FULL PAPER *Internal Medicine*

Evaluation of QT Interval Prolongation in Dogs with Heart Failure

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ABSTRACT. Comparison of the QT interval and corrected QT interval values that were calculated by the methods of Bazett (QTc1) and Fridericia (QTc2) were made between dogs with or without cardiac diseases to determine the influence of the QT interval on canine heart failure. Upon comparison of the measured values on ECG between the cardiac disease and non-cardiac disease groups, it was obse rved that the heart rate(HR) was significantly higher in the cardiac disease group than in the non-cardiac disease group, although th e QT interval was similar in the two groups. The QTc1 and QTc2 were significantly longer in the cardiac disease group than in the non-cardiac disease group. With the progression of the New York Heart Association Class, the HR tended to increase. The QTc1 and QTc2 beca me significantly prolonged with the progression of heart failure. Nevertheless, because Bazett's correction formula is known to overcorrect when the HR is high, it was considered that the QTc1 was actually overcorrected by high HR with the progression of heart failure . The QTc2, on the other hand, was only slightly influenced by HR, suggesting that the prolongation was due to the progression of heart failure. These results suggest that the prolongation of QTc2 in cardiac disease reflects the substantial prolongation of the QT interval without the influence of HR. It is suggested that the QTc2 could be a useful parameter for assessing the degree of heart failure in dogs with cardiac disease.

KEY WORDS: canine electrocardiogram, heart failure, QT interval.

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The length of the QT interval is associated with the duration of the action potential of ventricular muscles and is one of the important parameters used in the diagnosis of cardiac diseases through electrocardiography. The length of the QT interval is affected by the serum K^+ and Ca^{2+} levels, digitalis, agents that stimulate beta-receptors, and antiarrhythmic drugs. In humans, the QT interval is known to be prolonged in patients suffering from heart failure with valvular diseases [13, 18], myocarditis [19], and ischemic heart disease [1, 12, 20]. There have only been a few reports on the relationship between heart failure and QT interval prolongation in dogs, and the relationship remains unknown. In dogs with heart failure, the heart rate (HR) increases to various degrees to compensate for heart failure, and therefore, the length of the QT interval varies, making it difficult to evaluate the QT interval. Among many physiologic and pathologic factors, the HR has a large influence on the QT interval. Hence, when comparing the QT interval of dogs with different HRs, it is essential to exclude the influence of the HR. Many correction formulas have been developed to exclude the influence of HR in humans, and among them, the most widely used is Bazett's square root formula [2] because of its simplicity. Although this formula is also used in dogs; there were some problems encountered when using this formula in cardiac disease of dogs [5–8, 15,16]. Other methods of correcting the QT interval for HR in dogs have been developed, but they are not yet widely used [9,21]. Although the methods of correcting the QT interval for HR are not perfect, they could be useful in various situations, including assessment of the effects of various interventions and diseases. In studies on beagles and dogs at a veterinary clinic, it has been established that Fridericia's correction formula [4] using the cube root of the RR interval is simple and effective in excluding the effect of HR on the QT interval in dogs [7, 17]. In the present study, the effect of HR on the QT interval in dogs with or without cardiac diseases was investigated. In addition, the relationship between the QT interval and the corrected QT interval obtained from Fridericia's correction formula with the severity of heart failure was studied.

MATERIALS AND METHODS

The present study consisted of 562 dogs (248 males, 300 females, 14 unknown) that visited the following four veterinary clinics: as follows [1)]Veterinary Teaching Hospital of Nippon Veterinary and Animal Science University in Tokyo, Japan, [5)]Ina Veterinary Clinic of Animal ME Research Center, Tokyo, Japan, [3)]Sun Valley Animal Hospital, Fukuoka, Japan; and [4)]Clinique Veterinaire St Quentin en Yvelines, Paris, France. Each dog was examined for the presence of cardiac disease by studying the past medical history and conducting physical examinations. Dogs which did not exhibit cardiac diseases (non-cardiac disease group) included 291 dogs with no disorders of the liver, kidney or the respiratory tract as determined by blood and radiographic examinations. The cardiac disease group included 271 dogs diagnosed with mitral valve insufficiency (n-226),

filariasis (n=33), patent ductus arteriosus (n=5), pericardial effusion (n=3), pulmonary stenosis (n=2), ventricular septal defect (n=1), aortic stenosis (n=1). The average age of the animals was 8.2 ± 5.2 years (n=229) in the non-cardiac disease group and 9.7 ± 4.7 years (n=265) in the cardiac disease group. The average body weight was 10.5 ± 6.7 kg (n=211) in the non-cardiac disease group and 8.4 ± 6.5 kg (n=221) in the cardiac disease group. The dogs diagnosed with cardiac disease were divided into four classes (I-IV) according to the New York Heart Association (NYHA) classification of cardiac patients and a comparative study was performed. Following the NYHA Classification, the dogs were divided as follows: Class I, 58 dogs (age 6.0 ± 5.7 years; weight 6.7 ± 3.1 kg); Class II, 56 dogs (age 9.1 ± 3.9 years; weight 7.9 ± 4.6 kg); Class III, 104 dogs (age 10.9 ± 3.8 years; weight 9.3 ± 8.5 kg); and Class IV, 53 dogs (age 12.0 ± 3.2 years; weight 9.0 ± 6.3 kg).

Electrocardiogram (ECG) of dogs in right lateral recumbency were recorded using an automated electrocardiograph (α 6000AXD, Fukuda ME Kogyo Co., Chiba , Japan). The standard limb leads were used for recording and 5 consecutive heart beats were recorded on lead II. The following parameters were automatically measured on the ECG by the recording device and were analyzed in this study: HR, RR interval, QRS duration and QT interval. For each parameter, the median value of 5 consecutive heart beats was used in the analysis. Corrected QT intervals were calculated from these values by two different methods. The values of the parameters were checked for errors and if errors were found, repeat remeasurements were done manually on the ECG by ruler (paper speed of 50 mm/sec). Dogs with arrhythmia which affected the cardiac rhythm, such as premature contraction, were excluded from this study. Corrected QT intervals were calculated by two different formulas:

$$QTc1 = \frac{QT}{\sqrt{RR}}$$

$$QTc2 = \frac{QT}{\sqrt[3]{RR}}$$

The results were expressed as mean ± standard deviation. For statistical analysis, Student's *t*-test was used for comparison between groups. To assess correlations between QT, QTc1 or QTc2 with RR interval, linear regression analysis was used. Statistical significance was set at $p<0.05$.

RESULTS

The ECGs obtained from dogs with or without cardiac disease were studied. Comparison of the ECG parameters between the non-cardiac and cardiac disease groups showed that there were significant differences in the HR, RR, QRS, QTc1 and QTc2. The HR was significantly higher in the cardiac disease group; the RR was significantly shorter than in the non-cardiac disease group; and the QRS, QTc1 and QTc2 were significantly longer in the cardiac disease group but the QT intervals of two groups were similar (190.6 ± 19.4 msec for the cardiac disease group vs. 191.9 ± 21.1 msec for the non-cardiac disease group) (Table 1). Table 2 summarizes the ECG parameters of the dogs classified according to the NYHA Classification. Among the non-cardiac disease group and the four NYHA Class groups, the HR

Table 1. Measured values on ECG in the Non-cardiac disease dogs and Cardiac disease dogs

	HR (bpm)	RR (msec)	QRS (msec)	QT (msec)	QTc1 (msec)	QTc2 (msec)
Non-cardiac disease	118.0	540.5	41.9	191.9	264.4	237.2
(n=291)	± 27.5	± 149.9	± 8.1	± 21.1	± 24.1	± 18.4
Cardiac disease	137.0*	460.9*	48.3*	190.6	283.7*	248.0*
(n=271)	± 29.3	± 110.8	± 10.5	± 19.4	± 25.3	± 19.2

*, vs Non-cardiac disease $p<0.001$.

Table 2. Measured values on ECG according to the NYHA Classification of the dogs with cardiac disease

		Non-CD	NYHA I	NYHA II	NYHA III	NYHA IV
HR	(bpm)	118.0	121.7	136.0[a,b)]	143.3[a,b)]	142.1[a,b)]
		± 27.5	± 27.2	± 33.4	± 24.0	± 31.0
RR	(msec)	540.5	518.6	470.0[a,b)]	431.8[a,b,c)]	445.2[a,b)]
		± 149.9	± 119.0	± 124.6	± 81.9	± 113.0
QRS	(msec)	41.9	45.3[a)]	45.8[a)]	50.2[a,b,c)]	50.4[a,b,c)]
		± 8.1	± 9.5	± 9.0	± 11.5	± 10.0
QT	(msec)	191.9	186.4	187.8	190.6	198.3[a,b,c,d)]
		± 21.1	± 15.1	± 17.7	± 19.2	± 23.5
QTc1	(msec)	264.4	261.5	277.7[a,b)]	291.2[a,b,c)]	299.3[a,b,c,d)]
		± 24.1	± 19.4	± 25.0	± 22.7	± 16.8
QTc2	(msec)	237.2	233.2	243.2[a,b)]	252.6[a,b,c)]	260.5[a,b,c,d)]
		± 18.4	12.7	± 17.0	± 19.0	± 15.6

a) vs Non-CD, b) vs I, c) vs II, d) vs III. Non-CD: non-cardiac disease.

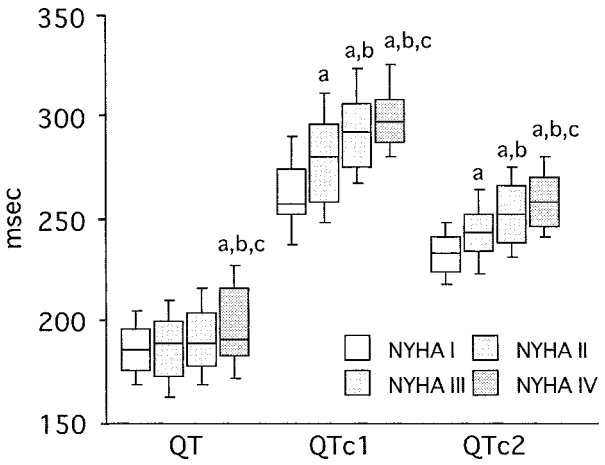

Fig. 1. Comparison of the QT and corrected QT intervals (QTc1, square root; QTc2, cube root) among the dogs in the four NYHA Class groups and the Non-cardiac disease dogs. QTc1 and QTc2 exhibited significant prolongation with the progression of the NYHA Class (a: vs I, b: vs II, c: vs III).

was lowest in the non-cardiac disease group (118.0 ± 27.5 bpm), this figure was not significantly different from the NYHA Class I group. The HR tended to increase as the NYHA class increased. The dogs in Classes II, III, and IV had a significantly higher HR than the dogs in Class I and non-cardiac disease groups.

The QRS duration tended to increase with the progression of NYHA Class. The QRS duration in the non-cardiac disease group was 41.9 ± 8.1 msec. The duration was significantly longer in Class I (45.3 ± 9.5 msec) and II (45.8 ± 9.0 msec) groups compared with the non-cardiac disease group ($p<0.01$). The QRS duration of Class III and Class IV groups was 50.2 ± 11.5 msec and 50.4 ± 10.0 msec, respectively. These figures were significantly higher than in Class II group ($p<0.05$). The difference in the QRS duration between Class III and Class IV groups was not significant.

The QT interval of the Class IV group was the longest among the groups at 198.3 ± 23.5 msec, showing significant differences in comparison with that in the other groups (non-cardiac disease group ($p<0.05$); Class I group ($p<0.01$); Class II group ($p<0.01$) and Class III group ($p<0.05$)). There were no significant differences in the QT interval between the other Classes. The QTc1 did not significantly differ between the non-cardiac disease group and the Class I group, but increased with the progression of NYHA Class. The QTc1 in the Class IV group was 299.3 ± 16.8 msec. There was no significant difference between the QTc2 of the non-cardiac disease group (237.2 ± 18.4 msec) and the Class I group (233.2 ± 12.7 msec). The QTc2 of the Class II group (243.2 ± 17.0 msec) was significantly longer than in the non-cardiac disease group and the Class I group ($p<0.05$). The QTc2 increased with progression of heart failure to Classes III (252.6 ± 19.0 msec) and IV (260.5 ± 15.6 msec). There were significant correlations between the QT interval and RR interval ($p<0.001$) in both the non-cardiac disease group ($r=0.692$) and cardiac disease group ($r=0.632$) (Fig. 1). There were also significant correlations ($p<0.001$) between the QTc1 interval and RR interval in both the non-cardiac disease ($r=–0.517$) and cardiac disease groups ($r=–0.528$). The correlation coefficient (r) between the QTc2 interval and RR interval was –0.104 in the non-cardiac disease group and –0.141 in the cardiac disease group, the latter being statistically significant ($p<0.05$).

DISCUSSION

The changes in the length of the QT interval depend on the HR and various other factors. Shorting of the QT interval typically occurs in pathological conditions such as hypercalcemia and digitalis intoxication. QT interval prolongation can be caused by various factors, including imbalance of electrolytes such as hypokalemia and hypocalcemia, or the administration of antiarrhythmic or psychotropic drugs. In humans, heart failure is known to prolong the QT interval but most studies on the QT interval in dogs have dealt with basic investigations [9–11, 21], including the effect of sinus arrhythmia or respiratory arrhythmia and the effect of change in HR caused by drug such as atropine. So far, there has been no report on the relationship between the length of the QT interval and heart diseases in dogs. Hence, in this study, the change in the QT interval in dogs with heart diseases was investigated.

Comparison of the measured parameters on ECG between the non-cardiac disease and cardiac disease groups showed that the HR of cardiac disease dogs was significantly higher than that of the non-cardiac disease dogs. However, the QT intervals of the two groups were similar. The QRS duration, QTc1 interval and QTc2 interval were all significantly prolonged in the cardiac disease group than in the non-cardiac disease group. While QT prolongation has not been reported in dogs with heart failure, it is known to be associated with ischemic heart disease [1, 12, 20], mitral valve prolapse syndrome [13, 18], cardiomyopathy [23] and myocarditis [19] in humans. Puddu *et al.* reported that patients suffering mitral valve prolapse syndrome with prolonged QT interval had elevated serum catecholamine levels [13]. Ahnve *et al.* reported that the one-year survival rate was low in patients with myocardial infarction accompanied by QT interval prolongation, and emphasized the importance of QT interval prolongation in predicting the occurrence of arrhythmia and prognosis [1]. They also reported that among patients with chronic ischemic heart disease, patients who exhibit prolonged QT interval had a significantly higher rate of sudden death. They concluded that the QT interval was a simple and useful parameter for following the course of patients with chronic ischemic heart disease [12]. In the present study of dogs with or without cardiac disease, the QT intervals of the cardiac disease and non-Cardiac disease groups did not significantly differ because the HR varied in each group. However, the corrected values of QT interval, i.e., QTc1 and QTc2, in the

cardiac disease group were significantly longer than in the non-cardiac disease group. It can, therefore, be considered that cardiac diseases in dogs induce QT interval prolongation, but because the QRS duration was also significantly prolonged in the cardiac disease group, the QRS complex may have probably contributed to prolonging the QT interval. Also, when Bazett's formula is used, it is known that an increase in HR overcorrects the value of the QT interval [14, 21], suggesting that increased HR contributed to the prolongation of QTc1 in the cardiac disease dogs. On the other hand, the correlation coefficient between QTc2 and RR interval was very low. It is, therefore, concluded that the increased HR in the cardiac disease group had a small influence on the prolongation of QTc2, but instead, QRS prolongation associated with cardiomegaly in heart failure and the change in electrophysiological characteristics of cardiac myocytes caused the prolongation of QTc2.

When the ECG measurements were evaluated according to the severity of heart failure, it was found out that the HR was significantly higher in NYHA Class II, III and IV dogs compared with the NYHA Class I dogs and the non-cardiac disease dogs, suggesting that the HR increased in the stage where exercise intolerance developed as a result of the progression of heart failure. The QT intervals were similar in the NYHA Class I, II and III groups, but were significantly prolonged in the Class IV group. On the other hand, the QTc1 and QTc2 significantly prolonged in the NYHA Class II, III and IV groups, with progression of heart failure (Fig. 2). However, because the HR increased with the progression of heart failure up to NYHA Class III, it was considered that the increase in HR, which was associated with the progression of heart failure, contributed to the prolongation of QTc1. When using the QTc1 to evaluate congestive heart failure, the degree of the increase in HR must be taken into consideration. The QTc2 and QTc1 showed a significant increase with the progression of the NYHA Class. However, it was reported that the value of QTc2 was less likely to be affected by HR than the value of QTc1 [7, 17], suggesting that the prolongation of QTc2 with the progression of heart failure is more closely associated with the pathologic condition of heart failure. Davey *et al.* demonstrated in human heart failure patients a correlation between the QT interval and degree of fractional shortening, and suggested that the QT interval prolongation was associated with left ventricular dysfunction [3]. They also reported that QT interval prolongation in human heart failure patients was not associated with the QRS duration [3]. In the present study in dogs, however, the QRS duration increased with the progression of heart failure. The QRS complex significantly differed among the groups of non-cardiac disease group, NYHA class I /II and NYHA class III/IV, but the difference was not significant between NYHA Class I and II nor between NYHA Class III and IV. Hence, it was suggested that although the QRS duration increased with progression of heart failure, factors other than prolongation of QRS duration might have contributed to QT interval prolongation. In a study of dogs with pacing-induced heart failure

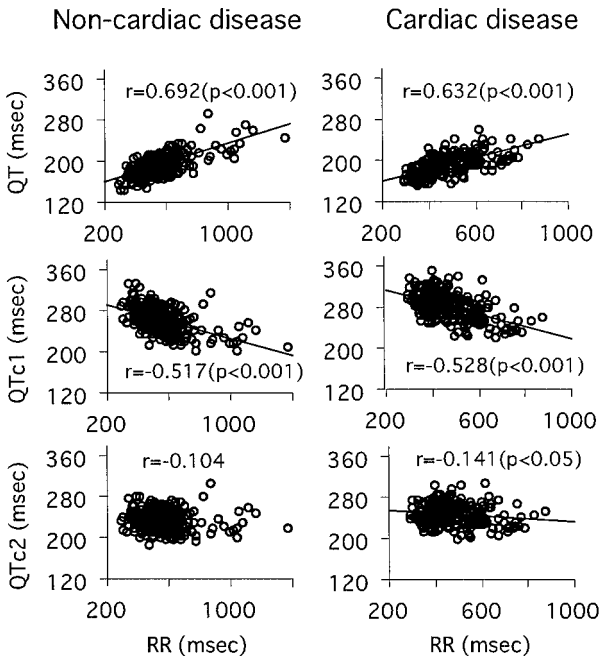

Fig. 2. Correlation between the QT/corrected QT interval and RR interval among the Non-cardiac disease dogs and among the Cardiac disease dogs. There was a strong correlation between the QT/QTc1 and RR interval, but the QTc2 was not associated with the RR interval.

and volume overload, the heart failure dogs had QT interval prolongation whereas the control dogs did not show any change in the length of the QT interval [22]. The QT interval prolongation in the aforementioned study was documented by both surface ECG and local electrogram, suggesting that prolonged repolarization of the ventricular myocardium was the cause of prolongation. QT interval prolongation may be caused by alterations in the regulation of autonomic nerves, alteration in ion channels of ventricular myocytes, or alteration in baroreceptors, although the cause remained uncertain in the present study.

Generally, since the classification of NYHA has many subjective factors, it is lacking in objectivity. The other methods of evaluating the severity of heart failure in dogs include echocardiogram and cardiovascular catheterization, in addition to conventional physical examination and chest X-ray. Nevertheless, these special examinations are difficult to perform in routine practice because of the risks to the animal and the requirement of special equipment. The QTc2 used in this study was calculated by the cube root of the RR interval, and the value of QTc2 can be determined by routine ECG. The present study suggests that since the value of QTc2 is not greatly affected by the variation in HR, QTc2 can be a simple and useful parameter for evaluating the QT interval in dogs with heart failure and which show variation in HR. And it is also suggested that the QTc2 could be a useful parameter for assessing the degree of heart

failure in dogs with cardiac disease.

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