How to approach the QT interval in dogs – state of the heart: a review

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ABSTRACT: The QT interval has been the objective of exhaustive attention in the past and also in recent times. A number of conditions, congenital and acquired, can have a direct effect on cardiac repolarization. Also drug regulatory agencies have showed increasing interest in the topic because certain drugs can prolong the QT interval to a level that produces ventricular arrhythmias. The dog is a species that shares some similarities with the human electrical system and has been used in human and veterinary research. We here present the current recommendations for QT measurement in dogs for use in clinical and experimental practice.

Keywords: electrocardiography; QT interval; repolarization; dogs

Contents

1. Introduction

The QT interval (QTi) on the electrocardiogram (ECG) represents the time required to achieve ventricular depolarization and the time required to complete the repolarization processes. The QTi is a dynamic physiological variable that can be affected by the velocities of both the ventricular conduction and repolarization (Moss, 1999; Sheridan, 2000; De Ponti et al., 2002). Multiple factors have been described to affect the QTi such as the cardiac cycle length, autonomic nervous system activity, age, gender, circadian rhythm, plasma electrolyte concentrations and variations in ion channels involved in cardiac repolarization (De Ponti et al., 2002; Luo et al., 2004). Different studies in dogs have shown that baseline uncorrected QT values are within the physiological range at similar heart rates (HR) suggesting that QTi are being measured accurately. This is consistent with emerging data showing that the accuracy of ECG parameter measurement in dogs is highly reproducible between and within individuals and is independent of the number of cycles measured (Hamlin et al. 2004; Tattersall et al., 2006).

2. Measurement of the QT interval

It is recommended to make a short pause before registering definitive ECG values after a change in the environmental conditions that could influence parameters like the HR. Studies involving abrupt changes in constant pacing rates showed that the QTi takes on average two to three minutes to reach a new steady state (Malik, 2004). Also it is desirable that tests are done within a narrow time

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window (usually less than 3 h) thus excluding any major influence of nycthemeral QT or HR variation (Tattersall et al., 2006).

The optimal approach to measuring the QTi should utilize a multi-channel ECG to record limb and precordial leads simultaneously, preferably at a speed of at least 50 mm/s. Most reports in the human literature measure one QTi in the lead II at a speed of 25mm/s (Moss, 1999; Friedman et al., 2003), which can compromise the accuracy of measurement. Other reports recommend this measurement in leads II, V_2 and V_3, because the T wave is always well defined and often reaches the maximal amplitude in these leads (Elming et al., 2003; Viskin et al., 2003; Vohra, 2003; Fenichel et al., 2004; Charbit et al., 2006). A similar situation has been determined in dogs, where the lead CV_5RL seems to produce less intra- and inter-animal variability as it well defined at the end (Nahas and Geffray, 2004). Other authors claim that the QTi can be measured from the longest QT period in a strip if the lead is well defined or not (Fenichel et al., 2004). Careful superimposition of different digitally and simultaneously recorded leads seems to solve the problem of lead selection and frequently makes the Q wave onset on T wave offset easier to detect (Fenichel et al., 2004). This is an interesting method for validation because dogs can show different T wave configurations that can change on a daily basis in simultaneous leads, including precordial leads, and has been the selected method in our practices.

The QTi should be measured from the earliest onset of the QRS complex to the latest end of the T wave (it should be determined from a straight line extrapolation of the terminal portion of the T wave to the point where it intersects the baseline) (Moss, 1999; Friedman et al., 2003; Charbit et al., 2006; Schmitt et al., 2007). In cases of biphasical T wave, it must be measured to its end as well. The small U waves, though rare in dogs, should not be included in the measurement (Haverkamp et al., 2000; Toivonen, 2002; Friedman et al., 2003; Vohra, 2003). For ease of measurement a tangent against the steepest part of the end of the T wave could be done (Figure 1). In practice this method may be more demanding but it improves the possibility in detecting changes in the QT. If the T wave has two positive deflections, the taller deflection should be chosen. If the T wave is biphasic, the end of the taller deflection should be selected. In many cases the end of the T wave is somewhat indistinct, either because of the presence of a low amplitude T wave or a somewhat prominent U wave. This can represent early afterdepolarizations (EAD) and should be included in the measurement (Moss, 1999; Toivonen, 2002; Viskin et al., 2003). Accurate determination of the QT interval, especially the T-wave termination, is sometimes challenging for both the trained eye and computer algorithms (Luo et al., 2004). Thus, quantification of the QTi is affected by the imprecision inherent in identifying the end of the T wave on the ECG (Moss, 1999; Malik, 2004). It is important to remember that T wave morphology and RR intervals are highly variable in dogs and must be analyzed by an expert veterinarian (De Ponti et al., 2002).

Other reports on humans recommend measuring three cardiac cycles and averaging these values to get the greatest precision (Moss, 1999; Malik, 2001). We believe that this method cannot be extrapolated for dogs. Compared with humans, QTi measurement seems to be more inaccurate in dogs. Even the most modern ECG equipment uses simple and imprecise algorithms for interval measurement. These algorithms are obviously influenced by marked sinus arrhythmia (SA) and highly irregular size and shape of T waves in dogs. Most relaxed, conscious dogs experience cyclic waxing and waning of parasympathetic efferent activity with respiration that produces the cyclic speeding and slowing of the heart rate known as respiratory SA. Currently, 12 consecutive cardiac cycles gener-

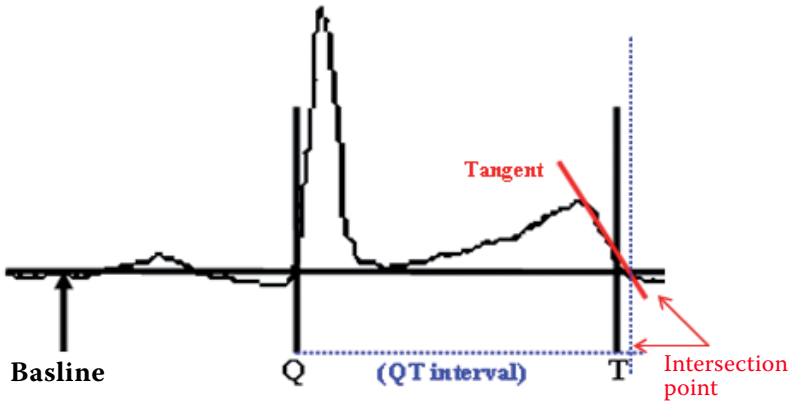

Figure 1. Measurement of the QTi according to the tangential approach of the T wave. Note that the QTi is actually longer when compared with the line intersecting the baseline

ally cover a time period equivalent to at least three respiratory cycles to minimize the effects of SA in dogs (Hamlin et al., 2004). When HR is regular and recordings are of good quality, there is little question that measuring parameters from one cardiac cycle would produce values very similar to values obtained by measuring a greater number and averaging. However, when respiratory SA occurs it might be expected that RR and QT would vary substantially and for this reason QTi measurements are corrected for HR (QTc) (Moss, 1999; Sheridan, 2000; Hamlin et al., 2004). Also, if the ECG after an acclimatization period does not reach a steady state we use the correction for HR (Malik, 2004). A general rule of thumb states that the QTi should generally be less than half of the preceding R-R interval. This rule, however, only holds true for HR in the 60 to 90/min range (Makaryus et al., 2006). One study showed that this rule was not adequate as an index of normal QTc (Koehler et al., 2004).

Measuring the QTi is complicated by a number of factors, both technical and physiological, which can compromise the accuracy of QT measurement. QTi can vary with the lead, the heart rate, the gender, time of day, drug induced changes, and clinical conditions like electrolyte abnormalities, myocardial ischemia or infarction, bradyarrhythmias, hypothermia, myocarditis, etc (Hamlin et al., 2004; Luo et al., 2004). The QTi also appears to be affected by the phase of menstrual cycle in human beings (Taylor, 2003). Interestingly, some reports have demonstrated that females exhibit a longer rate-corrected QTi and increased propensity toward drug-induced arrhytmias compared to males. Sex hormones are suspected to play a key role in this process. These findings were contradicted by the results of another study, although this should be interpreted with caution since the animals were not sexually mature at the initiation of some of these studies (Tattersall et al., 2006). Perhaps these notions deserve more attention since castration is a common practice in dogs and this influence has not been yet studied.

2.1. Methods of QTc assessment

Because of the numerous sources of inaccuracy with regard to QT measurement, it is difficult to evaluate the clinical and biological significance of minor QT changes, even when they are statistically significant (Moss, 1999). Differences in HR can be a consequence not only of autonomic conditioning but also of an external factor, like a drug (Malik, 2004). It is very interesting that even during the highly variable HR of SA in the dog the QT does not change due to QT "memory." QT memory holds that QT is determined by the average HR measured from the three to six beats preceding the QT being measured (Hamlin et al., 2004).

Several recommendations have been proposed on how to normalize the QTi for variations in HR (named corrected QT, QTc) and the issue remains a topic of debate. There are a number of mathematical possibilities for describing the QT/RR relationship but frequently, only very primitive approaches to HR correction are used despite the wide consensus on their inappropriateness (Malik, 2001). The most common approaches to the QTc use logarithmic expressions that adjust the QTi for HR. These include Bazzet's formula, which utilizes a square root adjustment for the RR cycle length, and Fridericia's formula, which utilizes a cube root adjustment for the RR interval. This calculation represents the QTi normalized to a HR of 60 beats per minute (bpm) and provides the analyst with a single metric to assess changes in the QT trend (Raunig et al., 2001). Both methods have their limitations when trying to compare subjects that have different HR. Bazett's formula is still the most popular in clinical practice, research, and education despite the fact that it was

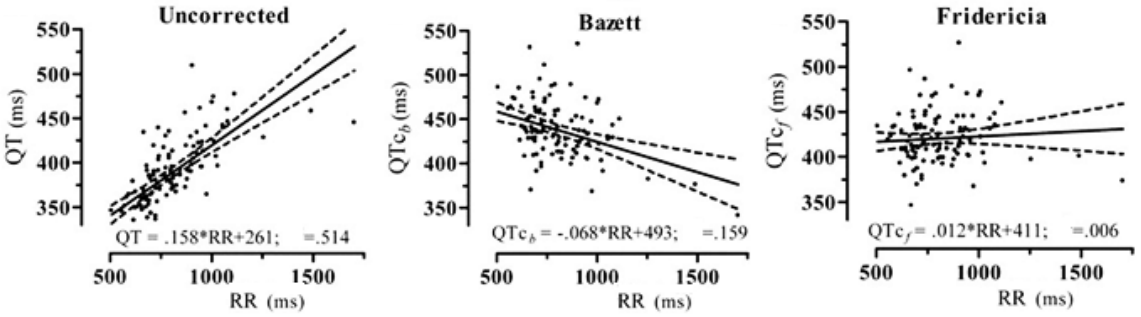

Figure 2. The Fridericia formula, although still imperfect, corrects QTi better than does the Bazett formula when HR diverges from 60 beats/min (from: Charbit et al., 2006)

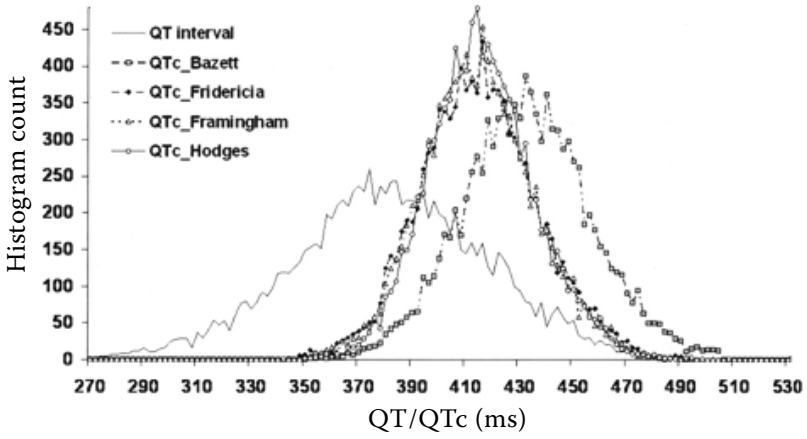

Figure 3. Distribution of the uncorrected QT measures and the QTc values from four formulae based on all 10 303 data samples, presented as histograms (from: Luo et al., 2004)

established many years ago (1961) that it should not be recommended (Luo et al., 2004).

Bazett's and Fridericia's formulae as well as other single-coefficient models fail to describe the QT to RR functional relationship in the dog. HR has much greater range and the QT-RR relationship flattens at low HR (high RR) in dogs. Therefore these monotonically increasing formulae should be avoided for correcting QTi duration for changes in HR in conscious dogs (Tattersall et al., 2006; Schmitt et al., 2007)'. Despite this fact, veterinary studies have preferred Fridericia's approach to the QTc because it is simple and effective in excluding the effect of HR on QTi in dogs (Hamlin et al., 2004; Koyama et al., 2004; Ghaffari and Parsamehr, 2009) (Figures 2 and 3). HR is nearly independent of the RR interval in dogs. In fact, the QT for normal dogs is rarely greater than 260 ms, even at RR intervals of 2000 ms (Hamlin et al., 2004). More interesting still is the observation that during respiratory SA when a dog is breathing 15 times a minute, the interbreath interval is 4000 ms, which would include between four and five heartbeats. When the RR interval changes dramatically, as with respiratory SA, but the QT does not change, then the QTc $[QT/(RR)^{1/3}]$ should vary proportionally according to the degree of SA (Hamlin et al., 2004).

One large study in humans compared four QTc corrected distributions. A corrected distribution in practical terms will be narrower than the original distribution. By simply applying a common approach, QT/QTc averages and the corresponding standard deviations show that all four QTc distributions are narrower than the original QT distribution (smaller SD). However Bazett's formula is relatively wider and 30% of apparently normal ECGs would be reported as prolonged QTi. Globally, Hodge's QTc correction remains the best choice with the smallest correlation coefficient (Luo et al., 2004). When these similar approaches are compared at two different values of QTi, Bazett's formula overcorrects values of QTc above 60 bpm compared to the other formula and generally lowers values below 60 bpm (Figure 4, Table 1). The Framingham formula has less correction above 100 bpm. This observation shows that the performance of the formulae are different with regard to HR values calculated and seems to imply that some QT correction formulae

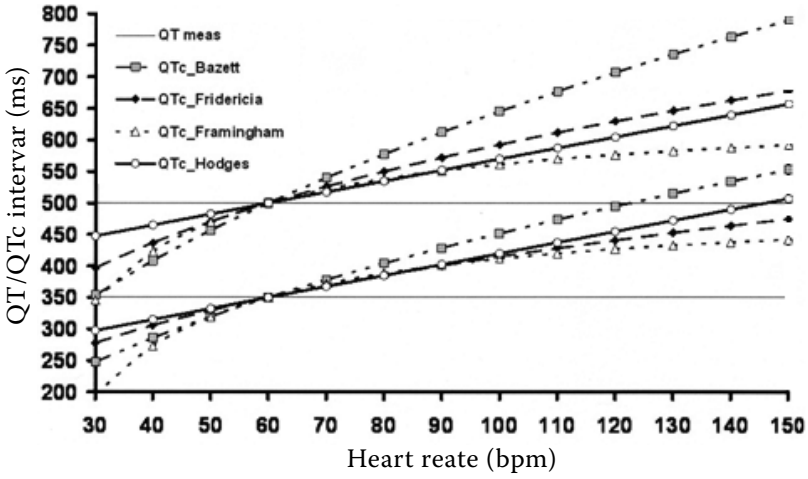

Figure 4. Comparison of four different QTc formulae based on two values of QT, namely 350 ms and 500 ms (from: Luo et al., 2004)

Table 1. The most popular formulae for correcting QTi

Name and year	Abbreviation	Formulae
Bazzet (1920)	QTc(B)	= QT/√RR
Fridericia (1920)	QTc(F)	= QT/^{3}√RR
Sagie et al. (the Framingham study) (1992)	QTc(S)	= QT + 0.154(1-RR)
Van de Water (1989)	QTc(VdW)	= QT – 0.087{(60/HR)-1}
Hodges et al. (1983)	QTc(H)	= QT + 1.75 (HR-60)
Ashman (1942)	QTc(A)	= K1 × log(10 × [RR + K2])

are good for sinus bradycardia while others are better for sinus rhythm or sinus tachycardia.

Charbit et al. (2006) reported a combination of Bazzet's (QTc_b) and Fridericia's (QTc_f) approach. First, the QTc_b is calculated. If the value is less than 430 ms (in human beings), patients are at a very low risk of having a prolonged QTi. If it is longer than 430 ms, the QTc_f calculation should be made to reduce the number of falsely prolonged QTi. The proposed new way to correct QTc_f would be both easily memorizable and calculable. The HR for which no correction is needed is, by definition, 60 bpm. For each increase of 10 bpm from 60 bpm, the correction factor increases by one multiple of 5%, i.e., 1 × 5 = 5%, 2 × 5 = 10%, 3 × 5 = 15%, and so forth, and inversely when the HR is below 60 (Figure 5). Finally, the QTc_f is easily calculated by adding or subtracting a multiple of 5 % of uncorrected QTi (easily calculable as QT divided by 10 and then by two).

Another useful method is Van de Water's formula. One study in Beagle dogs found that this formula showed a statistically superior correction and therefore was identified for use in the evaluation of compound effects (Tattersall et al., 2006). Also this method is preferred for small samples because the bias associated with a fixed formula is likely to be less than the variance obtained by estimating β from a small sample (Batey and Doe, 2002). This formula can be used in toxicology assessments to correct QTi duration for increases in HR33. Furthermore, unpublished data suggest that Van de Water's method appropriately corrects nycthemeral QT variation (Tattersall et al., 2006). Other approaches used to adjust QT for HR, like the Fridericia, Framingham, and Hodges formulae, are also popular in the field.

Another practical method for QTc calculation was described by Schmitt et al. (2007). First, Van de Water's method is applied. Then, the largest (QTc_{max}) and the shortest (QTc_{min}) individual QTc for each animal in treatment are obtained. The largest individual difference (QTc_{max} – QTc_{min}) observed during the treatment is then calculated. Two reference criteria are used to identify individual animals as responders to a given treatment: (1) $QTc_{max}R$ (= QTc_{max} + 10) – obtained by adding 10 ms to the largest value of QTc_{max} observed during a treatment, and (2) (QTc_{max} – QTc_{min})maxR which is defined as the largest value of (QTc_{max} – QTc_{min}) observed during the five control sessions increased by 50% (Schmitt et al., 2007). The decision to increase the experimentally determined values of $QTc_{max}R$ and (QTc_{max} – QTc_{min}) max by 10 ms and 50%, respectively, was designed to establish a reliable threshold that would clearly rule out a risk of delayed cardiac repolarization in the event that none of the drug-treated animals was a positive responder (Schmitt et al., 2007).

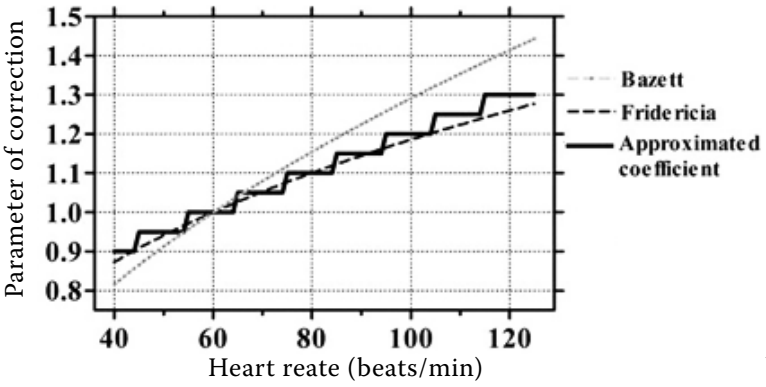

Figure 5. Correction factors for a given HR using QTc_f proposed by Charbit et al. (2006)

QTc values can be obtained also in individual studies. An equation relating QT to RR interval and its regression coefficient (*r2*) can be calculated using a simple regression model of the generic form $QT = \beta \times RR\alpha$. QTc can be normalized for the preceding RR interval using the formula $QTc = QT/RR\alpha$, where α is the adjustment to produce a regression line with a slope of zero, indicating that this correction removes the influence of HR (Kijtawornrat et al., 2006). This method could be suitable for a population with a wide range of HR variation providing good correction and allows precise determination of drug-induced changes in QT (Tattersall et al., 2006). Such methods, however, require the collection of a large volume of data over a long period of time to cover a wide range of HRs. This is typically not feasible in toxicology studies using traditional approaches. In contrast to this high inter-individual variation in humans, the QT/RR relationship in dogs is remarkably similar from day to day within a single animal, and despite the curvilinearity of the relationship, there is close agreement between animals (Batey and Doe, 2002).

More complicated exponential equations have also been described by various groups. Some data have showed clear curvilinearity; however, these correction formulae based on a logarithmic relationship, although valuable, are in the majority of cases excluded from analysis since their use presents practical and interpretational difficulties with respect to extrapolating a drug-related effect (Tattersall et al., 2006).

The failure of these classical methods to adequately adjust the QTi for changes in HR has lead to the application of a plethora of linear or nonlinear fitting equations, which force a mathematical function into the QT/RR relationship with varying degrees of success. However, many of these techniques exhibit species dependence and the fitting parameters cannot easily be interpreted in terms of the electrophysiological events associated with ventricular repolarization (Batey and Doe, 2002). Several other methods have been described for estimating the QTc. Their description is beyond of the scope of this paper since they have few applications for dogs, and the reader is encouraged to consult the literature (Malik, 2001; Luo et al., 2004).

There is a growing consensus among experts that the QTi should not be corrected for HR (Raunig et al., 2001). The QTi's from each patient are grouped according to the HR, in 'bins' of (arbitrarily) 10 bpm width and comparisons are made between bins with similar HR's. Thus, one obtains one bin for $QT_{HR\ 60–80\ bpm}$ intervals, one for $QT_{HR\ 80–100\ bpm}$ intervals, another for $QT_{HR\ 100–120\ bpm}$ intervals, and so on. The QTi's in each bin are then compared. This approach is highly valid because it accounts for QT variation with HR but does not assume a mathematical relationship, thus making no assumptions about the nature of the QT-HR relationship. This approach, however, requires many data points, either acquired from many, or from one individual (Davey, 2002; Fossa et al., 2002). A continuous evaluation of QT can be accomplished with a better-fitting mathematical model than the single-coefficient model. Numerous multicoefficient formulae have been proposed to better describe the relationship between QT and the RR interval.

Table 2. Data showing the average QT interval for four animals over four separate days, at three different RR intervals (from: Batey and Doe, 2002)

Animal	RR interval (ms)	QT interval (ms)				
		day 1	day 2	day 3	day 4	mean
1	500	229	235	231	–	231 ± 2
	1000	242	245	243	–	243 ± 1
	1500	262	268	254	–	261 ± 4
2	500	219	227	224	220	223 ± 2
	1000	235	245	242	236	240 ± 2
	1500	251	256	253	256	254 ± 1
3	500	227	233	223	227	227 ± 2
	1000	248	258	252	256	254 ± 2
	1500	256	262	261	260	260 ± 1
4	500	227	229	227	232	229 ± 1
	1000	250	254	246	253	251 ± 2
	1500	255	259	253	258	256 ± 1

However, these multicoefficient formulae ideally require a measurement of QT over a wide range of RR intervals to accurately assess the function coefficients and they are not widely used (Raunig et al., 2001).

QTi can be also analyzed from ambulatory QT recordings (Davey, 2002; Hamlin et al., 2004). This approach uses data obtained from 24-h ECG monitors ('Holter' monitors). QTi are measured on a beat-to-beat basis and plotted out against instantaneous HR. Beat-to-beat analysis provides a simple but potent tool for unravelling the rate dependency of drug-induced QT prolongation without recourse to mathematical modelling (Batey and Doe, 2002).

The HR varies significantly over a 24-h period in most patients, particularly when they are active. However, even inactive or sleeping subjects have spontaneous variations in their HR of 30 bpm or more. Dogs show a marked curvilinearity in the QT/RR relationship. The curve exhibits three distinct phases, a very steep section at high HR, a much flatter area at low HR, and an inflection zone linking the two, with a moderate slope. This triphasic relationship has been noted in humans also. This suggests that canine and human QT/RR relationships may share a similar trend, albeit with different HR ranges for each of the segments (Batey and Doe, 2002). A nomogram approach (Table 2) may provide more accurate results than mathematical correction (Batey and Doe, 2002). The data obtained is conventionally plotted out as a 'scatter plot' and, using a least-squares fitting technique, the QT60 and the QT/HR slope are obtained. Interestingly, there is evidence that the QT/HR slope varies according to the activity of the autonomic nervous system and hence varies diurnally. This not only enables the determination of the long-term effects of drugs in dogs, but also the free-living animal provides a more realistic environment, similar to man, in which autonomic control of the heart can vary enormously over a short space of time (Batey and Doe, 2002). Ambulatory QTi analysis can shed light on diurnal differences in QTi and its HR-dependent behaviour and this could be promising in experimental and clinical canine models. One often encountered difficulty with computerised analysis of the ECG is the accurate determination of ECG intervals (Batey and Doe, 2002).

In conclusion, we believe that it is important not only to understand the limitations of the correction formula and to avoid applying multiple formulae, but also that the most appropriate correction factor should be determined in each organisation using its own QT data collected from its particular strain of dog and under defined experimental conditions (Tattersall et al., 2006). We recommend selecting a homogeneous population for study having in mind circadian rhythm, ECG positioning, leads used, gender and breed to better fit QTc measurement. Also it has been suggested that a possible confounding factor is the use of a predetermined algorithm to correct the measured QTi for HR. When a treatment produces substantial changes in HR, QT rate-correction algorithms are not satisfactory, and may provide inaccurate QTc estimations (Schmitt et al., 2007).

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