

# Correlation of QT dispersion with indices used to evaluate the severity of familial ventricular arrhythmias in Boxers

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**Objective**—To measure QT interval duration and QT dispersion in Boxers and to determine whether QT variables correlate with indices of disease severity in Boxers with familial ventricular arrhythmias, including the number of ventricular premature complexes per day, arrhythmia grade, and fractional shortening.

**Animals**—25 Boxers were evaluated by ECG and echocardiography.

**Procedure**—The QT interval duration was measured from 12-lead ECG and corrected for heart rate (QTc), using Fridericia's formula. The QT and QTc were calculated for each lead, from which QT and QTc dispersion were determined. Echocardiography and 24-hour ambulatory ECG were performed to evaluate for familial ventricular arrhythmias. Total number of ventricular premature complexes, arrhythmia grade, and fractional shortening were determined and used as indices of disease severity.

**Results**—There was no correlation between any QT variable and total number of ventricular premature complexes, arrhythmia grade, or fractional shortening. No difference between QT dispersion and QTc dispersion was identified, and correction for heart rate did not affect the results.

**Conclusions and Clinical Relevance**—QT interval duration and dispersion did not correlate with indices of disease severity for familial ventricular arrhythmias. Heart rate correction of the QT interval did not appear to be necessary for QT dispersion calculation in this group of dogs. QT dispersion does not appear to be a useful noninvasive diagnostic tool in the evaluation of familial ventricular arrhythmias of Boxers. Identification of affected individuals at risk for sudden death remains a challenge in the management of this disease. (*Am J Vet Res* 2001;62:1481–1485)

**F**amilial ventricular arrhythmias (FVA) of Boxers is a commonly encountered disorder in veterinary medicine and is characterized by the development of ventricular tachyarrhythmias resulting in sudden death.<sup>1,2</sup> The mechanism of the arrhythmias in Boxers is unknown. There are 3 mechanisms postulated for the genesis of ventricular tachyarrhythmias, including enhanced automaticity, triggered activity, and reentry. In people, the predominant mechanism of ventricular tachyarrhythmias resulting in sudden cardiac death is

believed to be reentry.<sup>3</sup> Reentrant circuits are created when adjacent myocardial tissues have various electrophysiologic properties, allowing for the development of abnormal impulse conduction. The disparity in electrophysiologic properties may be caused by structural abnormalities or functional changes. Anatomic abnormalities, including hypertrophy, fibrosis, and ischemia, create areas of differing excitability and electrophysiologic properties resulting from abnormal tissue. Functional reentry occurs in the absence of any identifiable anatomic substrate, presumably as the result of inherent electrophysiologic differences in membrane and ionic properties of excitable tissue. Differences in the electrophysiologic properties of excitable tissue may manifest as inhomogeneity of ventricular depolarization and repolarization.<sup>4</sup>

The QT interval, measured from the surface ECG, is an electrocardiographic variable of ventricular repolarization.<sup>5</sup> The duration of the QT interval is not identical in all leads; this interlead difference between the maximum and minimum QT durations is known as QT dispersion.<sup>6</sup> It is hypothesized that the degree of variation in QT interval duration among leads (dispersion) reflects regional differences of ventricular repolarization.<sup>5,6</sup> Increased QT dispersion reflects increased inhomogeneity of ventricular repolarization.<sup>7</sup> Dispersion of ventricular repolarization reduces the threshold for ventricular fibrillation and facilitates the development of reentrant ventricular tachyarrhythmias. Consequently, QT dispersion may be used as a marker of arrhythmogenicity and may support a reentrant mechanism.<sup>5,8,9</sup>

QT dispersion may be an indicator of reentry and serve as a noninvasive means to identify electrical dispersion in Boxers with FVA. This could provide evidence for an arrhythmogenic substrate and can be useful in identifying dogs at risk for arrhythmia development and sudden cardiac death. In humans, QT dispersion has been used with some success for identifying patients at risk for developing ventricular tachyarrhythmias associated with a number of cardiovascular diseases, including chronic heart failure, hypertrophic cardiomyopathy, myocardial ischemia, aortic stenosis, mitral valve prolapse, and long QT syndrome.<sup>6,10-14</sup> The development of a noninvasive diagnostic test capable of identifying patients who are most severely affected with FVA that may be at highest risk for developing ventricular tachyarrhythmias and sudden death would represent a substantial advancement in the management of FVA in Boxers.

The purpose of the study reported here was to measure QT interval duration and QT dispersion in

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Boxers and to determine whether QT variables correlate with indices of disease severity of FVA, including the number of ventricular premature complexes, grade of arrhythmia, and left ventricular function (as measured by fractional shortening).

## Materials and Methods

**Animal selection**—A group of Boxers was evaluated as part of a screening program for FVA. Twenty-five dogs meeting the following entry criteria were included in the study: completion of a 12-lead ECG, 24-hour ambulatory ECG, and 2-dimensional echocardiography. Historical information regarding exercise tolerance and episodes of syncope was also obtained. No attempt was made to classify dogs as affected or unaffected, but dogs with and without cardiac arrhythmias were included.

**Twelve-lead ECG**—A 12-lead ECG was obtained in unsedated dogs positioned in right lateral recumbency. Tracings were recorded at paper speeds of 25 and 50 mm/s with a gain of 10 mm/mV. In some instances, the recording of precordial leads overlapped with the limb leads, and in these cases, the gain of the precordial leads was decreased to 5 mm/mV. The QT interval durations were measured manually as the duration from the onset of the QRS complex to the termination of the T wave.<sup>6</sup> Three consecutive beats were measured, and the RR interval immediately preceding each complex was recorded. A **heart rate-corrected QT interval (QTc)** was calculated for each beat as the duration of the QT interval divided by the cube root of the RR interval (measured in seconds) of the preceding cardiac cycle.<sup>15</sup> Mean QT and QTc were calculated for each lead on the basis of the 3 measured beats, from which QT and QTc dispersion were determined. The QT and QTc dispersion were defined as the difference between the maximum and minimum value of the mean QT and QTc for each lead, respectively.<sup>6</sup> In addition to QT and QTc dispersion, **mean values for QT and QTc (QT<sub>mean</sub> and QTc<sub>mean</sub>)** were calculated for each dog, using the mean values from each of the 12 leads.

**24-hour ambulatory ECG**—Twenty-four hour ambulatory ECG was performed, using 3-channel cassette recorders, and analyzed with a Holter analysis system with prospective user interaction.<sup>8</sup> Total number of **ventricular premature complexes (VPC)** and duration of recording were obtained. Only those recordings at least 20 hours in duration were included. If VPC were identified, the arrhythmia was graded on the basis of a modification of the Lown grading scheme as follows: grade 1 = single uniform VPC only; grade 2 = bigeminy, trigeminy, or multiform VPC; grade 3 = couplets or triplets; and grade 4 = R-on-T phenomenon or ventricular tachycardia. Animals in which no VPC were identified were classified as grade 0.<sup>16</sup>

**Echocardiography**—Two-dimensional echocardiography was performed in unsedated dogs positioned in right lateral recumbency, using standard techniques. **Fractional shortening (FS)** was calculated as the percentage difference between diastolic (LVIDd) and systolic (LVISd) left ventricular dimensions according to the formula  $FS = (LVIDd - LVISd) / LVIDd \times 100$ .<sup>17,18</sup>

**Statistical evaluation**—The QT variables (QT and QTc dispersion, QT<sub>mean</sub>, and QTc<sub>mean</sub>) were evaluated for correlation to total number of VPC, arrhythmia grade, and FS. For the purpose of statistical calculations, arrhythmia grade was converted to a numeric ordinal scale as described. The non-parametric Spearman correlation coefficient was used to identify significant correlation between the QT variables and indices of disease severity. A Mann-Whitney rank sum test was used to identify a difference between QT dispersion and QTc dispersion. Significance was tested at  $\alpha = 0.05$ .

## Results

Twelve-lead ECG, ambulatory ECG, and echocardiography were performed in 25 Boxers (20 females, 5 males). In addition to the QT variables (QT and QTc dispersion, QT<sub>mean</sub>, and QTc<sub>mean</sub>), descriptive statistics for the total number of VPC on 24-hour ambulatory

Table 1—Median, SD, minimum (min), maximum (max), and range values for QT variables, indices of disease severity, age, and heart rate of 25 Boxers evaluated by 12-lead ECG, ambulatory ECG, and echocardiography

Variable	Median	Mean	SD	Min	Max	Range
QT disp (ms)	0	3.9	12.5	0	50	50
QTc disp (ms)	0	4.8	15.6	0	61.3	61.3
QT <sub>mean</sub> (ms)	213	218.0	18.6	180	253	73
QTc <sub>mean</sub> (ms)	261	264.5	21.5	230	317	87
Age (y)	4	4.5	3.2	1	10	9
FS (%)	31.0	30.5	4.0	20.0	36.0	16.0
VPC (No./d)	5	2,776	12,489	0	62,622	62,622
Arrhythmia grade (range, 0 to 4)	1	2.0	1.4	0	4	4
Heart rate (beats/min)	111	109	19.9	65	148	83

QT disp = QT dispersion. QTc disp = QTc dispersion. QT<sub>mean</sub> and QTc<sub>mean</sub> = Mean QT and QTc values for each dog, using the mean values for each of the 12 leads. FS = Fractional shortening. VPC# = Total number of ventricular premature complexes per day.

Table 2—QT variables, signalment, and indices of disease severity for 3 Boxers in which QT and QTc dispersion were not zero

QT disp	QTc disp	QT <sub>mean</sub> *	QTc <sub>mean</sub> *	Age (y)	Sex	FS	VPC	Arrhythmia grade	Heart rate (beats/min)
50	61.3	224	280	1.5	M	28	1	1	110
7	7.9	223	262	2	F	36	6	3	97
40	50.6	225	276	1.5	F	35	24	2	111

\*Values for QT<sub>mean</sub> and QTc<sub>mean</sub> are within 1 SD of the mean, and indicators of disease severity do not suggest presence of disease.  
M = Male. F = Female.  
See Table 1 for key.

ECG, grade of arrhythmia, and FS were determined (Table 1). In 22 of 25 dogs, QT dispersion (and consequently QTc dispersion) was 0. Data for the 3 dogs with QT dispersion not equal to 0 were collected (Table 2). Values for  $QT_{\text{mean}}$  and  $QTc_{\text{mean}}$  were within 1 SD of the mean, and indicators of disease severity did not suggest presence of disease. Two of the 25 dogs had a history of syncope. In both dogs, QT and QTc dispersion were 0, and QT variables were either less than the mean or were within 1 SD of the mean. None of the dogs with non-zero QT dispersion had a history of syncope.

QT dispersion, QTc dispersion,  $QT_{\text{mean}}$ , and  $QTc_{\text{mean}}$  were evaluated for any correlation to total number of VPC, arrhythmia grade, and FS. No significant correlations between any of the QT variables and the indices of disease severity were found.

Evaluation of heart rate correction for QT interval duration revealed that individual measurements of QT intervals often did not change on a beat-to-beat basis, despite beat-to-beat variation in heart rate. A Mann-Whitney rank sum test failed to identify a difference between QT dispersion and QTc dispersion.

Two of the dogs (a 6-year-old male and a 10-year-old female) had syncope. Both had QT dispersion of 0, and  $QT_{\text{mean}}$  (213, 200 milliseconds) and  $QTc_{\text{mean}}$  (230, 259 milliseconds) were less than and within 2 SD of the mean. The total number of PCV and grade from Holter recordings were 68 VPC and grade 2 and 505 VPC and grade 3, respectively. The FS (32%, 25%) were within reference ranges for each dog.

## Discussion

This is the first study to report the role of QT dispersion in the assessment of FVA in Boxers. Results obtained in our study indicate that QT interval duration and dispersion of QT do not correlate with total number of VPC, arrhythmia grade, or FS. Most dogs had QT dispersion equal to 0, implying that substantial dispersion of repolarization was not observed in this group of dogs and would not be expected to discriminate dogs on the basis of disease severity. There was no difference between dispersion of QT and QTc intervals, and individual measurements of QT intervals did not change on a beat-to-beat basis, despite beat-to-beat variation in heart rate resulting from respiratory sinus arrhythmia. Thus, heart rate correction of the QT interval did not appear to be necessary for QT dispersion calculation in this group of dogs.

Human studies<sup>5,6,10-12,14</sup> evaluating QT dispersion have revealed potential clinical utility in predicting arrhythmic episodes or sudden death associated with cardiovascular diseases such as coronary artery disease, hypertrophic cardiomyopathy, chronic heart failure, aortic stenosis, mitral valve prolapse, and long-QT syndrome. Despite studies that claim clinical usefulness of QT dispersion in identifying patients at risk for future arrhythmic episodes or sudden death, much controversy still remains. Not all studies evaluating QT dispersion have arrived at the same conclusions.<sup>19,21</sup> Disparity in findings could result from evaluation of QT dispersion using retrospective study designs or having protocols that were subject to selection bias. This lack of standardization of the use of QT dispersion as a diag-

nostic tool makes comparison between studies difficult, which may account for some of the differences observed.<sup>19</sup>

One of the difficulties in evaluating QT dispersion is with the method of QT interval measurement itself. There is little difficulty in identifying the onset of the QRS, but there can be some ambiguity in determining the termination of the T wave. Low T wave amplitude, variations in T wave appearance, and the presence of a U wave are all factors that can contribute to the inability to accurately identify termination of the T wave, resulting in difficulty of QT interval measurement.<sup>6</sup> Some studies, in an effort to eliminate this uncertainty, have excluded leads in which these problems exist. Because QT dispersion is the difference between the largest and smallest QT interval between leads, eliminating 1 or more leads may have an effect on its value. Other efforts used to avoid complications associated with accurate determination of T wave termination include measurement of the QT interval from the onset of the QRS complex to the peak of the T wave ( $QT_{\text{peak}}$ ). The peak of the T wave can be more reliably identified than the end of the T wave, and is thus associated with less ambiguity.<sup>22</sup> Studies using various techniques to improve the accuracy of QT measurement have also created a lack of standardization that contributes to the inability to compare studies.

Results of our study indicate a lack of correlation between QT variables and indices of disease severity. As in other studies, the methods used may contribute to these findings. In our study, QT interval durations were measured manually. Manual measurement in previous studies<sup>13,23</sup> has been aided by the use of a digitizer coupled with magnification to improve resolution and enhance accurate identification of T wave termination. Using these criteria, error of measurement has been determined to be on the order of 20 milliseconds.<sup>24</sup> With the use of caliper measurement in our study, accuracy of measurement was estimated to be 0.25 mm, which corresponds to 10 milliseconds for recordings made at 25 mm/s and 5 milliseconds for recordings made at 50 mm/s. However, this is an unsubstantiated estimate that only takes into account the perceived error of measurement with the calipers and does not reflect accurate identification of T wave termination. In our study, we did not appreciate difficulty in identification of T wave termination and did not observe unusual T wave morphology (biphasic T waves, notching, changes in polarity) or presence of U waves. As a result, we did not use a digitizer or magnification, nor did we calculate  $QT_{\text{peak}}$  intervals. Validation of computer-free manual measurements may be necessary to fully appreciate the degree of measurement error. However, the frequency of QT dispersion values of 0 and the magnitude of nonzero measurements suggest that measurement error is unlikely to significantly affect the conclusions of our study.

Duration of the QT interval is affected by heart rate, and QT measurements are frequently corrected for heart rate. There are many ways in which QT interval duration can be corrected for heart rate; 2 of the most commonly used are Bazett's formula and Fridericia's formula.<sup>15</sup> Correcting for heart rate in

humans may be unnecessary, as adjustments made on the basis of Bazett's formula (square root) are negligible at heart rates between 50 and 80 beats/min.<sup>25</sup> In dogs, clinically normal heart rates are higher, with rates greater than 120 beats/min commonly developing in dogs in our study. Because Bazett's formula is believed to be less accurate at higher heart rates, we chose to correct the QT interval, using Fridericia's (cube root) method.<sup>26</sup> However, the importance of heart rate correction for the purpose of QT dispersion calculation in dogs is unclear. Furthermore, because of the relatively slow response of QT duration changes as a result of changing heart rate, the practice of measuring RR intervals immediately preceding each beat may be complicated by respiratory sinus arrhythmia, which commonly is found in dogs.<sup>25,27</sup> The necessity of heart rate correction for QT dispersion is also unclear.<sup>25,28</sup> In some investigators' opinion, the most serious drawback to the use of heart rate-corrected QT durations is that studies evaluating QT dispersion identify differences between patient populations on the basis of differences in underlying heart rate and not true differences in repolarization.<sup>25</sup> Most studies examining QT dispersion have reported values in terms of QTc, which may represent a confounding factor in the interpretation of their results.

In our study, QT and QTc measurements were determined, and no difference between QT and QTc dispersion was identified. Furthermore, individual measurements of QT intervals did not change on a beat-to-beat basis, despite beat-to-beat variation in heart rate resulting from respiratory sinus arrhythmia. Therefore, the use of heart rate correction of the QT interval did not appear to be necessary for QT dispersion calculation in this group of dogs.

Limitations in our study may arise from the assumption that FS obtained from 2-dimensional echocardiograms and the frequency and severity (grade) of the arrhythmia taken from 24-hour ambulatory ECG are useful in quantifying the severity of FVA in Boxers. The association between echocardiographic and electrocardiographic variables and FVA has not been demonstrated. The lack of correlation between QT dispersion and the results of these diagnostic tests may imply the lack of significant heterogeneity of repolarization in dogs with FVA, or it may simply reflect the inability of these diagnostic variables to quantify disease severity. However, these variables are commonly used in the diagnosis of FVA and serve to guide treatment and provide prognostic information in the clinical management of the disease.<sup>1,2</sup> The sex distribution in this group of dogs was skewed (20 female, 5 male), which may have influenced the results. The discrepancy most likely is a result of the fact that breeders owned most dogs evaluated, and females were more commonly evaluated. However, no evidence supporting a difference in QT variables on the basis of sex exists in dogs. Furthermore, previous evaluation of the total number of VPC and arrhythmia grade did not identify significant differences on the basis of sex.<sup>b</sup> The low numbers of dogs available for evaluation may have also contributed to our inability to demonstrate significant correlations between QT variables and these indices of

disease severity. More studies that include a greater number of animals may be needed to validate these findings.

The results of our study suggest that QT interval duration and QT dispersion do not correlate with indices of disease severity for FVA, including FS, number of VPC, and grade of arrhythmia. Furthermore, heart rate correction of the QT interval for the purpose of calculating QT dispersion may not be necessary.

<sup>a</sup>Del Mar Avionics, Irvine, Calif.

<sup>b</sup>Spier AW, Meurs KM, Lehmkuhl LB, et al. Evaluation of ambulatory ECG monitoring in asymptomatic Boxer dogs (abstr). *J Vet Intern Med* 1999;13:248.

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