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Original Research Article

Investigation of the Effects of Different Anesthesia Combinations on Cardiovascular Parameters in White New Zealand Rabbits

Key words

electrocardiography;
radiography;
rabbit;
VHS

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Abstract: The objective of this study is to assess the morphological and physiological alterations in the heart resulting from four distinct anesthesia combinations, with midazolam, medetomidine, and dexmedetomidine applied as preanesthetics in White New Zealand rabbits. For the study, a total of 32 white New Zealand rabbits were divided into four different groups. The vertebral heart score was measured in rabbits before (T_0) and at 5 (T_5), 10 (T_{10}), 30 (T_{30}), 50 (T_{50}) and 70 (T_{70}) minutes during the experiment. Concurrently, measurements were taken for the electrocardiographic parameters, all at consistent time intervals. Heart frequency, respiratory rate, rectal temperature, mean arterial pressure and peripheral blood oxygen saturation were measured for a total of 60 minutes with 5 minutes intervals before and during preanesthesia. The vertebral heart score changed in all groups except the Mid+Med group. In the electrocardiographic assessment, in the Mid+Med, Dex, and Mid+Dex groups, an extension in the duration of the QRS wave and QT interval was observed, while no significant change was detected in the durations of the PR interval and T wave. Conversely, in the Me group, a distinct prolongation was observed in the duration of the P wave. Peripheral blood oxygen saturation values increased, heart frequency, mean arterial pressure and rectal temperature parameters decreased in entire groups. Following a thorough analysis of all the data in this study,it was observed that the morphological and physiological effects on the heart induced by the Mid+Med group resulted in less pronounced changes compared to the other groups.

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Introduction

Among the various species, the New Zealand white rabbit is less aggressive than other species, has short life cycles and minimal health problems, and is easily accessible and affordable (1). Many experimental studies require sedation or anesthesia. Since the mortality rate due to anesthesia in rabbits is quite high (2), various anesthetic drugs and routes of administration have been investigated for protocols that minimize complication rates (3).

Pre-anesthesic drugs essentially, medetomidine and dexmedetomidine are highly selective, specific, and strong α2-adrenoreceptor agonists used mainly to provide sedation, analgesia, and antinociception. Adverse cardiovascular effects such as bradycardia, arrhythmia, hypertension or hypotension, and reduced cardiac output are also seen similarly to other α2-adrenoreceptor agonists. Medetomidine and dexmedetomidine cause a dose-dependent decrease in heart rate (HR), mean arterial pressure (MAP), and respiratory frequency (fR) in rabbits (4,5). Midazolam is a gamma-aminobutyric acid A receptor allosteric modulator that provides sedation without analgesia. In rabbits, midazolam administration induces sedation with excellent muscle relaxation, although depression of the cardiovascular and respiratory systems is minimal (6).

Radiography is the standard method for assessment of the respiratory tract anatomy as well as cardiac size and shape (7). Electrocardiography (ECG) is another non-invasive technique for assessing cardiac rhythm and electrical activity. These diagnostic methods are complementary in clinical practice (8).

Medetomidine, dexmedetomidine, and combinations of these sedatives with midazolam have been used for premedication in previous studies (6,9,10,11). However, studies comparing the effects of these drugs on the cardiovascular system are limited. This experiment was conducted to compare some cardiovascular effects of medetomidine (Med) and dexmedetomidine (Dex) alone and in combination with midazolam (Mid+Med, Mid+Dex) for premedication in White New Zealand rabbits. We hypothesized that the use of medetomidine and dexmedetomidine as preanesthetics would cause minimal cardiovascular effects, and in addition, the use of midazolam in combination with preanesthetics would further reduce the complications.

Material and methods

Animals

All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and approved by Ataturk University Local Board of Ethics Committee for Animal Experiments (no. 274/2021).

Thirty-two male New Zealand white rabbits (American Society of Anesthesiologists physical status I), aged 12–36 months and weighing 4.3 ± 0.4 kg, were obtained from the Medical Experimental Application and Research Centre of Ataturk University (Erzurum, Turkey). All rabbits were housed in individual stainless steel cages (60 × 50 × 60 cm high) without bedding material in a single room (temperature of 22 ± 2°C, humidity of 40%–60%, and illumination 12:12 hours light:dark cycle). The animals were fed a commercial pelleted diet and were provided water ad libitum.

Anesthesia Protocol

Rabbits that were not water-restricted before anesthesia but fasted for 4 hours were randomly divided into 4 groups. The groups were as follows: Medetomidine (0.3 mg/kg, Zoetis, New Zeland) (Group Med), Midazolam (1mg/kg, Zolamid 15 mg/3ml, Mefar Farma, Turkey) + Medetomidine (0.05 mg/kg, Zoetis, New Zeland) (Group Mid+Med), Dexmedetomidine (0.05 mg/kg, Sedadomid 200 µg/2ml, Kocak Farma, Turkey) (Group Dex), Midazolam (1 mg/kg) + Dexmedetomidine (0.025 mg/kg) (Group Dex). Preanesthetic agents were injected intramuscularly (IM) (5 ml/22 G cannula, Ayset, Tepefarma, Turkey) into the musculus quadriceps muscle group after T_0 measurement. At T_5, ketamine (30 mg/kg, ketasol 10%, Interhas, Turkey) was administered IM in entire groups to provide induction. For intubation, 10% local anesthetic spray (Vemcaine 10% pump oral spray, VEM, Tekirdag, Turkey) was used. After the rabbits were placed on the table in the dorsal position with the head and spine in a straight alignment, the intubation step was performed blindly using a laryngeal mask (No. R4, V-Gel Advanced Veterinary Airway Management System, Docsinnovet, London, UK), and the cuff of the laryngeal mask was inflated with 1 ml of room air through a syringe without using a manometer when sufficient depth of anesthesia was obtained (no swallowing reflex). Anesthesia maintenance isoflurane (Forane 99.9%, Aesica, Queenborough, UK) was administered in 100% oxygen at an oxygen flow rate of 2%/1L/min.

Radiographic Analysis

A radiographic evaluation of the VHS values of rabbits was performed in the right laterolateral position. For radiographic examinations, a 5 kilowatt (kW), 110 kilovolt (kV)/100 milliampere (mA) stationary X-ray machine (Mex-100, Oberhausen, Germany) was used. Radiographs were taken with a 35x43 x-ray cassette (DRx, Carestream, New York, United States of America) at 50 KV, 4.00 mAs, 100 mA dose, and at a distance of 80 cm from the tissue to be examined. The measurements were performed in the right lateral position before anesthesia (T_0), 5 (T_5), 10 (T_{10}), 30 (T_{30}), 50 (T_{50}), and 70 (T_{70}) minutes after anesthesia.

The vertebral heart score (VHS) was measured according to the protocol established by Ljubica (12). On the x-rays, the long heart axis (LA) was found by measuring from the farthest point in the ventral contour of the heart's x-ray image to the base of the heart, which is where the carina cranioventral border is. The short axis (SA) was measured at the widest cardiac image point on a line perpendicular to the long axis at the level of the clavicle vena cava. Both measurements (long and short axes) were compared with the distance from the cranial edge of the 4th thoracic vertebra (T4) to the cranial edge of the 5th thoracic vertebra. The VHS was calculated according to the formula given below:

$$VHS = (LA/T4) + (SA/T4)$$

Electrocardiographic Analysis

Biopac Systems, Inc Mp 150 400 kHz (Aero Camino, Goleta, United States of America) ECG device was used for electrocardiography measurement. The standard alligator clip electrodes, with the teeth curled outward, were applied just caudoproximal to each elbow and mid-caudal to the skin fold between the hocks and buttocks. The electrodes were placed in accordance with the manufacturer's instructions, similar to their placement in cats and dogs. Approximately 1 ml of alcohol was applied to each skin-electrode interface to enhance conductivity.

Electrocardiographic measurements were taken in the minutes specified in the VHS measurement. The evaluation of ECG analysis was performed with the Acqknowledge program (version 4.1.1.1 AcqKnowledge for MP Systems) (Intel® Core I5 CPU M460 2.53 Ghz, HP, California, United States of America). All measurements were taken for an average of 3 minutes, and the results were recorded. The amplitudes (mV) and durations (ms) of the P wave, QRS wave, and T wave were measured, while the durations (ms) of the PR interval and QT intervals were recorded by the same person at the same time.

Monitoring

In all animals, the HR and peripheral oxygen saturation (SpO_2) were monitored from the patient monitor (Comen C80-V, China) throughout the study by placing the tongue probe of the bedside patient on the tongue of the rabbits. Rectal temperature (T) was measured from the dorsal wall of the rectum with a digital thermometer throughout the study. *f*R was monitored on the patient monitor throughout the study by placing crocodile-tipped clips after shaving the skin on the musculus triceps on the forelimbs, the skin on the musculus quadriceps on the hindlimbs, and finally the skin dorsally (Heiniger Saphir, Switzerland). MAP was monitored on the patient monitor throughout the study using a size 2 cuff (4-6 cm) of the patient monitor after shaving the proximal tarsal joint of the left hind leg. These physiologic parameters of the rabbits were measured and recorded every 5 minutes for a total of 60 minutes with the aforementioned methods.

Statistical Analysis

Power analysis was performed to determine the minimum number of animals required in each group (PS-Power and Sample Size Calculation, Version 3.1.2, Vanderbilt University, TN, USA). Accordingly, in a calculation with a Type I error (α) of 0.05 and a Type II error (power, β) of 0.95, it was determined that 8 rabbits were required in each group for a difference of 0.2 (standard deviation ± 0.1) between the measured VHS values to be considered statistically significant between the groups. The difference in VHS values due to the administration of medetomidine in rabbits was investigated as a preliminary study before the main study. This preliminary study was utilized to generate the data for the current study.

All data used in the study were analyzed using SPSS software (IBM Company, SPSS Inc., IL, USA). The Shapiro-Wilk test was used before the analysis to determine the normal distribution of the data. Normally distributed data were analyzed using repeated analysis of variance (ANOVA). In cases where the assumption of sphericity was not met, the Greenhouse-Geisser or Huynh-Feldt value was used as the basis for the data obtained from the test results. Subsequently, differences between the groups were determined using the post-hoc Tukey test. For non-normally distributed data, the Kruskall-Wallis test followed by Dunn's multiple comparison test was used. All data were presented as mean ± standard deviation (SD), and p values <0.05 were considered statistically significant.

Table 1: VHS measurements before and during the experiment

	Time					
Groups	**T_0**	**T_5**	**T_{10}**	**T_{30}**	**T_{50}**	**T_{70}**
Med	7.75	7.8	7.8	7.8	7.85	7.95
	(6.7-7.8)[ab]	(6.8-8.5)*	(6.8-8.2)	(6.8-8.3)*	(6.9-8.4)*	(7-8.5)*[#]
Mid+Med	7.8	7.75	7.7	7.7	7.75	7.75
	(7.5-8.1)[a]	(7.5-8)	(7.6-8.2)	(7.3-7.9)	(7.3-7.9)	(7.4-7.9)
Dex	7.4	7.45	7.55	7.65	7.45	7.3
	(7-7.9)[b]	(7-8)	(7.2-8)*	(7.2-8)*	(7.1-7.9)	(6.9-7.8) [#]
Mid+Dex	7.7	7.7	7.9	7.65	7.65	7.5
	(7.5-7.9)[ab]	(7.5-8)	(7.5-8.1)*^	(7.3-7.9)[#]	(7.3-8)[#]	(7.3-7.8)*^[#]

Note: Measurements were recorded before drug administration (baseline) and every 5 minutes under anesthesia. Data are expressed as median (range). Different letters indicate differences in the same time period ($p<0.05$). Different letters indicate differences within the same time period ($p<0.05$). * indicates a within-group difference with T_0 ($p<0.05$). ^ indicates a within-group difference with T_5 ($p<0.05$). # indicates a within-group difference with T_{10} ($p<0.05$). The difference between groups for the same time period is indicated with [a and b].

Results

During the study, one of the rabbits in the Med group developed dyspnea at 55 minutes during anesthesia, and breathing became regular with pure oxygen support. Two rabbits in the Mid+Med group showed intermittent apnea for an average of 1 minute after ketamine administration. These rabbits were included in the study. At T_{15}, one rabbit in the Mid+Med group died. A new rabbit was used to replace the deceased rabbit, and the study was continued.

VHS measurement increased from T_0 to T_{70} following sedation in the Med group. The VHS value did not change in the Mid+Med group ($p<0.05$). In the Dex and Mid+Dex groups, an increase was observed until T_{10} and T_{30}, respectively, and then a decrease was observed. There was no statistically significant difference between the groups ($p>0.05$, Table 1).

P wave duration measurements showed a statistically significant increase at T_{50} in the Med group compared to T_5. In PR interval duration, QRS wave amplitude duration, and QT interval duration measurements, there was no statistically significant difference between groups. In T wave duration measurements, an inter-group difference was found at T_{70} ($p<0.05$, Table 2).

There was a gradually decrease in HR and T measurements in all groups until T_{60}. In addition, there was a difference between the groups in HR measurements from T_5 to T_{50} and in T measurements at T_{35} ($p<0.05$). In *f*R measurement, a statistically significant decrease was observed in the Med group at T_{40} and T_{60} compared to T_0 ($p<0.05$). In MAP value measurements, there was an increase in the Mid+Dex group at T_5 compared to T_0 and a gradual decrease after T_5 until T_{60} ($p<0.05$). There was a difference between the groups in MAP between T_{20} and T_{60}. Hypotension (MAP below 60 mmHg) was observed only in the Mid+Dex group. While no change was observed in the Med group in SpO_2 measurements, an increase was observed in the Mid+Med, Dex and Mid+Dex groups until T_{60}. There was also a statistically significant difference between the groups between T_5 and T_{20} (Table 3).

Discussion

The midazolam-medetomidine (Group Mid+Med) anesthesia combination was found to cause smaller changes in morphological and physiological effects on the heart compared to the other groups. An increase was observed in the VHS parameter in the Med group. While no change was observed in the Mid+Med group, an increase and then a decrease were observed in the Dex and Mid+Dex groups. The study revealed that P wave duration increased solely in the Med group. Prolongation in QRS wave and QT interval durations was observed, with no change in PR interval or T wave duration. Although not reaching statistical significance, the Mid+Med, Dex, and Mid+Dex groups exhibited a trend towards prolonged QRS wave and QT interval durations. Heart rate (HR), temperature (T), respiratory rate (*f*R), and mean arterial pressure (MAP) values decreased in all groups, while oxygen saturation (SpO_2) increased in all groups except the Med group.

During the study, the occurrence of dyspnea in one rabbit in the Med group and apneic respiration in two rabbits in the Mid+Med group was attributed to respiratory system depression following ketamine administration. This association was previously noted in a scientific study conducted on Wistar rats (13).

Moarabi et al. found an average VHS value of 7.8±0.33 in their radiographic assessment of New Zealand rabbits in the right lateral position. (14). Our study revealed that the Med, Mid+Med, and Mid+Dex groups exhibited a similar trend in T_0 measurement data compared to Moarabi et al.'s findings; however, the Dex group showed a comparatively lower VHS measurement. The underlying cause of this discrepancy is postulated to be the higher intrathoracic fat volume observed in rabbits as compared to other species. This results in a more cranial positioning of the rabbit's heart on lateral radiographs, leading to the superimposition of the fat layer with the cranial aspect of the heart and the consequent formation of artifacts. Fractional shortening (FS) is an index used to assess left ventricular systolic performance, and it has been reported to significantly decrease after dexmedetomidine administration in a study (14). In another study, it was reported that medetomidine administration led to a decrease in fractional shortening similar to that observed with dexmedetomidine administration (15). In parallel with these findings, it has been stated that the use of medetomidine and dexmedetomidine leads to an increase in E-point septal separation, resulting in left ventricular dilation and an observed enlargement in the cardiac silhouette. (15,16,17). Similarly, it was hypothesized that the increase in VHS measurement in the Med, Dex, and Mid+Dex groups in our study is related to cardiomegaly resulting from left ventricular dilation due to delayed atrioventricular conduction. The reason for the absence of any changes in the Mid+Me group is speculated to be the antiarrhythmic effect shaped by midazolam usage, as also suggested by Dupras et al., which may prevent slowing of cardiac conduction (18). The decrease in VHS at T_{50} and T_{70} time intervals in the Dex group, as well as at T_{30}, T_{50}, and T_{70} time intervals in the Mid+Dex group, is concluded to be potentially attributed to the shortened half-life of dexmedetomidine, as defined in previous studies (19), and the reduction in vascular resistance by ketamine, which may alleviate the atrioventricular delay caused by dexmedetomidine (20,21).

In the electrocardiographic assessment, the recording in Lead II indicated a positive P wave, QRS complex, and T wave. In mice administered with xylazine and ketamine, a decrease in the amplitude and an increase in the duration of the P wave have been reported (22). On the other hand,

Table 2: ECG parameter measurements before and during the experiment

		Time					
	Groups	**T_0**	**T_5**	**T_{10}**	**T_{30}**	**T_{50}**	**T_{70}**
P-Wave Amplitude	Med	0.05±0.03	0.05±0.02	0.04±0.01	0.03±0.01	0.04±0.02	0.03±0.01
	Mid+Med	0.08±0.02	0.07±0.02	0.06±0.02	0.06±0.02	0.06±0.05	0.04±0.02
	Dex	0.06±0.02	0.07±0.02	0.05±0.02	0.07±0.02	0.06±0.05	0.04±0.02
	Mid+Dex	0.06±0.01	0.05±0.01	0.06±0.01	0.04±0.02	0.06±0.02	0.15±0.28
P-Wave Duration	Med	0.03±0.01	0.03±0.01	0.04±0.02	0.04±0.01	0.04±0.01^	0.06±0.05
	Mid+Med	0.03±0.06	0.03±0.01	0.03±0.01	0.03±0.01	0.05±0.02	0.05±0.02
	Dex	0.03±0.01	0.03±0.01	0.03±0.01	0.05±0.01	0.05±0.03	0.04±0.01
	Mid+Dex	0.03±0.03	0.03±0.01	0.03±0.01	0.03±0.01	0.03±0.01	0.03±0.01
PR Interval Duration	Med	0.05±0.03	0.04±0.01	0.06±0.03	0.05±0.01	0.05±0.01	0.05±0.01
	Mid+Med	0.04±0.01	0.04±0.01	0.04±0.01	0.04±0.01	0.06±0.02	0.06±0.01
	Dex	0.04±0.01	0.04±0.01	0.05±0.01	0.06±0.02	0.06±0.02	0.05±0.01
	Mid+Dex	0.04±0.01	0.04±0.01	0.04±0.01	0.04±0.01	0.04±0.01	0.05±0.01
QRS Complex Amplitude	Med	0.12±0.07	0.12±0.04	0.10±0.06	0.10±0.05	0.07±0.02	0.07±0.02
	Mid+Med	0.14±0.04	0.12±0.04	0.13±0.04	0.11±0.04	0.09±0.05	0.08±0.04
	Dex	0.13±0.04	0.13±0.03	0.12±0.03	0.11±0.04	0.12±0.03	0.13±0.04
	Mid+Dex	0.11±0.02	0.11±0.02	0.11±0.02	0.11±0.01	0.12±0.03	0.22±0.31
QRS Complex Duration	Med	0.16±0.04	0.15±0.03	0.14±0.03	0.14±0.027	0.14±0.04	0.14±0.05
	Mid+Med	0.13±0.01	0.13±0.01	0.13±0.01	0.15±0.023	0.14±0.03	0.15±0.03
	Dex	0.14±0.02	0.15±0.01	0.14±0.02	0.15±0.028	0.16±0.03	0.17±0.03
	Mid+Dex	0.13±0.02	0.13±0.01	0.14±0.02	0.15±0.025	0.15±0.02	0.15±0.02
QT Interval Duration	Med	0.22±0.06	0.22±0.05	0.21±0.06	0.21±0.07	0.22±0.09	0.24±0.06
	Mid+Med	0.18±0.02	0.17±0.02	0.18±0.01	0.20±0.04	0.21±0.04	0.21±0.04
	Dex	0.18±0.02	0.20±0.02	0.19±0.03	0.20±0.06	0.21±0.04	0.23±0.04
	Mid+Dex	0.18±0.02	0.18±0.02	0.18±0.02	0.20±0.03	0.20±0.02	0.21±0.02
T-Wave Amplitude	Med	0.06±0.04	0.06±0.03	0.05±0.01	0.07±0.05	0.06±0.06	0.04±0.01
	Mid+Med	0.08±0.03	0.08±0.03	0.07±0.02	0.06±0.03	0.06±0.04	0.05±0.02
	Dex	0.07±0.02	0.07±0.03	0.06±0.02	0.08±0.05	0.07±0.03	0.07±0.02
	Mid+Dex	0.05±0.02	0.06±0.02	0.06±0.02	0.06±0.02	0.06±0.02	0.09±0.09
T-Wave Duration	Med	0.05±0.03	0.06±0.04	0.05±0.03	0.06±0.02	0.07±0.03^{a}	0.07±0.02^{a}
	Mid+Med	0.03±0.01	0.04±0.01	0.03±0.01	0.04±0.01	0.05±0.02^{ab}	0.06±0.02^{ab}
	Dex	0.03±0.01	0.03±0.01	0.04±0.01	0.05±0.04	0.04±0.01^{ab}	0.04±0.01^{b}
	Mid+Dex	0.03±0.01	0.03±0.01	0.03±0.01	0.04±0.01	0.04±0.01^{b}	0.04±0.01^{b}

Note: Measurements were recorded before drug administration (baseline) and every 5 minutes under anesthesia. Data are expressed as mean ± standard deviation. Different letters indicate differences in the same time period ($p<0.05$). Different letters indicate differences a within the same time period ($p<0.05$). * indicates a within-group difference with T_0 ($p<0.05$). ^ indicates within-group difference with T_5 ($p<0.05$). # indicates a within-group difference with T_{10} ($p<0.05$). The difference between groups for the same time period is indicated with [a and b]

Table 3: Measurement of heart frequency (HR), rectal temperature (*T*), respiratory rate (*f*R), noninvasive mean arterial pressure (MAP) and peripheral arterial hemoglobin saturation (SpO_2) before and after administration of Medetomidine (Med), Midazolam+Medetomidine (Mid+Med), Dexmedetomidine (Dex) or Midazolam+Dexmedetomidine (Mid+Dex)

		Time												
	Groups	T_0	T_5	T_{10}	T_{15}	T_{20}	T_{25}	T_{30}	T_{35}	T_{40}	T_{45}	T_{50}	T_{55}	T_{60}
HR	Med	226 ±50	202±34^{a}	187 ±29^{a}	170±39^{a}	182±33^^{a}	178±32^{a}	170±25^{a}	171±25^{a}	163±37	166±35	162±31^{a}	166±31	167±37
	Mid+Med	244±36	236±37^{ab}	234±45^{ab}	217±46^{ab}	219 ±52^{ab}	213 ±52^{ab}	198±51$^{\#ab}$	185±54$^{\#ab}$	198±64	164±40	167±32^$^{\#ab}$	166±33^$^{\#}$	152 ±27*^
	Dex	268±15	262±25^{b}	255±28^{b}	214±79^{ab}	229±31$^{\#ab}$	231±24^{b}	220±25^{ab}	214±30^{ab}	206±32	197±35*^	187±34*^^{ab}	184±35*^	179±31*^$^{\#}$
	Mid+Dex	262±30	275±28^{b}	266±33^{b}	258±30^{b}	248±30^{b}	249±38^{b}	238±35^{b}	227±31^{b}	219±38	214±37	209±34^{b}	207±36	200±27*^
T	Med	39.2±0.5	38.8±0.8	38.4±0.8	38.2±0.6	38.2±0.7*	37.9±0.51*	37.7±0.5*	37.7±0.3*^{ab}	37.6±0.6	37.5±0.6	37.5±0.5*	37.4±0.3*	37.3±0.4*
	Mid+Med	38.7±1	38.5±0.9	38.3±0.9	38.1±1.2	37.9±1.1*	37.7±1*	37.6±0.9*^$^{\#}$	37.5±0.9*^^{a}	37.2±0.9*^$^{\#}$	37.2±0.9*^	36.9±0.9*^$^{\#}$	36.7±0.8*^$^{\#}$	36.6±0.8*^$^{\#}$
	Dex	39±0.44	38.8±0.4	38.7±0.4	38.6±0.4*	38.4±0.5*	38.1±0.4*^$^{\#}$	37.9±0.5*^	37.6±0.5*^$^{\#ab}$	37.4±0.5*^$^{\#}$	37.3±0.5*^$^{\#}$	37.1±0.5*^$^{\#}$	37.0±0.4*^$^{\#}$	36.7±0.3*^$^{\#}$
	Mid+Dex	39.3±0.2	39.2±0.2	39.0±0.2*	38.8±0.2*	38.7±0.3	38.6±0.2*^$^{\#}$	38.4±0.3*^$^{\#}$	38.3±0.3*^$^{\#b}$	38.1±0.4*^$^{\#}$	37.8±0.3*^$^{\#}$	37.6±0.4*^$^{\#}$	37.5±0.5*^$^{\#}$	37.4±0.5*^$^{\#}$
***f*R**	Med	55±19^{a}	45±20	33±13	31±12	34±13	32±16	31±14	37±17	31.9±15*	32±11	36±13	35±13	29±11*
	Mid+Med	40±25^{ab}	50±26	49±23	45±20	46±14	42±11	40±15	39±18	30±13	35±12	35±14	36±16	31±13
	Dex	31±14^{ab}	43±19	43±13	31±20	46±11	49±16	51±13	48±10	37±13	40±9	41±7	37±8	36±12
	Mid+Dex	30±6^{b}	46±17	41±19	55±29	46±29	39±22	38±18	36±6	29±10	32±5	32±6	27±10	28±8
MAP	Med	93±12^{a}	105±40	109±43	123±39	123±41^{a}	117±46^{a}	107±37	124±66^{a}	127±54^{a}	118±30^{a}	99±12^{a}	81±16	82±12^{a}
	Mid+Med	70±11^{b}	81±28	72±28	74±28	62±14^{b}	70±18^{b}	83±21	82±13^{ab}	79±14^{ab}	79±14^{ab}	82±20^{ab}	85±17	84±21^{a}
	Dex	74±12^{b}	77±12	85±19	104±47	106±34^{ab}	110±41^{ab}	108±61	109±62^{ab}	109±59^{ab}	109±63^{a}	98±53^{a}	87±40	74±33^{ab}
	Mid+Dex	77±12^{ab}	100±34*	96±34*^	97±57*$^{\#}$	95±41*^$^{\#ab}$	75±18^{ab}	64±22	56±27*^$^{\#b}$	56±31*^$^{\#b}$	56±34*^$^{\#b}$	50±25*^$^{\#b}$	57±44*^$^{\#}$	50±24*^$^{\#b}$
SpO_2	Med	91±6	95±3^{ab}	97 ±2^{a}	96±4	97±2^{ab}	96±4	98.5±1	96±5	96±5	97±4	97±4	97±3	96±6
	Mid+Med	95±1	97±1^{a}	97±1^{a}	98±1	98.5±1^{a}	97±1	98±1	98±1	98±1*	98±1	98±1*	98±1	99±1
	Dex	92±3	94±2^{b}	96±1^{ab}	97±1*	96±2^{b}	98±1*	97±1*^$^{\#}$	98±1	98±1	97±1	97±1	97±1	98±1*
	Mid+Dex	92±1	94±1*^{ab}	94±1*^{b}	96±1*^	96±1*^^{ab}	97±1*^$^{\#}$	98±1*^$^{\#}$	97±1*	97±1*	96±1*$^{\#}$	97±1*^$^{\#}$	97±1*^$^{\#}$	97±1*^$^{\#}$

Note: Measurements were recorded before drug administration (baseline) and every 5 minutes under anesthesia. Data are expressed as mean ± standard deviation. Different letters indicate differences in the same time period ($p<0.05$). Different letters indicate differences a within the same time period ($p<0.05$). * indicates a within-group difference with T_0 ($p<0.05$). ^ indicates within-group difference with T_5 ($p<0.05$). # indicates a within-group difference with T_{10} ($p<0.05$). The difference between groups for the same time period is indicated with [a and b]

administration of medetomidine in dogs has been reported to result in a decrease in both the duration and amplitude of the P wave (23). The prolongation of the P wave duration indicates left atrial dilation, while the increase in amplitude suggests right atrial dilation (24). In studies conducted, it has been reported that the amplitude and duration of the P wave in rabbits varied between 0.04 to 0.12 mV and 0.01 to 0.05 s, respectively (25,26). In our study, although the prolongation of P wave duration in the Med group was not statistically significant, the elongation at T_{70} time may be related to left atrial dilation and consequently, a slowdown in impulse conduction in the SA.

Although statistically significant differences were not observed in intra-group and inter-group comparisons of QRS complex durations, an elongation in QRS complex durations was identified in all groups in our study compared to the reported QRS complex durations in healthy rabbits (0.02-0.06 s) from a previous study (26). Cave et al. (27) investigated the effects of hypertonic fluid therapy following treatment with lipid emulsion on bupivacaine toxicity in New Zealand rabbits. In their study, they described that a wide QRS complex reflects left-sided intraventricular conduction delay, while a prolonged QRS complex reflects delayed depolarization of ventricular function. In light of the above information, in our study, it is contemplated that the prolongation of QRS complex durations following the administration of medetomidine and dexmedetomidine may be attributed to left-sided intraventricular delay. Our hypothesis is supported by the findings of Shekidef and colleagues, who reported an elongation in QRS complex durations in calves associated with the use of α2-adrenergic

receptor agonists. They attributed this phenomenon to delayed ventricular depolarization (28).

In a study assessing the risk factors for prolonged QT (0.15-0.17s) and cardiac arrhythmias in female rabbits due to drug administration, it was emphasized that the measurement of the QT interval is crucial in detecting cardiac repolarization abnormalities. The study highlighted that the prolongation of this interval is associated with the emergence of arrhythmias (29). In our study, the prolongation of the QT interval duration, compared to the data found in healthy rabbits by Lord et al. (26) (average 0.12s), was considered to be attributable to cardiomyopathy resulting from the delay between ventricular depolarization and repolarization, as also suggested by Yılmaz (24). Our hypothesis is supported by the findings of Drici et al., who described the prolonged QT syndrome in cats due to the use of antipsychotic drugs as being associated with drug-induced ventricular arrhythmias (30). Similarly, Kinjavdekar et al. reported that the subarachnoid administration of α2-adrenergic receptor agonists in goats could lead to the prolongation of the QT interval, suggesting that this prolongation may be attributed to delayed ventricular depolarization. (31).

In our study, it was observed that the average heart rate at T_0 is similar to the previously reported average heart rate for rabbits (32) (200-300 bpm), and it was found that the heart rate decreased over time in all groups. We hypothesized that the reason for this is attributed to the bradycardia induced by medetomidine and dexmedetomidine, as stated in the study conducted by Murrell and colleagues (33). Similarly, Yamashita et al. have reported a significant reduction in heart rate with the use of α2 adrenergic receptor agonists in horses. (34). In our study, the decrease in heart rate can be explained by sinus bradycardia induced by α2 adrenergic receptor agonists, which is thought to result from the reduction in sympathetic neurotransmitter release from the central nervous system. In addition, England et al. have reported a decrease in heart rate due to sinus bradycardia as a result of the use of α2-adrenergic receptor agonists (35). The heart rate in the Mid+Dex group was found to be higher than the heart rate in the Med group. It was hypothesized that the regulatory effect of midazolam, attributed to its antiarrhythmic properties, played a role in the occurrence of this difference in heart rates (36). Granholm et al., in their study investigating the reliability of medetomidine and dexmedetomidine in cats, reported an increase in heart rate in the group where dexmedetomidine was used compared to the group where medetomidine was used. They attributed this phenomenon to the reduction in sympathetic tone, shaped by inhibiting norepinephrine release in the central nervous system (37). Therefore, in our study, it was concluded that the higher heart rate in the Mid+Dex group could be attributed to the combined effects of both midazolam and dexmedetomidine administration.

Before the experiment, T was within the reference range (37.4-39.6°C) in all groups (38). It was observed that over time, all values gradually decreased but remained within the reference range. The gradual decrease in T observed over time after the administration of dexmedetomidine and medetomidine was considered to be associated with a reduction in muscle activation and the impact on thermoregulation following the administration of α2-adrenergic receptor agonists. These results were consistent with the findings of Ansah et al. and Selmi et al.(39,40). It has been reported that hypothermia develops in cats following the administration of α2-adrenergic receptor agonists, and this condition is attributed to a decrease in heat production due to reduced muscle activity during sedation. It is suggested that the direct effects of α2-adrenergic receptor agonists on thermoregulation may be responsible for this phenomenon. (41). Furthermore, in dogs, it has been reported that the administration of medetomidine and dexmedetomidine affects thermoregulation through central α2-adrenoreceptors, leading to a decrease in T. (42). However, in the study by Granholm and colleagues, no significant difference was found between the administrations of dexmedetomidine and medetomidine. In our study, a significant difference was observed at T_{35} between the Mid+Med and Mid+Dex groups, with the group receiving dexmedetomidine having a higher temperature than the group receiving medetomidine. We considered that this situation could be attributed to the difference in levels of muscle activity and the generation of heat through muscle activity. Our hypothesis is supported by the detection of intergroup differences in T following the administration of medetomidine and dexmedetomidine in cats. This was reported to be attributed to the difference in levels of muscle activity (39).

In rabbits, the normal *f*R during rest is between 30 and 60 breaths per minute. (43). n our study, all *f*R measurements recorded, except for the Med group, were within the normal range. In the Med group, a significant decrease was observed at T_{40} and T_{60} compared to T_0. The decrease observed in our study was considered to be related to a reduction in sympathetic tone, possibly due to the effects of medetomidine, as also indicated by Granholm et al. (37). A similar observation was reported in a study conducted in sheep, where bradypnea was noted between the T_5 and T_{60} minutes following the administration of medetomidine, attributed to a decrease in sympathetic tone. (44).

The report has documented that, for the identification of anesthesia-induced hypotension in rabbits, the non-invasive MAP value should be above 60 mmHg. (45). In our study, no statistically significant change was observed in MAP values evaluated with the non-invasive method over time in the Med, Mid+Med, and Dex groups. In the Mid+Dex group, an increase in MAP values was observed between T_5 and T_{20} minutes, followed by a gradual decrease after T_{35}. The initial increase in MAP was attributed to an elevation in vascular resistance and contraction of vascular smooth muscles, as indicated by Brunton et al. (46). The subsequent decline was considered to be influenced by dexmedetomidine activating presynaptic α2-adrenoreceptors, thereby

reducing plasma norepinephrine absorption (45). Additionally, the hypotensive effect of isoflurane, used for maintaining anesthesia, was presumed to contribute to the decrease in arterial blood pressure (33). Similarly, a study conducted in dogs (39) reported the hypotensive effects of dexmedetomidine while noting that medetomidine did not have a significant impact on this hemodynamic response.

Pulse oximetry is a non-invasive monitoring method that provides information about lung ventilation and can be utilized to assess a patient's oxygenation and perfusion (47). In rabbits, an SpO_2 reference value of 94% and above is considered acceptable, while measurements below 90% are interpreted as indicative of hypoxia. (48). In our study, all SpO_2 measurements in each group were within the reference range. In the T_{10} time interval, the lower measurement of the SpO_2 parameter in the Mid+Dex group compared to the Mid+Med groups may be attributed to the stronger sedative effect of dexmedetomidine. Indeed, supporting our hypothesis, a study conducted in dogs (49) reported that dexmedetomidine provided stronger and more predictable sedation and analgesia compared to an equivalent dose of medetomidine. Similarly, Yanmaz et al. (11) reported a gradual decrease in SpO_2 over time in their study using intranasal combinations of dexmedetomidine and midazolam in New Zealand rabbits. Despite the administration of oxygen, they observed that SpO_2 remained below 90%. On the other hand, Wei et al. (50) found a higher SpO_2 value after the intranasal administration of medetomidine compared to the SpO_2 measurement reported by Yanmaz and colleagues. As observed, these studies indicate the role of dexmedetomidine in the detection of low SpO_2 values. Additionally, a study conducted in rabbits reported that midazolam had less respiratory depression compared to dexmedetomidine. (45). In light of these findings, the SpO_2 values of animals in our study being within reference ranges and the highest SpO_2 values being observed in the Mid+Med group, can be interpreted as the combination of midazolam and medetomidine used in our study causing less respiratory depression.

The primary limitation of our study stems from the method of selecting two rabbits from each group and studying them on the same day, as opposed to examining all animals within a single group on a unified day. This approach could have minimized pre-experimental differences arising from the capture and handling method, allowing for greater control over potential variations between the groups.

Conclusion

Upon comprehensive examination of all the data in the study, it was observed that the anesthesia combination of midazolam and medetomidine (Group Mid+Med) induced comparatively fewer morphological and physiological alterations in the heart when contrasted with the other groups..

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Conflicts of interest. The authors declare no competing interests.

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Raziskava učinkov različnih kombinacij anestezije na kardiovaskularne parametre pri belih novozelandskih kuncih

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Izvleček: Cilj te študije je bil ovrednotiti morfološke in fiziološke spremembe srca, nastale zaradi štirih različnih kombinacij anestezije, pri čemer so bili kot sedativi uporabljeni midazolam, medetomidin in dexmedetomidin pri belih novozelandskih kuncih. V študiji smo 32 živali razdelili v štiri različne skupine. Vrednost vertebralnega srčnega indeksa je bila merjena pri zajcih pred poskusom (T0) in po 5 (T5), 10 (T10), 30 (T30), 50 (T50) in 70 (T70) minutah med poskusom. Hkrati so bile v enakih časovnih intervalih opravljene meritve elektrokardiografskih parametrov. Srčno frekvenco, frekvenco dihanja, rektalno temperaturo, srednji arterijski tlak in nasičenost periferne krvi s kisikom smo merili skupaj 60 minut, s 5-minutnimi presledki pred in med sedacijo. Vrednost vertebralnega srčnega indeksa se je spremenila v vseh skupinah, razen v skupini Mid+Med. Pri elektrokardiografski oceni smo v skupinah Mid+Med, Dex in Mid+Dex opazili podaljšanje trajanja vala QRS in intervala QT, medtem ko pri trajanju intervala PR in vala T nismo zaznali bistvenih sprememb. Nasprotno smo v skupini Me opazili izrazito podaljšanje trajanja vala P. Vrednosti nasičenosti periferne krvi s kisikom so se povečale, srčna frekvenca, srednji arterijski tlak in parametri rektalne temperature so se v vseh skupinah znižali. Po temeljiti analizi vseh podatkov v tej študiji je bilo ugotovljeno, da so morfološki in fiziološki učinki na srce, zaznani v skupini Mid+Med, povzročili manj izrazite spremembe v primerjavi z drugimi skupinami.

Ključne besede: elektrokardiografija; radiografija; kunec; VHS