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Analysis of repolarization parameters in healthy Great Danes

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Summary

The aim of the study was the analysis of the repolarization period in Great Dane dogs. Fifty-eight clinically healthy Great Danes (30 males, 28 females) between 1 and 9 years old (3.2 ± 1.8 years old on average) were included in the study. A resting ECG with the use of limb (I, II, III, aVR, aVL, aVF) and precordial leads (V1, V2, V4) in the right lateral position was performed in each dog. Fifty-eight ECG curves were analyzed. The following parameters were assessed: rhythm, heart rate (HR), duration of the P wave, PQ duration interval, duration of QRS, and the R-wave amplitude. The repolarization period was assessed using 7 parameters: duration of the QT interval, adjusted duration of the QT interval (acc. to Fridericia formula), the T-wave amplitude, total repolarization time, duration of early and late (TpTe) repolarizations, and the Te/QT ratio. Statistical analysis was carried out by the U Mann-Whitney test and Spearman rank correlation, and a significance level of $p < 0.05$ was adopted. All parameters used for the standard assessment of the ECG curve were within reference values for giant dog breeds. A higher average duration of QRS (66 ms ± 4.9) was observed, but in no dog did it exceed 70 ms. No significant sex differences in the QT (203 ms ± 19.1 vs 204.5 ms ± 15.7) or QTcF (259.4 ms ± 14.2 vs 263 ms ± 13.7) intervals were observed. The T-wave amplitude was positive in 31 (53.44%), negative in 14 (24.14%), and biphase in 13 (22.42%) of the ECG recordings. A correlation of TpTe and TpTe/QT with the sex of the dogs was observed. Statistically significant differences in the values of TpTe and TpTe/QT were observed between males and females. Sex-related norms for these parameters were calculated (average ± 2 SD). They were TpTe 18-42 ms, TpTe/QT 0.1-0.2 for females and TpTe 16-54 ms, TpTe/QT 0.1-0.25 for males. No correlation of TpTe and TpTe/QT with age was observed.

Keywords: repolarization period, Tpeak, Tend, T wave

Repolarization disorders in dogs are a serious diagnostic challenge. The duration of repolarization seen in the ECG shows heterogeneity, the T wave can be positive, negative or biphasic (10). Owing to the large diversity in correct T-wave morphology, the diagnostic value of this parameter remains limited. It has also been shown that the duration and amplitude of segments and intervals can vary from standard reference values in deep-chested dogs (1, 13). Therefore, studies concerning new parameters that may aid in the diagnosis of repolarization disorders are under way. The corrected QT interval (QTc), QT dispersion, and QTc are helpful in the diagnosis of repolarization. The Fridericia formula is most often used to obtain a heart-rate corrected QT interval, where $QTcF=QT/RR^{1/3}$(6). The interval from the peak to the end of the T wave (TpTe) and the TpTe/QT coefficient are some of the most recent available ECG markers. They are used to determine the risk of ventricular arrhythmias (2, 3).

The TpTe time interval reflects the transmural dispersion of repolarization, which occurs as a result of differences in the duration of the action potential between the epicardial, M cell and endocardial layers of the myocardium (15). The T-wave peak value (Tpeak) represents the end of the repolarization of epicardial cells, whereas the end of the T wave (Tend) signifies the end of the repolarization in the M cells. The TpTe/QT ratio is an even more sensitive arrhythmic risk marker, eliminating factors such as the heart rate and variability in the duration of the QT interval (7, 14). Both the TpTe interval and TpTe/QT ratio are commonly used in human medicine to determine the risk of sudden cardiac death and ventricular arrhythmia in acquired, particularly drug-induced, long QT syndrome in coronary heart disease, Brugada syndrome, and resynchronization therapy (2, 3). In veterinary medicine, there are single reports describing the application of these markers, and they are not yet widely

used. Therefore, there is a need for further studies to determine their reference values and usefulness (19).

The aim of the study was to analyze the repolarization time in healthy Great Dane dogs by evaluating the QT and QTcF intervals, the T wave, the TpTe interval, and the TpTe/QT ratio, as well as to determine reference values for these parameters in Great Dane dogs.

Material and methods

The study was carried out on a group of 58 clinically healthy Great Dane dogs (30 males, 28 females) between 1 and 9 years old (mean 3 ± 1.88). Each dog underwent a full clinical examination with particular focus on the cardiovascular system. Moreover, all dogs had a complete blood count, biochemistry analysis (ALT, AST, urea, creatinine, electrolytes), and echocardiography examination. Upon confirmation that all dogs were healthy, they underwent an electrocardiographic examination. Standard limb (I, II, III, aVR, aVL, aVF) and precordial (V1, V2, V4) lead configurations were used. Limb electrodes were placed on the elbows (yellow electrode – left thoracic limb, red electrode – right thoracic limb) and knees (green electrode – left pelvic limb, black – right pelvic limb). Electrodes for the precordial leads were placed on the chest in the following configuration: V1 – fifth intercostal space to the right of the sternum, V2 – sixth intercostal space to the left of the sternum, V4 – sixth intercostals space at the costochondrial junction to the left of the sternum. In order to ensure good conduction between the skin and the electrode clips, the skin of each dog was degreased with alcohol. No pharmacological restraint was used to perform the examination. Recordings were obtained at a paper speed of 50 mm/s and were calibrated at 10 mm/mV. In total, 58 recordings were obtained. BTL SD 08 software was used to analyze the electrocardiograms. The whole ECG curve was assessed in all leads. The measurements were taken from lead II. The QT interval (the interval between the start of the Q wave and the end of the T wave), the corrected QT interval - QTc according to Fridericia's formula, the T-wave amplitude (the distance from the isoelectric line to the peak of the T wave), the duration of late repolarization (TpTe – measured from the peak to the end of the T wave), and the TpTe/QT coefficient were analyzed. The mean, standard deviation (SD), and reference range (mean ± 2 SD) were calculated for each parameter. Statistical analysis was performed by the non-parametric Mann-Whitney U test, and correlations were analyzed by Spearman's rank correlation. The significance level was set at $p < 0.05$. Statistical analysis was conducted with STATISTICA software.

Results and discussion

The clinical examination of the dogs revealed no abnormalities. The complete blood count and blood biochemistry results were within reference ranges. None of the dogs had any congenital heart defects. The size of the heart chambers, left ventricular systolic function, as well as aortic and pulmonary blood flow examined by echocardiography, were within reference ranges in all the dogs. There were no defects in the atrioventricular, aortic, or pulmonary valves in any of the animals. The ECG parameters (P wave duration, P amplitude, PQ duration, QT) were within reference ranges for giant breed dogs (Tab. 1). No statistically significant differences between males and females were noted in the duration of the QT (203 ± 19.1 ms vs. 204.5 ± 15.7 ms) and QTcF (259.4 ± 14.2 ms vs. 263 ± 13.7 ms) intervals (Tab. 2). The QT and QTcF were not correlated with the age of the dogs. The T-wave amplitude was positive in 31 (53.44%), negative in 14 (24.14%), and biphasic in 13 dogs (22.42%).

There was a correlation between TpTe ($r = 0.51$) and TpTe/QT ($r = 0.56$) and sex. Statistically significant differences were noted between males and females in the values of TpTe ($p = 0.04$) and TpTe/QT ($p = 0.01$) (Fig. 1 and 2). TpTe was 18-42 ms and TpTe/QT ranged from 0.1 to 0.2 in females, whereas in males TpTe was 16-54 ms and TpTe/QT ranged from 0.1 to 0.25. TpTe and TpTe/QT did not correlate with age.

Proper ventricular repolarization is essential for correct ventricular relaxation and filling in diastole (4, 5). There is a physiological difference in the duration of

Tab. 1. The values of ECG parameters

	HR (bpm)	P time (ms)	P amp. (mV)	PQ (ms)	QRS (ms)	R amp. (mV)	QT (ms)	QTcF (ms)	Early repolarization	TpTe	T amplitude +	T amplitude –	TpTe/QT
mean	128.90	53.17	0.19	53.17	53.17	53.17	53.17	261.29	86.92	32.72	–0.32	0.32	0.16
SD	20.38	7.31	0.07	7.31	7.31	7.31	7.31	13.94	15.78	8.17	0.15	0.18	0.03

Tab. 2. The values of repolarization in males and females

		Age (years)	QT (ms)	QTcF	TpTe (ms)	Positive amplitude (ms)	Negative amplitude (ms)	TpTe/QT
males	mean	3.06	204.53	263.03	34.93*	–0.36	0.35	0.17*
	SD	1.76	15.73	13.68	9.41	0.15	0.19	0.04
	Reference value			to 300	16-54*			0.1-0.25*
females	mean	3.53	203.00	259.43	30.36*	–0.28	0.28	0.15*
	SD	2.01	19.09	14.22	5.89	0.15	0.15	0.02
	Reference value			to 300	18-42*			0.1-0.2*

Explanation: * statistically significant difference

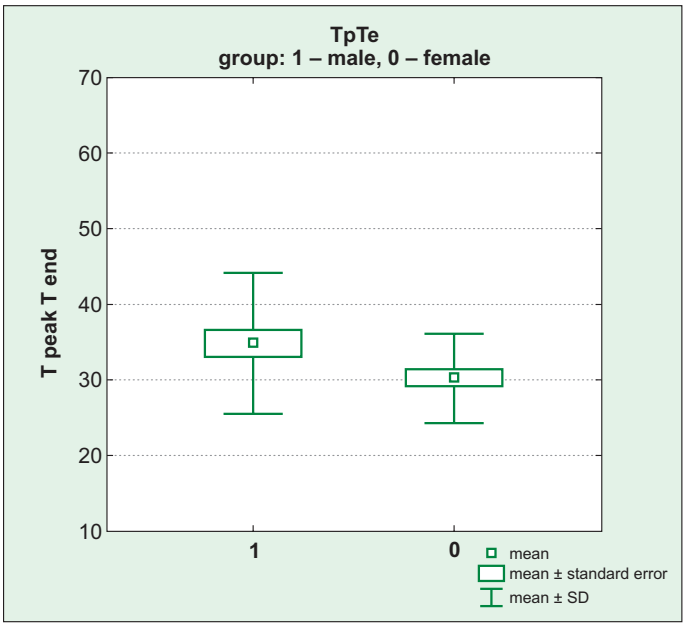

Fig. 1. Differences in the TpTe parameter between males and females (p = 0.04)

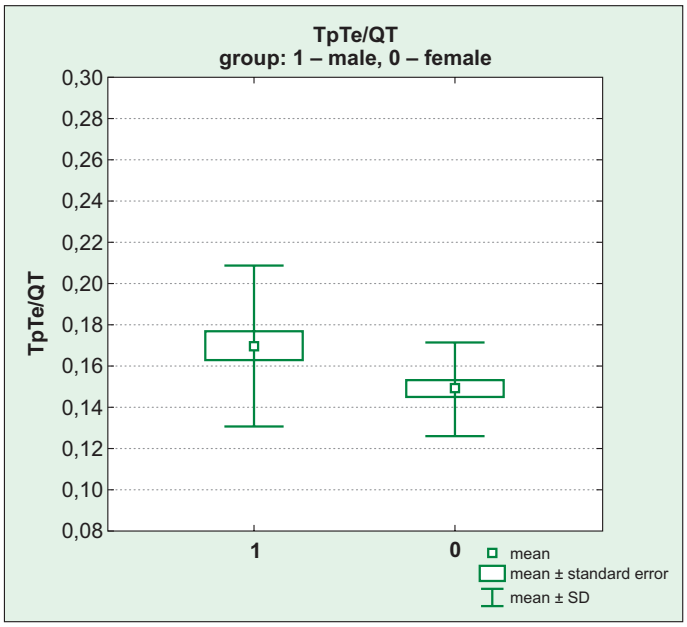

Fig. 2. Differences in the TpTe/QT parameter between males and females (p = 0.01)

the action potential between various areas of the myocardium and different layers of the ventricular wall. Under certain conditions, this can lead to triggered activity and the formation of a reentry-type arrhythmia (18). The duration of the QT interval, QTc, and QT dispersion are normally used to assess repolarization (9, 17). In this study, there was no difference in the duration of the QT interval between males and females, nor was it correlated with age. However, the value of the QT interval is strictly dependent on the heart rate. Therefore, in order to eliminate this dependence, the corrected QT interval is calculated. In the present study, the QT interval was corrected using the Fridericia formula, which is considered optimal for dogs. There was no statistically significant difference between males and females in the duration of the QTcF interval, nor was this parameter correlated with age. Furthermore, there were no differences in the dispersion of QT. QT dispersion (QTd) refers to the variability of the QT interval between individual ECG leads. In humans, it is used as a marker of arrhythmogenesis. At present, QTd is believed to be a weak indicator of repolarization abnormalities and to reflect only non-specific T-wave changes (11). Moreover, determination of QTd is time consuming, and the repeatability of manual measurements is low.

The T wave represents ventricular repolarization, and its variable morphology in dogs is a result of a less orderly repolarization, compared to humans, whose organized repolarization always leads to a positive T wave in the ECG. The repolarization sequence across the ventricular walls affects the T-wave polarity (24). In dogs, the assessment of the T-wave morphology has a limited diagnostic value because of its variability (8). The literature emphasizes the usefulness of TpTe (Tpeak-Tend) in assessing the transmural dispersion of repolarization (12, 15). This parameter illustrates various times of the completion of repolarization in successive ventricular wall muscle layers. Tpeak represents the end of repolarization in the epicardium, whereas Tend represents the end of repolarization in the M-cell layer of the endocardium. A prolonged duration of TpTe is associated with an increased risk of ventricular arrhythmias. This is attributed to an increased susceptibility of M cells to factors influencing the duration of the action potential. Under certain conditions, such as electrolyte imbalances and hypoxia, afterdepolarization and the subsequent formation of reentrant loops may occur, which results in ventricular tachycardia and even ventricular fibrillation (18). In this study, a statistically significant difference in the values of TpTe was found between males and females. In humans, the duration of TpTe was found to be longer in men than women. This is due to a greater transmural dispersion of repolarization in men, and explains the higher risk of developing an arrhythmia and sudden cardiac death in men than in women (21). In Great Dane dogs, sudden cardiac death occurs particularly in males with dilated cardiomyopathy, which is a sex-dependent disorder in this breed. In the current study, there was no correlation between TpTe and age. Similar results were obtained in humans, in whom no association between TpTe and age was found (16).

TpTe/QT is another parameter useful for assessing repolarization (7). This parameter is believed to be a more sensitive indicator of repolarization abnormalities than TpTe, making it possible to assess the dispersion of repolarization relative to the total duration of repolarization. This parameter has been shown to have relatively constant values for different species and does not depend on the heart rate. In this study, a statistically significant difference in the values of TpTe/QT between

males and females was found. In male dogs, as in men, the TpTe/QT coefficient had higher values (24). TpTe/QT was not correlated with age. Studies in humans suggest that TpTe/QT is a better prognostic indicator of the Torsade de Pointes form of ventricular tachycardia than QTc and QTd in patients with an acquired long QT syndrome (such as drug-induced QT prolongation) and in patients subjected to cardiac resynchronization therapy (2, 14). An extended duration of TpTe and TpTe/QT was found in patients with a congenital or acquired long QT syndrome, hypertrophic cardiomyopathy with a mutation in cardiac troponin I, the Brugada syndrome, and in patients subjected to a percutaneous coronary intervention (20, 22, 23, 25).

The study on a group of Great Dane dogs made it possible to carry out a thorough analysis of the repolarization phase in this breed, which is predisposed to dilated cardiomyopathy. The reference values of TpTe and TpTe/QT, which have been determined in this study, may be used for an early detection of repolarization disorders, and, together with other ECG parameters, may be used to evaluate the efficacy of antiarrhythmic therapy and the safety of antiarrhythmic drugs. Prolongation of the TpTe and TpTe/QT intervals is associated with an increase in the transmural dispersion of repolarization, which may increase the risk of ventricular arrhythmias. In the future, these parameters may be used as non-invasive markers of arrhythmogenesis both in healthy animals and in those with a diagnosed heart disease.

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