Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2018.115

RESEARCH ARTICLE

Determination of Corrected QT Interval in Kangal Breed Dogs

R Gonul, L Koenhemsı*, K Yıldız and ME Or

Istanbul University-Cerrahpaşa, Faculty of Veterinary Medicine, Department of Internal Medicine, Avcilar, Istanbul, Turkey
*Corresponding author: lomekoh@istanbul.edu.tr

ARTICLE HISTORY (18-209)

Received: June 24, 2018
Revised: October 08, 2018
Accepted: October 10, 2018
Published online: December 21, 2018

Key words:
Formulas
Kangal dogs
QT intervals

A B S T R A C T

QT interval is one of the important reasons of severe and life threatening ventricular arrhythmias in humans and animals. Many formulas have been developed for correcting the QT interval however the best formula did not define yet by the researchers. For this reason, forty-nine clinically healthy Kangal dogs without cardiac problems other than sinus arrhythmia were included to the study. In this study corrected QT interval was determined by Bazet (QTcB = QT/√RR), Fridericia (QTcF = QT/³√RR), Famingham (QT+0.154(1-RR)), Van der Water (QTcVdW = QT–0.087((60/HR)-1)), Hodges (QT+0.00175(HR-60)), Matsunaga (QTcM = log600 QT/logRR) formulas. As a result, Bazett's formula showed the best consistency because the slope curve of the regression line was closest to zero (-0.00743) in our study.

©2018 PVJ. All rights reserved

To Cite This Article: Gonul R, Koenhemsı L, Yıldız K and Or ME, 2019. Determination of corrected QT interval in Kangal breed dogs. Pak Vet J, 39(1): 86-90. http://dx.doi.org/10.29261/pakvetj/2018.115

INTRODUCTION

Accuracy of electrocardiogram (ECG) has a very important role in the assessment of the heart (Matsubara *et al.,* 2018). The QT interval in the electrocardiogram (ECG) shows the duration of ventricular depolarization and repolarization (Brüler *et al.,* 2018). The prolongation of the QT interval indicates that the duration of ventricular repolarization is prolonged electrocardiographically, which is a risk factor for the development of various severe and life-threatening ventricular arrhythmias, including torsades de pointes (Matsunaga *et al.,* 1997; Ackerman, 1998; Raunig *et al.,* 2001; Chiang *et al.,* 2006; Schmitt *et al.,* 2007; Agudelo *et al.,* 2011; Patel *et al.,* 2017). Short QT syndrome is a recently described disease characterized by shortening of the QT interval and it is associated with paroxysmal atrial or ventricular fibrillation, fainting seizures and can cause sudden death in healthy people (Kijtawornrat *et al.,* 2010; Brüler *et al.,* 2018). QT interval depends on the heart rate, many physiological, pathological factors and medications, so that making interpretation of the data is very difficult (Matsunaga *et al.,* 1997; Spence *et al*., 1998; Raunig *et al.* 2001; Batey and Doe, 2002; Chiang *et al.,* 2006; Watanabe and Miyazaki 2006; Schmitt, 2007; Fossa, 2008; Agudelo *et al.,* 2011; Patel *et al.,* 2017). For this reason, it is very important to determine a true QT interval (QTc), and various studies have been carried out recently (Spence *et al.,* 1998; Raunig *et al.,* 2001; Batey and Doe 2002; Chiang *et al.,* 2006; Watanabe and Miyazaki 2006; Fossa, 2008; Patel *et al.,* 2017).

Since it is known that the QT interval depends on the RR interval, many formulas have been developed for correcting the QT interval for the heart rate (Bazett, 1920; Fridericia, 1920; Sarma *et al.,* 1984; Matsunaga *et al.,* 1997; Chiang *et al.,* 2006; Watanabe and Miyazaki 2006; Patel *et al.,* 2017). The relationship between QT and RR intervals was first investigated by Bazett in the early 20th century with a regression formula QTb = a√RR (Bazett, 1920; Matsunaga *et al.,* 1997; Batey and Doe, 2002). Fridericia (1920) defined the cube root correction factor (QTf = QT / RR1 / 3), which leads to more accurate results (Spence *et al.,* 1998; Batey and Doe, 2002; Watanabe and Miyazaki, 2006). While Bazett's and Fridericia's formulas are the most commonly used models for validating QT interval for clinical and non-clinical studies of heart rhythm changes, these models confirm the QT interval at 60 beats / min, so that they overestimate the QT interval at fast heart rates and underestimate it at slow heart rates (Spence *et al.,* 1998; Raunig *et al.,* 2001; Batey and Doe, 2002; Watanabe and Miyazaki, 2006; Patel *et al.,* 2017). Bazett's and Fridericia's formulas are created for humans, and later Van de Water have developed the formula QTcVdW = QT-0.087 {(60 / HR) -1} on anesthetized dogs (Van de Water *et al.,* 1989; Batey and Doe, 2002). Various covariance formulas have also been developed for the detection of QTc and they are generally categorized as linear regression (QT = α + β HR) or logarithmic (log (QT) = log (α) + β log (Matsunaga *et al.,* 1997; Spence *et al.,* 1998; Chinag *et al.,* 2006).

Various models have been developed to explain the relationship between the heart rate and the QT interval, the specific value of the parameters can vary widely depending on the population and their condition (Spence *et al.,* 1998; Chiang *et al.,* 2006; Agudelo *et al.,* 2011). Currently the best formula is not defined, and there is a need for new studies using high-quality ECG machines and various formulas on a large number of populations (Chiang *et al.*, 2006; Watanabe and Miyazaki, 2006; Patel *et al.,* 2017). For this reason, we have determined the corrected QT interval for the first time in Kangal dogs, considering different rate and sinus arrhythmias, age and sex-related changes.

MATERIALS AND METHODS

Forty-nine Kangal dogs found healthy as a result of clinical, laboratory and electrocardiographic studies were included to our study. Cases with sudden changes in the heart rhythm were excluded from the study.

ECGs were recorded in conscious dogs restrained lateral recumbency. Electrode gel was applied and the electrodes were placed through aligator clips to improve conduction. ECGs were recorded by CONTEC ECG600G model class I type CF Electrocardiography machine. When the dogs were settled short time ECGs recorded in accordance with the standard operating procedures.

Traces were recorded at a speed of 25 and 50 mm/sn with a ECG sensitivity at 1 mV. 6 leads electrocarido-graphy were recorded which including at least 12 consecutive cardiac cycles and QRS, RR and QT intervals were measured from lead II. In this way, the effects of respiratory sinus arrhythmia were also considered. The measurements were made manually using an ECG chart and the averages were determined. QT interval was measured from the earliest onset of the Q wave to the latest end of the T wave. In cases where the end of the T wave and the beginning of the P wave are conjugate due to the rapid heart rhythm, the last part of the T wave is measured. U waves are rarely encountered in dogs. Dogs with U waves were excluded from our study.

Different formulas were used to determine corrected QT intervals (Bazet; QTcB = QT/√RR, Fridericia; QTcF = QT/^{3}√RR, Famingham; QT + 0.154(1-RR), Van der Water; QTcVdW = QT – 0.087 ((60/HR)-1), Hodges; QT+0.00175 (HR-60), Matsunaga; QTcM = log600 QT/logRR).

The QTc-RR regression line slope for each QTc formula was detected and a comparison of the QTc formulas was made. Regression line slopes were close to zero, showed the consistency of the QTc formulas calculated against changes in heart rate. Animals were divided into various groups according to age, gender and heart rhythm (<1 year,> 1 year,> 120 beats per minute heart rate, <120 beats per minute heart rate, female, male). The QTc-RR regression line slope, mean, standard deviation, and changes were calculated for each group. In a similar way, a linear regression model was used to examine the variables.

RESULTS

ECG recordings of 49 Kangal breed dogs were compared in our study. For all groups (heart rate, gender, age) 6 different QTc formulas calculated and parameters (mean, standard deviation, difference, slope and p-value) shown in Table 1. All samples revealed a positive correlation between uncorrected QT interval and the RR interval (Fig 1). Best results of QTc-RR interval regression slope of the graph paper drawings in some groups are given in Fig. 2, 3 and 4.

As a result, it was found that Bazett's formula showed the best consistency because the slope curve of the regression line was closest to zero (-0.00743). Regression lines for other formulas; Fridericia (0.085595), Famingham (0.049507), Van der Water (0.114146), Hodges (0.37147) and Matsunaga (0.14213) showed consistency at different levels because these formulas were different distances from zero.

To consider the data according to the heart rate (>120 beat / minute), sex (male and female), and age (<1 year); Bazett's formula showed the best consistency that regression line was near to zero (0.062542, 0.018934, -0.02655, 0.042822, respectively). Fridericia's formula (0,006203) in the group with heart rate <120 beats / minute and Van der Water and Fridericia's formulas (0,022936 and 0,02865) with animals >1 years old group showed the best consistency. However, Hodges' formula showed the least consisty because it was highly statistically significantly different from zero.

In addition, Bazetts' formula is the best verifying method for QT interval according to the p-value (P=0,838369) as regression line. Because it was not statistically significantly different from zero. Also, similar results with regression lines were determined in other groups according to p-value (Table 1).

DISCUSSION

Several studies were made to compare different formules of QTc (Matsunaga *et al.,* 1997; Chiang *et al*., 2006; Watanabe and Miyazaki, 2006; Agudelo *et al.,* 2011; Patel *et al.,* 2017). QT interval is shortened in cases of increased cardiac rhythm under physiological conditions (Chiang *et al.,* 2006; Brüler *et al.,* 2018). Although the heart rhythm can change at high rates due to sinus arrhythmia caused by SA node in dogs, QT interval does not change due to QT "memory" (Hamlin *et al*., 2004; Patel *et al.,* 2017; Matsuba *et al.,* 2018). If the heart rhythm suddenly increases or decreases, it takes 2-3 seconds for the dogs to adapt to QT and it'll take least 70% to steady state, which can take 2-3 minutes in humans (Matsunaga *et al.,* 1997; Hamlin *et al.,* 2004). Matsunaga *et al.* (1997) have excluded the data from sudden cardiac rhythm in order to minimize the effects of time delay because the time delay is so short in dogs. However, the effects of respiratory sinus arrhythmias are seen spontaneously in dogs, they are not removed (Matsunaga *et al.,* 1997). Hamlin *et al.* (2004) reported that 12 consecutive cardiac cycles in sinus arrhythmia dogs generally equate to at least 3 respiratory cycle periods, so that measurements made from short continuous electrocardiographic monitoring with 12 consecutive

Table 1: QTc (mm / sec) values calculated for all groups in Kangal dogs

Parametreler	QTc Formula	Slope	Mean	SD	Min.-Max.	p-value	%95 Confidence limit	
All samples	Bazett's	-0,007	0,279	0,020	0,243-0,334	0,8384	-0,08035	0,06548
(n=49)	Fridericia's	0,086	0,242	0,019	0,206-0,288	0,0095	0,02189	0,14929
	Framingham's	0,050	0,27	0,014	0,245-0,305	0,0456	0,00100	0,09801
	Van de Water's	0,114	0,231	0,016	0,200-0,277	0,0000	0,06619	0,16209
	Hodges'	-0,371	0,327	0,037	0,261-0,421	0,0000	-0,44006	-0,30287
	Matsunaga's	0,142	0,192	0,019	0,156-0,241	0,0000	0,09121	0,19305
Heart Rate >120	Bazett's	0,063	0,28	0,022	0,243-0,334	0,3580	-0,07398	0,19906
(n=35)	Fridericia's	0,157	0,239	0,021	0,206-0,288	0,0100	0,04015	0,27428
	Framingham's	0,111	0,269	0,016	0,245-0,305	0,0132	0,02486	0,19759
	Van de Water's	0,180	0,227	0,017	0,200-0,264	0,0001	0,09675	0,26328
	Hodges'	-0,445	0,342	0,031	0,283-0,421	0,0000	-0,55799	-0,33155
	Matsunaga's	0,203	0,187	0,019	0,156-0,228	0,0001	0,11113	0,29541
Heart Rate <120	Bazett's	-0,084	0,276	0,018	0,25-0,314	0,2835	-0,24747	0,07915
(n=14)	Fridericia's	0,006	0,248	0,015	0,222-0,287	0,9285	-0,14129	0,15370
	Framingham's	-0,019	0,273	0,012	0,254-0,304	0,7327	-0,14030	0,10151
	Van de Water's	0,063	0,239	0,013	0,22-0,277	0,3024	-0,06482	0,19172
	Hodges'	-0,139	0,289	0,019	0,261-0,319	0,0923	-0,30474	0,02658
	Matsunaga's	0,074	0,204	0,013	0,181-0,241	0,2122	-0,04842	0,19659
Male	Bazett's	0,019	0,284	0,021	0,249-0,334	0,7115	-0,08501	0,12288
(n=29)	Fridericia's	0,109	0,245	0,020	0,206-0,288	0,0200	0,01866	0,20031
	Framingham's	0,069	0,273	0,015	0,245-0,305	0,0489	0,00037	0,13802
	Van de Water's	0,135	0,233	0,017	0,2-0,277	0,0003	0,06717	0,20191
	Hodges'	-0,344	0,330	0,035	0,263-0,421	0,0000	-0,44652	-0,24175
	Matsunaga's	0,162	0,194	0,019	0,156-0,241	0,0001	0,08960	0,23448
Female	Bazett's	-0,027	0,272	0,019	0,243-0,311	0,5954	-0,12974	0,07664
(n=20)	Fridericia's	0,068	0,236	0,018	0,208-0,272	0,1283	-0,02162	0,15775
	Framingham's	0,035	0,266	0,013	0,247-0,293	0,3025	-0,03385	0,10301
	Van de Water's	0,098	0,227	0,015	0,204-0,255	0,0090	0,02759	0,16763
	Hodges'	-0,402	0,324	0,041	0,261-0,405	0,0000	-0,50009	-0,30424
	Matsunaga's	0,127	0,188	0,017	0,159-0,218	0,0015	0,05553	0,19901
1 age >	Bazett's	-0,126	0,281	0,024	0,253-0,334	0,0980	-0,27929	0,02705
(n=14)	Fridericia's	-0,029	0,249	0,019	0,215-0,288	0,6497	-0,16269	0,10539
	Framingham's	-0,046	0,274	0,015	0,251-0,305	0,3456	-0,14795	0,05604
	Van de Water's	0,023	0,238	0,015	0,209-0,264	0,6403	-0,08130	0,12718
	Hodges'	-0,287	0,303	0,031	0,261-0,354	0,0004	-0,41605	-0,15739
	Matsunaga's	0,046	0,202	0,015	0,158-0,228	0,3657	-0,06091	0,15336
1 age <	Bazett's	0,043	0,278	0,020	0,243-0,314	0,3818	-0,05547	0,14111
(n=35)	Fridericia's	0,137	0,239	0,020	0,216-0,287	0,0023	0,05277	0,22156
	Framingham's	0,096	0,268	0,015	0,245-0,304	0,0040	0,03266	0,15855
	Van de Water's	0,163	0,228	0,017	0,200-0,277	0,0000	0,10153	0,22425
	Hodges'	-0,407	0,337	0,036	0,281-0,421	0,0000	-0,50587	-0,30797
	Matsunaga's	0,187	0,188	0,019	0,156-0,241	0,0000	0,12027	0,25381

cardiac cycles accurately reflect the physiological changes that can occur with respiration. It is also reported that even measurements from 1 heart cycle, where heart rhythm is regular (no respiratory arrhythmia) and good quality recordings (no artifacts), show similar results to a large number of measurements (Hamlin *et al*., 2004). On the other hand, some researchers performed measurements of QT and RR intervals from normal and high frequency heart rhythms, in short-term ECG recordings in anesthetized dogs (Van de Water *et al*., 1989), and some researchers performed short and long-term ECG recordings in awake beagle dogs (Matsunaga *et al.,* 1997; Batey and Doe, 2002, Schmitt *et al*. 2007; Kijtawornrat *et al*., 2010; Patel *et al.,* 2017; Matsuba *et al.,* 2018;). Suden rhythm changes were excluded from our study. 12 consecutive ECGs of Kangal dogs without an anestesia were used in our study parallel to the study of Hamlin *et al.* (2004) to determine the influence of respiratory sinus arrhythmia. Calculations were made manually. Patel *et al.* (2017) reported that the digital ECG measurements were more accurate than the manual measurements, but we observed that manual measurements were more accurate in comparative measurements, especially when the heart rhythm was fast and there was slight oscillation in the isoelectric line. Also, in manual measurements there are no errors that can be caused by automatic measurements when the T and U waves are combined or cannot be distinguished, or when the T and P waves are combined. Hamlin *et al.* (2004) also reported that no computer system today is completely reliable for the measurement of ECG parameters, and that even if measured by a computer, these measurements must be repeated by a person.

Bazett's square root formula used in correcting the QT interval for heart rhythm is generally accepted because of its simplicity and usability (Matsunaga *et al.,* 1997). However, investigators have reported that QT interval in Bazett's formula is corrected to 60 beats / min heart rate, which is less reliable for awake dogs with rapid heart rhythm (Batey ve Doe, 2002; Chiang *et al.,* 2006; Agudelo *et al.,* 2011).

It is known that Bazett's formula in both humans and dogs to overestimate the true value of short RR intervals and underestimate the long RR intervals (Matsunaga *et al.,* 1997; Batey and Doe, 2002; Agudelo *et al.,* 2011). For this reason, some researchers have supported the cube root formula of Fridericia (Matsunaga *et al.,* 1997). However, researchers have reported that the errors in the Fridericia's formula are similar to those in the Bazett's formula, are inadequate for different heart rates, have some conflicting results, and are not suitable for awake dogs (Matsunaga *et al.,* 1997; Raunig *et al*., 2001; Batey and Doe, 2002;

Agudelo *et al.*, 2011; Patel *et al.*, 2017;). The formula (QTc = QT-0.087 x [(60 / HR) -1] developed by Van de Water *et al.* (1989) is the correction formula used in anesthetized dogs and others are designed for humans. The researchers compared different correction formulas (Bazett, Fridericia, Framingham, Van der Water, Hodges, etc.) (Agudelo *et al.*, 2011; Patel *et al.*, 2017). They have found that Van de Water's correction factor is statistically superior, more consistent, and less variable in the increased heart rhythm, which can be used to correct the QT interval time and is widely varied in heart rhythms (Hamlin *et al.*, 2004; Agudelo *et al.*, 2011; Patel *et al.*, 2017). Nevertheless, Batey and Doe (2002) reported that the Van de Water formula showed similar results to the Fridericia's formula when the RR interval was 700-1300 ms, but that these errors were smaller than the Fridericia's formula, even at high and low heart rates besides these values. The Framingham formula can be used in normal heart rhythms but has been found unsuccessful in extreme rhythms (Batey ve Doe, 2002; Agudelo *et al.*, 2011). Hodges QTc is reported to be a good choice due to the small correlation coefficient (Agudelo *et al.*, 2011). Spence *et al.* (1998) reported that QT values were best assessed in the beagle study with log (QT) = α + β log (HR) formula, especially when populations were large, and Van de Water's formula could be preferred for small numbers of groups. Nevertheless, it is reported that Van de Water is still superior to others that Bazett, Fridericia and Van der Water formulas still maintain their popularity (Spence *et al.*, 1998). The discussion on this subject has still continued and has not yet reached a definite conclusion.

In our study, we found that all of the samples with high heart rhythm (average heart rate: 143.26±30.02 beats/min (minimum 90 beats/min - maximum 215 beats/min)) and in all subgroups with high heart rate (HR> 120, male, female, <1 yr) Bazett 's formula gave the best results when Fridericia's formula was better in subgroups with low heart rhythm (HR <120 and 1 year). Hodges' formula showed the least consistency between the other formulas acoording to the slope curve near to zero, and the highest statistical significance because it had higher p value cause differentiation from zero. Therefore, we found that the QTc Hodges was insufficient to correct QTc interval.

The change quantity parameter (minimum-maximum), is the narrowest QTc change interval in all samples (0.06) in the Framingham's formula, and is the largest QTc change interval in all samples (0.16) and in all subgroups except HR <120 in the Hodges' formula.

Some researchers prefer the linear regression model for QTc (Matsunaga *et al.*, 1997; Spence *et al.*, 1998; Chiang *et al.*, 2006). When the heart rhythm is unusually high or low, the relationship between QT interval and cardiac rhythm is thought to be linear (Chiang *et al.*, 2006). Matsunaga *et al.* (1997) compared the results of 14 different formulations of beagle dogs in their study. The results show that exponential formulas gave better results than linear regression formulas but are not practical because of the complexity of interpretation of parameters due to lack of linearity. Therefore, it is reported that one parameter logarithmic formula (QTc = log600 * QT / logRR msn) is more appropriate and normalized the QT

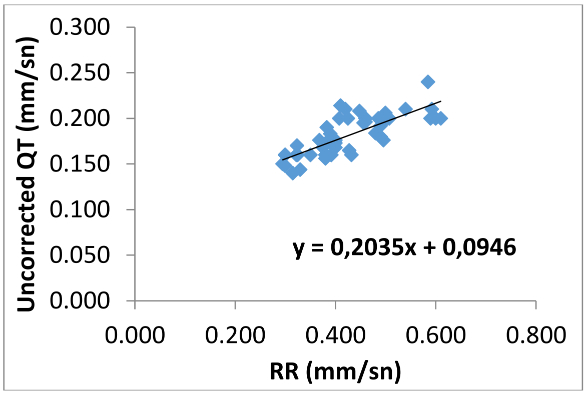

Fig. 1: Uncorrected QT and RR interval.

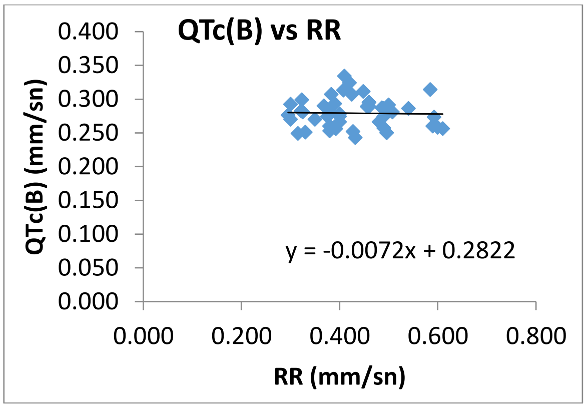

Fig. 2: Bazett's Formula for all sampels.

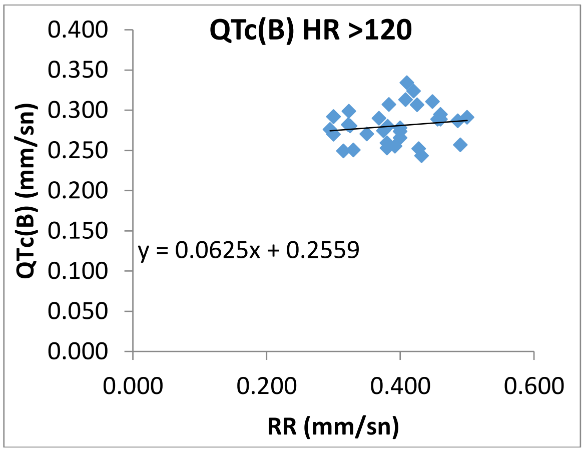

Fig. 3: Bazett's Formula for HR>120.

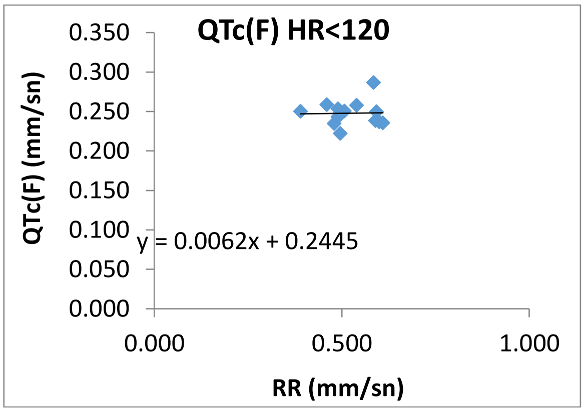

Fig. 4: Fridericia's Formula for HR<120.

interval to 100 rpm, thus indicating that the one parametric equations are superior to multiparameter formulas (Matsunaga *et al.,* 1997). Matsunaga *et al.* (1997) reported that bradycardia is a major problem due to the prolongation of QT, and they found that the logarithmic formulation is well suited to confirm the QT interval even in the large RR states of bradycardia. However, even with moderate changes in heart rhythm, it is still difficult to interpret the results, and correction for fast and slow heart rhythms is required (Batey and Doe, 2002). The relationship between the QT and RR intervals is far from linear and any mathematical correction attempt at a precise heart rhythm inevitably fails (Matsunaga *et al.,* 1997; Batey and Doe, 2002). Logarithmic formula of Matsunaga is inadequate, especially in fast heart rhythms, in our study.

The researchers found that gender evaluations did not affect the QT interval correction studies (Patel *et al.,* 2017). However, it has been found that the age effect is very slight on the p-value in the formula, in which case Fridericia's formula is more appropriate than the Bazett's formula (Patel *et al.,* 2017). Similar to the study of Patel *et al.* (2017) gender did not affect evaluations but, HR <120 and >1 age groups with significantly lower heart rhythm were significant changes in p value.

Minor QT changes are clinically and biologically important, but detection is difficult (Patel *et al.,* 2017). It is known that changes in heart rhythm may not only result from autonomic status, but various factors such as electrolyte impairment, drug therapy, inherited and acquired harvests may affect the QT and RR relationship (Matsunaga *et al.,* 1997; Spence *et al.,* 1998; Patel *et al.,* 2017). The QT-RR relationship also varies depending on free walking status, rest state, anesthesia status, sampling or analysis methods of the data (Spence *et al.,* 1998; Chiang *et al.,* 2006; Watanabe and Miyazaki, 2006). That's why each validation formula has its own outstanding or underperforming performance (Watanabe and Miyazaki, 2006). Especially in dogs with rapid heart rhythms, it was known that QT-RR relation exhibits a sharp curve, and therefore new studies are being made to reveal the relationship level in different heart rhythms (Watanabe and Miyazaki, 2006; Fossa, 2008). Although many authors have reported that Bazett's and Fridericia's formulas are insufficient to correct QT interval especially in awake dogs, Patel *et al.* (2017) found that Bazett's formula is more appropriate than the others in HR>120 cases.

Conclusions: we found that even in dogs with high cardiac rate (HR, mean 156 ± 25 beats / min), the linear curve was obtained and similar to the Patel *et al.* (2017), we have observed that Bazett's formula gave the best result. Although it has been suggested that the QT interval should be corrected to an average of 100 beats per minute for dogs with higher heart rhythm (Matsunaga *et al.,* 1997; Chiang *et al.,* 2006), a consensus has emerged recently that QT should not be corrected for cardiac rhythm (Rauning *et al.,* 2001). In this study, it is concluded that Bazett's and Fridericia's formulas, which do not have such corrections, retain superior from Mastsunaga's logarithmic formula and other formulas.

Authors contribution: RG designed the study, made the statistical analysis; LKH wrote the study, KY collected the patients, made the ECGs, MEO has decided if the patients is suitable for study.

REFERENCES

Agudelo CF, Scheer P and Tomenendalova J, 2011. How to approach the QT interval in dogs – state of the heart: a review. Vet Med 56:14-21.

Batey AJ and Doe CPA, 2002. A method for QT correction based on beat-to-beat analysis of the QT/RR interval relationship in conscious telemetred beagle dogs. J Pharmacol Toxicol Methods 48:11-9.

Bazett J, 1920. An analysis of time relation of electrocardiograms. Heart 7:353-67.

Brüler BC, Jojima FS, Dittrich G, *et al*., 2018. QT instability, an indicator of augmented arrhthmogenesis, increases with the progression of myxomatous mitral valve disease in dogs. J Vet Cardiol 20:254-66.

Chiang AY, Holdsworth DL and Leishman DJ, 2006. A one-step approach to the analysis of the QT interval in conscious telemetrized dogs. J Pharmacol Toxicol Methods 54:183-8.

Fossa AA, 2008. Assessing QT prolongation in conscious dogs: Validation of a beat-to-beat method. Pharmacol Ther 119:133-40.

Fridericia L, 1920. Dir systolendaeur in elektrokardiogram bei normalen menchen und bei herzkranken. J Intern Med 53:469-86.

Hamlin RL, Kijtawornrat A and Keene BW, 2004. How many cardiac cycles must be measured to permit accurate RR, QT and QTc estimates in conscious dogs? J Pharmacol Toxicol Methods 50:103-8.

Kijtawornrat A, Panyasing Y, del Rio C, *et al*., 2010. Assesment of ECG interval and restitution parameters in the canine model of short QT syndrome. J Pharmacol Toxicol Methods 61:231-7.

Matsubara F, Kazuhide O, Miyazaki S, *et al.,* 2018. Investigation of individual analysis of QT interval in beagle dogs. J Phamacol Toxicol Methods 93:157-72.

Matsunaga T, Mitsui T, Harada T, *et al*., 1997. QT corrected for heart rate and relation between QT and RR ıntervals in Beagle dogs. J Pharmacol Toxicol Methods 38:201-9.

Patel S, Bhatt L, Patel R, *et al*., 2017. Identifiction of appropriate QTc Formula in beagle dogs for nonclinical safety assesment. Regul Toxicol Pharmacol 89:118-24.

Raunig D, DePasquale MJ, Huang CH, *et al*., 2001. Statistical analysis of QT interval as a function of changes in RR interval in the coscious dog. J Pharmacol Toxicol Methods 46:1-11.

Sarma JSM, Sarma RJ, Bilitch M, *et al*., 1984. An exponential Formula for heart rate dependence of QT interval during exercise and cardiac pacing in humans: reevaluation of Bazett's Formula. Am J Cardiol 54:103-8.

Schmitt MW, Landenberg FV, Poth H, *et al*., 2007. Simple-to-use, reference criteria for revealing drug-induced QT interval prolongation in conscious dogs. Eur J Pharmacol 554:46-52.

Spence S, Soper K, Hoe CM, *et al*., 1998. The Heart Rate-Corrected QT Interval of Conscious Beagle Dogs: A formula based on analysis of covariance. Toxicol Sci 45:247-58.

Van de Water A, Verheyen J, Xhonneux R, *et al*., 1989. An improved method to correct the QT interval of the electrocardiogram for changes inheart rate. J Pharmacol Methods 22:207-17.

Watanabe H and Miyazaki H, 2006. A new approach to correct the QT interval for changes in heart rate using a nonparametric regression model in beagle dogs. J Pharmacol Toxicol Methods 53:234-41.