QT interval instability and variability in dogs with naturally-occurring hypercortisolism

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Abstract

Hypercortisolism 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 naturally-occurring hypercortisolism (NOHC), indices of variability and instability of the QT interval were retrospectively studied in 38 dogs with NOHC and prospectively studied in 12 healthy dogs: variance (QTv), total instability (TI), short-term (STI) and long-term (LTI), and mean (QTm). Except for QTm, all parameters studied were higher in the NOHC group than in the control group. In addition, STI and QTv showed moderate positive correlation with left ventricle wall thickness. The NOHC group was subdivided according to cortisol suppression pattern in the low-dose dexamethasone suppression test. All electrocardiographic indices of partial and absent suppression patterns were numerically higher than healthy dogs. QTv and TI were lower in the control group than in both NOHC subgroups. LTI and STI were lower in the CG than in the group with the partial suppression pattern. There was no statistical difference between sex groups in any of the electrocardiographic parameters studied. This result might indicate that the etiology of NOHC, 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 and the long-term stability; however further studies are necessary to understand the role of cortisol on electrical instability in dogs.

Introduction

Hypercortisolism the most common endocrine disorders in dogs, with prevalence ranging from 0.17 to 1.46% (O'Neill et al. 2016; Carotenuto et al. 2019; Schofield et al. 2021). 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).

Compared to people, veterinary literature has less information related to cardiovascular risk in dogs with NOHC. Nevertheless, cardiac disease has been reported as the main cause of death in dogs with pituitary-dependent hypercortisolism (Chen et al. 2016). Most dogs with hypercortisolism develop systemic arterial hypertension (Vidal et al. 2018; García San José et al. 2020, 2021), and are prone to present left ventricular hypertrophy (Chen et al. 2014; Takano et al. 2015), and systolic dysfunction (Chen et al. 2014). Although no association with atherosclerosis was previously reported (Hess et al. 2003), dogs with hypercortisolism are also at risk for thromboembolic disease, with a prevalence of 6.1% in that population (Hoffman et al. 2018).

In addition to functional and structural complications in the cardiovascular system secondary to hypercortisolism, 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 this condition are lacking. Nonetheless, owing to the clear evidences in people and the high incidence of NOHC in dogs, investigation of markers 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 (Hondeghem 2008b, a). 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 (Limprasutr et al. 2018).

In dogs with myxomatous mitral valve disease, 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 hypercortisolism 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 of chronic hypercortisolism on myocardial repolarization in dogs. Thus, this study aimed at evaluating QT interval indices in dogs with NOCH. 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 NOHC between January 2013 and April 2016 at a veterinary teaching facility were retrospectively analyzed. The inclusion criteria for the hypercortisolism group (HG) were the diagnosis of hypercortisolism through the low-dose dexamethasone suppression test (LDDST) (0.01 mg/kg IV) in dogs with clinical and clinicopathological signs of hypercortisolism, in addition to the presence of an electrocardiographic tracing performed within seven days of confirmation of NOHC. The LDDST in our teaching veterinary facility is performed using the following protocol: collection of the first blood sample (T0h); administration of dexamethasone (0.01 mg/kg IV); collection of the second blood sample 4h after the dexamethasone administration (T4h); collection of the third blood sample 8h after the dexamethasone administration (T8h). The blood samples are centrifuged, their serum is separated, and then subjected to cortisol measurement using the radioimmunoassay method (minimum cortisol concentration measured = 0.01 µg/dL). Due to the retrospective nature of this study, we were unable to classify the etiology of the NOHC as either pituitary-dependent hypercortisolism or adrenal tumor hypercortisolism. Not included in the study were dogs that did not have electrocardiographic tracing,

suspected of having iatrogenic hypercortisolism, that were receiving any medication with possible impact on the QT interval, or that were already receiving any treatment for NOHC at the time of electrocardiographic recording. The cortisol concentration results that were available on the medical records of the dogs of HG were included in the analyses. Those LDDST results were classified according to the five patterns of described by Bennaim and colleagues: absence of suppression (T4h and T8h > 1µg/dl and both > 50% T0h), partial suppression (T4h and T8h > 1µg/dl, but either < 50% T0h), complete suppression (T4h and T8h < 1 µg/dL), escape (T8h > 1 µg/dL and T4h < 1 µg/dL) or inverse (T4h > 1 µg/dL and T8h < 1 µg/dL) (Bennaim et al. 2018). To evaluate 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). Due to the retrospective nature of the study, the exams were performed by different veterinary cardiologists with equivalent level of training. For the control group (CG), healthy dogs from a Beagle research colony were prospectively enrolled. Only dogs without clinical characteristics compatible with NOHC or any other systemic disease were included in this group. These dogs underwent a thorough clinical examination as well as electrocardiographic evaluation. In both groups, demographic data (breed, sex, age, body weight) was recorded.

Electrocardiographic Analysis

In all animals, the electrocardiographic tracing was obtained using computer-based equipment[a]. 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 heart rate, duration of the RR interval, and 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); QTc (QT corrected for heart rate); QTv (variance of QT intervals); TI (total instability); LTI (long-term instability); and STI (short-term instability). QTc was calculated according to the formula proposed by Fridericia (Fridericia 1920):

$$\mathrm{QTc} = \frac{\mathrm{QTinterval}}{\mathrm{RRinterval}^{1/3}}$$

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:

$$\mathrm{TI}_{QT_n} = \sqrt{[(\mathrm{CG(x)} - \mathrm{QT}_n)^2 + (\mathrm{CG(y)} - \mathrm{QT}_{n+1})^2]}$$

$$\mathrm{TI} = \mathrm{Median}(\mathrm{TI}_{QT_1} \ldots \mathrm{TI}_{QT_{49}})$$

Where:

$$\text{Xaxiscenterofgravity}: \text{CG(x)} = \sum_{i=m}^{m+49} \left(\text{QT}_\text{i}\right) / 50 \right)$$

$$\text{Yaxiscenterofgravity}: \text{CG(y)} = \sum_{i=m+1}^{m+50} \left(\text{QT}_\text{i}\right) / 50 \right)$$

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

$$\text{LTI}_{QT_n} = \text{CG(x)}_{Rot} - \left[\left(\cos\theta \bullet \text{QT}_{n+1} \right) - \left(\text{sen}\theta \bullet \text{QT}_n \right) \right]$$

$$\text{LTI} = \text{Median}(\text{LTI}_{QT_1} ... \text{LTI}_{QT_{49}})$$

$$\text{STI}_{QT_n} = \text{CG(y)}_{Rot} - \left[\left(\text{sen}\theta \bullet \text{QT}_{n+1} \right) + \left(\cos\theta \bullet \text{QT}_n \right) \right]$$

$$\text{STI} = \text{Median}(\text{STI}_{QT_1} ... \text{STI}_{QT_{49}})$$

Where:

$$\text{CG(x)}_{Rot} = [\cos\theta \bullet \text{CG(x)}] - [\text{sen}\theta \bullet \text{CG (y)}]$$

$$\text{CG(y)}_{Rot} = [\text{sen}\theta \bullet \text{CG(x)}] + [\cos\theta \bullet \text{CG(y)}]$$

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. Unpaired t test or Mann-Whitney test was used to assess differences between CG and HG, depending on the results of normality test. Chi-square test was used to evaluate difference between both groups regarding sex. 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 scalling (Cornell et al. 2004):

$$IVSdN: \frac{diastolicIVS}{bodyweight^{0,241}}$$

$$LVDdN: \frac{diastolicLVD}{bodyweight^{0,294}}$$

$$LVFWdN: \frac{diastolicLVFW}{bodyweight^{0,232}}$$

$$IVSsN: \frac{systolicIVS}{bodyweight^{0,24}}$$

$$LVDsN: \frac{systolicLVD}{bodyweight^{0,315}}$$

$$LVFWsN: \frac{systolicLVFW}{bodyweight^{0,222}}$$

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 0.9 to 1 (very strong) (Schober et al. 2018).

In addition, depending on the results of normality test, Kruskal-Wallis test followed by Dunn's post hoc test or analysis of variance (ANOVA) followed by Tukey's multiple comparison test was used to check for differences between the suppression patterns in the 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 NOHC (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). HC had significantly higher weight (10.5 kg; IQR 8.8-16.1 kg; p=0.0224) and older age (11 years; IQR 10-13 years; p<0.0001), when compared to CG (8.85kg; IQR 8.6-9.25 kg; 1 year). There was no statistical difference between both groups regarding sex prevalence.

Regarding the plasma cortisol concentration in the LDDST, 23 (60.53%) dogs had the results of T0h and T8h, and 19 (50%) dogs had the results of T4h (Table 1). Among the dogs with this data available, the complete suppression pattern was observed in one dog (4.35%), the escape pattern in one dog (4.35%), the absent suppression pattern in six dogs (26.09%), and the partial suppression pattern in 12 dogs (52.17%). The three dogs that only had the T0h and the T8h results could not be classified because the absence of the T4h results hinders the differentiation between absence, partial, escape patterns in those cases.

Concentric hypertrophy was observed in 66.67% (16/24) dogs with NOHC.

Heart rate, QT mean, variability and instability indices

With the exception of QTm and heart rate, a significant difference was documented between CG and HG in all parameters studied. QTv, QTc, LTI, STI and TI were higher in HG than in CG (Table 2). There was no statistical difference of heart rate between both groups. 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).

Since the partial and the absent suppression patterns were observed in the majority of the HG, the comparison of the electrocardiographic indices was performed between those two HG subgroups and CG. All electrocardiographic indices of both partial and absent suppression patterns were numerically higher than healthy dogs. Except for QTm and QTc, there was significant difference between CG and either or both HG subgroups in all analyzes (Table 3). QTv and TI were lower in the CG than in both HG subgroups. LTI and STI were lower in the CG than in the group with the partial suppression pattern.

When comparing the results according to the sex of HG, 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 NOHC 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 NOHC compared to healthy dogs. In addition, also compared to healthy dogs, most indices derived from the QT interval were statistically higher in the partial suppression pattern in the LLDST, and QTv and TI were also higher in the absent suppression pattern.

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; Brüler 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 2008b; 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 NOHC as compared to healthy dogs (Tables 2 and 3 and Fig. 2) points to a higher risk for cardiovascular events in that population.

Higher arrhythmogenic and death risk in people with hypercortisolism 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 hypercortisolism (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 NOHC, 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 NOHC and LV hypertrophy might present greater fluctuation of the QT interval and susceptibility to cardiovascular complications.

Dogs with hypercortisolism may exhibit different patterns of suppression of hypothalamic-pituitary-adrenal axis during LDDST, depending on the etiology of the disease (Zeugswetter et al. 2021). Bennaim and colleagues described five cortisol suppression patterns in the LLDST of dogs with NOHC and well as the prevalence of NOHC etiology in each group. All dogs with adrenal tumor hypercortisolism showed absence of suppression pattern, while the dogs with pituitary-dependent hypercortisolism were distributed among five patterns: absence of suppression, partial suppression, complete suppression, escape or inverse (Bennaim et al. 2018). In our study, most electrocardiographic indices derived from QT interval (QTv, TI, LTI, and STI) were significant higher in dogs with partial suppression pattern (i.e., likely to have pituitary-dependent hypercortisolism (Bennaim et al. 2018) than in the CG (Table 3). In addition, QTv and TI were also higher in dogs with absent suppression pattern (i.e., likely to present adrenal tumor and/or

pituitary-dependent hypercortisolism (Bennaim et al. 2018) than in the CG. Although the LDDST result alone is not capable of determining the etiology of NOHC in all cases (Bennaim et al. 2018), the different results in the analyzes cited above might indicate that the etiology of hypercortisolism, and its consequent influence on hypothalamic pituitary-adrenal axis (HPAA), could interfere on the heterogeneity of ventricular repolarization parameters in different ways. Since dogs with the partial suppression pattern might present pituitary-dependent hypercortisolism, it could be hypothesized that the short-term and the long-term stability could have higher specificity and be more influenced by this etiology of NOHC. At least in people with either adrenal tumor or pituitary-dependent hypercortisolism, 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. Further studies are necessary to understand the role of NOHC 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 implies data collection carried out by different observers, and limits the acquisition of some data, such as the presence of comorbidities and the results of exams other than the LDDST. Although all the veterinary cardiologists who performed the cardiological exams had an equivalent level of training, echocardiographic measurements can be influenced by interobserver variation (Hsue and Visser 2020). 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), electrolyte disturbances (Yelamanchi et al. 2001), as well as with antiarrhythmic drugs administration (Shantsila et al. 2007). Since LDDST cannot distinguish the etiology of the NOCH in all cases (Bennaim et al. 2018), the lack of results of other exams, including adrenal or pituitary imaging impairs the classification of the NOCH and represents the major limitation of this study. This fact does not allow the differentiation between dogs with adrenal tumor hypercortisolism, pituitary-dependent hypercortisolism or both, which may significantly impair the discussion regarding the influence of the origin of the NOHC in repolarization abnormalities. 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 NOHC. Finally, since repolarization indices are influenced by age (Piccirillo et al. 2013) and obesity (Nigro et al. 2010) in people, weight and specially age differences between CG and HG could have induced a bias in the analyses comparing them.

This study demonstrated that NOHC play a role on temporal heterogeneity of the QT interval, since the QT variability and instability indices were higher in dogs with NOHC 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 NOHC are encouraged to better understand the relationship between HPAA and cardiac electrical instability.

Declarations

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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.

Footnotes

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References

Ahmad K, Dorian P (2007) Drug-induced QT prolongation and proarrhythmia: an inevitable link? Europace 9:iv16–iv22. https://doi.org/10.1093/europace/eum167

Armstrong HF, Lovasi GS, Soliman EZ, Heckbert SR, Psaty BM, Austin JHM, Krishnan JA, Hoffman EA, Johnson C, Budoff MJ, Watson KE, Barr RG (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, Chortis V, Delivanis DA, Erickson D, Natt N, Terzolo M, Arlt W, Young WFJ, Murad MH (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, Malik M, Couderc J-P, Laguna P, Piccirillo G, Smith GL, Tereshchenko LG, Volders PGA (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. Europace 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, Brandes A, Richardt G, Potratz J (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, Houtman MJC, De Boer TP, Wilders R, Beekman JD, Maessen JG, Van Der Hulst FF, Van Der Heyden MAG, Van Veen TAB, Van Rijen HVM, De Bakker JMT, Vos MA (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, Sahebzadah N, Køber L (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, Giannico AT, Sousa MG (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, Brugnoli F, Giannuzzi P, Semprini G, Tosolini P, Fracassi F (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, Agarwal V, Krishnamoorthy P, Grodzicki T, Messerli FH (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

Chen H-Y, Lien Y-H, Huang H-P (2016) Association of Renal Resistive Index, Renal Pulsatility Index, Systemic Hypertension, and Albuminuria with Survival in Dogs with Pituitary-Dependent Hyperadrenocorticism. Int J Endocrinol 2016:1–7. https://doi.org/10.1155/2016/3814034

Chen H-Y, Lien Y-H, Huang H-P (2014) Assessment of left ventricular function by two-dimensional speckle-tracking echocardiography in small breed dogs with hyperadrenocorticism. Acta Vet Scand 56:88. https://doi.org/10.1186/s13028-014-0088-5

Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, Marzullo P, Cerbone G, Siciliani M, Lombardi G (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

Cornell CC, Kittleson MD, Della Torre P, Häggström J, Lombard CW, Pedersen HD, Vollmar A, Wey A (2004) Allometric scaling of M-mode cardiac measurements in normal adult dogs. J Vet Intern Med 18:311–321. https://doi.org/10.1892/0891-6640(2004)18<311:asomcm>2.0.co;2

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, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, Pereira AM, Sørensen HT (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, Beuschlein F, Reincke M (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

Fridericia LS (1920) Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 53:469–486

García San José P, Arenas Bermejo C, Alonso-Miguel D, Clares Moral I, Cuesta-Alvaro P, Pérez Alenza MD (2021) Changes in systolic blood pressure in dogs with pituitary dependent hyperadrenocorticism during the first year of trilostane treatment. J Vet Intern Med 35:130–141. https://doi.org/10.1111/jvim.15978

García San José P, Arenas Bermejo C, Clares Moral I, Cuesta Alvaro P, Pérez Alenza MD (2020) Prevalence and risk factors associated with systemic hypertension in dogs with spontaneous hyperadrenocorticism. J Vet Intern Med 34:1768–1778. https://doi.org/10.1111/jvim.15841

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

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 and TdP. QT: an unreliable predictor of proarrhythmia. Acta Cardiol 63:1–7. https://doi.org/10.2143/AC.63.1.2025324

Hondeghem LM (2008b) QT prolongation is an unreliable predictor of ventricular arrhythmia. Heart Rhythm 5:1210–1212. https://doi.org/https://doi.org/10.1016/j.hrthm.2008.05.006

Hondeghem LM (2011) QTc prolongation as a surrogate for drug-induced arrhythmias: fact or fallacy? Acta Cardiol. 66:685–689

Hsue W, Visser LC (2020) Reproducibility of echocardiographic indices of left atrial size in dogs with subclinical myxomatous mitral valve disease. J Vet Intern Med 34:1779–1786. https://doi.org/10.1111/jvim.15850

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, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, Wu J, Hasegawa K, Mastantuono E, Dagradi F, Pedrazzini M, Yamagishi M, Berthet M, Murakami Y, Shimizu W, 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, Iliescu C, Lopez-Mattei JC (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, Micíc S, Stojanovic M, Zdravkovic M, Kostic T, Koracévic M, Kutlešic M, Pavlovic M, Dakic S (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, Kumada H, Fukuda K, Mitani S, Rousselot JF, Hirose H, Uchino T (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, Schunkert H, Bonnemeier H (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, Bilker WB, Kimmel SE, Strom BL, Hennessy S (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 Cardiolog 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, Curtis AB, Deisenhofer I, Furokawa T, Gillis AM, Haugaa KH, Lip GYH, Van Gelder I, Malik M, Poole J, Potpara T, Savelieva I, Sarkozy A, Fauchier L, Kutyifa V, Ernst S, Gandjbakhch E, 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. Europace 20:1565-1565ao. https://doi.org/10.1093/europace/euy067

Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G (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

Niemeijer MN, van den Berg ME, Deckers JW, Franco OH, Hofman A, Kors JA, Stricker BH, Rijnbeek PR, Eijgelsheim M (2015) Consistency of heart rate-QTc prolongation consistency and sudden cardiac death: The Rotterdam Study. Heart Rhythm 12:2078–2085. https://doi.org/10.1016/j.hrthm.2015.07.011

Nigro G, Russo V, Di Salvo G, De Crescenzo I, Rago A, Perrone L, Golino P, Russo MG, Calabrò R (2010) Increased Heterogenity of Ventricular Repolarization in Obese Nonhypertensive Children. Pacing Clin Electrophysiol 33:1533–1539. https://doi.org/https://doi.org/10.1111/j.1540-8159.2010.02889.x

O'Neill DG, Scudder C, Faire JM, Church DB, McGreevy PD, Thomson PC, Brodbelt DC (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, Gavallér H, Csanády M, Forster T, Papp JG, Varró A, Lengyel C, Sepp R (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, Metinidou A, De Martin M, Scacchi M, Stramba-Badiale M, Cavagnini F (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

Piccirillo G, Moscucci F, Pascucci M, Pappadà MA, D'Alessandro G, Rossi P, Quaglione R, Di Barba D, Barillà F, Magrì D (2013) Influence of aging and chronic heart failure on temporal dispersion of myocardial repolarization. Clin Interv Aging 8:293–300. https://doi.org/10.2147/CIA.S41879

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, Csík N, Farkas AS, Papp JG, Varró A, Forster T, Curtis MJ, Farkas A (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, Linz K, Jahnel U (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

Schofield I, Brodbelt DC, Niessen SJM, Church DB, Geddes RF, O'Neill DG (2021) Frequency and risk factors for naturally occurring Cushing's syndrome in dogs attending UK primary-care practices. J Small Anim Pract. https://doi.org/10.1111/jsap.13450

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. Europace 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, Lehmkuhl LB, Hamlin RL (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, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MCJM, Stricker BHC, Witteman JCM (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, Sunahara H, Aoki T, Fijii Y (2015) Left ventricular structural and functional abnormalities in dogs with hyperadrenocorticism. J Vet Cardiol 17:173–181. https://doi.org/10.1016/j.jvc.2015.07.002

Terzolo M, Allasino B, Pia A, Peraga G, Daffara F, Laino F, Ardito A, Termine A, Paccotti P, Berchialla P, Migliaretti G, Reimondo G (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 C, Heeringa J, Brusselle GG, Hofman A, Witteman JCM, Kingma JH, Sturkenboom MCJM, Stricker BHC (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, Van Deuren B, Lu HR, Van Ammel K, Peeters M, Gallacher DJ (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, Bentivoglio M, Borgioni C, Angeli F, Carluccio E, Sardone MG, Porcellati C (2003) Atrial fibrillation in hypertension: predictors and outcome. Hypertension 41:218–223. https://doi.org/10.1161/01.hyp.0000052830.02773.e4

Vidal PN, Miceli DD, Arias ES, D'Anna E, García JD, Castillo VA (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

Yelamanchi VP, Molnar J, Ranade V, Somberg JC (2001) Influence of Electrolyte Abnormalities on Interlead Variability of Ventricular Repolarization Times in 12-Lead Electrocardiography. Am J Ther 8:117–122. https://doi.org/10.1097/00045391-200103000-00006

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

Tables

Table 1. Data of cortisol plasma concentration in the LDDST of dogs with NOCH, and classification of the suppression pattern, according to Bennaim and colleagues (2018).

Dog	Cortisol T0h (µg/dL)	Cortisol T4h (µg/dL)	Cortisol T8h (µg/dL)	% T4h	% T8h	Suppression pattern
1	3.5	2.5	2.6	71.43	74.29	Absent
2	4.1	2.1	3.5	51.22	85.37	Absent
3	5.5	3.6	4.1	65.45	74.55	Absent
4	5.8	3	4.8	51.72	82.76	Absent
5	5.3	2.8	5.2	52.83	98.11	Absent
6	5.6	4.8	5.4	85.71	96.43	Absent
7	8.3	<1	<1	<12.05	<12.05	Complete
8	1.7	<1	1.3	<58.82	76.47	Escape
9	9.4	1	1.2	10.64	12.77	Partial
10	2.9	1.3	1.2	44.83	41.38	Partial
11	5	1	1.6	20.00	32.00	Partial
12	9.1	1.2	1.8	13.19	19.78	Partial
13	5.3	2.3	2	43.40	37.74	Partial
14	10.6	1.4	2.2	13.21	20.75	Partial
15	7.8	2.5	5.4	32.05	69.23	Partial
16	9.1	3.7	5.7	40.66	62.64	Partial
17	13.1	3.4	7.2	25.95	54.96	Partial
18	18.1		7.3		40.33	Partial
19	11.2	5.5	7.8	49.11	69.64	Partial
20	14.4	4.6	11	31.94	76.39	Partial
21	2.2		1.9		86.36	Unknown
22	2.1		1.9		90.48	Unknown
23	5.71		14.83		259.72	Unknown

LDDST: low-dose dexamethasone suppression test; NOHC: naturally-occurring hypercortisolism; T0h: basal plasma cortisol concentration; T4h: plasma cortisol concentration 4 hours after dexamethasone administration during LDDST; T8h: plasma cortisol concentration 8 hours after dexamethasone administration during LDDST.

Table 2 Descriptive statistics of heart rate, mean, variance and QT instability parameters in dogs with NOHC and healthy dogs.

	QTm (ms)		QTc (ms)		QTv (ms)		TI		LTI		STI	
	HG	CG	HG	CG	HG	CG	HG	CG	HG	CG	HG	CG
Minimum value	162.5	170.4	100.7	102.0	16.7	9.8	6.2	4.2	3.8	4.2	2.1	2.0
25 percentil	185.2	183.8	114.5	107.3	45.5	11.0	7.6	5.6	5.3	4.8	3.5	2.2
Median	201.0	194.5	119.6	112.5	90.5	14.6	9.7	6.5	6.7	5.5	4.7	2.4
75 percentil	214.9	197.1	128.3	117.8	156.8	31.3	13.2	7.5	9.6	5.7	6.8	2.8
Maximum value	274.4	211.5	155.9	122.0	746.6	64.8	25.8	10.0	15.3	7.0	13.8	4.9
Mean	201.9	191.6	121.8	112.3	126.3	22.9	11.1	6.6	7.7	5.4	5.3	2.6
Standard deviation	22.6	11.1	13.5	6.286	136.9	16.8	4.6	1.5	3.0	0.8	2.8	0.8
Standard error	3.7	3.2	2.5	1.8	22.5	4.8	0.7	0.4	0.5	0.2	0.5	0.2
Inferior CI 95%	194.4	184.6	115.1	107.0	80.6	12.2	9.5	5.7	6.7	4.9	4.3	2.1
Superior CI 95%	209.4	198.7	125.2	118.0	171.9	33.5	12.6	7.6	8.7	5.9	6.2	3.1
CV (%)	11.2	5.8	11.09	5.596	108.4	73.3	41.5	22.5	39.2	14.8	53.2	29.9
p	0.1738*		0.0261*		<0.0001**		<0.0001**		0.0072**		0.0002**	

NOHC: naturally-occurring hypercortisolism; QTm: mean of QT intervals; QTc: QT interval corrected for heart rate; QTv: variance of QT intervals; TI: total instability; LTI: long-term instability; STI: short-term instability; HG: hypercortisolism group; CG: control group; IC: confidence interval; CV: coefficient of variation. *: Unpaired t test; **: Mann-Whitney test

Table 3 Mean and standard deviation (median; percentil 25/75) QT interval parameters in healthy dogs and in dogs with NOCH, subdivided according to the cortisol concentration suppression pattern of in the LDDST.

	CG	HG		p
		Partial suppression pattern	Absent suppression pattern	
QTm	191.6 ± 11.1	195.6 ± 20.92	207 ± 23.24	0.2520*
	(194.5; 183.8/197.1)	(197.6; 183.4/207.4)	(200; 190.1/231)	
QTc	115.5 ± 5.6	116.4 ± 12.2	121.1 ± 8.9	0.6081**
	(116; 110.7/117.3)	(116.7; 105.4/121.8)	(120.1; 113.7/129.4)	
QTv	22.9 ± 16.8	151.8 ± 205.6	127.2 ± 96.7	0.0008**
	(14.6; 11.0/31.3)^{A}	(66.7; 41.2/201.1)^{B}	(111; 43.61/216.3)^{B}	
TI	6.6 ± 1.5	11.6 ± 5.6	11.2 ± 4.4	0.0015**
	(6.5; 5.6/7.5)^{A}	(9.5; 7.5/13.9)^{B}	(9.7; 7.5/15.2)^{B}	
LTI	5.4 ± 0.8	8.1 ± 3.6	8.7 ± 3.9	0.0376*
	(5.5; 4.8/5.7)^{A}	(6.5; 5.5/11.1)^{B}	(8.1; 5.6/11.5)^{AB}	
STI	2.6 ± 0.8	5.9 ± 3.7	4.3 ± 2	0.0104**
	(2.4; 2.2/2.8)^{A}	(4.7; 3.1/6.9)^{B}	(4.5; 2.2/5.5)^{AB}	

NOHC: naturally-occurring hypercortisolism; LDDST: low-dose dexamethasone suppression test; QTm: mean QT interval; QTc: QT interval corrected for heart rate; QTv: variance of the QT interval; TI: total instability; LTI: long-term instability; STI: short-term instability; HG: hyperadrenocorticism group; CG: control group. *: ANOVA followed by Tukey's multiple comparison test; **: Kruskal-Wallis test followed by Dunn's post hoc test. Values followed by the same letter do not differ from each other by Tukey's or Dunn's test (p>0.05).

Figures

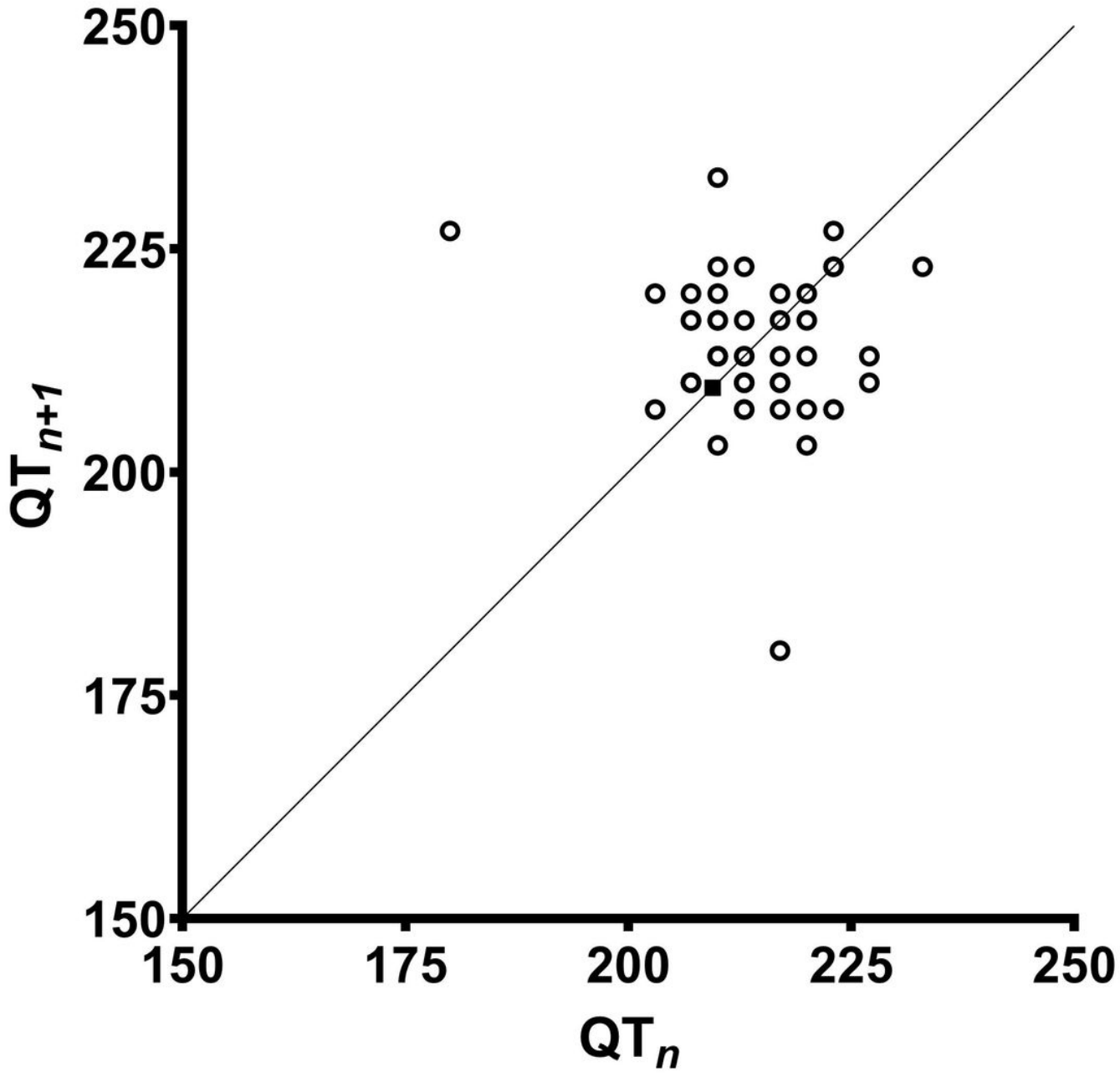

Figure 1

Poincaré plot constructed from the intersection between QTn (X axis) and QTn+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

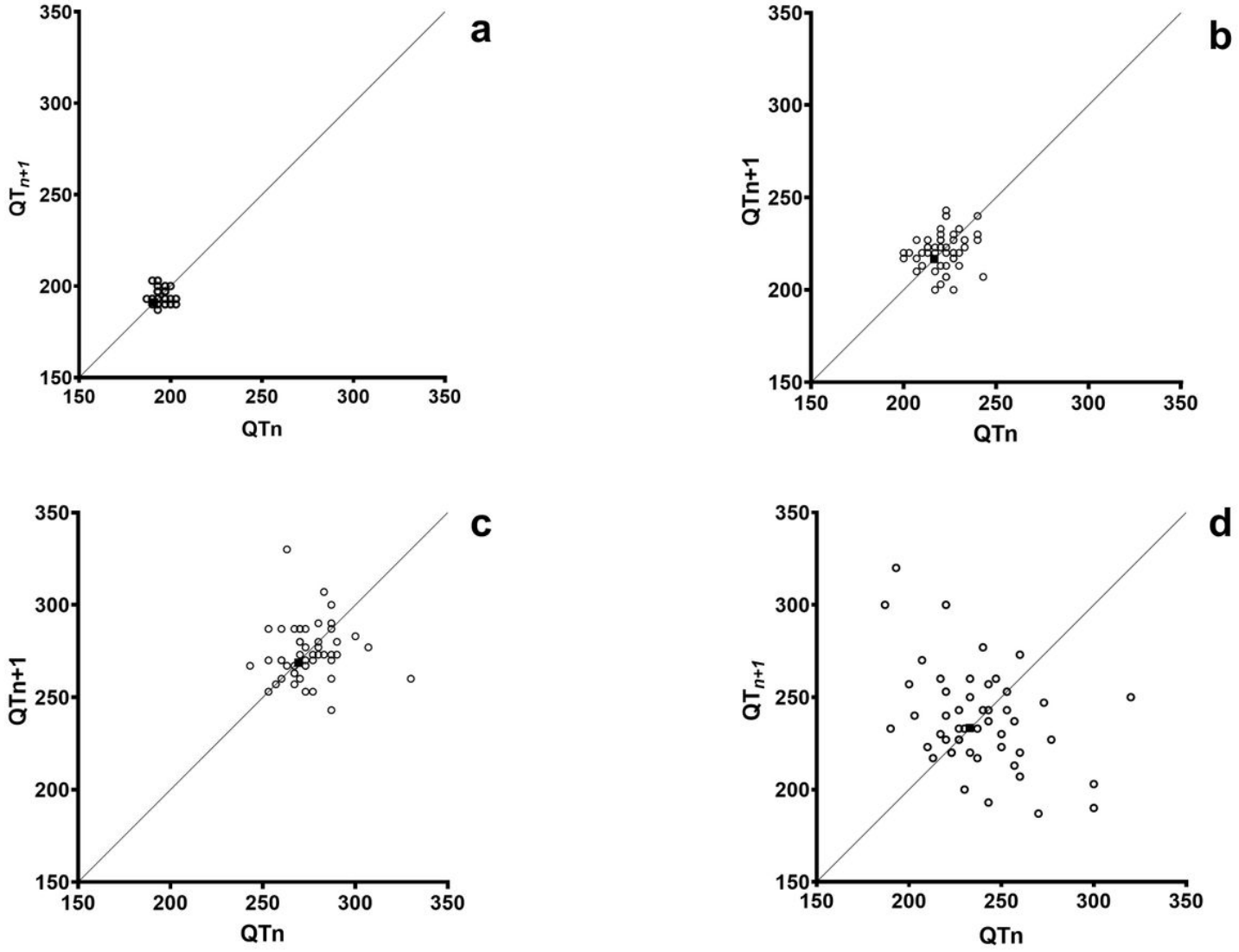

Figure 2

Poincaré plots showing the dispersion of the intersection points between QTn (X axis) and QTn+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