ISTANBUL UNIVERSITY CERRAHPASA

Frontal QRST Angle as a Marker of Arrhythmogenesis and Disease Progression in Dogs with Myxomatous Mitral Valve Disease

Bruna Cristina BRÜLER, Amália Turner GIANNICO, Marlos Gonçalves SOUSA

Department of Veterinary Medicine, Laboratory of Comparative Cardiology, Federal University of Paraná (UFPR), Paraná, Brazil

Cite this article as: Brüler, B. C., Giannico, A. T., & Sousa, M. G. (2024). Frontal QRST angle as a marker of arrhythmogenesis and disease progression in dogs with myxomatous mitral valve disease. *Acta Veterinaria Eurasia*, 50(2), 128-134.

Abstract

The objective of this study was to investigate if an increased frontal QRST angle (fQRSTa), an electrocardiographic derived index, can predict ventricular arrhythmias in dogs with myxomatous mitral valve disease, as well as to assess its role as a marker of disease progression. One hundred six dogs with myxomatous mitral valve disease and 20 control dogs underwent clinical and echocardiographic examination, along with 3-minute six-lead electrocardiographic recordings. The fQRSTa was calculated for each one of the 126 dogs. Differences between disease stages were investigated, along with possible correlations of the fQRSTa and other electrocardiographic variables associated with increased arrhythmogenesis. Interclass and intraclass correlation tests were applied to investigate repeatability. Finally, the sensitivity and specificity of fQRSTa in identifying arrhythmia predisposition and cardiac remodeling were calculated. An increase related to disease progression was documented for fQRSTa, with significant difference between groups C and B2 from control, and group C from B1. A fQRSTa >126.5 was able to discriminate B1 and control from B2 and C dogs with a sensitivity of over 79% and specificity of 60.66%. A fQRSTa >122.00 also discriminated the presence of arrhythmias from sustained sinus rhythms with a sensitivity of 88.24% and specificity of 70.00%. Finally, the index showed excellent repeatability, and positive correlations with previously reported ECG markers of arrhythmogenesis in dogs with myxomatous mitral valve disease. In conclusion, the fQRSTa is positively corelated to arrhythmogenesis and cardiac remodeling in dogs with myxomatous mitral valve disease. Dogs stages B2 and C show increased fQRSTa, which allows to infer that repolarization is affected as disease progresses.

Keywords: Arrhythmias, electrocardiography, heart disease, repolarization

Introduction

Structural heart disease is the number one cause of sudden unexpected death in dogs (Olsen & Allen, 2000). Myxomatous mitral valve disease (MMVD) is well established as the most frequent acquired cardiac disease in this species, accounting for around 75% of heart disease in documented populations (Keene et al., 2019). Although congestive heart failure is the main concern in this disease, dogs with MMVD have an increased risk of sudden cardiac death from ventricular arrhythmias (VA), and research focused on electrocardiography (ECG) and Holter recordings have documented that VAs become significantly more frequent as the disease progresses (Crosara et al., 2010).

It is assumed that unstable repolarization dynamics play a major role in the genesis of VA in dogs with structural heart disease (Barr et al., 1994; Berger et al., 1997) especially due to the increased beat-to-beat variability of repolarization secondary to cardiac remodeling (Thomsen et al., 2005). The elucidation of the electrophysiological events involved in rhythm disorders may lead to the identification of ECG markers that provide early identification of life-threatening arrhythmias, resulting in improved strategies for prevention and/or optimized clinical approach (Chen et al., 2013). Recently, our group has investigated novel ECG variables that reflect impaired repolarization, especially due to their prognostic value, along with their inexpensive, noninvasive, and quick-to-perform nature. Markers including prolongation and instability of the QT interval, as well as T-wave peak-end interval (Tpte) and the ratio of T-wave peak-end intervals and QT intervals (Tpte/QT) have all shown positive correlations with arrhythmogenesis, as well as prognostic value in dogs with MMVD (Brüler et al., 2018; Vila et al., 2021). In humans, the frontal QRST angle (fQRSTa) is a known repolarization parameter derived from vectorcardiography that reflects transmural dispersion and can play a role in arrhythmia risk stratification in a variety of clinical settings (Borleffs et al., 2009; Chua et al., 2016; Palaniswamy et al., 2009) Nonetheless, the use of fQRSTa in veterinary medicine is yet to be documented.

In this study, the authors hypothesized that MMVD dogs would exhibit an increased fQRSTa along with disease progression, making them more prone to developing VA. Therefore, the purpose of this study was to investigate possible correlations of increased fQRSTa and cardiac remodeling, and to assess the role of this variable as a marker of arrhythmogenesis in this disease.

Materials and Methods

Dogs recruited for this prospective cross-sectional observational study were selected among patients admitted for regular cardiac evaluation at a wide range of private veterinary clinics.

Corresponding Author: Bruna C. BRÜLER • **E-mail:** bbruler@gmail.com

Received: October 13, 2023 • **Revision Requested:** December 14, 2023 • **Last Revision Received:** January 26, 2024 • **Accepted:** February 8, 2024 • **Publication Date:** May 2, 2024 • DOI: 10.5152/actavet.2024.23078

Available online at actavet.org

All procedures received verbal client consent and were previously approved by the institutional Animal Use Committee, which complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

The primary inclusion criterion was the diagnosis of MMVD, based on clinical history and the echocardiographic criteria of impaired valve anatomy and function (Chetboul & Tissier, 2012). Dogs recruited were then staged as B1, B2, and C, in accordance with the ACVIM consensus guidelines for the diagnosis and treatment of MMVD (Keene et al., 2019). Dogs with echocardiographic evidence of any congenital or acquired cardiac disease other than MMVD were excluded from the study, along with patients with bundle branch block on ECG, and patients undergoing antiarrhythmic therapy. Dogs with clinical and/or laboratory evidence of debilitating systemic diseases at the time of diagnosis were also not included. Finally, healthy dogs that lacked valve disease were also gathered to be used as controls. Echocardiographic parameters such as left atrium-to-aorta ratio (LA/Ao) and normalized left ventricular internal diameter at end-diastole (nLVDd) were recorded for each dog (Cornell et al., 2004). The LA/Ao was measured in a two-dimensional short-axis view obtained from the right parasternal window and calculated using a previously described method (Hansson et al., 2002). Cardiac remodeling was defined as LA/Ao > 1.6 and nLVDd > 1.7 (Keene et al., 2019). All echocardiograms were carried out by two experienced veterinary cardiologists using an ultrasonography system (MySono U6—Samsung, Suwon, South Korea) equipped with 3.0-8.0 MHz and 2.0-4.0 MHz phased array transducers (P2-4 and P3-8 reference—Samsung, Suwon, South Korea). Also, ECG tracings were acquired for each patient using a computer-based six-lead surface ECG (InCardio®—Inpulse Animal Health Ltda., São Paulo, SP, Brazil), with the dogs placed in right lateral recumbency and maintained in position by gentle physical restraint. Alcohol was applied to the electrodes to improve electrical conduction. ECG was performed continuously and uninterrupted for 3 minutes.

The fQRSTa was calculated for each dog, which is represented by the absolute value of the difference between QRS axis and T-wave axis (Chua et al., 2016). Whenever the difference exceeded 180 degrees, the fQRSTa was calculated as 360° minus the absolute value of the difference between the frontal plane QRS axis and T axis (Borleffs et al., 2009). The calculation of the axis using the InCardio® software was semi-automatized, with the possibility of manually adjusting the reference line and wave intervals as needed. The QRS duration was defined as the interval from the start of the QRS complex until the J point. The T wave was defined as the interval from the first deflection, back to the point where it reaches the reference-line, with no future deflection (in case of biphasic morphologies). Positive, negative, and biphasic T waves were accepted. The step-by-step calculation of the fQRSTa in two canine ECGs with different T-wave morphologies are shown in Figures 1 and 2.

Also, whenever non-sinus rhythms or ectopic ventricular depolarizations occurred, they were recorded for future analyses, along with the prevailing baseline sinus rhythms. Other known electrocardiographic variables that reflect impaired repolarization such as T-wave peak-end interval (Tpte) and the ratio of T-wave peak-end intervals and QT intervals (Tpte/QT) in leads II and aVR were calculated, using a previously reported technique (Vila et al., 2021). A single investigator, who was also blinded to the patient's heart condition, was responsible for all ECG measurements. Finally, 19 out of 126 (15%) animals were randomly selected for remeasuring, and a second investigator was then recruited to determine the fQRSTa in these selected patients, to check for intra and interobserver repeatability, respectively.

For statistical purposes, the dogs were divided in accordance with the stage of MMVD (B1, B2, and C) proposed by the consensus statement of the American College of Veterinary Internal Medicine (Keene et al., 2019), which depended on clinical signs attributable to congestive heart failure, as well as the echocardiographic evidence of cardiac remodeling. Healthy dogs that lacked valvular thickening were used as controls. All data underwent the Shapiro-Wilk normality test. An analysis of variance followed by Tukey´s multiple comparison test was used to investigate differences between disease stages in the studied population. Pearson's test was used to assess whether correlations existed between fQRSTa and/or age and body weight, as well as between LA/Ao, nLVDd, Tpte (lead II), Tpte/QT (lead II), Tpte (aVR), and Tpte/QT (aVR). Interclass and intraclass correlation coefficient tests were applied to determine Cronbach's alpha and check index repeatability. Finally, receiver operating characteristic (ROC) curves were constructed to investigate the sensitivity and specificity of fQRSTa to differentiate dogs with and without previously recognized arrhythmias, and to distinguish patients with dilated hearts from those without remodeling. All analyses were performed using the software GraphPad Prism (version 9.0—San Diego, CA, USA) and Statistica (Version 10—TIBCO Software, CA, USA) using default settings. The level of significance was defined as $p < .05$.

Results

One hundred twenty-six client-owned dogs were recruited by the end of the study. Although mixed breed dogs were the majority of the studied population (24.0%), several breeds were represented, including Miniature Poodle (18.4%), Lhasa Apso (12.0%), Shih-tzu (12.8%), Maltese (9.6%), Dachshund (4.8%), Yorkshire terrier (4.8%), Miniature Schnauzer (2.4%), French Bulldog (2.4%), German Spitz (1.6%), Miniature Pinscher (1.6%), Cocker Spaniel (1.6%), Pug (0.8%), Whippet (0.8%), Bichon Frisé (0.8%), and Cotton de Tulear (0.8%). The age and body weight of the animals ranged from 1-17 years and 1.8-16 kg, respectively. Forty-two out of 126, 34/126, and 30/126 dogs were classified as stages B1 (32.8%), B2 (28.0%), and C (23.2%), respectively, along with 20/126 controls (16.0%). No difference existed between stages regarding sex ($p = .0527$) and weight ($p = .4744$), but a significant and expected age difference was documented between the controls and all the other groups ($p = .0001$). Demographic data are summarized in Table 1.

When it comes to rhythm analyses, sinus arrhythmia was the predominant background rhythm. Ten of 126 dogs (7.9%) had ventricular premature complexes (VPCs), all of which presented with a right bundle branch block morphology. Six of them (60%) were classified as ACVIM stage C patients, three (30%) were B2, and one (10%) was B1. All VPCs identified were isolated, except for one stage C dog that presented a paroxysmal ventricular tachycardia. The occurrence of supraventricular arrhythmias was also higher in stage C patients (four dogs [13.3%] with atrial fibrillations and three dogs [10%] with atrial premature complexes). One stage C patient (0.33%) had both atrial fibrillation and VPCs. Two stage B2 patients (0.58%) had atrial premature complexes and one (0.29%) had atrial fibrillation.

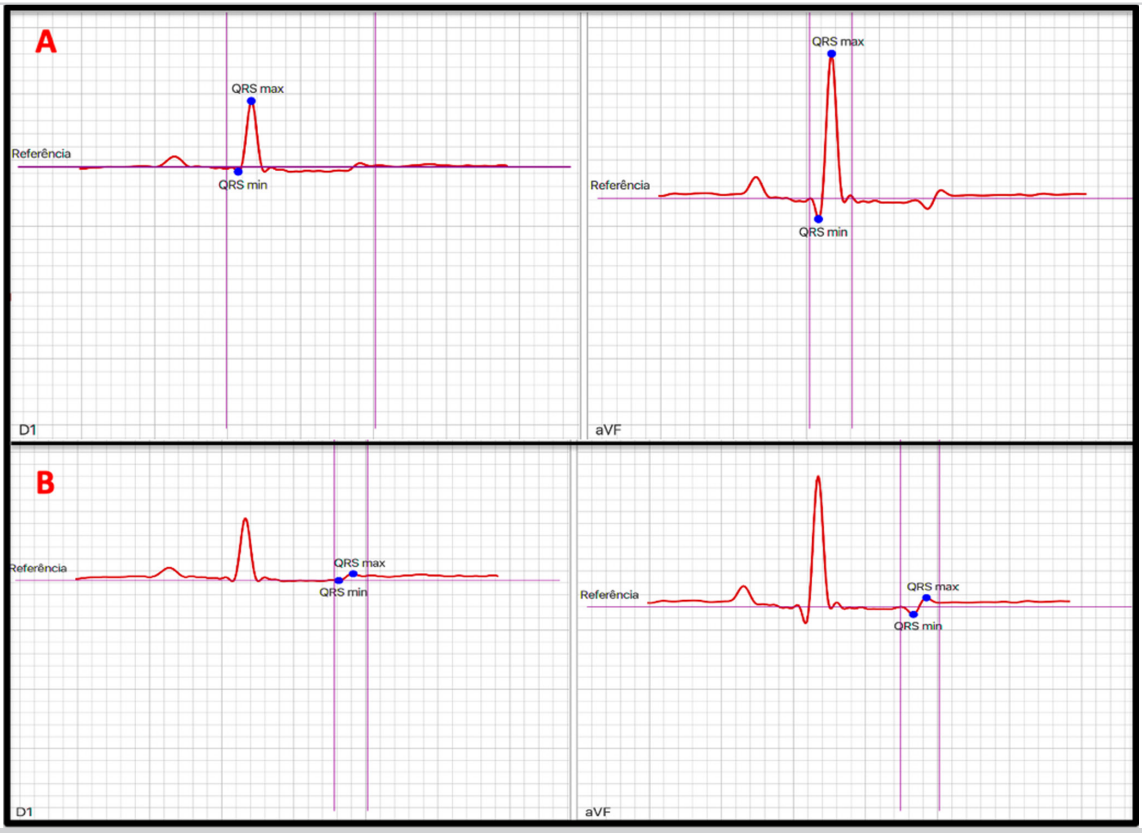

Figure 1.
The Semi-automated Method for Determining the QRS Axis and the T Wave Axis Through Leads D1 and avF, Using the Software's Tool Originally Built to Determine the QRS Axis. The T Wave Is Defined as the Interval From the First Deflection, Back to the Point Where It Reaches the Reference-Line, with No Future Deflection (in Case of Biphasic Morphologies). The Peaks Are Defined as the Time Point Where the T Wave Reaches the Maximal and Minimal Amplitudes. The frontal QRST angle (fQRSTa) Corresponds to the Absolute Value of the Difference Between the QRS Axis and T-Wave Axis, Corrected for Its Smallest Equivalent in 360°. QRS Axis in A = *67°. T Wave Axis in* B = *15°. fQRSTa = 67–15 = 52°. fQRSTa = frontal QRST angle.*

Therefore, a total of 19/126 patients (15%) were identified with arrhythmias of non-sinus origin during ECG recording, none of which was from the control group.

The fQRSTa showed a significant difference between controls and B2 and C, and also between B1 and C. No significant difference was found between groups control and B1, as well as between B1 and B2 (p = .0001). The mean values of the index for each group increased from 74.90 (control) to 149.07 (C), as shown in the box-plots in Figure 3.

Regarding correlations, fQRSTa was positively correlated with LA/Ao (ρ = .3900), Tpte(lead II) (ρ = .3411), Tpte/QT (lead II) (ρ = .3134), Tpte(avR) (ρ = .3801), and Tpte/QT (aVR) (ρ = .3811). Significant correlations are represented as Scatter Plots in Figure 4.

For repeatability assessment, the interclass and intraclass correlation coefficient test generated Cronbach's alpha of 0.987 and 0.903 for intraobserver and interobserver variability, respectively, with p = .0001

Finally, regarding ROC curves, an area under the curve (AUC) of 0.8000 was obtained when using fQRSTa to differentiate dogs with rhythm disorders from dogs in the control group with absolute sinus rhythms at the time of diagnosis. Also, to distinguish dogs with remodeled hearts from those without remodeling, an AUC of 0.6707 was documented. The corresponding curves are shown in Figure 5.

The best cut-off values to identify remodeling and rhythm disorders, with the respective sensitivity, specificity, and odds ratio values are shown in Tables 2 and 3.

Discussion

In this investigation, we sought to assess fQRSTa in dogs with MMVD to identify repolarization instabilities in the ventricular myocardium. Our results demonstrated that fQRSTa, a previously acknowledged marker of impaired repolarization in medicine, can not only identify arrhythmogenesis in MMVD dogs but also plays a role as an indicator of disease progression and cardiac remodeling.

The fQRSTa is derived from vectorcardiography, a method that is based on the identification of heart vectors through the cardiac cycle as loops. The QRS loop reflects depolarization, whereas the T loop reflects repolarization. By vectorcardiography, it is possible to measure a spatial angle between depolarization and repolarization, or, in other words, an angle between the QRS and T vector. Projection of three-dimensional spatial QRS and T vectors onto the frontal

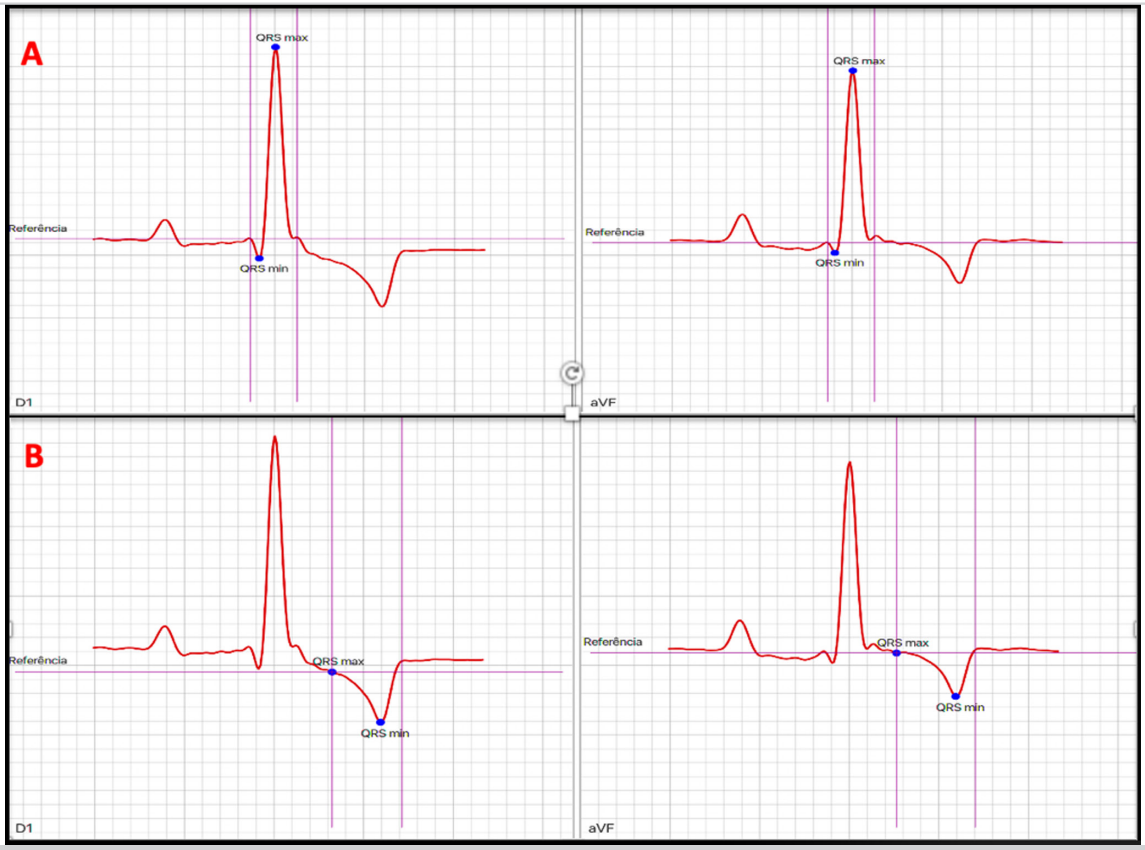

Figure 2.
The Semi-automated Method for Determining the QRS Axis and the T-Wave Axis Through Leads D1 and avF, Using the Software's Tool Originally Built to Determine the QRS Axis. The T wave Is Defined as the Interval From the First Deflection, Back to the Point Where It Reaches the Reference Line, with No Future Deflection (in Case of Biphasic Morphologies). The Peaks Are Defined as the Time Point Where the T Wave Reaches the Maximal and Minimal Amplitudes. The fQRSTa Corresponds to the Absolute Value of the Difference Between QRS Axis and T-wave Axis, Corrected for Its Smallest Equivalent in 360°. QRS Axis in A = 47°. T-wave axis in B = −135°. fQRSTa = 47 − (−135) = 182°. Correcting for the smallest equivalent in 360° → fQRSTa = 178°. fQRSTa = Frontal QRST angle.

Table 1.
Demographic Features of Healthy Control Dogs and Dogs with MMVD

	Groups										
	B1		B2		C		Control		Total		
Variables	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p***
Sex											.0527
Male	24	19.2	20	16.0	9	7.2	7	5.6	60	48.0	
Female	17	13.6	15	12.0	20	16.0	13	10.4	65	52.0	
	Mean±SD										
Age (years)	11.3 ± 3.0[A]		12.5 ± 2.3[A]		12.3 ± 1.8[A]		5.5 ± 3.0[B]		11.9±3.10		.0001
Weight (kg)	7.8 ± 4.2		7.1 ± 3.6		6.9 ± 3.5		8.5 ± 4.1		6.7±3.3		.4744

Note: Results of age and weight are presented as mean ± SD. Values followed by the same letter do not differ from each other by chi-square test ($p > .05$).

plane produces the fQRSTa (Oehler et al., 2014). An abnormally wide fQRSTa reflects impaired repolarization dynamics, and a series of studies have shown that this finding stratifies arrhythmogenic risk in a variety of medical settings (Borleffs et al., 2009; Chua et al., 2016; Palaniswamy et al., 2009). Hence, the clinical use of this resource may impact decision-making when it comes to selecting patients who would benefit from a cardioverter implantation in the general population (Güner et al., 2020).

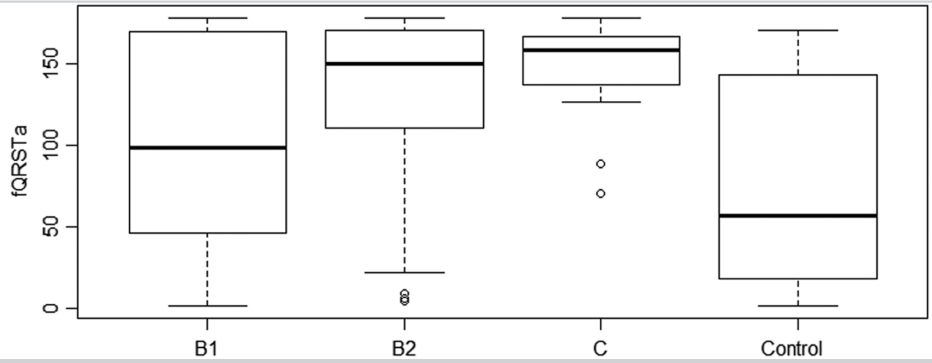

Figure 3.
Box Plots Depicting the Medians, Interquartile Ranges, and Amplitude of the fQRSTa in Dogs in Different Stages of Myxomatous Mitral Valve Disease and Healthy Control Dogs. Outliers Are Shown. fQRSTa = Frontal QRST Angle.

In MMVD dogs, although precise mechanisms are yet to be underlined, the etiology of VA seems multifactorial and includes anatomical substrate (myocardial stimulation through prolapsed leaflets and ventricular dilation) and a disrupted autonomic nervous system, similar to mitral valve prolapse in humans (Zuppiroli et al., 1994). At a cellular level, in chronic structural heart diseases, there is an increase in beat-to-beat variability in an otherwise uniform action potential duration, resulting from increased membrane instability (Haigney et al., 1998). Recent studies have shown that repolarization disorders are exposed in the ECG in the form of progressive prolongation and instability of the QT interval, as well as increases in Tpte and Tpte/QT (Brüler et al., 2018; Vila et al., 2021). These findings most likely explain the impaired repolarization dynamics involved in the generation of VA in MMVD dogs, which become significantly more prevalent with disease progression (Crosara et al., 2010).

In our study, when used to identify rhythm disorders, the fQRSTa produced an ROC curve with an AUC of 0.8000 when discriminating dogs with arrhythmias from those of the control group with absolute sinus rhythms. Dogs with fQRSTa >122.0 (sensitivity: 88.24%/specificity: 70.00%) were shown to be more prone to developing rhythm disorders. In addition, our study identified significant correlations of fQRSTa with previously documented ECG markers of VA in MMVD, such as Tpte (Vila et al., 2021). This finding strengthens the role of this variable as a marker of arrhythmogenesis in canine valvular degeneration.

Also, fQRSTa discriminated MMVD dogs with remodeled and non-remodeled hearts. A fQRSTa > 126.5 was able to discriminate B1 and control from B2 and C dogs with a sensitivity of 79.7% and specificity of 60.7%, with dogs being 4.5 times more likely to exhibit cardiac dilatation. Although echocardiography remains the gold standard

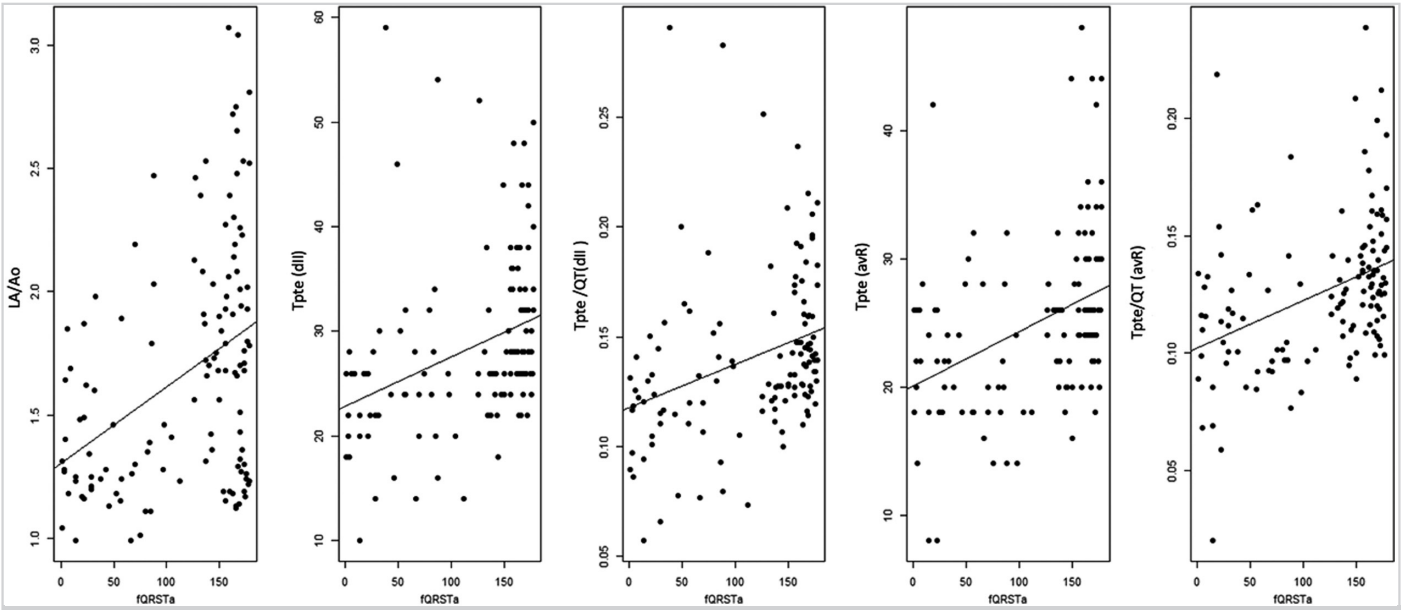

Figure 4.
Scatter-Plots Depicting Significant Positive Correlations Between fQRSTa and LA/Ao (ρ = .3900), Tpte(lead II) (ρ = .3411), Tpte/QT(lead II) (ρ = .3134), Tpte(avR) (ρ = 0.3801), Tpte/QT(avR) (ρ = 0.3811). LA/Ao Ratio of the Left Atrial to Aortic Root Diameters; Tpte: T-Wave Peak-End Interval; Tpte/QT: Ratio of Tpte and QT Intervals.

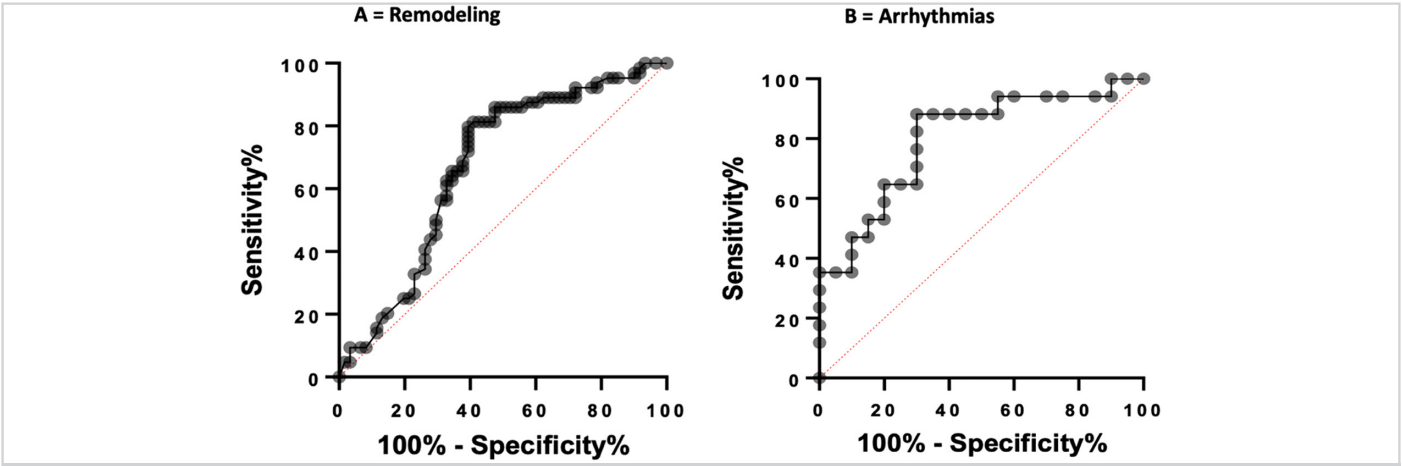

Figure 5.
Receiver Operating Characteristic Curves Constructed to Assess Sensitivity and Specificity of the fQRSTa in Differentiating Dogs with Either Remodeled (MMVD Stages B2 and C) or Non-remodeled (MMVD Stage B1 and Control) Hearts (AUC = 0.6707) and Sensitivity and Specificity of the fQRSTa in Differentiating Dogs With and Without Arrhythmias (B) (AUC = 0.8000). fQRSTa = Frontal QRST Angle; AUCs = Areas Under the Curve.

for evaluation of cardiac anatomy and function, markers of remodeling obtainable from conventional ECG tracings may aid in clinical screening when echocardiography in unavailable. Also, the identification of significant correlations of fQRSTa and LA/Ao supports the finding that the fQRSTa increases with disease progression. In severe cases of mitral valve regurgitation, volume overload leads to left atrial remodeling and increases left atrial filling pressure, which are all associated with the onset of clinical signs of heart failure (Reynolds et al., 2012). The significant correlation with LA/Ao is supportive of repolarization disorders increasing as clinical signs become overt (Haigney et al., 1998).

Table 2.
Cutoff Values, Sensitivity, Specificity, Positive Predictive Value (PPV), Accuracy, and Odds Ratio Obtained When Using the fQRSTa to Differentiate Dogs with Remodeled (MMVD Stages B2 and C) and Non-remodeled (MMVD Stage B1 and Control) Hearts

Cutoff	Sensitivity (%)	Specificity (%)	PPV	Accuracy (%)	Odds Ratio
> 21.00	95.31	18.3	92.86	20.80	1.72
> 23.00	93.75	21.31	94.12	23.20	2.19
> 126.5	79.69	60.66	96.00	48.00	4.57
> 169.5	20.31	85.25	90.29	77.60	2.07
> 170.5	18.75	86.89	90.48	79.20	2.38

Note: fQRSTa = Frontal QRST angle; PPV = Positive predictive value.

Table 3.
Cut-Off Values, Sensitivity, Specificity, Positive Predictive Value (PPV), Accuracy, and Odds Ratio Obtained When Using the fQRSTa to Differentiate Dogs with Arrhythmias From Dogs From the Control Group with Only Sinus Rhythms

Cutoff	Sensitivity (%)	Specificity (%)	PPV	Accuracy (%)	Odds Ratio
> 86.00	88.24	60.00	14.29	27.03	0.09
> 104.5	88.24	65.00	13.30	24.32	0.07
> 122.0	88.24	70.00	12.50	21.62	0.06
> 142.5	64.71	75.00	28.51	29.72	0.18
> 146.5	64.71	80.00	27.27	27.02	0.14

Note: fQRSTa = Frontal QRST angle; PPV = Positive predictive value.

It is important to note that electrolyte disturbances, especially associated with potassium and calcium disorders, may interfere with repolarization dynamics, potentially affecting the fQRSTa, regardless of primary cardiac conditions (Feldman & Ettinger, 1977). Although patients with significant hematological and biochemical findings were not recruited for this study, a thorough electrolyte panel was not available for every patient, which should be pointed out as a limitation for this study. Another important limitation involves the use of standard ECG recordings, instead of a 24-hour Holter monitoring. As we know, the paroxysmal nature of most arrhythmias may lead to false-negative diagnosis when relying on 3-minute tracings. The use of a 24-hour Holter monitoring would certainly improve identification of rhythm disorders, leading to an increase in sensitivity and specificity values. Another limitation is related to the fact that the ECG parameters in this study rely on the use of specific software, attributed to its corresponding digital ECG machine. From this point, there is no way to predict how the index will behave in equipment from different vendors. Lastly, the true prognostic potential of this index in predicting the development of arrhythmias and sudden cardiac death requires future longitudinal studies.

Conclusion and Recommendations

Although sudden cardiac death is not considered a common outcome in MMVD patients, it's surely the most devastating complication, and it is agreed that VA plays a major role (Crosara et al., 2010; Olsen & Allen, 2000). This study has shown that fQRSTa increases with progression of MMVD in dogs, and may detect increased predisposition to arrhythmia development in these patients. Values for fQRSTa of 122 and 126 performed as the most precise cutoffs to identify the presence of rhythm disorders and remodeling, respectively.

The prognostic applicability of fQRSTa in dogs with MMVD is yet to be investigated.

Ethics Committee Approval: The present study is in accordance with the precepts of Law no 11.794, of October 8, 2008, under Decree number 6.899 of July 15th 2009, and with the edited rules from Conselho Nacional de Controle da Experimentação Animal (CONCEA), and approval was granted by the Animal Use Ethics Committee of the Agricultural Sciences Campus of The Federal University of Paraná (Approval No: 094/2018, Date: December 5, 2018).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.C.B., M.G.S.; Design – B.C.B., M.G.S.; Supervision – M.G.S.; Resource – B.C.B., A.T.G.; Materials – B.C.B., A.T.G.; Data Collection and/or Processing – B.C.B., A.T.G.; Analysis and/or Interpretation – B.C.B.; Literature Search – B.C.B. Writing – B.C.B.; Critical Review – A.T.G., M.G.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

Barr, C. S., Naas, A., Freeman, M., Lang, C. C., & Struthers, A. D. (1994). QT dispersion and sudden unexpected death in chronic heart failure. *Lancet*, *343*(8893), 327–329. [CrossRef]

Berger, R. D., Kasper, E. K., Baughman, K. L., Marban, E., Calkins, H., & Tomaselli, G. F. (1997). Beat-to- beat QT interval variability. Novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. *Circulation*, *96*(5), 1557–1565. [CrossRef]

Borleffs, C. J., Scherptong, R. W., Man, S. C., van Welsenes, G. H., Bax, J. J., van Erven, L., Swenne, C. A., & Schalij, M. J. (2009). Predicting ventricular arrhythmias in patients with ischemic heart disease: Clinical application of the ECG-derived QRS-T angle. *Circulation. Arrhythmia and Electrophysiology*, *2*(5), 548–554. [CrossRef]

Brüler, B. C., Jojima, F. S., Dittrich, G., Giannico, A. T., & Sousa, M. G. (2018). QT instability, an indicator of augmented arrhythmogenesis, increases with the progression of myxomatous mitral valve disease in dogs. *Journal of Veterinary Cardiology*, *20*(4), 254–266. [CrossRef]

Chen, X., Tereshchenko, L. G., Berger, R. D., & Trayanova, N. A. (2013). Arrhythmia risk stratification based on QT interval instability: An intracardiac electrocardiogram study. *Heart Rhythm*, *10*(6), 875–880. [CrossRef]

Chetboul, V., & Tissier, R. (2012). Echocardiographic assessment of canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*, *14*(1), 127–148. [CrossRef]

Chua, K. C. M., Teodorescu, C., Reinier, K., Uy-Evanado, A., Aro, A. L., Nair, S. G., Chugh, H., Jui, J., & Chugh, S. S. (2016). Wide QRST angle on the 12-lead ECG as a predictor of sudden death beyond the LV ejection fraction. *Journal of Cardiovascular Electrophysiology*, *27*(7), 833–839. [CrossRef]

Cornell, C. C., Kittleson, M. D., Della Torre, P., Häggström, J., Lombard, C. W., Pedersen, H. D., Vollmar, A., & Wey, A. (2004). Allometric scaling of M-mode cardiac measurements in normal adult dogs. *Journal of Veterinary Internal Medicine*, *18*(3), 311–321. [CrossRef]

Crosara, S., Borgarelli, M., Perego, M., Häggström, J., La Rosa, G., Tarducci, A., & Santilli, R. A. (2010). Holter monitoring in 36 dogs with myxomatous mitral valve disease. *Australian Veterinary Journal*, *88*(10), 386–392.

Feldman, E. C., & Ettinger, S. J. (1977). Electrocardiographic changes associated with electrolyte disturbances. *Veterinary Clinics of North America*, *7*(3), 487–496. [CrossRef]

Güner, A., Kalçık, M., Çelik, M., Uzun, F., Çizgici, A. Y., Ağuş, H. Z., Aslan, S., Güner, E. G., Ulutaş, A. E., Bayam, E., & Kalkan, M. E. (2020). Impaired repolarization parameters may predict fatal ventricular arrhythmias in patients with hypertrophic cardiomyopathy (from the CILICIA Registry). *Journal of Electrocardiology*, *63*, 83–90. [CrossRef]

Haigney, M. C., Wei, S., Kääb, S., Griffiths, E., Berger, R., Tunin, R., Kass, D., Fisher, W. G., Silver, B., & Silverman, H. (1998). Loss of cardiac magnesium in experimental heart failure prolongs and destabilizes repolarization in dogs. *Journal of the American College of Cardiology*, *31*(3), 701–706. [CrossRef]

Hansson, K., Häggström, J., Kvart, C., & Lord, P. (2002). Left atrial to aortic root indices using two-dimensional and m-mode echocardiography in cavalier king charles spaniels with and without left atrial enlargement. *Veterinary Radiology and Ultrasound*, *43*(6)(6), 568–575. [CrossRef]

Keene, B. W., Atkins, C. E., Bonagura, J. D., Fox, P. R., Häggström, J., Fuentes, V. L., Oyama, M. A., Rush, J. E., Stepien, R., & Uechi, M. (2019). ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *Journal of Veterinary Internal Medicine*, *33*(3), 1127–1140. [CrossRef]

Oehler, A., Feldman, T., Henrikson, C. A., & Tereshchenko, L. G. (2014). QRS-T angle: A review. *Annals of Noninvasive Electrocardiology*, *19*(6), 534–542. [CrossRef]

Olsen, T. F., & Allen, A. L. (2000). Causes of sudden and unexpected death in dogs: a 10-year retrospective study. *The Canadian Veterinary Journal = La Revue Veterinaire Canadienne*, *41*(11), 873–875.

Palaniswamy, C., Singh, T., Aronow, W. S., Ahn, C., Kalapatapu, K., Weiss, M. B., Pucillo, A. L., & Monsen, C. E. (2009). A planar QRS-T angle> 90 degrees is associated with multivessel coronary artery disease in patients undergoing coronary angiography. *Medical Science Monitor*, *15*(12), MS31–MS34.

Reynolds, C. A., Brown, D. C., Rush, J. E., Fox, P. R., Nguyenba, T. P., Lehmkuhl, L. B., Gordon, S. G., Kellihan, H. B., Stepien, R. L., Lefbom, B. K., Meier, C. K., & Oyama, M. A. (2012). Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: The PREDICT cohort study. *Journal of Veterinary Cardiology*, *14*(1), 193–202. [CrossRef]

Thomsen, M. B., Truin, M., van Opstal, J. M., Beekman, J. D., Volders, P. G., Stengl, M., & Vos, M. A. (2005). Sudden cardiac death in dogs with remodeled hearts is associated with larger beat-to-beat variability of repolarization. *Basic Research in Cardiology*, *100*(3), 279–287. [CrossRef]

Vila, B. C. P., Camacho, A. A., & Sousa, M. G. (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. *Journal of Veterinary Cardiology*, *35*, 25–41. [CrossRef]

Zuppiroli, A., Mori, F., Favilli, S., Barchielli, A., Corti, G., Montereggi, A., & Dolara, A. (1994). Arrhythmias in mitral valve prolapse: Relation to anterior mitral leaflet thickening, clinical variables, and colour Doppler echocardiographic parameters. *American Heart Journal*, *128*(5), 919–927. [CrossRef]