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Normal QT interval in Ukrainian Riding Horses at rest and during exercise

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Summary

Measurement of the main parameter of cardiac repolarization, namely QT interval, has a very high diagnostic value in human medicine, since its irregularities may indicate severe life-threatening ventricular tachyarrhythmias. The QT interval may vary not only with heart rate, age, sex, and autonomic tone, but also with horse breeds. Therefore, the description of its reference values for a specific breed is of great importance. The Ukrainian Riding Horse was bred as a show jumping, dressage and three-day eventing breed on the basis of Hanoverian, Thoroughbred and Trakehner stallions and local mares, as well as Hungarian Furioso, Gidran Arab and Nonius mares. Twenty-three horses of the Ukrainian riding breed were included in the study: 8 geldings, 8 mares, and 7 stallions aged 3-11 years. The electrodes for ECG recording were placed according to an adapted base-apex system. The ECG was registered during rest, exercise, and recovery periods. QT intervals were measured from resting to peak exercise levels on the traces of the 2nd lead and plotted against RR intervals. The piecewise regression model was fitted to the data plot. The values of $Slope_1$, $Slope_2$, and RR_{bend} were compared to those of other breeds. The QT/RR relationship was relatively described by the piecewise linear regression model for all sexes ($0.95 < r^2 < 0.97$). The sex of horses of the Ukrainian riding breed had a significant effect on the model. In terms of $Slope_1$, $Slope_2$, and RR_{bend} values, Ukrainian riding horses are closest to Warmbloods, Standardbreds, and Thoroughbreds. The QT interval in horses should be corrected for breed and sex.

Keywords: equine, Ukrainian Riding Horse, ECG, QT correction

The QT interval is the only measurement of ventricular repolarization on the surface ECG (13). QT measurements may be performed manually or automatically, but manual methods are recommended. The manual measurement of a QT interval can be complicated, especially if the reader is inexperienced, or ECG traces are of low resolution (12). Manual measurement is usually performed by caliper or ruler methods on printed traces or digitally. The end of the T wave is visually determined where it returns to the isoelectric line (12, 37). Difficulties in determining the end of the T wave may occur due to the U wave changing the morphology of the T wave and a high heart rate, where T waves are closely followed by P waves and the isoelectric baseline is unclear.

There are several methods used in human medicine for determination of the end of the T wave. One of the most common is the threshold method, in which the T wave offset is determined as the point where it reaches the isoelectric baseline (21, 33). Another is a tangent method, which involves a tangent drawn along the steepest part of the descending slope of the T wave. The intersection of the tangent with the baseline defines the end of the T wave and the QT interval (17, 21, 33). Most reference values were determined by the threshold method, and measurements by the tangent method may be up to 10 ms shorter than those by the threshold method (21).

As the QT interval changes with the heart rate (HR), a correction formula based on HR is used to calculate a corrected value independent of HR, which is referred to as QTc. In human medicine, correction formulae are used for any QT interval with HR other than 60 bpm (11, 18).

Over the past few centuries many correction formulae have been proposed by different authors, but no single method has been generally agreed upon (1, 5, 10-12, 15, 18, 20, 33). Some authors suggest that QT intervals should be compared only with other QT data obtained using the same algorithm (3). Since hoofed animals differ from humans in the Purkinje fibre distribution, correction formulae designed for humans cannot be applied to equine QT intervals. This was confirmed by a recent study performed by Pedersen et al. on 30 Standardbred racehorses. It was shown that the piecewise linear regression model describes the

QT to RR relationship in this breed more accurately than Bazett and Fridericia's formulae, linear and three-parameter monoexponential regression models (24).

The disorders of heart repolarization in humans include early repolarization syndrome (ERS), short-QT syndrome (SQTS), and long-QT syndrome (LQTS). Only LQTS appears to be relevant to horses, and it is characterized by a delayed repolarization of cardiac cells resulting in prolonged action potentials and QT intervals on the surface ECG. Two forms of LTQS are distinguished: inherited and acquired ones. LTQS has been associated with syncopal episodes, life-threatening cardiac arrhythmias, including torsades de pointes, and sudden death syndrome (9).

A recent study performed by Buhl et al. (7) on 51 stallions revealed that the inherited form of LQTS in horses occurs under specific medications and after castration. The medications that potentially induce prolongation of the QT interval include class I and class III antiarrhythmic drugs, as well as a variety of non-cardioactive drugs: psychotherapeutic, antihistamine, antimicrobial, and prokinetic agents (9). Proarrhythmia is one of the common adverse effects of class IA and class III antiarrhythmics, because all the above-mentioned drugs prolong the APD by antagonism of repolarizing K1 currents (14). Quinidine intoxication has been associated with QT prolongation and induction of torsades de pointes in horses and humans (4, 30). Dofetilide (Tikosyn) is a class III antiarrhythmic agent that blocks IKr with relative specificity (15). In order to assess the QT interval in horses of a specific breed, it is important to have reference values to compare it to.

Recent studies have described the QT interval and approved the piecewise linear regression as a correction method for Thoroughbred, Icelandic, Arabian, Warmblood (show jumping), Warmblood (dressage), and Standardbred horses, as well as Coldblood trotters (25). In view of the results presented, the QT interval in horses should be corrected for breed. The dependence of the QT interval on the sex of the animal has also been proven in horses (24).

The Ukrainian Riding Horse, or the Ukrainian Saddle Horse, also known as the Ukrainian Warmblood, is a relatively young Ukrainian breed of warmblood sport horses. Breeding began after World War II, and the genetic base consists of Hanoverian, Thoroughbred, and Trakehner stallions and local mares, as well as Hungarian Furioso, Gidran Arab, and Nonius mares (8). It was bred as a show jumping, dressage and three-day eventing breed, but is also suitable as a general riding horse (31).

The goal of the current study was to validate the piecewise linear regression for correction of the QT interval in horses of the Ukrainian riding breed, to examine the possible influence of body weight (BW) on the QT model, and to describe reference values for a normal QT interval in the Ukrainian Riding Horse for mares, stallions, and geldings.

Material and methods

Animals. Twenty-three horses of the Ukrainian riding breed, also known as the Ukrainian Warmblood, were included in this research. The group included 8 geldings aged 4-10 years, 8 mares aged 4-11 years, and 7 stallions aged 3-10 years. Ten of the horses competed in dressage, 8 were in training for show jumping, and 5 were used for pleasure riding, but had regular longeing training. BW was determined with a weight band as 440 kg ± 19 kg. To assess the effect of BW, the horses were divided into three groups: BW < 433 kg (n = 6), BW of 434-447 kg (n = 12), and BW > 448 kg (n = 5). Since 19 animals (83%) were in a narrow range of age (7-11 years), this parameter was not considered as an effect in models. Anamnesis was collected prior to ECG recordings with a focus on the health status and performance of the animal within the preceding six months. The condition of the cardiovascular system of the animals was evaluated by a physical examination, which included examination of mucous membranes (conjunctiva of the eyes), filling time of the capillaries, apical heartbeat (precordial area), arterial pulse (maxillary and digital arteries), and auscultation of the heart. All horses underwent a regular (annual) standardized echocardiographic examination. Animals showing signs of illness, reduced performance, or cardiac disease were excluded from the research.

ECG recordings. ECG registration was performed with a digital telemetric ECG system [a portable ECG monitor developed by researchers of The National Technical University of Ukraine, Igor Sikorsky Kyiv Polytechnic Institute]. An adapted base-apex system for electrode placement was used. Four electrodes were arranged as follows: the negative (red) electrode was placed on the right in front of the scapula, 5-7 cm below the withers; the positive (green) electrode – on the left directly behind the area of the apical beat caudally from the elbow; the positive-negative (yellow) electrode – 5-10 cm above the green one; and the refractive (black) electrode – on the left in the area of the scapula (28). Disposable electrode pads with a gel layer and a sticky base were used [SKINTACT F-55 electrodes with aqua-wet gel, Innsbruck, Austria]. The skin areas were not clipped, and the electrodes were attached directly to the fur. For better contact of the electrodes with the body of the animal, an elastic lunging girth was fastened, covering all electrodes. The ECG recordings were stored on SD memory cards and subsequently uploaded to a cloud storage. The ECG traces were analyzed with the software provided, and time intervals were analyzed manually using on-screen calipers [Cardio Calipers 3.3, ICONICO, New York, NY, USA].

Exercise. The outdoor activities were performed during spring and fall mornings with the temperature from 13 to 20°C. The registration of ECGs was performed in three stages:

I) Registration of an ECG at rest before exercise for 10-15 minutes.

II) ECG registration during exercise for 30-40 minutes.

III) ECG registration during rest immediately after exercise for 15 minutes.

The exercise stage included warm-up and exercise itself. The exercise protocol included seven intervals: two at walk, two in trot, two in canter, and one in gallop. Each interval lasted 3-10 min with a distance of 2000-4000 m. Three leads were recorded: 1st lead – between the red and yellow elec-
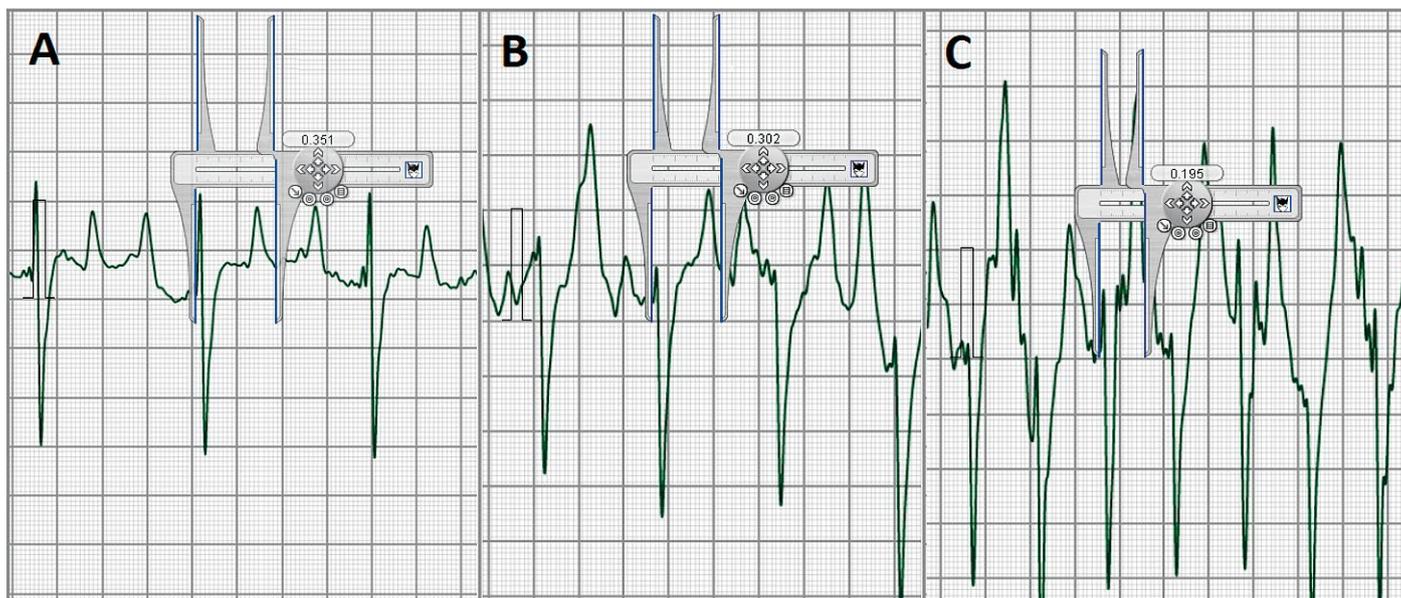
Fig. 1. Measurements of the QT interval at different heart rates on the ECG of a 7-year-old mare with screen calipers. A – HR = 80 bpm, QT interval = 0.35 s; B – HR = 113 bpm, QT interval = 0.30 s; C – HR = 200 bpm, QT interval = 0.19 s. Speed: 50 mm/s, 1 mV = 20 mm

trodes, 2nd lead – between the red and green electrodes, and 3rd lead – between the yellow and green electrodes.

ECG analysis. The tracings of the 2nd lead were used in the analysis. The time intervals were measured manually with on-screen calipers as described by Pedersen et al. (24). Eight recording periods with a stable HR for at least 30 seconds were identified with the purpose of minimizing the possible effect of the QT lag and hysteresis (24). Each period represented the heart rate from minimal (at rest) to peak (during exercise). HR within each period was calculated based on 10 consecutive beats. In the five following complexes, QT intervals were measured from the earliest onset of the Q wave to the end of the T wave (T$_{end}$). For the detection of T$_{end}$, the threshold method was used, and T$_{end}$ was visually determined as a point where the downward leg of the T wave reaches the isoelectric baseline (24). Measurements were performed on the tracings with 20 mm/mV amplitude and 50 mm/s sweep speed (Fig. 1).

Data analysis. The measured values of HR and QT were transferred to a data management program. For QT/RR regression estimation, the measured HR was converted to the RR interval: RR = 60/HR. Obtained RR and measured QT intervals were transferred to SAS [SAS University Edition, NC, USA] for statistical analysis and to GraphPad Prism [version 8, GraphPad Software, San Diego, CA, USA] for graphic presentation.

QT correction. The piecewise linear regression model, introduced by Pedersen et al. (24), was used for QT interval correction. This model is described as two straight lines joined at a bending point (RR$_{bend}$). It can be given by two equations:

QT = a + Slope$_1$ × (RR – RR$_{bend}$), for RR ≤ RR$_{bend}$;
QT = a + Slope$_2$ × (RR – RR$_{bend}$), for RR > RR$_{bend}$.

For calculation of the bending point and line slopes, a PROC NONLIN procedure with a modified Newton-Gauss method was run in the SAS program.

For graphical presentation, QT intervals were plotted against RR values in the GraphPad Prism software.

To verify the accuracy of the fit and to test the influence of sex and BW on the plot, an ANCOVA analysis of the data

was performed in the SAS program. The results were given as mean and standard deviation. The results with a p-value lower than 0.05 were considered significant.

Results and discussion

According to the above methodology, the QT/RR relationship was described for horses of the Ukrainian riding breed. The QT interval for all sexes appeared to have a clear piecewise linear relationship with the RR interval. The correlation coefficient of the data was high for all animals: $0.95 < r^2 < 0.97$ with $P < 0.0001$. Based on solution estimates from Table 1, regression lines were drawn (Fig. 2). The ANCOVA analysis confirmed the validity of the piecewise regression model and the effect of sex on slopes ($P < 0.0001$) and the bending point ($P = 0.0002$). Geldings had a shorter QT interval than stallions or even mares, most notably at $0.8 < RR < 1.3$ s. BW had no systematic effect on slopes ($P = 0.1$) or the bending point ($P = 0.43$). Calculated reference QT intervals for all sexes with 95% prediction intervals at different HR and RR values are presented in Table 2.

This research is the first systematic analysis of the QT interval at HR ranging from rest to heavy exercise in Ukrainian riding horses. Earlier studies of QT were conducted within a specific (often low) HR range and/or included other breeds (2, 22-25, 36).

The piecewise linear regression described for Standardbred horses by Pedersen et al. (24) clearly describes the QT/RR relationship in horses of the Ukrainian riding breed. This relationship in horses differs markedly from the linear QT/RR relation in humans (29).

Slope$_1$ represents the QT/RR relationship on HR from the bending point value to maximal exercise values, whereas Slope$_2$ is representative of HR from resting values to the bending point value. The incline of Slope$_1$ is greater, than that of Slope$_2$, indicating faster short-

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

Sex	$Slope_1$	$Slope_2$	RR_{bend}	a
Mare	0.384 [0.369; 0.398]	0.067 [0.044; 1.039]	1.011 [0.984; 1.039]	0.450 [0.442; 0.459]
Gelding	0.357 [0.345; 0.370]	0.095 [0.074; 0.115]	1.000 [0.970; 1.030]	0.427 [0.419; 0.436]
Stallion	0.387 [0.376; 0.398]	0.056 [0.036; 0.076]	1.045 [1.023; 1.067]	0.472 [0.465; 0.479]
Mean for breed	0.377 [0.368; 0.385]	0.080 [0.067; 0.094]	1.012 [0.995; 1.030]	0.447 [0.442; 0.453]

Tab. 2. Calculated reference QT intervals (s) with a 95% prediction interval at different heart rates

| HR (bpm)	RR interval (s)	Mare	Gelding	Stallion
200	0.30	0.17 [0.16; 0.18]	0.17 [0.15; 0.18]	0.19 [0.16; 0.20]
190	0.32	0.18 [0.17; 0.19]	0.18 [0.17; 0.18]	0.20 [0.17; 0.20]
180	0.33	0.19 [0.17; 0.20]	0.19 [0.17; 0.22]	0.21 [0.17; 0.21]
170	0.35	0.20 [0.18; 0.22]	0.21 [0.19; 0.22]	0.22 [0.19; 0.22]
160	0.38	0.22 [0.20; 0.23]	0.22 [0.21; 0.23]	0.23 [0.22; 0.24]
150	0.40	0.23 [0.21; 0.23]	0.23 [0.20; 0.24]	0.24 [0.23; 0.25]
140	0.43	0.24 [0.22; 0.25]	0.24 [0.22; 0.24]	0.25 [0.23; 0.25]
130	0.46	0.25 [0.23; 0.26]	0.24 [0.22; 0.24]	0.26 [0.24; 0.26]
120	0.50	0.27 [0.25; 0.27]	0.27 [0.25; 0.28]	0.27 [0.24; 0.26]
110	0.55	0.29 [0.27; 0.29]	0.28 [0.27; 0.29]	0.29 [0.28; 0.31]
100	0.60	0.31 [0.29; 0.32]	0.28 [0.25; 0.29]	0.30 [0.28; 0.31]
90	0.67	0.34 [0.32; 0.35]	0.33 [0.32; 0.34]	0.35 [0.32; 0.36]
80	0.75	0.37 [0.35; 0.38]	0.35 [0.33; 0.36]	0.37 [0.36; 0.38]
70	0.86	0.40 [0.38; 0.41]	0.39 [0.38; 0.40]	0.40 [0.38; 0.41]
60	1.00	0.46 [0.44; 0.47]	0.44 [0.42; 0.44]	0.47 [0.46; 0.48]
50	1.20	0.47 [0.46; 0.49]	0.46 [0.45; 0.47]	0.50 [0.48; 0.50]
40	1.50	0.49 [0.47; 0.50]	0.48 [0.46; 0.49]	0.51 [0.49; 0.51]
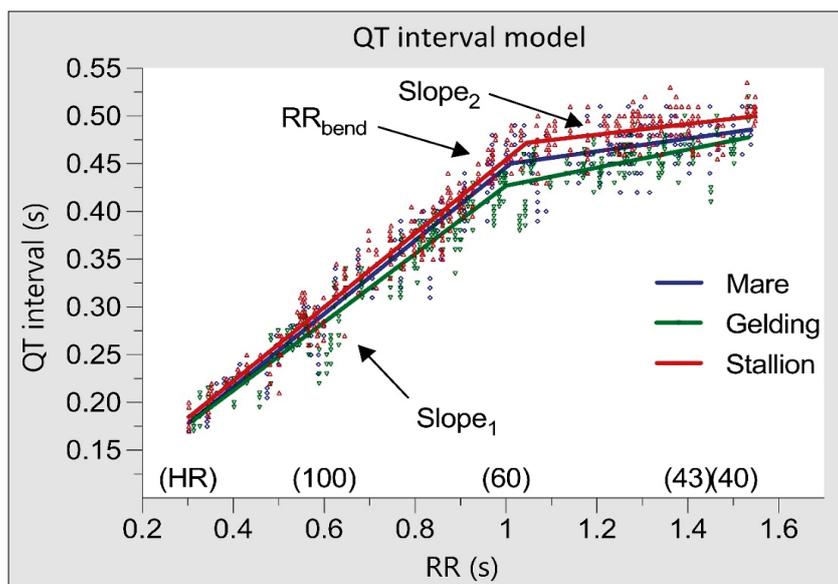
Fig. 2. Data plot of QT/RR intervals with fitted ($0.95 < r^2 < 0.97$) piecewise linear regression lines with variations by sex. $Slope_1$ represents the QT/RR relation on heart rate over the bending point value (RR_{bend}), and it has a higher incline, indicating a quicker shortening of the QT interval. HR – heart rate

ening of the QT interval with higher HR. Comparison of the value of $Slope_1$ (0.377) for the Ukrainian Riding Horse with data presented by Pedersen shows it is in a similar range for some other horse breeds. It is closest to $Slope_1$ for show jumping Warmbloods (0.351) from one side and to Standardbreds (0.380) from another. The value of $Slope_2$ for the Ukrainian Riding Horse (0.080) is also similar to values for Thoroughbreds (0.071) and dressage Warmbloods (0.087). The bending point (1.012) value is close to those for Thoroughbreds (0.955) and show jumping Warmbloods (1.013).

The explanation of biophysical processes behind piecewise linear regression models is still lacking. Pedersen et al., who qualitatively studied QT variations and proved a piecewise linear regression model for the QT/RR relationship in horses, speculated that the bending point represents the HR at which the contribution of the slow delayed rectifier channels (KCNQ1) becomes significant. The KCNQ1 channels, found in both human and equine cardiac tissue, are activated by beta-adrenergic stimulation (19).

Variations in the QT interval may be explained by previously described phenomena: the QT lag and hysteresis, and QT dispersion. The QT lag is a delay in QT adaptation during rapid changes in HR. QT adapts more slowly to decelerations than to accelerations of HR. Since the measurements of QT intervals were performed during periods with a constant HR, the influence of the QT lag is considered to be minimal. The second phenomenon – QT hysteresis – is a loop formed on the plot of QT versus RR intervals during dynamic adaptation of repolarization with heart rate changes. One of the mechanisms for the occurrence of QT hysteresis in humans may involve the residual sympatho-adrenal activity following the cessation of exercise (35). QT hysteresis is also known to be influenced by the parasympathetic nervous system (26). The physiology of horses is characterized by a high vagal tone and its strong impact on the heart. The QT interval was measured during exercise as well as during the post-exercise period. Therefore, QT hysteresis may be considered significant in this study.

QT dispersion is the variation of the QT interval in length between different ECG leads for the same ECG cycle due to differences in lead perspective. Dispersion is calculated by measuring the difference between the shortest and longest QT intervals

in a 12 lead ECG (6). The QT interval was measured on traces of the 2nd lead only, and QT dispersion was not calculated. Therefore, minor differences in electrode placement between individuals in this study may have induced some variability in QT intervals.

The solution estimates of the QT/RR model showed no significant effect of BW. In human medicine, there is a proven effect of obesity on QTc prolongation (27). A recent study performed on 250 horses of different breeds at rest revealed a significant (yet weak) relationship between BW and the QT interval, in which QTc was independent of BW, suggesting that BW influences mostly HR, but not QT itself (36). To prove a systematic effect of BW on the QT interval at rest and during exercise, a wider range of BWs should be presented in a study, and the obesity of the horses should be assessed.

The effect of age was not considered in this study, since most horses were of similar age (7-11 years). A recent study on 203 horses of the American Miniature Horse breed revealed that QT intervals were shorter in foals than in other age groups, suggesting that with a smaller heart size the ventricular conduction velocity is slower (34). To prove the effect of age on the QT interval, horses of all age groups should be presented in the study, including foals, yearlings, adults, and elderly horses.

The main finding of the study is the description of reference values for QT intervals in all sexes of horses of the Ukrainian riding breed. The influence of sex on Slope$_1$, Slope$_2$, and RR$_{bend}$ in this breed was significant, which is similar to the results of studies conducted on Standardbreds. With a lower HR, geldings seem to have the shortest QT interval, and stallions have the longest one.

Judging by the values of Slope$_1$, Slope$_2$, and RR$_{bend}$, Ukrainian riding horses are close in patterns of cardiac repolarization to Warmbloods, Standardbreds, and Thoroughbreds.

The results of this study support the piecewise linear regression model presented by Pedersen et al. (24) as a description of the relationship between QT and RR intervals in horses.

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