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Original Scientific Article

EVALUATION OF THE CORRECTED QT INTERVAL WITH BAZETT'S METHOD IN CAVALIER KING CHARLES SPANIEL DOGS WITH MYXOMATOUS MITRAL VALVE DISEASE

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ABSTRACT

Myxomatous mitral valve disease (MMVD) is one of the most common heart diseases in dogs. The disease progresses faster in Cavalier King Charles Spaniel (CKCS) dogs and occurs at an earlier age. QT interval length reflects abnormalities in ventricular repolarization which may predispose to the formation of fatal arrhythmias such as torsades de pointes. A fast and accurate assessment is therefore essential. The study aimed to examine the changes in QT duration in MMVD cases of CKCS and to calculate the corrected QT durations with Bazett's formula in various stages of the disease. The study included 20 CKCS dogs of both genders, various ages and weights, and different stages of MMVD (n=6 in B1 stage, n=6 in B2 stage, and n=8 in C stage), and 5 healthy CKCS which were included in the control group. Clinical, radiological, hematological, biochemical, echocardiographic, and electrocardiographic examinations were performed. The corrected QT interval duration in the MMVD group was longer than the control ($p<0.05$). However, there was no significant difference between B1, B2, and C. It was concluded that the corrected QT interval can give a significant distinction between healthy and MMVD CKCS dogs.

Key words: Cavalier, myxomatous, mitral valve, QT

INTRODUCTION

Myxomatous mitral valve disease (MMVD) is one of the most common cardiac diseases in small and medium-sized dog breeds (1, 2). In dogs of the Cavalier King Charles Spaniel breed, the disease progresses more rapidly and occurs at an earlier age, and genetic reasons are thought to be responsible (3, 4). The average age of MMVD onset in CKCS is 6.25 years, whereas in other dog breeds 12 years (5). The clinical findings range from mitral regurgitation to exercise intolerance, respiratory distress, cyanosis, ascites, and syncope, depending on the severity of the disease. The severity of the systolic murmur detected on auscultation is directly proportional to the severity of mitral regurgitation (6, 7). In humans and dogs with MMVD, the histopathology findings on the mitral valve included nodular thickening, lipid deposition, and mucoid degeneration of fibrotic tissue (8).

The QT interval, which reflects the total time for depolarization and repolarization of the ventricles, comprises the interval between the onset of QRS conduction and the end of the T wave (9). The duration of the QT interval, measured as a ventricular activation time, is one of the cardiac parameters commonly used to describe cardiac abnormalities and assess drug safety (10). The QT interval is inversely proportional to the R-R interval and heart rate. For proper evaluation of the electrocardiogram, the lower and upper limits of the normal QT interval must be known (11). The QT interval should be less than half of the R-R interval. In dogs, QT>0.25 mm/second is defined as interval prolongation and <0.15 mm/second as interval shortening. QT prolongations may

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occur as a result of hypocalcemia, hypokalemia, quinidine toxicity, ethylene glycol intoxication, central nervous system problems, hypothermia, myocardial ischemia, left ventricular hypertrophy, right or left bundle branch block, myocarditis, and pericarditis (12). Variations in the heart rate can affect the QT and can lead to misinterpretation. QT interval length reflects abnormalities in ventricular repolarization which may predispose to the formation of fatal arrhythmias such as torsades de pointes. Therefore, fast and accurate assessment is essential (13). The corrected QT interval (QTc) is often used in clinical applications by utilizing Bazett, Fredericia, Framingham, and Hodges formulas which correct for the heart rate (14, 15, 16). Henry Cuthbert Bazett's formula, published in 1920, is most commonly used for humans and dogs, (14, 15, 17).

The study aimed to investigate the changes in QT duration in MMVD of CKCS dogs and to differentiate the corrected QT by Bazett's formula in different MMVD stages (B1, B2, and C).

MATERIAL AND METHODS

Twenty CKCS dogs diagnosed with MMVD were included in the survey group and five CKCS healthy dogs were included in the control group. The dogs in the control group were classified as group A because of their predisposition to myxomatous mitral valve disease. The age and sex of the dogs in both groups were recorded.

All examinations were performed after obtaining consent from the patient's owner and were approved by the Ethics committee of the Veterinary Faculty, Istanbul University-Cerrahpaşa (March 16, 2021, No 2021/15). Clinical, radiological, hematological, biochemical, echocardiographic, and electrocardiographic examinations were performed on MMVD and control groups.

Dogs with MMVD were classified into A (n=5), B1 (n=6), B2 (n=6), and C groups (n=8) according to the American College of Veterinary Internal Medicine (ACVIM) standards. Group D patients with severe respiratory distress, cyanosis, ascites, and syncope were not included in the study because of the difficulty of ECG imaging. Laterolateral chest radiographs were obtained using a digital radiography unit SMS-CM -N (EcoRay, Korea). The vertebral heart score (VHS) of each patient was measured using the technique established by Buchanan (18). Pulmonary edema was graded according to severity as 0, +1, +2, and +3. The echocardiographic and Doppler echocardiographic examination was performed on the right parasternal long axis, right parasternal short axis, right parasternal heart base acoustic windows, left apical 4 chambers, and apical 5 chambers. It was performed on the SIUI Apogee 3500V model Doppler ultrasound machine (Shantou Institute of Ultrasonic Intstruments, China). Systolic and diastolic measurements of LA/Ao (left atrial to aortic root ratio), IVS (interventricular septal thickness), LVID (left ventricular internal dimension), LVPW (left ventricular posterior wall thickness), FS (fractional shortening), and EF (ejection fraction) were calculated by the Teicholz method in M-mode echocardiography. Pulmonary artery Doppler measurements were performed at the base frame of the right parasternal heart. Mitral measurements were performed in the apical four-chamber view on the left side. Echocardiographic measurements were performed according to ACVIM standards (19).

Electrocardiographic recordings were performed on conscious animals in the lateral position according to the technique described by Edward (9). Alcohol and electrolyte gel was applied to the area during the placement of the electrocardiogram clips to ensure conductivity. Electrocardiograms were recorded with the CONTEC ECG600G class I electrocardiography machine (Contect Medical System, China) at paper speeds of 25 to 50 mm/s and an amplitude sensitivity of 10 mm=1 mV. Patients with sudden changes in respiratory rhythm and ECG waveforms with artifacts, such as a shift in the isoelectric line, were not included in the study. Measurements of P, PR, QRS, RR, QT, and T durations and P, Q, R, S, and T amplitudes were made manually from an ECG trace of the lead II. Mean values were obtained from five consecutive ECG waveforms with steady beats. The QT range was measured from the beginning of the Q wave to the end of the T wave. Areas of arrhythmia were not evaluated in the QT interval measurements. The Bazett formula ($QTcb=QT/\sqrt{RR}$) was used to determine the corrected QT interval.

Blood was sampled (3 mL) from the cephalic vein. A complete blood count was performed using the Idexx ProCyte Dx Model blood scanner (IDEXX Laboratories, USA). Biochemical analyses were reviewed using the Idexx Catalyst One instrument (IDEXX Laboratories, USA).

Statistical analyses of the data obtained at the end of the study were performed using the SPSS statistical software package (version 28 Windows, IBM Corporation, NY). The One-way ANOVA was used for the comparative assessment of normally distributed parameters, and the chi-square test was

used for cross-group comparison of nonparametric qualitative data.

RESULTS

There were two female (40%) and three male (60%) dogs in the A group. In the MMVD groups, seven (35%) were female and thirteen (65%) were male. The mean age was 8.26 years in A, 5.66 years in B1, 7.66 years in B2, and 9 years in C group.

Significant differences were observed for the level of pulmonary edema between the groups (p=0.001). B2 and C groups had a significantly higher probability of pulmonary edema compared to A and B1 (p<0.05) (Table 1).

Table 1. Pulmonary edema level observed in different stages of mitral myxomatous valve disease in Cavalier King Charles Spaniel dogs

Level of pulmonary edema	A Stage (n:5)	B1 Stage (n:6)	B2 Stage (n:6)	C Stage (n:8)	p value
0	5 (100%)	5 (83.3%)	0 (0.0%)	0 (0.0%)	**0.001***
1	0 (0%)	1 (16.7%)	5 (83.3%)	3 (37.5%)	
2	0 (0%)	0 (0.0%)	1 (16.7%)	3 (37.5%)	
3	0 (0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	

*p<0.05

Table 2. Echocardiographic values in different stages of mitral myxomatous valve disease in Cavalier King Charles Spaniel dogs

Parameters	A Stage (n:5)	B1 Stage (n:6)	B2 Stage (n:6)	C Stage (n:8)	p value
IVSd (cm)	0.63±0.06	0.67±0.04	0.74±0.05	0.68±0.05	0.537
LIVDd (cm)	2.63±0.18^{b}	2.44±0.14^{b}	3.14±0.25^{b}	4.27±0.25^{a}	**<0.001**
LVPWd (cm)	0.65±0.07	0.85±0.06	0.77±0.09	0.80±0.11	0.589
IVSs (cm)	0.96±0.07	1.14±0.13	1.09±0.12	1.23±0.14	0.524
LVIDs (cm)	1.44±0.10^{bc}	1.20±0.10^{c}	1.78±0.15^{b}	2.34±0.12^{a}	**<0.001**
LVPWs (cm)	0.82±0.10	1.19±0.07	1.08±0.07	1.17±0.14	0.152
EF (%)	78.30±1.63	86.74±1.54	78.34±4.45	79.78±1.81	0.114
FS (%)	45.17±1.62	51.51±2.31	42.87±3.69	44.87±1.32	0.089
EPSS (cm)	0.25±0.03^{b}	0.35±0.06^{ab}	0.31±0.03^{ab}	0.58±0.10^{a}	**0.019**
Ao Root (cm)	1.26±0.08^{b}	1.38±0.06^{b}	1.42±0.06^{ab}	1.68±0.07^{a}	**0.002**
LA (cm)	1.48±0.10^{b}	1.88±0.11^{b}	2.07±0.17^{b}	3.64±0.29^{a}	<0.001
LA/Ao (cm)	1.19±0.06^{b}	1.38±0.09^{b}	1.45±0.07^{b}	2.15±0.12^{a}	**<0.001**
PV (cm/sec)	73.08±4.89	79.32±6.54	80.08±7.99	70.01±3.94	0.538
AV (cm/sec)	101.50±13.39	107.71±12.55	119.01±14.47	98.51±6.22	0.585
MV E Vel (cm/sec)	63.03±2.85^{b}	57.67±3.91^{b}	60.28±4.73^{b}	134.52±17.95^{a}	**<0.001**
MV A Vel (cm/sec)	58.73±1.99	54.27±5.91	54.27±5.83	88.82±15.31	0.066

Values are expressed as mean ± SD. Values with different superscripts within a row differ significantly. IVSd: interventricular septal thickness at end-diastole; IVSs: interventricular septal thickness at end-systole; LVIDd: left ventricular internal dimension at end-diastole, LVIDs: left ventricular internal dimension at end-systole, LVPWd: left ventricular posterior wall thickness at end-diastole, LVPWs: left ventricular posterior wall thickness at end-systole, Ao: aortic root, LA/Ao: left atrial to aortic root ratio, FS: fractional shortening, EF: ejection fraction, PV: pulmonary velocity, AV: aortic velocity, MV E Vel: mitral E wave peak velocity, MV A Vel: mitral E wave peak velocity

Table 3. Electrocardiographic values for different stages of mitral myxomatous valve disease in Cavalier King Charles Spaniel dogs

Parameters	A Stage (n:5)	B1 Stage (n:6)	B2 Stage (n:6)	C Stage (n:8)	p value
P amp. (mV)	0.23±0.02	0.26±0.04	0.23±0.03	0.22±0.03	0.892
Q amp. (mV)	(-)0.30±0.04	(-)0.27±0.06	(-)0.17±0.06	(-)0.39±0.06	0.124
R amp. (mV)	1.56±0.29	1.77±0.29	1.95±0.15	2.59±0.28	0.058
T amp. (mV)	(-)0.12±0.05	(-)0.20±0.08	(-)0.13±0.08	(-)0.35±0.08	0.199
P dur. (mm/sec)	0.100±0.062	0.040±0.002	0.040±0.001	0.05±0.005	0.374
PR interval (mm/sec)	0.080±0.005^{b}	0.090±0.004^{b}	0.100±0.004^{ab}	0.110±0.004^{a}	**0.003**
QRS dur. (mm/sec)	0.040±0.004	0.050±0.005	0.050±0.003	0.150±0.078	0.391
T dur. (mm/sec)	0.060±0.008	0.080±0.007	0.060±0.007	0.070±0.007	0.089
QT interval (mm/sec)	0.180±0.007	0.180±0.007	0.180±0.004	0.180±0.005	0.705
RR interval (mm/sec)	0.50±0.05	0.44±0.02	0.47±0.02	0.40±0.02	0.199
QTcb (mm/sec)	0.250±0.002^{b}	0.280±0.006^{a}	0.270±0.004^{a}	0.28±0.002^{a}	**0.002**
Heart rate (bpm)	126.00±5.14^{a}	128.16±8.98^{ab}	130.33±6.54^{ab}	153.00±4.77^{b}	**0.017**

Values are expressed as mean ± SD. Values with different superscripts within a row differ significantly. Amp: amplitude, dur: duration, bpm: beats per minute, QTcb: corrected QT with Bazett's formula

Table 4. Hemogram and biochemical values for different stages of mitral myxomatous valve disease in Cavalier King Charles Spaniel dogs

Parameters	A Stage (n: 5)	B1 Stage (n: 6)	B2 Stage (n: 6)	C Stage (n: 8)	p value
RBC (x 10^{12}/L)	5.85±0.16	6.28±0.12	6.13±0.21	5.83±0.21	0.402
HCT (%)	38.22±0.88	39.95±0.74	39.02±1.66	36.89±1.22	0.321
HGB (g/dL)	14.14±0.42	15.25±0.74	14.61±0.69	13.55±0.45	0.214
MCV (fL)	65.38±1.10	63.63±1.18	63.85±0.90	63.35±0.71	0.501
MCH (pg)	24.16±0.47	24.28±1.11	23.88±0.14	23.27±0.28	0.600
MCHC (g/dL)	36.98±0.24	38.07±1.20	37.45±0.44	36.72±0.29	0.475
WBC (x 10^{9}/L)	13.19±0.89	13.37±1.42	11.99±1.85	11.91±1.50	0.856
PLT (x 10^{9}/L)	143.40±47.33	173.83±73.04	230.67±64.60	161.50±58.07	0.799
GLU (mg/dL)	106.20±7.32	109.50±5.53	111.50±5.68	110.25±7.59	0.963
CREA (mg/dL)	0.88±0.66	0.73±0.04	0.62±0.08	0.77±0.11	0.269
BUN (g/dL)	17.32±3.57	12.67±1.48	16.50±4.77	18.75±2.87	0.602
TP (g/dL)	6.64±0.27	7.38±0.22	6.90±0.25	6.57±0.15	0.054
ALB (g/dL)	3.15±0.12	3.71±0.22	3.30±0.17	3.20±0.15	0.130
GLOB (g/dL)	3.47±0.29	3.67±0.11	3.62±0.88	3.39±0.14	0.508
ALT (U/L)	34.20±8.20	57.33±6.76	49.50±7.34	58.28±12.49	0.364
ALKP (U/L)	48.00±13.37	43.33±14.05	92.83±45.22	120.50±52.22	0.480

Values are expressed as mean ± SD. WBC: white blood cell, RBC: red blood cell, MCV: mean corpuscular volume, HCT: hematocrit, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, HGB: hemoglobin, PLT: platelet, ALT: alanine aminotransferase, ALKP: alkaline phosphatase, TP: total protein, BUN: blood urea nitrogen, GLU: glucose, ALB: albumin, GLOB: globulin

VHS was higher in the C group compared to the other groups ($p<0.001$). The VHS was 10.28 in group A, 10.70 in group B1, 11.11 in group B2, and 12.17 in group C.

The echocardiographic values LA, LA/AO, LVIDd, LVIDs, EPSS, and MV E Vel were significantly higher in patients with stage C heart disease compared to the other groups ($p<0.001$) (Table 2).

The heart rate was higher in group C than in groups A, B1, and B2 ($p<0.05$) (Table 3). While sinus rhythm was noted in almost all healthy (group A), B1, and B2 dogs, sinus tachycardia was noted in only one dog from the B1 group. In the C group, 2

had sinus rhythm, 2 had sinus tachycardia, 1 had atrial tachycardia, 1 had sinus arrhythmia, and 2 had SA block.

The corrected QT duration was longer in the MMVD groups than in the control ($p<0.05$) (Table 3), however, there was no significant difference between them. No significant differences were observed for the RR interval, blood count, and biochemistry (Table 3 and 4).

DISCUSSION

MMVD is the most commonly diagnosed cardiovascular disease in dogs and accounts for more than 70% of all cardiovascular diseases in dogs (1). The studies conducted in the CKCS breed have reported a prevalence of 56.6% in dogs older than 4 years (5, 20). The data from our study shows that the disease occurs in animals older than 5 years and the stage of the disease increases with age. Several studies have reported that clinical signs occur at an earlier age in CKCS due to genetic predisposition (4, 21). Due to the long preclinical phase, it can lead to death in the early stages before congestive heart failure occurs (22).

Increased ALT and creatine levels may be observed in congestive heart failure (23, 24). The current research observed a slight increase in ALT levels at different stages of MMVD similar to other reports.

QT prolongation is associated with myocardial ischemia, cardiomyopathies, and hypertension (25). It is a marker of myocardial electrical instability and is associated with sudden death in people with congestive heart failure (10). Because the QT interval depends on the heart rate, the values obtained at different heart rates are used as the "corrected" QT interval (QTc) in the analysis of patients' electrocardiographic data (26). Universal QT - correction methods, such as the Bazett method, are widely used in clinical and preclinical safety studies because of their ease of use and broad support in the literature (27). Studies have reported that QTc prolongation is associated with malignant arrhythmias and a high risk of mortality in cardiac patients (27, 28). In our study, arrhythmias were found to be more common in patients with QTc prolongation, especially in stage C.

Bazett's formula is most applicable in dogs with high heart rates (12, 29). In another study (30), a significant prolongation of the QTc value calculated by the Bazett method was observed with the progression of heart failure. In our study, although there was no significant prolongation of QT duration between the groups, an increase in QTc value was observed in MMVD groups compared to the control. It has been suggested that the Fridericia and Hodges formulas can be applicable in patients with rapid heart rates (25). Although many authors (31, 32, 33) reported that the Bazett formula was not sufficient to correct the QT interval in dogs, Patel et al. (29) reported that it is more appropriate in cases where the heart rate exceeds 120. Similarly, we concluded that Bazett's formula is suitable for distinguishing MMVD from healthy dogs with high heart rates.

The limitations of Bazett's formula are well known and may lead to over- or under-correction in slow and fast heartbeats. Nevertheless, it remains the most important parameter for the evaluation of cardiac electrical function because of its high diagnostic value (34). In the current study, the use of Bazett's formula proved that it can be useful in distinguishing MMVD from healthy animals, especially in the more advanced stages of the disease when the heart rate is increasing.

CONCLUSION

Although the QTcb value was not significantly different among B1, B2, and C groups, it can be used in cases with high heart rates. Bazett's formula correction of the QT interval can discriminate between healthy and MMVD-affected CKCS dogs when pulmonary edema, cough, and exercise intolerance have not yet occurred or when echocardiography cannot be performed. In conclusion, we believe that long-term studies with a larger number of patients are needed to obtain more reliable results.

CONFLICT OF INTEREST

The authors declare that they have no potential conflict of interest with respect to the authorship and/or publication of this article.

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AUTHORS' CONTRIBUTIONS

RG designed the study, HS, EMA, SM and ASNA collected the patients, made ECGs, and echocardiography, LK and HS wrote the study, LK made the translation from Turkish to English, MEO has decided if the patients is stuitable for study.

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