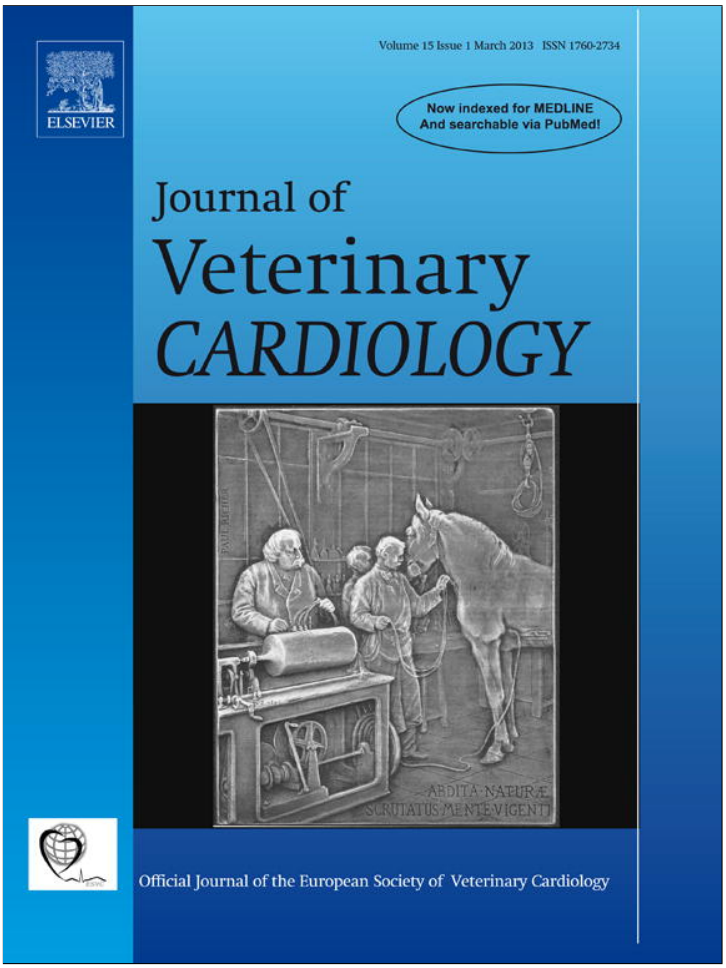

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Normal electrocardiographic QT interval in race-fit Standardbred horses at rest and its rate dependence during exercise

Philip J. Pedersen, DVM [a,*], Joergen K. Kanters, MD [b], Rikke Buhl, DVM, PhD [c], Dan A. Klaerke, MD [a]

[a] *Department of Veterinary Clinical and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark*
[b] *Laboratory of Experimental Cardiology, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark*
[c] *Department of Large Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark*

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KEYWORDS
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Arrhythmia;
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LQTS

Abstract *Objectives:* Cardiac repolarization, measured as QT and T_{peak} to T_{end} (T_pT_e) intervals on the ECG, is important, as irregularities caused by diseases, ventricular hypertrophy, drugs and genetic defects can trigger arrhythmias which predispose human patients to syncope and sudden cardiac death. In horses, repolarization is not well described and therefore QT analysis cannot yet be used diagnostically. Therefore, we sought to describe reference values for the normal QT and T_pT_e intervals in Standardbreds and to determine the best method for heart rate (HR) correction.
Animals: 30 Standardbreds.
Methods: QT and T_pT_e intervals were measured during rest and exercise and plotted against HR converted to R_{peak} to R_{peak} interval (RR). Data were fitted with relevant regression models. Intra- and inter-observer agreement was assessed using Bland—Altman analyses.
Results: Data were best described by a piecewise linear model ($r^2 > 0.97$). Average prediction error of this model was smaller than for both Bazett and Fridericia corrections. Coefficient of repeatability of intra- and inter-observer variability was

* Corresponding author.
E-mail address: philip@sund.ku.dk (P.J. Pedersen).

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8.76 ms and 5.64 ms respectively and coefficient of variation was 1.77% and 2.76% respectively. T_pT_e increased with RR in stallions.
Conclusions: The QT interval in Standardbred horses shortens with decreasing RR interval (increasing HR) as in humans, but in a markedly different order as it clearly follows a piecewise linear model. The equine QT interval can be measured easily and there is small intra- and inter-observer variability. This model of the equine QT interval provides clinicians with a method that could support a diagnosis of repolarization disturbances in horses.

Abbreviations

CR	coefficient of repeatability
CV	coefficient of variability
HR	heart rate
LOWESS	locally weighted scatterplot smoothing
LVH	left ventricular hypertrophy
PE	prediction error
QT_c	QT interval corrected for heart rate
RR	R_{peak} to R_{peak} interval
SCD	sudden cardiac death
T_pT_e	T wave peak to T wave end interval

Introduction

Quantification of the heart's repolarization is important since disturbances have been shown to predispose to arrhythmias and sudden death in human patients. Repolarization disturbances are commonly induced by heart disease, ventricular hypertrophy or administration of drugs that block the potassium channels responsible for repolarization.[1] Disturbance of repolarization in humans can also be inherited as mutations in genes coding for the ion channels directly involved in repolarization or for proteins involved in ion channel regulation, like in the genetic disorder long QT syndrome.[2]

The QT interval is the only routinely used measure of ventricular repolarization,[3] and drug studies have proven that changes in the QT interval as low as 10 ms are of clinical importance in man.[4] However, the QT interval is notably heart rate (HR) dependent and therefore it is corrected for HR in humans (QT_C) before evaluation using different formulas.[5] Other indicators of repolarization can also be identified on the ECG.[6] One is the T_{peak} to T_{end} interval (T_pT_e), measuring the distance from the top of the T wave (T_{peak} or T_p) to the point at which the T wave reaches the baseline (T_{end} or T_e), which reflects repolarization dispersion (regional repolarization variation). Longer T_pT_e intervals have been related to increased mortality in humans.[6,7]

Since HR in the horse can vary between 30 and 250 beats per minute, rate adaptation of the QT interval must be more efficient than in humans. The QT interval in horses has previously only been investigated within a limited HR range.[8,9] As a consequence, no formula for equine QT correction for HR is available and some researchers have used human correction methods.[10] Furthermore, the range of T_pT_e is unknown. This makes it difficult to establish toxicological safety margins of drugs used in equine practice. Practitioners treating horses with drugs such as quinidine, which is known to prolong the QT interval in humans and which has been described to widen the QRS complex in horses,[11] do not monitor cardiac function based on QT interval, as they have no reference values; rather they have to rely on clinical signs of intoxication.[12] Unfortunately, sudden death is a well-known problem in horses,[13] and it has a big impact on animal welfare, rider safety, finances and public relations. Up to 68% of racehorses suffering sudden death do not have structural lesions sufficient to account for death on necropsy and such cases are frequently attributed to sudden cardiac death (SCD).[14] Although it is well described that spontaneous arrhythmias are common in the horse,[15] studies coupling specific arrhythmias to SCD are sparse.[16] Therefore, it can be speculated that repolarization disorders may underlie some of these SCD, as in humans, but without knowledge about repolarization adaptation, diagnostics in the horse are impossible.

The purpose of this study was to describe reference values for the normal QT and T_pT_e intervals in race-fit Standardbred horses and to determine the best method for rate correction of the QT interval in exercising horses. Furthermore, the study aimed to specify observer agreement for QT interval measurements and finally to describe and discuss the normal range of the equine T_pT_e interval.

Animals, materials and methods

Horses

Thirty randomly selected race-fit Standardbred horses were included in the study. All were of the Standardbred American light type. The group included 10 stallions aged 3–7 years, 10 geldings aged 3–6 years and 10 mares aged 3–6 years. Body weight was 510 kg ± 34 kg (estimated with a weight band) with no significant difference between groups. To ensure general health and race fitness prior to the ECG recording, all horses were subjected to a physical examination and a standardized echocardiographic examination as previously described,[17] and the trainer was asked a series of questions concerning the performance and health status of the horse within the past six months. Horses showing signs of illness, cardiac disease or reduced performance were excluded.

ECG recordings

The ECGs were recorded with a digital veterinary telemetric ECG system.[d] Surface electrodes[e] were placed with only a slight modification of the manufacturer's instructions: the sternal electrode was placed 5 cm caudal to the xiphoid process at the same circumference level (girth line) as the left trunk, right trunk and ground electrodes. The left trunk electrode was placed 30 cm ventral to the withers on the left side of the horse in the sixth or seventh intercostal space. The ground electrode was placed 10 cm ventral to the left trunk electrode. The right trunk electrode was placed at the level of the left trunk electrode but on the right side of the horse. All skin areas covered by the electrodes were clipped, shaved and rinsed for optimal contact. The electrodes were further taped to the skin with a patch of sticky foam.[f] Before the horses were rigged with the harness, an elastic lunging girth was fastened, completely covering all electrodes. ECGs were recorded and stored on a memory card, followed by digital storage on a laptop computer. The ECG tracings were subsequently analyzed using the provided software[d] and time intervals were analyzed manually using on screen calipers.[g]

[d] Televet 100, Televet 100 version 4.2.0, Roesch & Associates Information Engineering GmbH, Frankfurt am Main, Germany.
[e] KRUUSE ECG electrodes, Jørgen KRUUSE, Langeskov, Denmark.
[f] Snögg, Jørgen KRUUSE, Langeskov, Denmark.
[g] Cardio Calipers 3.3, ICONICO, New York, NY, USA.

Exercise

Continuous ECGs were recorded with the horse at rest, during a warm up period, during a competition harness race and during the post exercise recovery period. The harness races performed were 1600 m sprints.

ECG analysis and agreement

Seven recording periods with a constant HR for at least 30 s were identified to minimize the possible effect of QT lag and hysteresis. Heart rates ranged from resting HR to peak HR. The HR within each period was determined as an average of 10 consecutive beats, and then converted to a calculated RR interval (RR = 60/HR). QT intervals were measured on the following five complexes from the onset of the Q wave to the end of the T wave (QT). The end of the T wave was determined visually as the point where it reaches the isoelectric baseline.[18] Time intervals from the onset of the Q wave to the peak of the T wave (QT_p) were also measured and used to calculate the T_pT_e interval over the entire RR range (Fig. 1). Measurements were performed in lead II with a 40 mm/mV amplitude and a 200 mm/s sweep speed, by a veterinarian specialized in equine medicine with particular interest in equine cardiology and 4 years' experience in ECG reading (Observer 1).

To test intra- and inter-observer agreement, six random horses (two of each sex) were measured again by Observer 1 and by a veterinary student inexperienced in equine cardiology and ECG reading who had undergone a short training session to learn the specific definitions of the QT interval

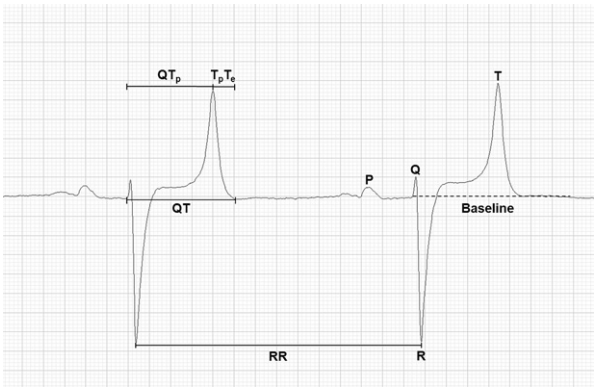

Figure 1 Raw data (lead II, 40 mm/mV amplitude, 200 mm/s sweep speed) with illustration of the QT interval. The end of the T wave is determined visually as the point where the T wave reaches the isoelectric baseline. The Q to T_{peak} (QT_p), T_{peak} to T_{end} (T_pT_e) and RR intervals are also illustrated.

(Observer 2). Observers were independent and blinded to the results of previous ECG readings and the results of the other observer. Observers were not blinded to the measured result as this was registered manually.

Data analysis

QT correction

To estimate QT/RR regression lines and their goodness of fit, an SAS[h] program that fitted data to the most commonly used formulas in human medicine was used. These formulas included the HR correction formulas Bazett ($QT_C = QT/\sqrt{RR}$) and Fridericia ($QT_C = QT/\sqrt[3]{RR}$). Further, a linear and a three parameter monoexponential ($QT = a + b*e^{(c*HR)}$) regression analysis was performed. Ultimately a piecewise linear regression line was tested in SAS[h] due to the appearance of the equine QT/RR plot. The piecewise linear regression model is described as two straight half lines joined at a bending point (RR_{Bend}) given by the equations

$$QT = Slope_1 * RR + Intercept_1, \text{ for } RR = RR_{Bend}$$

$$QT = Slope_2 * RR + Intercept_2, \text{ for } RR > RR_{Bend}$$

Since the bending point is given, the intercepts are redundant and the model can be reduced to three parameters ($Slope_1$, $Slope_2$, RR_{Bend}).

To validate the best regression model and test the effect of sex, an ANCOVA analysis was run in SAS.[h] Age was not considered as an effect in the models, since all horses included in the study were relatively young and in quite a narrow age range. Further, it has previously been shown that age only has an effect on QT interval in the young or elderly in both humans and horses.[19,20] Body weight was constant in the horses included in the study and was not considered as an effect.

To assess the best HR correction method for equine QT measurements an average prediction error (PE) was calculated $\left(PE_{avg} = \frac{1}{n}\sum_{i=1}^{n}|\widehat{QT} - QT_i|\right)$ for the Bazett and Fridericia correction formulas and the best equine regression model found in the study. $\widehat{QT}$ is the predicted QT interval by the model used and QT_i is the manually measured QT interval. For the Bazett and Fridericia correction formulas this was done by first calculating an average QT_C for each horse $\left(\text{e.g. Bazett: } QT_{Cavg} = \frac{1}{n}\sum_{i=1}^{n}\frac{QT_i}{\sqrt{RR_i}}\right)$. This average QT_C was again used to calculate the $\widehat{QT}$ by the models (e.g. Bazett: $\widehat{QT} = QT_{Cavg} \times RR$).

Further PE's were plotted over the entire RR range using a locally weighted scatterplot smoothing (LOWESS) plot in SAS.[h] Here a low-degree polynomial was fitted to a local subset of the data surrounding each point in the data set, giving more weight to points near the point for which the response was being estimated and less weight to points further away. The LOWESS plot is very flexible, making it ideal for modeling data for which no theoretical models exist.

T_pT_e analysis

To assess the timing of the late phase repolarization of the horse, all T_pT_e intervals covering the descending limb of the T wave were plotted against RR for all three sexes. A linear regression fit was performed on these data to estimate T_pT_e/RR dependence.

Inter- and intra-observer variability

Observer agreement was determined using the method described by Bland and Altman.[21] The repeatability of QT measurements was estimated using the coefficient of repeatability (CR) defined as $1.96*\sqrt{(2*SD_w^2)}$ (SD_w is the standard deviation within measurements). This value describes the value below which the difference between to measurements will lie with a probability of 95%. Further, the within measurements coefficient of variation (CV) was calculated in percent. Results were considered significant if $P < 0.05$.

Results

QT correction

With the described methodology applied to equine ECG analysis, we determined the QT/RR relationship of a relatively homogeneous population of horses. The raw data plot is shown in Fig. 2 and QT appears to have a clear piecewise linear relationship with RR, with a high homogeneity between individuals. From our data analysis, we found that the best descriptive model divided by sex and type was indeed the piecewise linear regression fit ($0.97 < r < 0.99$: $P < 0.0001$ for all sexes). From the solution estimates of the piecewise linear regression (Table 1), the regression lines could be drawn (Fig. 2). The ANCOVA analysis confirmed the validity of the piecewise linear model and showed a significant effect of sex on the slope ($P = 0.025$) and bending point ($P = 0.010$) of the models. Stallions

[h] SAS system version 9.2 for Windows, SAS Institute Inc., Cary, NC, USA.

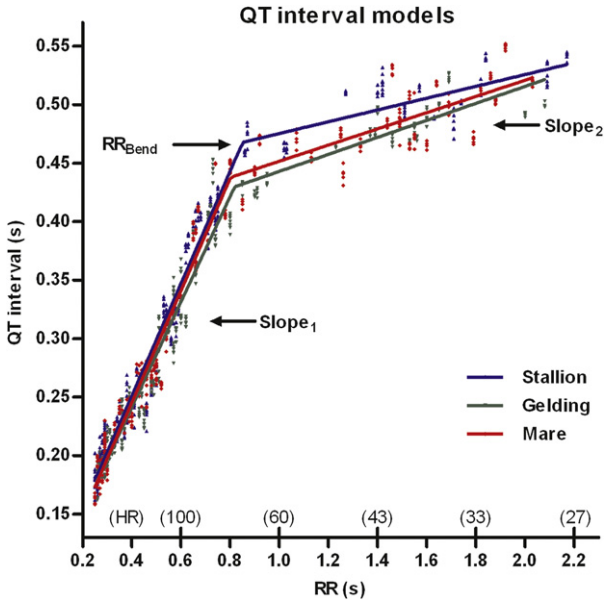

Figure 2 For equine QT/RR plots the correlation coefficient corresponded best with a piecewise linear regression fit ($0.97 < r < 0.99$). The fitted lines based on sex are superimposed on all the QT/RR plots of the QT measurements. Heart rate (HR).

have a longer QT interval than both mares and geldings, being most pronounced for RR > 0.8 s. A table of calculated reference QT intervals with 95% prediction intervals at different HR/RR values for the different sexes can be seen in Table 2.

The average PEs of the QT measurements corrected with the Bazett, Fridericia and piecewise linear regression models were calculated as 28.1 ms, 46.1 ms and 14.2 ms respectively, showing that the piecewise linear regression model is the best HR correction model for the equine QT interval. A LOWESS plot illustrating the tendencies for systematic mis-correction of the formulas over the entire range of RR intervals is presented in Fig. 3.

T_pT_e analysis

T_pT_e, dependence on RR and sex was estimated by linear regression (Fig. 4). Results show that the slopes of all regression lines are significantly different (stallion vs. gelding $P = 0.01$, stallion vs. mare $P < 0.0001$, gelding vs. mare $P < 0.0001$). Stallions and geldings have longer T_pT_e intervals than mares. The slopes of the stallion and gelding regression lines have a significant deviation from zero ($P < 0.0001$), and RR explained 12% and 20% of the T_pT_e variation respectively. In the mare, the slope did not have a significant deviation from zero ($P = 0.052$) and RR only explained 1% of the T_pT_e variation.

Intra- and inter-observer agreement

Reproducibility of QT measurements (inter-observer variability) had a CR of 8.76 ms and a CV of 2.76%. Repeatability of the QT measurements (intra-observer variability) had a CR of 5.64 ms and a CV of 1.77%. Variability was similar over the entire QT range for both inter- and intra-observer measurements.

Discussion

This study presents the first systematic analysis of the equine QT interval from resting to maximal HR during exercise. The main finding is that the rate dependence of the equine QT interval fits a piecewise linear regression model and is therefore markedly different from that found in humans.

Studying the QT interval in exercising horses is superior to using vagolytic and/or sympathomimetic drugs, as these would strongly increase QT interval variability. Simply recording different heart rates in resting horses would give limited information about QT/RR dependency, and simple changes in posture have even been associated with increased QT interval variability in humans.[22]

The challenges when measuring equine QT intervals are very similar to the ones described in human medicine, especially getting a definitive determination of the end of the T wave. Factors which could make this particularly difficult in the horse are the physiological shifts in orientation and further conformational changes of the T wave during exercise. These should be well known by the observer and definitions of the end of the T wave should be in agreement amongst observers. In this study, we found agreement between observers to be very similar to what has been found in human studies.[18]

Table 1 Solution estimates with 95% confidence intervals of the piecewise linear QT regression lines.

Sex	$Slope_1$	$Slope_2$	RR_{Bend}
Stallion	0.480 [0.467; 0.493]	0.050 [0.042; 0.059]	0.852 [0.831; 0.872]
Gelding	0.450 [0.436; 0.464]	0.073 [0.062; 0.083]	0.818 [0.793; 0.843]
Mare	0.479 [0.463; 0.495]	0.069 [0.060; 0.079]	0.802 [0.780; 0.825]

Table 2 Calculated reference QT intervals (s) with 95% prediction interval at different heart rates (HR)/RR intervals.

HR (BPM)	RR (s)	Stallion	Gelding	Mare
30	2.00	0.53 [0.56; 0.49]	0.52 [0.55; 0.48]	0.52 [0.56; 0.48]
40	1.50	0.50 [0.53; 0.47]	0.48 [0.51; 0.45]	0.49 [0.53; 0.45]
50	1.20	0.49 [0.52; 0.45]	0.46 [0.49; 0.43]	0.47 [0.50; 0.43]
60	1.00	0.48 [0.51; 0.44]	0.44 [0.47; 0.41]	0.45 [0.49; 0.41]
70	0.86	0.47 [0.50; 0.43]	0.43 [0.47; 0.40]	0.44 [0.48; 0.40]
80	0.75	0.42 [0.45; 0.38]	0.40 [0.44; 0.36]	0.41 [0.45; 0.38]
90	0.67	0.38 [0.42; 0.35]	0.36 [0.40; 0.33]	0.37 [0.41; 0.34]
100	0.60	0.35 [0.38; 0.31]	0.33 [0.37; 0.29]	0.34 [0.38; 0.31]
110	0.55	0.32 [0.36; 0.29]	0.31 [0.35; 0.27]	0.32 [0.35; 0.29]
120	0.50	0.30 [0.33; 0.26]	0.29 [0.32; 0.25]	0.29 [0.33; 0.26]
130	0.46	0.28 [0.31; 0.25]	0.27 [0.30; 0.23]	0.27 [0.31; 0.24]
140	0.43	0.27 [0.30; 0.23]	0.25 [0.29; 0.22]	0.26 [0.29; 0.23]
150	0.40	0.25 [0.29; 0.22]	0.24 [0.28; 0.21]	0.25 [0.28; 0.21]
160	0.38	0.24 [0.28; 0.21]	0.23 [0.27; 0.20]	0.24 [0.27; 0.20]
170	0.35	0.23 [0.26; 0.19]	0.22 [0.26; 0.18]	0.22 [0.25; 0.19]
180	0.33	0.22 [0.25; 0.18]	0.21 [0.25; 0.17]	0.21 [0.25; 0.18]
190	0.32	0.21 [0.25; 0.18]	0.21 [0.24; 0.17]	0.21 [0.24; 0.17]
200	0.30	0.20 [0.24; 0.17]	0.20 [0.23; 0.16]	0.20 [0.23; 0.16]
210	0.29	0.20 [0.23; 0.16]	0.19 [0.23; 0.15]	0.19 [0.22; 0.16]
220	0.27	0.19 [0.22; 0.15]	0.18 [0.22; 0.15]	0.18 [0.22; 0.15]
230	0.26	0.18 [0.22; 0.15]	0.18 [0.22; 0.14]	0.18 [0.21; 0.14]
240	0.25	0.18 [0.21; 0.14]	0.17 [0.21; 0.14]	0.17 [0.21; 0.14]

Correction of the equine QT interval was performed with both the Bazett and the Fridericia formulas on each horse individually. The Bazett correction performed better than the Fridericia

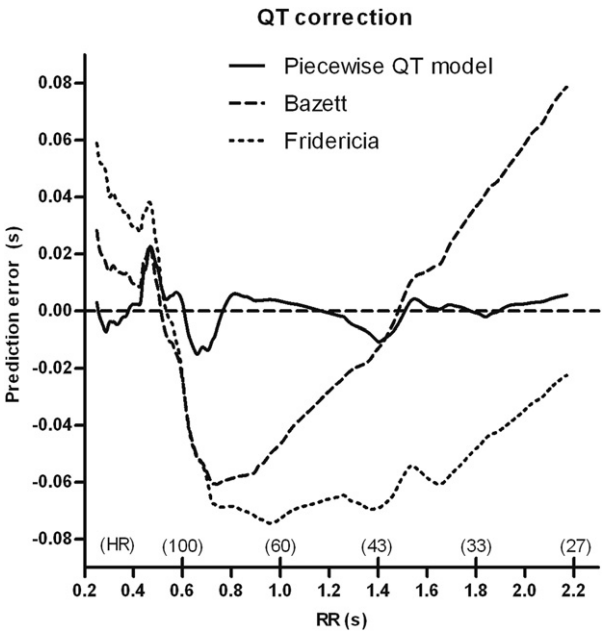

Figure 3 LOWESS plot of the prediction errors of all the corrected QT measurements based on correction method. This plot illustrates systematic tendencies to mis-correction (deviations from zero) of the formulas. It can be seen that the piecewise linear model performs best in almost all heart rate (HR)/RR ranges.

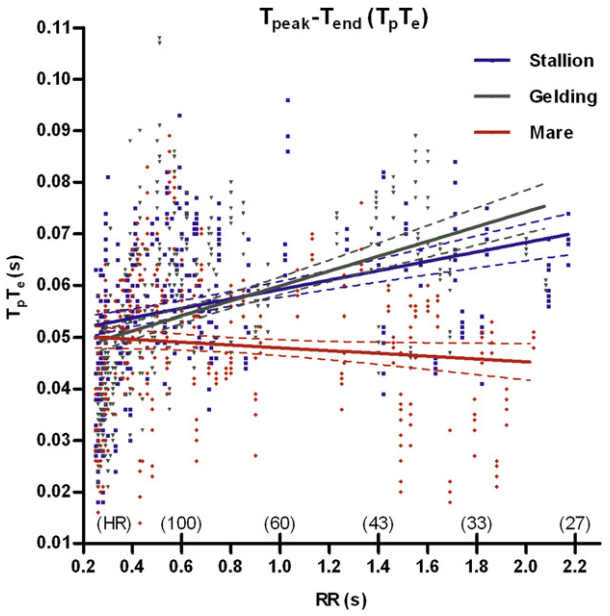

Figure 4 T_{peak} to T_{end} time interval (T_pT_e) plots with linear regression lines and 95% confidence intervals. Slopes of the linear regression lines are significantly different between the sexes (stallion vs. gelding $P = 0.01$, stallion vs. mare $P < 0.0001$, gelding vs. mare $P < 0.0001$). The slope of the stallion and gelding linear regression lines were significantly different from zero ($P < 0.0001$). In the mare, the slope was not significantly different from zero ($P = 0.052$). Variation explained by RR was given by $r^2_{\text{stallion}} = 0.12$, $r^2_{\text{gelding}} = 0.20$ and $r^2_{\text{mare}} = 0.01$. Heart rate (HR).

formula in the horse, which is in contrast to what has been described in human studies.[3] A piecewise regression model gives the best description of the equine QT/RR relationship, whereas in humans the QT intervals at different HRs have been shown to be well described by linear regression.[23] In healthy human subjects, the advantage of using nonlinear fits was marginal (0.5–1%)[24] and humans did not have as well-defined a bending point as is seen in the horse. Further, equine athletes exhibit a more homogeneous QT interval ($0.97 < r^2 < 0.99$) than human athletes ($r^2 = 0.91$).[23] Based on the average PE of the three models, the piecewise linear model again performs better when compared with the Bazett and Fridericia methods, despite the fact that it was determined from a pooled data group (sex wise) as opposed to an individual mean QT of each horse (Fig. 3).

The biophysical basis for this piecewise linear QT/RR relationship in horses remains unexplained. Since the maximal heart rate of horses is greater than in humans, it demands an increased repolarization power to allow proper QT shortening during tachycardia. The slow delayed rectifier potassium channel (KCNQ1), which has been found in both the human and equine heart,[25] is primarily activated upon β-adrenergic stimulation[26]; the bending point may reflect the HR where the contribution of the KCNQ1 channels becomes significant. To examine this hypothesis further, studies are being undertaken to assess whether the equine cardiac ventricles have a higher expression of KCNQ1 channels compared to humans or if equine KCNQ1 channels have altered kinetics compared to humans.

In humans, QT lag is described as a delayed adaptation of the QT interval following changes in RR interval.[27] QT hysteresis is characterized by longer QT intervals at a given RR interval when heart rates are increasing and shorter QT intervals at the same RR interval when heart rates are decreasing. Although the mechanisms of QT lag and hysteresis are not completely known, an influence of the autonomic nervous system has been found.[10] In horses, knowledge of the beat to beat dynamics of the QT interval is absent, but in analyzing QT intervals in periods with a constant HR, the possible effects of QT lag would have been minimized. As the autonomic nervous system has been described to have a high impact on equine cardiac function, QT hysteresis could potentially be present and significant in horses. Additionally, the influence of the autonomic nervous system could differ between sexes, which could potentially influence the results of this study.

A recent study in humans showed that both QT_c and T_pT_e were prolonged after strenuous exercise (a marathon race) immediately post-race. Likewise, changes in inflammatory markers and electrolytes were detected, but these were not correlated with changes in repolarization markers.[28] Changes in inflammatory markers or electrolyte status in the horses in this study were not evaluated.

Stallions, on average, have a longer QT interval at all measured HRs (resting to maximum) compared to mares and geldings. This sex difference is in clear contrast to what has been described in humans, in which the QT_C interval in males is, on average, 10 ms shorter than that of females.[29] In humans, the reduction is apparently influenced by male sex hormones, since the QT interval measured in prepubescent and elderly people is the same in males and females. Furthermore, castrated men have a prolonged QT interval that can be restored to normal by an injection of testosterone.[30] A possible explanation for this difference in the horse could be based on sex differences in left ventricular hypertrophy (LVH) caused by strenuous exercise as a part of the "athletes heart syndrome". It is well described in humans that intense training causes LVH averaging 30%,[31] which is associated with a prolonged QT interval.[32] In Standardbred racehorses, training also causes LVH, and stallions have an especially high degree of LVH, with an average increase in ventricular mass of 40%. In contrast, LVH is significantly lower in mares.[17] This could cause a prolonged QT interval in the athletic stallions compared to mares. So far, no large studies have examined LVH in castrated men or geldings in relation to training, but the present study shows that geldings have a surprisingly short QT interval. Our analysis of the equine T_pT_e interval related to RR could elucidate if this is related to a smaller left ventricular mass, as this interval increases with LVH in humans.[33] The analysis revealed that the equine T_pT_e interval in race-fit Standardbred mares behaved as in human control studies, in which the T_pT_e interval can be regarded as nearly rate independent.[6] In contrast, in stallions and geldings, a marked increase in T_pT_e interval correlated to decreasing RR interval (Fig. 4). It could be speculated that intense training in the horse causes LVH in stallions and geldings, promoting prolongation of the T_pT_e interval. The reason why Standardbred geldings do not show a prolonged QT interval like stallions do, and the question of whether or not the prolonged QT interval in stallions may cause arrhythmias or SCD, remain unknown.

Conclusions

The model of the equine QT interval in Table 1 and the reference QT interval values in Table 2 provide an easy diagnostic reference that can be applied to horses presenting with a history of syncope or other heart disease, as part of the examination of offspring from horses having suffered SCD, or as a marker of toxicity during treatment with QT prolonging drugs like quinidine. Since the intra- and inter-observer variability was within the range described in human medicine[18] for even inexperienced observers (as Observer 2 in this study), QT measurements in horses need not be reserved for referral hospital specialists.

Conflict of interest

The authors have no conflict of interest.

Acknowledgments

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