 min after induction, there was a significant difference in comparison with the value measured after the injection of midazolam ($p < 0.05$). The QRS duration, QT interval, T wave amplitude, ST segment and mean electrical axis changes were not statistically different from the values measured after midazolam injection.

In the isoflurane treatment group (group 3), the heart rate was significantly increased ($p < 0.01$) at 15th min after anesthesia induction. It then continued to decrease until the 60th min. However, at all timepoints, the heart rate was significantly higher than the value measured after midazolam injection ($p < 0.05$). The P wave duration and amplitude were increased and the PR interval decreased gradually after induction of anesthesia, but these changes

Table 1. Mean and standard error of mean for measured variables of dogs (30 measurements) at different time-points before drug injections and after medetomidine and midazolam injections.

Parameters	Baseline values	After medetomidine	P ₁	After midazolam	P ₂
Heart rate (beats per min)	106.00 ± 5.300	51.000 ± 3.400	*	49.000 ± 2.600	NS
P-wave duration (sec)	0.038 ± 0.002	0.037 ± 0.001	NS	0.040 ± 0.001	NS
P-wave amplitude (mv)	0.170 ± 0.012	0.130 ± 0.010	*	0.130 ± 0.010	NS
PR interval (sec)	0.120 ± 0.002	0.142 ± 0.004	*	0.144 ± 0.003	NS
R amplitude (mv)	0.941 ± 0.072	1.030 ± 0.077	*	1.050 ± 0.068	*
QRS duration (sec)	0.093 ± 0.002	0.094 ± 0.002	NS	0.094 ± 0.002	NS
QT interval (sec)	0.174 ± 0.005	0.196 ± 0.004	*	0.205 ± 0.006	NS
T wave amplitude (mv)	0.111 ± 0.041	0.213 ± 0.049	*	0.345 ± 0.052	*
ST segment (sec)	0.011 ± 0.019	0.022 ± 0.020	NS	0.053 ± 0.020	NS
Mean electrical axis (°)	61.000 ± 3.600	61.000 ± 4.500	NS	56.000 ± 5.900	NS

P₁ compares the values after medetomidine injection to the baseline values and P₂ compares the effects of midazolam injection to medetomidine injection.

* indicates significant difference at the $p < 0.01$ level; NS shows statistically non-significant differences ($p > 0.05$)

were not significantly different from the values measured after midazolam injection. The amplitude of the R wave was gradually decreased until min 45. At this timepoint, it was significantly different from the value measured after midazolam injection ($p < 0.01$). After that, it started to increase, however, at 60th min, it was significantly less than the value measured after midazolam injection ($p < 0.05$). The changes in QRS duration and QT interval were not significantly different from the values measured after midazolam injection. The amplitude of the T wave was significantly decreased at 15th ($p < 0.01$), 30th ($p < 0.05$), and 60th min ($p < 0.05$). The ST segment was gradually decreased until 30th min and reached its lowest value and became negative at this point, and then increased, reaching its highest value at 60th min. However, these changes were not statistically significant when compared to the measured amount after the injection of midazolam. The changes in the mean electrical axis were not statistically significant compared to the value measured after midazolam injection.

In the present study, 21 dogs showed 1st degree atrioventricular block after medetomidine injection, 27 dogs after midazolam injection, 10 dogs in the ketamine group at the beginning of anesthesia (15th min), and seven dogs at the end of anesthesia (60th min). Additionally, seven dogs in the propofol group showed 1st degree atrioventricular block at the beginning of anesthesia, and 6 dogs at the end of anesthesia. In the isoflurane group, five dogs showed 1st degree atrioventricular block at the beginning of anesthesia and six dogs at the end of anesthesia.

Also, five dogs exhibited 2nd degree atrioventricular block after medetomidine injection, six dogs after midazolam injection and one dog after anesthesia induction with ketamine.

Sinus arrhythmia was observed in all dogs after injection of medetomidine and midazolam. Additionally, it was observed in seven dogs in the ketamine group, five dogs in the propofol group and five dogs in the isoflurane group.

Table 2. Mean and standard error of mean for measured parameters in ten dogs. The measured parameters have been compared to the time-point of midazolam injection.

Parameters	Groups	After midazolam injection	Time-points after anesthetic administration (min)			
			15	30	45	60
Heart rate (beats per min)	Ketamine	43.000 ± 3.000	69.000 ± 6.000 [†]	70.000 ± 6.000 [†]	72.000 ± 7.000 [†]	78.000 ± 6.000 [†]
	Propofol	52.000 ± 5.000	77.000 ± 8.000 [†]	67.000 ± 6.000	65.000 ± 8.000	69.000 ± 6.000
	Isoflurane	52.000 ± 5.000	92.000 ± 6.000 [†]	88.000 ± 8.000*	88.000 ± 7.000*	84.000 ± 5.000 [†]
P-wave duration (sec)	Ketamine	0.042 ± 0.003	0.041 ± 0.002	0.040 ± 0.002	0.041 ± 0.002	0.040 ± 0.002
	Propofol	0.038 ± 0.002	0.040 ± 0.001	0.042 ± 0.001	0.043 ± 0.002	0.040 ± 0.001
	Isoflurane	0.039 ± 0.002	0.040 ± 0.001	0.042 ± 0.003	0.042 ± 0.003	0.041 ± 0.003
P-wave amplitude (mv)	Ketamine	0.145 ± 0.016	0.150 ± 0.017	0.130 ± 0.017	0.155 ± 0.016	0.150 ± 0.019
	Propofol	0.121 ± 0.021	0.155 ± 0.014	0.165 ± 0.021	0.150 ± 0.037	0.155 ± 0.017
	Isoflurane	0.135 ± 0.018	0.165 ± 0.024	0.156 ± 0.024	0.183 ± 0.024	0.161 ± 0.016
PR interval (sec)	Ketamine	0.151 ± 0.004	0.144 ± 0.004	0.143 ± 0.003	0.150 ± 0.007	0.138 ± 0.005*
	Propofol	0.148 ± 0.004	0.139 ± 0.006	0.138 ± 0.005*	0.137 ± 0.006	0.138 ± 0.006
	Isoflurane	0.133 ± 0.006	0.127 ± 0.008	0.133 ± 0.008	0.129 ± 0.006	0.124 ± 0.005
R amplitude (mv)	Ketamine	1.100 ± 0.132	1.035 ± 0.146	1.030 ± 0.143	1.050 ± 0.139	1.081 ± 0.145
	Propofol	1.045 ± 0.113	0.935 ± 0.111*	0.930 ± 0.129	0.883 ± 0.159*	0.895 ± 0.138
	Isoflurane	1.005 ± 0.120	0.985 ± 0.109	0.619 ± 0.141	0.683 ± 0.114 [†]	0.739 ± 0.145*
QRS duration (sec)	Ketamine	0.095 ± 0.003	0.098 ± 0.002	0.094 ± 0.003	0.094 ± 0.003	0.099 ± 0.001
	Propofol	0.092 ± 0.003	0.091 ± 0.003	0.091 ± 0.003	0.09 ± 0.003	0.091 ± 0.003
	Isoflurane	0.094 ± 0.003	0.089 ± 0.004	0.090 ± 0.005	0.092 ± 0.004	0.091 ± 0.004
QT interval (sec)	Ketamine	0.211 ± 0.011	0.199 ± 0.006	0.205 ± 0.009	0.201 ± 0.012	0.191 ± 0.008
	Propofol	0.203 ± 0.009	0.192 ± 0.011	0.203 ± 0.012	0.211 ± 0.013	0.220 ± 0.011
	Isoflurane	0.202 ± 0.010	0.208 ± 0.011	0.193 ± 0.011	0.204 ± 0.014	0.208 ± 0.010
T wave amplitude (mv)	Ketamine	0.365 ± 0.081	0.370 ± 0.073	0.315 ± 0.067	0.385 ± 0.049	0.431 ± 0.057
	Propofol	0.315 ± 0.082	0.300 ± 0.075	0.295 ± 0.087	0.300 ± 0.011	0.290 ± 0.096
	Isoflurane	0.355 ± 0.110	0.025 ± 0.113 [†]	0.022 ± 0.128*	0.067 ± 0.014	0.028 ± 0.137*
ST segment (sec)	Ketamine	0.035 ± 0.045	0.090 ± 0.033	0.090 ± 0.037	0.095 ± 0.027	0.113 ± 0.031
	Propofol	0.070 ± 0.029	0.050 ± 0.032	0.055 ± 0.029	0.033 ± 0.036	0.055 ± 0.035
	Isoflurane	0.055 ± 0.032	0.020 ± 0.035	-0.006 ± 0.038	0.050 ± 0.034	0.072 ± 0.042
Mean electrical axis (°)	Ketamine	66.000 ± 4.300	67.000 ± 5.800	64.000 ± 5.700	61.000 ± 4.600	67.000 ± 8.500
	Propofol	46.000 ± 15.600	38.00 ± 1 4.400	49.000 ± 11.800	43.000 ± 17.200	48.000 ± 17.800
	Isoflurane	57.000 ± 7.000	50.000 ± 9.600	58.000 ± 15.600	41.000 ± 20.400	46.000 ± 14.900

* Indicates a significant difference at the level of $p < 0.05$, and [†] indicates a significant difference at the level of $p < 0.01$.

Discussion

In the present study, we aimed to utilize anesthesia methods commonly practiced in clinics and examine the impact of certain routinely administered drugs on ECG. In the present study, after reaching the maximum effect of medetomidine, all dogs became motionless and assumed a lateral recumbent position. They did not react to manipulation and ECGs were taken at this time. In the case of midazolam, attempts were made to take the ECGs at the time when the drug showed its maximum effect. However, it was challenging to determine the exact time of the maximum effect of midazolam due to the prior use of medetomidine.

It seems that changes in the number of heartbeats can greatly impact other ECG indices. Therefore, drugs that affect the number of heartbeats may also change these ECG indices. In the present study, heart rates were significantly decreased after the injection of medetomidine which was consistent with previous studies.²³ The peripheral vasoconstriction effect of alpha-2 agonists increases arterial blood pressure leading to reflex bradycardia.²⁴ Additionally, these drugs decrease sympathetic activity and increase parasympathetic activity in the central nervous system that decrease the inhibitory effects on the cardiac vagal neurons mediated by GABA and glycine which may contribute to the bradycardia.²⁵ Moreover, the increase in the number of cases of sinus arrhythmia after the administration of medetomidine in the present study provided further evidence of the increase in parasympathetic tone.

In the present study, after the injection of medetomidine, only the decrease in the amplitude of the P wave was found to be significant. It has been found that the amplitude of the P wave in dogs is related to their heart rate. Specifically, a lower heart rate corresponds to a decrease in the recorded P wave amplitude.^{26,27} Alpha 2 agonists such as medetomidine can reduce the P wave amplitude by suppressing the sympathetic system.²⁸ In a study conducted by Sarchahi *et al.*, a decrease in P wave amplitude was observed after intramuscular injection of xylazine. Also, Rafee *et al.* and Mosallanejad *et al.* reported a decrease in P wave amplitude after intramuscular injection of medetomidine. Our study was consistent with their studies.^{29,30}

The significant increase in the PR interval observed after the injection of medetomidine in the present study might be attributed to the decrease in heart rate. The PR interval reflects the electrical conduction from the atria to the ventricles. Administration of alpha-2 agonists is associated with delayed conduction through the AV node which can sometimes lead to first-degree AV block.³¹ This condition is characterized by a prolongation of the PR interval exceeding 130 msec.¹ Stimulation of the parasympathetic nervous system causes a decrease in the heart

rate resulting in an increase in the PR interval. This increase in the PR interval has also been reported in previous studies.^{28,29,32} Sarchahi *et al.* reported a significant inverse correlation between heart rate and the PR interval after the administration of xylazine which is an alpha-2 agonist belonging to the same family as medetomidine.³⁰

The present study found that the increase in R wave amplitude and QRS duration after the injection of medetomidine was not significant. This finding was in consistent with the study conducted by Yaygingül and Belge who reported a non-significant increase in R wave amplitude and QRS duration after medetomidine injection.³³ On the other hand, Ahmad *et al.* reported an increase in R wave amplitude with dexmedetomidine alone and in combination with midazolam.³⁴ A higher R wave amplitude may indicate higher systolic pressure.³⁵

A significant increase in the QT interval has been reported in various other studies after the administration of alpha 2 agonists,²⁸⁻³⁰ which can indicate a slower repolarization of the ventricles.³⁶ A decrease in the heart rate can cause prolongation of the QT interval³⁷ while the heart rate and the QT interval may change independently of each other.³⁰ In the present study, the amplitude of the T wave was increased after administration of medetomidine. The increase in T wave amplitude has been observed in other studies that used medetomidine and dexmedetomidine.^{28,29}

Sinus arrhythmia and first- and second-degree heart block caused by alpha-2 agonists are due to the stimulation of the vagus nerve by these drugs. These cases were observed in the present study and have also been reported in other studies as well.^{29,38}

After administration of midazolam, only the increase in the amplitude of R and T waves was significant and changes in other indices were minor and not significant. Considering that midazolam was prescribed after medetomidine, it seems that many of its effects were masked by medetomidine and its overall effects were not observed. Since there were no significant changes in the duration and amplitude of the P wave after midazolam injection, it can be assumed that midazolam had no effect on the P wave.³⁴

In the present study, following the administration of ketamine, the heart rate started to increase, so that its value was significantly higher at all timepoints compared to the value measured after the injection of midazolam. Ketamine increases the heart rate due to its vagolytic effect.³² This increase in heart rate leads to a decrease in PR and QT intervals. In the present study, there was a gradual decrease in PR interval until 60 min after ketamine administration. Additionally, there was a slight and non-significant decrease in QT interval. These changes might be attributed to the increase in the heart rate.

In addition, it has also been observed that ketamine has antiarrhythmic properties³⁹ and combining ketamine with benzodiazepines achieves greater cardiorespiratory

stability.⁴⁰ In the present study, the administration of medetomidine and midazolam resulted in an increased PR interval while the administration of ketamine led to a decreased PR interval within the normal range (0.06 to 0.13 sec).³²

It has been reported that in dogs under ketamine-diazepam anesthesia, QRS duration was increased in cocker spaniels while decreased in German shepherds.²⁶ This suggests that the breed of dogs may affect QRS duration. A similar irregular pattern was observed in studies conducted on dexmedetomidine alone and also in combination with midazolam with ketamine or propofol by Ahmad *et al.*³⁴

After induction of anesthesia with propofol, there was a significant increase in heart rate and R wave amplitude in the 15th min. A dramatic and significant increase in heart rate has been reported in previous studies following administration of propofol.^{41,42} The reason for this increase in the number of heart rate could be attributed to the decrease in peripheral vascular resistance and vasodilation which occurs as a result of the inhibition of sympathetic tone by propofol. This increasing effect on heart rate is more noticeable in the first few min after injection of propofol, as observed in the present study at the 15th min, and then it was decreased. Cattai *et al.* have also reported a similar increase in heart rate during the initial minutes.¹³

On the other hand, Ikeno *et al.* reported that propofol had no direct effect on electrocardiographic variables. In their study, propofol had no effect on the conduction velocity of the electrical current in the atria and ventricles as well as in the SA and AV nodes. As a result, no changes were observed in heart rate, PR interval, QRS duration and QT interval.⁴³ It has been reported that dose of propofol may also affect the heart rate. Low doses of propofol have been found to increase the heart rate, while high doses have been found to decrease heart rate. In these studies, the effects of propofol on electrocardiographic variables have been investigated in various species and at different time intervals after administration of the drug. Therefore, it appears that further studies are still needed to conduct a comprehensive investigation of its effect.⁴⁴

After the induction of anesthesia with isoflurane, the heart rate was significantly increased so that at all timepoints following the induction of anesthesia it was remained significantly higher compared to the value measured after the injection of midazolam. However, the maximum increase in heart rate was observed at 15th timepoint ($p < 0.01$). The R wave amplitude was decreased after induction of anesthesia with isoflurane until 45 min. At this timepoint, there was a significant difference compared to the value measured after midazolam injection ($p < 0.01$). Afterward, the amplitude started to increase. This result was consistent with the results of Liu *et al.* However, in their study, the heart rate was

decreased when dexmedetomidine was administered before isoflurane.⁴⁵ In the present study, the heart rate was decreased significantly after administration of medetomidine and midazolam, but after administration of isoflurane, it was increased again and reached its normal level. These results showed that isoflurane neutralized the heart rate-lowering effect of medetomidine. The duration and amplitude of the P wave was not changed significantly in the present study, which was consistent with the findings of Liu *et al.* Additionally, changes in the PR and QT interval as well as QRS duration were corresponded to changes in heart rate. It means that with the increase in heart rate in 15 min after isoflurane induction, the PR and QT intervals were decreased. The decrease in the R wave amplitude indicated that isoflurane had an effect on the conduction of electric current in the ventricles. In the present study, isoflurane caused a significant decrease in T wave amplitude. The reduction of T wave amplitude in the present study was contrary to the results of the study by Liu *et al.* In the detailed examination of the T wave amplitude in the present study, it was observed that the direction of the T wave became negative in many dogs after the administration of isoflurane. However, the amplitude of the waves was not actually decreased. As a result, the overall summation of the T wave amplitude was decreased leading to a significant difference in the T wave amplitude. Isoflurane has been reported to cause myocardial ischemia through a mechanism that is not dependent on blood pressure and heart rate. Increased lactate production may be the cause of this ischemia.⁴⁶

The diagnostic value of T wave changes in dogs is very limited compared to humans as T wave morphology is highly variable in small animals.⁴⁷ The morphology of the T wave, *i.e.* the amplitude and duration, did not show any regular pattern during the entire observation period and remained in normal values. T wave may be positive, negative or biphasic^{1,32} and all three types were observed in the present study.

In the present study, despite minor changes in some cardiac variables, the electrical axis of the heart was not changed in any of the groups and was in the normal range. This finding was similar to the findings of Yaygingül and Begle.³³

In the present study, medetomidine and midazolam were administered separately as pre-anesthetic medications. We considered the measurement times based on the time of the peak effect of the drugs.^{31,48} Premedication drugs are typically administered simultaneously either mixed in the same syringe if they are compatible or in separate syringes if they are not compatible. But we wanted to assess the impact of each drug separately. In our study, we exclusively investigated the effects of medetomidine. In case of midazolam, the effects observed after its administration were attributed to midazolam compared to the effects observed after

administration of medetomidine. If we had mixed it, the effect would have been masked by midazolam, and the individual effects of both drugs would not have been clearly determined.

Our results showed that the drugs used in this study did not have many side effects on electrocardiographic variables and could be used without serious concern. The most important side effects were severe reduction in heart rate and 1st degree Atrioventricular (AV) block, and to a lesser extent, 2nd degree AV block caused by medetomidine and midazolam. These effects were masked and resolved by the anesthetics.

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Conflict of interest

The authors report no conflicts of interest.

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