

QT Interval Instability and Variability in Dogs with Hyperadrenocorticism

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QT interval instability and variability in dogs with hyperadrenocorticism

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Abstract

Hyperadrenocorticism is one of the most common endocrine diseases in dogs. In humans, it is clearly associated with a higher risk of cardiovascular events, but studies in dogs are scarce. To investigate the arrhythmogenic risk of dogs with hyperadrenocorticism, indices of variability and instability of the QT interval were studied in 38 dogs with hyperadrenocorticism and in 12 healthy dogs: variance (QT_v), total instability (TI), short-term (STI) and long-term (LTI), and mean (QT_m). Except for QT_m, all parameters studied were higher in the hyperadrenocorticism group than in the control group. In addition, STI and QT_v showed moderate positive correlation with left ventricle wall thickness. To a better understanding on the effect of the hypothalamus-pituitary-adrenal axis on ventricular repolarization, the hyperadrenocorticism group was subdivided according to the percentage of variation in plasma cortisol concentration (<30.1%; 30.1-60%; >60%) 8 hours after low-dose administration of dexamethasone. There was statistical difference in QT_v, TI and LTI indices between the control group and the <30.1% and >60% groups, and in STI index between the control group and the >60% group. There was no statistical difference between sex groups in any of the electrocardiographic parameters studied. This result may indicate that the etiology of hyperadrenocorticism, and its consequent influence on hypothalamus-pituitary-adrenal axis could interfere on the heterogeneity of ventricular repolarization parameters in different ways, especially in the short-term stability; however further studies are necessary to understand the role of cortisol on electrical instability in dogs.

Keywords

Hypercortisolism; Arrhythmia; Cortisol; QT variability; Cushing's disease

Introduction

Hyperadrenocorticism is one of the most common endocrine disorders in dogs, with prevalence ranging from 0.2 to 1.46% (O'Neill et al. 2016; Carotenuto et al. 2019). In people, it is clear that chronic excessive secretion of cortisol can lead to several complications such as diabetes mellitus, central obesity, hyperlipidemia, hypercoagulability, and systemic arterial hypertension (Mancini et al. 2004). These abnormalities promote a higher risk of cardiovascular events, such as coronary artery disease, acute myocardial infarction, stroke and heart failure, which may remain high five years after successful treatment of the disease (Colao et al. 1999; Dekkers et al. 2013; Terzolo et al. 2014; Di Dalmazi et al. 2014; Bancos et al. 2016).

In addition to the majority (80%) of people with hyperadrenocorticism having 'high' or 'very high' risk of cardiovascular complications (Mancini et al. 2004), the risk of cardiovascular disease in these patients is five times higher than the rest of the population, and the risk of death from cardiovascular complications doubles with each 20 mmHg increase in systolic blood pressure and 10 mmHg of diastolic blood pressure (Nieman 2019). Veterinary literature lacks information related to cardiovascular risk in dogs with hyperadrenocorticism. Despite no association with atherosclerosis (Hess et al. 2003), dogs with hyperadrenocorticism are at risk for thromboembolic disease, with a prevalence of 6.1% in that

population (Hoffman et al. 2018). Also, they are prone to developing systemic arterial hypertension, left ventricular hypertrophy, diastolic dysfunction, left atrial enlargement and congestive heart failure (De Caterina et al. 2010; Nieman 2019).

In addition to functional and structural complications in the cardiovascular system secondary to hyperadrenocorticism, there is evidence of a higher arrhythmogenic risk. In people, several studies have already demonstrated the association between hypercortisolism and atrial fibrillation (Huerta et al. 2005; van der Hooft et al. 2006; De Caterina et al. 2010; Koracevic et al. 2020), but studies evaluating the risk for arrhythmias in dogs with such condition are lacking. Nonetheless, owing to the clear evidences in people and the high incidence of hyperadrenocorticism in dogs, investigation of surrogates for cardiovascular events in this species are indeed warranted.

The electrocardiogram is a low-cost exam widely used in veterinary practice, which can provide precious information in these situations. QT interval corresponds to the duration of the ventricular action potential, being one of the most used electrocardiographic parameters for the diagnosis of cardiac abnormalities (Niemeijer et al. 2015). The prolongation of QT interval has been historically associated with a higher frequency of arrhythmic events (Boulaksil et al. 2011; Itoh et al. 2016). Of note, some studies have demonstrated the inaccuracy of the isolated QT interval for stratification of arrhythmogenic risk (Hondegem 2008a, b). However, parameters derived from QT, such as the instability and variability of QT, have been further studied, and proved more sensitive and specific for predicting the development of arrhythmias (Limprasut et al. 2018).

In dogs with myxomatous mitral valve disease, our research group recently demonstrated that QT interval instability increases with disease progression and have predictive value for the development of ventricular arrhythmias (Brüler et al. 2018). While in people with hyperadrenocorticism the prolongation of QT interval corrected by heart rate (QTc) has been confirmed (Pecori Giraldi et al. 2011), to the best of our knowledge no study has investigated the influence played by high serum cortisol levels on myocardial repolarization in dogs. Thus, this study aimed at evaluating QT interval indices in dogs with hyperadrenocorticism. We hypothesized that an increased prolongation and instability of QT interval would be associated with a higher risk of developing arrhythmias.

Materials and methods

Animals

Medical records of dogs diagnosed with hyperadrenocorticism between January 2013 and April 2016 at a veterinary teaching facility were retrospectively analyzed. The inclusion criteria for the hyperadrenocorticism group (HG) were the diagnosis of hyperadrenocorticism through the low-dose dexamethasone suppression test (LDDST) (0.01 mg/kg IV), in addition to the presence of an electrocardiographic tracing performed within seven days of confirmation of hyperadrenocorticism. Dogs that did not have electrocardiographic tracing or that were already receiving any hyperadrenocorticism drug therapy at the time of electrocardiographic recording were not admitted into this investigation. To

access the presence of left ventricle (LV) concentric hypertrophy, echocardiographic data were also collected from dogs that had this information available in their records. Concentric hypertrophy was defined as diastolic LV free wall (LVFW) and/or interventricular septum (IVS) thickness above the normal range for body weight (Gonçalves et al. 2002). For the control group (CG), healthy dogs from a Beagle research colony were prospectively enrolled. Only dogs without clinical characteristics compatible with hyperadrenocorticism or any other systemic disease were included in this group. These dogs underwent a thorough clinical examination as well as electrocardiographic evaluation. In either group, demographic data (breed, sex, age, body weight) was recorded.

Electrocardiographic Analysis

In all animals, the electrocardiographic tracing was obtained using a computer-based equipment. Bipolar (I, II and III), and unipolar (aVL, aVR and aVF) leads were recorded, with paper velocity adjusted to 50 mm/s and sensitivity calibrated to 1 mV/1 cm. The analysis of the electrocardiographic traces was performed in lead II, and included duration of the QT interval, which corresponds to the beginning of the Q wave to the end of the T wave (Santilli et al. 2019). Fifty consecutive QT intervals were measured and recorded, allowing the calculation of the following parameters: QTm (mean QT intervals); QTv (variance of QT intervals); TI (total instability); LTI (long-term instability); and STI (short-term instability). The variables TI, LTI and STI were calculated according to the methodology proposed by Van der Linde and colleagues (Van Der Linde et al. 2005), which is based on *Poincaré* plots (Fig 1) constructed from the intersection between QT_n (X axis) and QT_{n+1} (Y axis). TI was calculated by applying the equation described below:

$$TI_{QT_n} = \sqrt{[(CG(x) - QT_n)^2 + (CG(y) - QT_{n+1})^2]}$$

$$TI = \text{Median } (TI_{QT_1} \dots TI_{QT_{49}})$$

Where:

$$X \text{ axis center of gravity: } CG(x) = \sum_{i=m}^{m+49} (QT_i)/50$$

$$Y \text{ axis center of gravity: } CG(y) = \sum_{i=m+1}^{m+50} (QT_i)/50$$

The width and length of the *plot XY* were measured after rotating it in -45° (θ) around its origin. Thus, rotational centers of gravity were obtained, which were later used to calculate LTI and STI.

$$LTI_{QT_n} = CG(x)_{Rot} - [(\cos \theta \cdot QT_{n+1}) - (\sin \theta \cdot QT_n)]$$

$$LTI = \text{Median} (LTI_{QT_1} \dots LTI_{QT_{49}})$$

$$STI_{QT_n} = CG(y)_{Rot} - [(\sin \theta \cdot QT_{n+1}) + (\cos \theta \cdot QT_n)]$$

$$STI = \text{Mediana} (STI_{QT_1} \dots STI_{QT_{49}})$$

Where:

$$CG(x)_{Rot} = [\cos \theta \cdot CG(x)] - [\sin \theta \cdot CG(y)]$$

$$CG(y)_{Rot} = [\sin \theta \cdot CG(x)] + [\cos \theta \cdot CG(y)]$$

Statistical analysis

Shapiro-Wilk test was used to investigate normality of the data. Mean, standard deviation, median, interquartiles, minimum and maximum, confidence interval and coefficient of variation values were calculated. Mann-Whitney test was used to assess differences between CG and HG. To evaluate the correlation between echocardiographic LV measurements and QT mean, variability and instability indices, Spearman test was performed. To minimize body weight bias, systolic and diastolic IVS and LVFW were divided by LV internal diameter (LVD). In addition, diastolic and systolic IVS, LVD and LVFW were normalized for body weight using allometric scaling (CORNELL et al., 2004):

$$IVSdN: \frac{\text{diastolic IVS}}{\text{body weight}^{0,241}}$$

$$LVDdN: \frac{\text{diastolic LVD}}{\text{body weight}^{0,294}}$$

$$LVFWdN: \frac{\text{diastolic LVFW}}{\text{body weight}^{0,232}}$$

$$IVSsN: \frac{\text{systolic IVS}}{\text{body weight}^{0,24}}$$

$$LVDsN: \frac{\text{systolic LVD}}{\text{body weight}^{0,315}}$$

$$LVFWsN: \frac{\text{systolic LVFW}}{\text{body weight}^{0,222}}$$

For the interpretation of the Spearman correlation magnitude, the following classification was adopted: correlation coefficients 0 to 0.1 (negligible), 0.1 to 0.39 (weak), 0.4 to 0.69 (moderate), 0.7 to 0.89 (strong), and 09 to 1 (very strong)(Schober et al. 2018).

In addition, Kruskal-Wallis test followed by Dunn's post hoc test was used to check for differences in accordance to the percentage of reduction of basal cortisol in response to LDDST. Lastly, Mann-Whitney test was used to evaluate differences attributed to sex in HG. All statistical analyses were performed using the software *Graphpad Prism for Windows* (v.5.02), considering p<0.05 as significant.

Results

Animals

Data from 38 dogs with hyperadrenocorticism (7-20 years; 3.5-50.0 kg; 25 females) were retrospectively selected. Several breeds were represented, including Poodle (n=6), Lhasa Apso (n=4), Beagle (n=3), Cocker (n=3), Dachshund (n=3), Schnauzer (n=2), Boxer (n=1), Dogo Argentino (n=1), Labrador (n=1), Shih tzu (n=1) and Yorkshire (n=1), as well as mixed-breed dogs (n=12). The CG consisted of 12 healthy Beagle dogs (1-2 years; 8.6-10.0 kg; 6 females). Concentric hypertrophy was observed in 66,67% (16/24) dogs with hyperadrenocorticism.

QT mean, variability and instability indices

With the exception of QTm, a significant difference was documented between CG and HG in all parameters studied. QTv, LTI, STI and TI were higher in HG than in CG (Table 1). Fig 2 illustrates the greater dispersion of points in the *Poincaré* plot in HG dogs compared to one of the CG dogs, representing wider total QT instability.

There was moderate positive significant correlation between QTv and LVFW/LVDd ($p=0,043$; $r=0,46$), QTv and LVFWsN ($p=0,019$; $r=0,53$), and STI and LVFW/LVDd ($p=0,032$; $r=0,4$),

When dogs with hyperadrenocorticism were divided into three subgroups according to the percentage of variation in plasma cortisol concentration (<30.1%; 30.1-60.0%; >60.0%) 8 hours after the start of the LDDST, significant difference was found only in QTv, TI, LTI and STI (Table 2). QTv TI and LTI were lower in the control group in comparison with the <30.1% and >60% groups. Also, STI was lower in the control group compared to the >60% group. No difference was documented between the control and the 30.1-60% groups for any electrocardiographic parameter studied.

When comparing the results according to the sex of dogs with hyperadrenocorticism, there was no difference in any of the electrocardiographic parameters studied (QTm $p=0.5338$; QTv $p=0.9113$; TI $p=0.7625$; LTI $p=0.5349$; STI $p=0.7503$).

Discussion

In this study, we investigated the influence of hypercortisolism in some QT interval variables in dogs. Although QT interval was not prolonged, the variability and instability of total ventricular electric activity was higher in dogs with hyperadrenocorticism compared to healthy dogs. In addition, the indices derived from the QT interval varied according to the intensity of hypothalamic pituitary-adrenal axis (HPAA) suppression during the LDDST.

QT interval reflects the duration of cardiac action potential and its prolongation is considered proarrhythmic. The association between QT prolongation and a higher risk of ventricular arrhythmias and sudden death has been discussed in the literature for more than 40 years (Schwartz and Wolf 1978; Straus et al. 2006; Ahmad and Dorian 2007; Hondeghem 2011; Niemeijer et al. 2015). In dogs, the prolongation of QTc has been demonstrated with the progression of several heart diseases (Koyama et al. 2004; Brûler et al. 2018), which might potentially result in higher arrhythmogenic risk. Nonetheless, in spite of the progressive increase of QT interval along the worsening of mitral valve degeneration in dogs, we recently showed that QTc failed to predict the development of ventricular arrhythmias in those animals (Vila et al. 2021).

Curiously, several studies also suggest that prolongation of the QT interval and QTc are not reliable predictors of ventricular arrhythmia (Spier et al. 2001; Hondeghem 2008a, b; Leonard et al. 2013). In fact, the prolongation of the duration of the action potential can be antiarrhythmic, since it is the mechanism of class III antiarrhythmic agents (Brendorp et al. 2002). Thus, other factors must coexist with QT interval duration abnormalities for the promotion of proarrhythmic effects, such as spatial or temporal heterogeneity of cardiac repolarization (Schneider et al. 2005). Our results showed no difference between the HG and the CG in the mean duration of QT interval (QTm), but significant difference was found in the parameters that assess repolarization temporal heterogeneity through QT variability (QTV) and instability (TI, LTI and STI).

QT interval exhibits spontaneous fluctuations with each beat, reflecting subtle time variations in ventricular depolarization and repolarization. Because ventricular depolarization is much more stable than repolarization, QT variability may be used as a tool to measure the variance of ventricular repolarization duration (Baumert et al. 2016). Parameters derived from QT variability have already been shown to be useful tools to investigate pro-arrhythmogenic and non-arrhythmogenic effect of drugs in dogs (Schneider et al. 2005), and to be a strong predictor of ventricular fibrillation in rabbits anesthetized with myocardial ischemia, presenting greater sensitivity and specificity than the QT and QTc intervals (Sarusi et al. 2014; Limprasutr et al. 2018). Therefore, the greater variability and instability of QT in dogs with hyperadrenocorticism as compared to healthy dogs (Table 2 and Figure 2) points to a higher risk for cardiovascular events in that population.

Higher arrhythmogenic and death risk in people with hyperadrenocorticism has already been associated with cardiovascular complications, such as systemic arterial hypertension, left ventricular hypertrophy, cardiomegaly and myocardial ischemia (Verdecchia et al. 2003; Dekkers et al. 2013; Chatterjee et al. 2014). Systemic arterial hypertension is observed in 85% of people and 80% of dogs with

hyperadrenocorticism (Mancini et al. 2004; Vidal et al. 2018), leading to increased afterload and, consequently, LV concentric hypertrophy. In our study, although blood pressure data were not included, LV concentric hypertrophy was observed in 66,67% of dogs with hyperadrenocorticism, which was similar to previous reports (65%) (Takano et al. 2015). Myocardial hypertrophy results in structural disarray, including fibrosis, collagen accumulation, increased interstitial fibroblasts, and diastolic dysfunction (Shenasa et al. 2015), leading to a 3.4-fold and 2.8-fold increase in the risk of developing supraventricular arrhythmias and ventricular tachycardia/fibrillation in humans, respectively (Chatterjee et al. 2014). Indeed, left ventricular thickness variables correlated positively with QT variability and instability in this study, which has also already been shown in humans (Orosz et al. 2015). These results suggest that dogs with hyperadrenocorticism and LV hypertrophy might present greater fluctuation of the QT interval and susceptibility to cardiovascular complications.

When dogs with hyperadrenocorticism were divided in accordance with the percentage of reduction in plasma cortisol concentration during the LDDST, all indices were higher as compared to healthy dogs, with the exception of QTm. However, significant differences were only documented between controls and dogs which attained <30.1% and >60% cortisol suppression. Dogs with hyperadrenocorticism may exhibit different patterns of suppression of hypothalamic-pituitary-adrenal axis during LDDST, depending on the etiology of the disease (Zeugswetter et al. 2021). In a recent study, Bennaim and colleagues described five patterns of LDDST results, and found that 100% of dogs with adrenal tumor hyperadrenocorticism showed the absence of suppression pattern (T4h and T8h > 1 μ g/dL and both >50% T0), while dogs with pituitary-dependent hyperadrenocorticism were distributed among five patterns: absence of suppression, partial suppression (T4h and T8h > 1 μ g/dL, but either <50% T0), complete suppression (T4h and T8h < 1 μ g/dL), escape (T8h > 1 μ g/dL and T4h < 1 μ g/dL) or inverse (T4h > 1 μ g/dL and T8h < 1 μ g/dL) (Bennaim et al. 2018).

In our study, dogs with plasma cortisol reduction >60% (i.e., likely to have pituitary-dependent hyperadrenocorticism) and dogs with plasma cortisol reduction <30.1% (i.e., likely to present adrenal tumor and/or pituitary-dependent hyperadrenocorticism) showed similar results. QTv, TI and LTI were similar in these groups, and significantly higher than in CG. in. For STI, however differences existed only between the >60% group and the CG (Table 2). This result may indicate that the etiology of hyperadrenocorticism, and its consequent influence on HPAA, could interfere on the heterogeneity of ventricular repolarization parameters in different ways, especially in the short-term stability. At least in people with either adrenal tumor or pituitary-dependent hyperadrenocorticism, the risk of death and cardiovascular events was shown to be similar (Dekkers et al. 2013). Nevertheless, to the best of authors' knowledge, there are no studies which investigated such characteristic in dogs. It is not clear why the group of dogs with 30-60% of cortisol suppression did not differ from control dogs. Further studies are necessary to understand the role of hyperadrenocorticism etiology on electrical instability in dogs.

Lastly, while studies in people have reported that women have higher QTc than men (Linde et al. 2018), other studies have found no difference between sex in QT variability (Bonnemeier et al. 2003; Krauss et al. 2009), which is similar to our findings in dogs.

An important limitation of this study is its retrospective design, which limits the acquisition of some data, such as the presence of comorbidities. It is known that ventricular repolarization rates may change with heart diseases (Brüler et al. 2018; Vila et al. 2021), with non-cardiac diseases (Armstrong et al. 2017; Kim et al. 2021), as well as with antiarrhythmic drugs administration (Shantsila et al. 2007). In addition, information such as systemic blood pressure, blood gases, and 24 hours Holter recording to thoroughly investigate the presence of arrhythmias could enrich the understanding of the pathophysiological mechanisms involved in the development of cardiovascular complications in dogs with hyperadrenocorticism.

This study demonstrated that hypercortisolism play a role on temporal heterogeneity of the QT interval, since the QT variability and instability indices were higher in dogs with hyperadrenocorticism than in healthy dogs, and showed moderate positive correlation with left ventricle thickness. In addition, fluctuation of ventricular repolarization indices was observed according to the suppression of HPAA during the LDDST. Future studies that focus on the dynamics of cardiac repolarization in dogs with hyperadrenocorticism are encouraged to better understand the relationship between HPAA and cardiac electrical instability.

Declarations

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Conflict of interest statement: The authors have no conflict of interest to disclose.

Code or data availability (software application or custom code): Not applicable

Authors' Contributions: Beatriz de Carvalho Pato Vila, Marcela Sigolo Vanhoni¹, and Marlos Gonçalves Sousa contributed to acquisition of the data, participated in the statistical analysis, and wrote and edited the manuscript.

Ethics approval: The study was entirely conducted in a Veterinary Teaching facility following the guidelines outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Consent to participate: Due to the retrospective nature of this investigation, institutional policies do not require a written consent of animal owners prior to inclusion of data in the study, as well as to publish manuscripts.

Consent for publication: Due to the retrospective nature of this investigation, institutional policies do not require a written consent of animal owners prior to inclusion of data in the study, as well as to publish manuscripts.

References

- Ahmad K, Dorian P (2007) Drug-induced QT prolongation and proarrhythmia: an inevitable link? EP Eur 9:iv16–iv22. <https://doi.org/10.1093/europace/eum167>
- Armstrong HF, Lovasi GS, Soliman EZ, et al (2017) Lung function, percent emphysema, and QT duration: The Multi-Ethnic Study of Atherosclerosis (MESA) lung study. Respir Med 123:1–7. <https://doi.org/10.1016/j.rmed.2016.12.003>
- Bancos I, Alahdab F, Crowley RK, et al (2016) THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. Eur J Endocrinol 175:R283–R295. <https://doi.org/10.1530/EJE-16-0465>
- Baumert M, Porta A, Vos MA, et al (2016) QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrop. Eur Eur pacing, arrhythmias, Card Electrophysiol J Work groups Card pacing, arrhythmias, Card Cell Electrophysiol Eur Soc Cardiol 18:925–944. <https://doi.org/10.1093/europace/euv405>
- Bennaim M, Shiel RE, Forde C, Mooney CT (2018) Evaluation of individual low-dose dexamethasone suppression test patterns in naturally occurring hyperadrenocorticism in dogs. J Vet Intern Med 32:967–977. <https://doi.org/10.1111/jvim.15079>
- Bonnemeier H, Wiegand UKH, Braasch W, et al (2003) Circadian profile of QT interval and QT interval variability in 172 healthy volunteers. Pacing Clin Electrophysiol 26:377–382. <https://doi.org/10.1046/j.1460-9592.2003.00053.x>
- Boulaksil M, Jungschleger JG, Antoons G, et al (2011) Drug-Induced torsade de pointes arrhythmias in the chronic AV block dog are perpetuated by Focal Activity. Circ Arrhythmia Electrophysiol 4:566–576. <https://doi.org/10.1161/CIRCEP.110.958991>
- Brendorp B, Pedersen O, Torp-Pedersen C, et al (2002) A benefit-risk assessment of class III antiarrhythmic agents. Drug Saf 25:847–865. <https://doi.org/10.2165/00002018-200225120-00003>
- Brüler BC, Jojima FS, Dittrich G, et al (2018) QT instability, an indicator of augmented arrhythmogenesis, increases with the progression of myxomatous mitral valve disease in dogs. J Vet Cardiol 20:254–266. <https://doi.org/10.1016/j.jvc.2018.06.002>
- Carotenuto G, Malerba E, Dolfini C, et al (2019) Cushing's syndrome—an epidemiological study based on a canine population of 21,281 dogs. Open Vet J 9:27–32. <https://doi.org/10.4314/ovj.v9i1.5>
- Chatterjee S, Bavishi C, Sardar P, et al (2014) Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. Am J Cardiol 114:1049–1052. <https://doi.org/10.1016/j.amjcard.2014.07.015>

- Colao A, Pivonello R, Spiezio S, et al (1999) Persistence of Increased Cardiovascular Risk in Patients with Cushing's Disease after Five Years of Successful Cure. *J Clin Endocrinol Metab* 84:2664–2672. <https://doi.org/10.1210/jcem.84.8.5896>
- De Caterina R, Ruigómez A, Rodríguez LAG (2010) Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. *Arch Intern Med* 170:1450–1455.
<https://doi.org/10.1001/archinternmed.2010.305>
- Dekkers OM, Horváth-Puhó E, Jørgensen JOL, et al (2013) Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab* 98:2277–2284.
<https://doi.org/10.1210/jc.2012-3582>
- Di Dalmazi G, Berr CM, Fassnacht M, et al (2014) Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. *J Clin Endocrinol Metab* 99:2637–2645. <https://doi.org/10.1210/jc.2014-1401>
- Gonçalves AC, Orton EC, Boon JA, Salman MD (2002) Linear, logarithmic, and polynomial models of M-mode echocardiographic measurements in dogs. *Am J Vet Res* 63:994–999.
<https://doi.org/10.2460/ajvr.2002.63.994>
- Hess RS, Kass PH, Van Winkle TJ (2003) Association between Diabetes Mellitus, Hypothyroidism or Hyperadrenocorticism, and Atherosclerosis in Dogs. *J Vet Intern Med* 17:489–494.
[https://doi.org/10.1892/0891-6640\(2003\)017<0489:ABDMHO>2.3.CO;2](https://doi.org/10.1892/0891-6640(2003)017<0489:ABDMHO>2.3.CO;2)
- Hoffman JM, Lourenço BN, Promislow DEL, Creevy KE (2018) Canine hyperadrenocorticism associations with signalment, selected comorbidities and mortality within North American veterinary teaching hospitals. *J Small Anim Pract* 59:681–690. <https://doi.org/10.1111/jsap.12904>
- Hondeghem LM (2008a) QT prolongation is an unreliable predictor of ventricular arrhythmia. *Hear Rhythm* 5:1210–1212. <https://doi.org/https://doi.org/10.1016/j.hrthm.2008.05.006>
- Hondeghem LM (2008b) QT and TdP. QT: an unreliable predictor of proarrhythmia. *Acta Cardiol* 63:1–7. <https://doi.org/10.2143/AC.63.1.2025324>
- Hondeghem LM (2011) QTc prolongation as a surrogate for drug-induced arrhythmias: fact or fallacy? *Acta Cardiol*. 66:685–689
- Huerta C, Lanes SF, García Rodríguez LA (2005) Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology* 16:360–366. <https://doi.org/10.1097/01.ede.0000158743.90664.a7>
- Itoh H, Crotti L, Aiba T, et al (2016) The genetics underlying acquired long QT syndrome: Impact for genetic screening. *Eur Heart J* 37:1456–1464. <https://doi.org/10.1093/eurheartj/ehv695>
- Kim PY, Irizarry-Caro JA, Ramesh T, et al (2021) How to Diagnose and Manage QT Prolongation in Cancer Patients. *JACC CardioOncology* 3:145–149. <https://doi.org/10.1016/j.jaccao.2021.01.002>

Koracevic G, Micic S, Stojanovic M, et al (2020) High likelihood for atrial fibrillation in Cushing's syndrome. *Eur Rev Med Pharmacol Sci* 24:1391–1397.
https://doi.org/10.26355/eurrev_202002_20196

Koyama H, Yoshii H, Yabu H, et al (2004) Evaluation of QT interval prolongation in dogs with heart failure. *J Vet Med Sci* 66:1107–1111. <https://doi.org/10.1292/jvms.66.1107>

Krauss TT, Mäuser W, Reppel M, et al (2009) Gender effects on novel time domain parameters of ventricular repolarization inhomogeneity. *Pacing Clin Electrophysiol* 32 Suppl 1:S167-72.
<https://doi.org/10.1111/j.1540-8159.2008.02278.x>

Leonard CE, Freeman CP, Newcomb CW, et al (2013) Antipsychotics and the Risks of Sudden Cardiac Death and All-Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare Beneficiaries of Five States. *J Clin Exp Cardiol Suppl* 10:1–9. <https://doi.org/10.4172/2155-9880.S10-006>

Limprasutr V, Pirintr P, Kijtawornrat A, Hamlin RL (2018) An increasing electromechanical window is a predictive marker of ventricular fibrillation in anesthetized rabbit with ischemic heart. *Exp Anim* 67:175–183. <https://doi.org/10.1538/expanim.17-0100>

Linde C, Bongiorni MG, Birgersdotter-Green U, et al (2018) Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Eur Eur pacing, arrhythmias, Card Electrophysiol J Work groups Card pacing, arrhythmias, Card Cell Electrophysiol Eur Soc Cardiol* 20:1565–1565ao. <https://doi.org/10.1093/europace/euy067>

Mancini T, Kola B, Mantero F, et al (2004) High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. *Clin Endocrinol (Oxf)* 61:768–777.
<https://doi.org/10.1111/j.1365-2265.2004.02168.x>

Nieman LK (2019) Hypertension and Cardiovascular Mortality in Patients with Cushing Syndrome. *Endocrinol Metab Clin North Am* 48:717–725. <https://doi.org/10.1016/j.ecl.2019.08.005>

Niemeijer MN, van den Berg ME, Deckers JW, et al (2015) Consistency of heart rate-QTc prolongation consistency and sudden cardiac death: The Rotterdam Study. *Hear Rhythm* 12:2078–2085.
<https://doi.org/10.1016/j.hrthm.2015.07.011>

O'Neill DG, Scudder C, Faire JM, et al (2016) Epidemiology of hyperadrenocorticism among 210,824 dogs attending primary-care veterinary practices in the UK from 2009 to 2014. *J Small Anim Pract* 57:365–373. <https://doi.org/10.1111/jsap.12523>

Orosz A, Baczkó I, Nagy V, et al (2015) Short-term beat-to-beat variability of the QT interval is increased and correlates with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. *Can J Physiol Pharmacol* 93:765–772. <https://doi.org/10.1139/cjpp-2014-0526>

- Pecori Giraldi F, Toja PM, Michailidis G, et al (2011) High prevalence of prolonged qt interval duration in male patients with Cushing's disease. *Exp Clin Endocrinol Diabetes* 119:221–224.
<https://doi.org/10.1055/s-0031-1271628>
- Santilli RA, Moïse NS, Pariaut R, Perego M (2019) *Electrocardiography of the dog and cat: diagnosis of arrhythmias*. Edra, Trento
- Sarusi A, Rárosi F, Szűcs M, et al (2014) Absolute beat-to-beat variability and instability parameters of ECG intervals: biomarkers for predicting ischaemia-induced ventricular fibrillation. *Br J Pharmacol* 171:1772–1782. <https://doi.org/10.1111/bph.12579>
- Schneider J, Hauser R, Andreas J-O, et al (2005) Differential effects of human ether-a-go-go-related gene (HERG) blocking agents on QT duration variability in conscious dogs. *Eur J Pharmacol* 512:53–60. <https://doi.org/10.1016/j.ejphar.2005.01.042>
- Schober P, Boer C, Schwarte L (2018) Correlation Coefficients: Appropriate Use and Interpretation. *Anesth Analg* 126:1. <https://doi.org/10.1213/ANE.0000000000002864>
- Schwartz PJ, Wolf S (1978) QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 57:1074–1077. <https://doi.org/10.1161/01.cir.57.6.1074>
- Shantsila E, Watson T, Lip GYH (2007) Drug-induced QT-interval prolongation and proarrhythmic risk in the treatment of atrial arrhythmias. *Eur Eur pacing, arrhythmias, Card Electrophysiol J Work groups Card pacing, arrhythmias, Card Cell Electrophysiol Eur Soc Cardiol 9 Suppl 4:iv37-44.*
<https://doi.org/10.1093/europace/eum169>
- Shenasa M, Shenasa H, El-Sherif N (2015) Left ventricular hypertrophy and arrhythmogenesis. *Card Electrophysiol Clin* 7:207–220. <https://doi.org/10.1016/j.ccep.2015.03.017>
- Spier AW, Meurs KM, Muir WW, et al (2001) Correlation of QT dispersion with indices used to evaluate the severity of familial ventricular arrhythmias in Boxers. *Am J Vet Res* 62:1481–1485.
<https://doi.org/10.2460/ajvr.2001.62.1481>
- Straus SMJM, Kors JA, De Bruin ML, et al (2006) Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 47:362–367.
<https://doi.org/10.1016/j.jacc.2005.08.067>
- Takano H, Kokubu A, Sugimoto K, et al (2015) Left ventricular structural and functional abnormalities in dogs with hyperadrenocorticism. *J Vet Cardiol Off J Eur Soc Vet Cardiol* 17:173–181.
<https://doi.org/10.1016/j.jvc.2015.07.002>
- Terzolo M, Allasino B, Pia A, et al (2014) Surgical remission of Cushing's syndrome reduces cardiovascular risk. *Eur J Endocrinol* 171:127–136. <https://doi.org/10.1530/EJE-13-0555>
- van der Hooft CS, Heeringa J, Brusselle GG, et al (2006) Corticosteroids and the risk of atrial fibrillation.

Arch Intern Med 166:1016–1020. <https://doi.org/10.1001/archinte.166.9.1016>

Van Der Linde H, Van De Water A, Loots W, et al (2005) A new method to calculate the beat-to-beat instability of QT duration in drug-induced long QT in anesthetized dogs. J Pharmacol Toxicol Methods 52:168–177. <https://doi.org/10.1016/j.vascn.2005.03.005>

Verdecchia P, Reboldi G, Gattobigio R, et al (2003) Atrial fibrillation in hypertension: predictors and outcome. Hypertens (Dallas, Tex 1979) 41:218–223.
<https://doi.org/10.1161/01.hyp.0000052830.02773.e4>

Vidal PN, Miceli DD, Arias ES, et al (2018) Decrease of nitric oxide and increase in diastolic blood pressure are two events that affect renal function in dogs with pituitary dependent hyperadrenocorticism. Open Vet J 8:86–95. <https://doi.org/10.4314/ovj.v8i1.14>

Vila B de CP, Camacho AA, Sousa MG (2021) T-wave peak-end interval and ratio of T-wave peak-end and QT intervals: novel arrhythmogenic and survival markers for dogs with myxomatous mitral valve disease. J Vet Cardiol 35:25–41. <https://doi.org/10.1016/j.jvc.2021.02.004>

Zeugswetter FK, Carranza Valencia A, Glavassevich K, Schwendenwein I (2021) Patterns of the low-dose dexamethasone suppression test in canine hyperadrenocorticism revisited. Vet Clin Pathol 50:62–70. <https://doi.org/10.1111/vcp.12958>

Figure Captions

Fig 1 Poincaré plot constructed from the intersection between QT_n (X axis) and QT_{n+1} (Y axis) in one of the dogs with hyperadrenocorticism included in the study. The circles represent the 49 cartesian combinations formed between 50 sequenced QT intervals (QT₁ to QT₅₀), and the black square represents the projection of the gravity center coordinates of the QT intervals on the X and Y axes

Fig 2 Poincaré plots showing the dispersion of the intersection points between QT_n (X axis) and QT_{n+1} (Y axis) in one of the healthy dogs (a), whose total calculated instability was 6.4, and in three dogs with hyperadrenocorticism, whose calculated total instability was 11.6 (b), 16.9 (c) and 25.8 (d). The black squares represent the projection of the center of gravity coordinates of the QT intervals on the X and Y axes

Figures

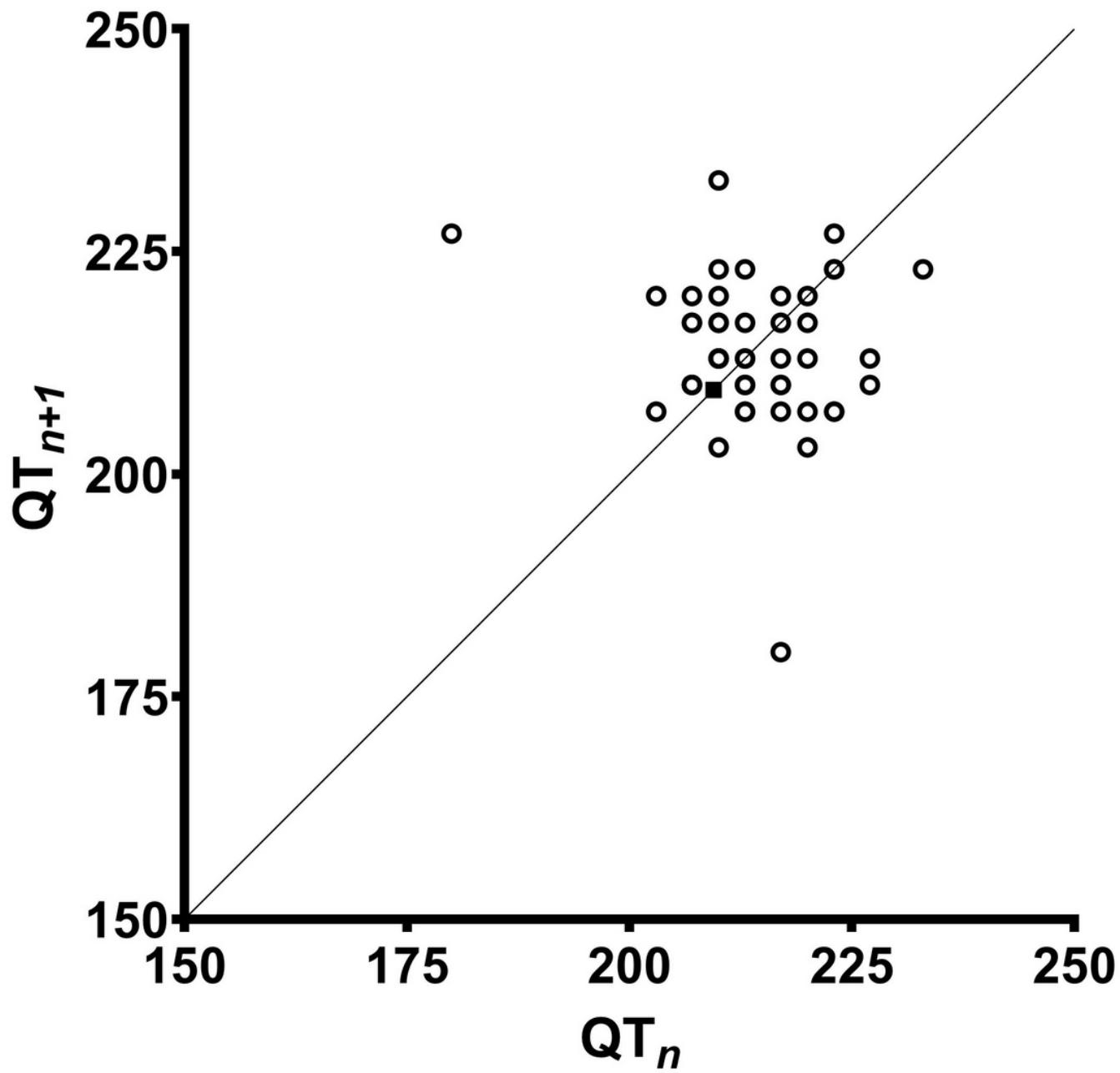


Figure 1

Poincaré plot constructed from the intersection between QT_n (X axis) and QT_{n+1} (Y axis) in one of the dogs with hyperadrenocorticism included in the study. The circles represent the 49 cartesian combinations formed between 50 sequenced QT intervals (QT_1 to QT_{50}), and the black square represents the projection of the gravity center coordinates of the QT intervals on the X and Y axes

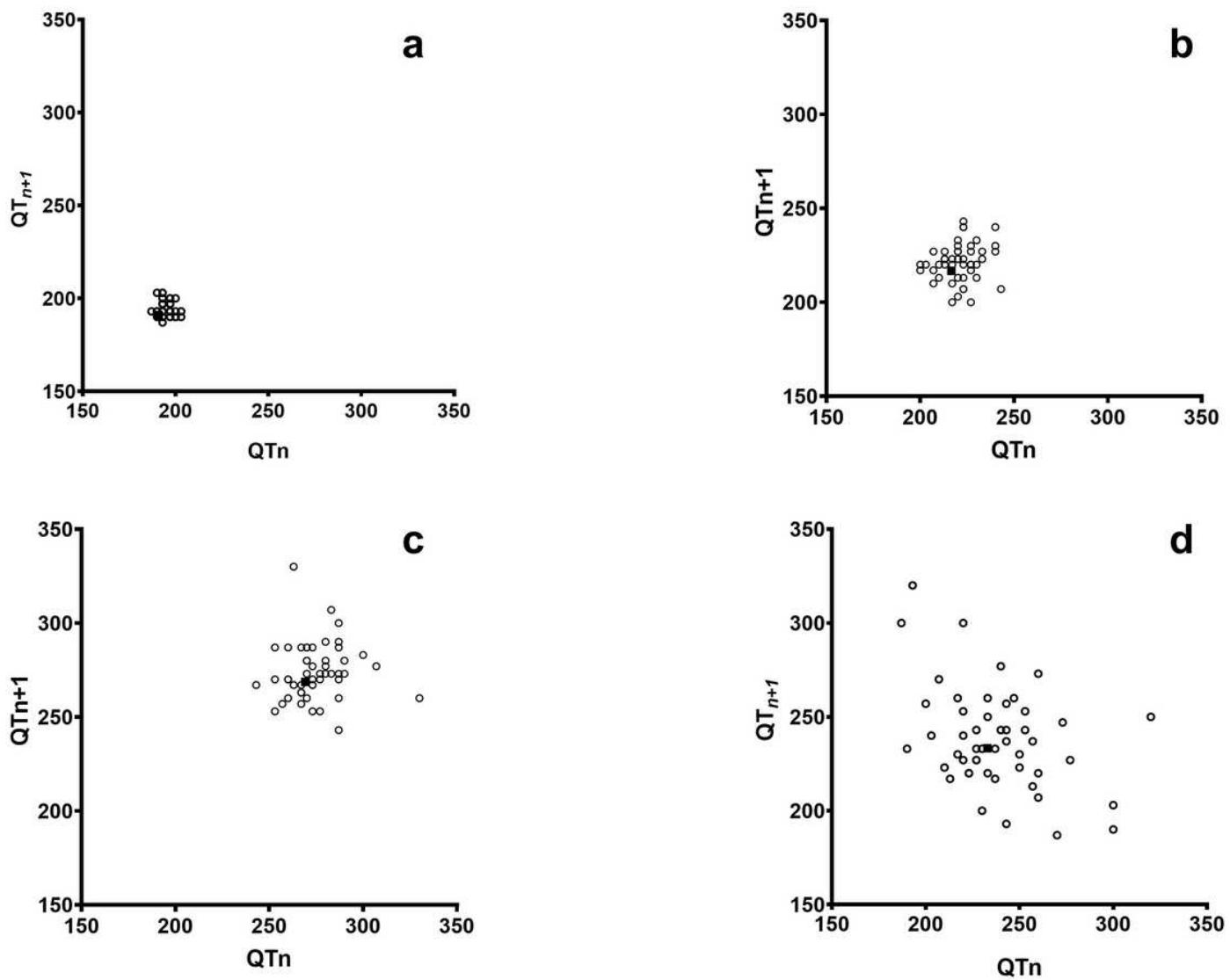


Figure 2

Poincaré plots showing the dispersion of the intersection points between QT_n (X axis) and QT_{n+1} (Y axis) in one of the healthy dogs (a), whose total calculated instability was 6.4, and in three dogs with hyperadrenocorticism, whose calculated total instability was 11.6 (b), 16.9 (c) and 25.8 (d). The black squares represent the projection of the center of gravity coordinates of the QT intervals on the X and Y axes