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R-peak time in different clinical stages of canine myxomatous mitral valve disease

Tempo para pico da onda R (R-peak time) em diferentes estágios da doença mixomatosa da valva mitral canina

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ABSTRACT: Myxomatous mitral valve disease (MMVD) is highly prevalent in dogs. An accurate diagnosis and staging are crucial for effective treatment. While echocardiography is the gold standard for diagnosis, it is operator-dependent and its availability is limited. Conversely, electrocardiography (ECG) is a low-cost widely accessible technology, and variables such as R-peak time (RPT) have been underexplored in MMVD. This study investigated RPT in dogs with MMVD, correlations with disease stages and echocardiographic measures, and its diagnostic performance. Records of 81 dogs were analyzed. RPT differed between stages (A vs. C and D; B1 vs. C and D; B2 vs. C and D), showing a positive correlation with disease stage (ρ=0.830) and cardiac dimensions (LVEDdn - ρ=0.719; LA/Ao - ρ=0.760). The optimal RPT cut-off points and ROC curve AUCs to differentiate dogs with and without MMVD were: 29ms; Youden's index - 0.739; AUC - 0.892, and to distinguish between the treatment-beneficial group (B2, C, and D) and the healthy/non-beneficial group (A and B1) - 30ms; Youden's index - 0.850; AUC - 0.935. Although RPT is not suggested as a replacement for echocardiography, the preliminary results indicate its potential use for MMVD screening, especially where echocardiography is unavailable. Prospective studies with larger samples are needed to further investigate these findings and explore additional factors influencing RPT.

KEYWORDS: electrocardiography; intrinsicoid deflection; dog.

RESUMO: A degeneração mixomatosa da valva mitral (DMVM) é altamente prevalente em cães. O diagnóstico e estadiamento são cruciais para o tratamento. A ecocardiografia é o diagnóstico padrão-ouro, porém, o exame é operador-dependente e tem disponibilidade limitada. Por outro lado, o eletrocardiograma (ECG) é uma tecnologia de baixo custo e amplamente disponível e variáveis como o tempo para o pico da onda R (RPT) têm sido pouco investigadas na DMVM. Este estudo investigou o RPT em cães com DMVM, sua correlação com estágios da doença e medidas ecocardiográficas e seu desempenho diagnóstico. Registros de 81 cães foram analisados. O RPT diferiu entre os estágios (A *vs.* C e D; B1 *vs.* C e D; B2 *vs.* C e D), mostrando uma correlação positiva com o estágio da doença (ρ=0,830) e dimensões cardíacas (LVEDdn - ρ=0,719; LA/Ao - ρ=0,760). Pontos de corte ótimos do RPT e AUC da curva ROC para diferenciar cães com e sem DMVM foram: 29ms; índice de Youden - 0,739; AUC - 0,892), e para distinguir entre o grupo que se beneficia do tratamento (B2, C e D) e grupo saudável/não beneficiado (A e B1) - 30ms; índice de Youden - 0,850; AUC - 0,935. Embora não indiquem o RPT como um substituto da ecocardiografia, os resultados preliminares sugerem um potencial na triagem do diagnóstico da DMVM, especialmente na indisponibilidade da ecocardiografia. Estudos prospectivos e com amostras maiores são necessários para investigar esses achados e explorar fatores adicionais que influenciam o RPT.

PALAVRAS-CHAVE: eletrocardiografia; deflexão intrinsecoide; cão.

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INTRODUCTION

Myxomatous mitral valve disease (MMVD) is a highly prevalent heart condition affecting dogs (Keene *et al.*, 2019). Progressive and chronic derangement of mitral valve apparatus causes blood backflow from the left ventricle (LV) to the left atrium (LA), leading to congestive heart failure (CHF) (Boswood *et al.*, 2016; Keene *et al.*, 2019; O'Brien; Beijerink; Wade, 2021). Early diagnosis allows the clinician to classify the patient according to the ACVIM (American College of Veterinary Internal Medicine) consensus (Keene *et al.*, 2019) and to start the treatment when recommended. Correct treatment may prolong the preclinical disease period, improving the patient's quality of life (Boswood *et al.*, 2016).

Currently, the gold standard in MMVD diagnosis is echocardiography (Keene *et al.*, 2019). This test aids identification of mitral valve insufficiency and cardiac remodeling, particularly the atrial and ventricular dimensions and left atrium to aorta ratio (LA/Ao). Notwithstanding, echocardiographic measurements may also have prognostic value, helping to predict mortality in MMVD (Sargent *et al.*, 2015).

Despite the undisputable fact that echocardiography is the gold standard, it presents important practical limitations. First, it is not an ubiquitously available exam and even when available, it is not a cheap exam. Second, it is an operator dependent exam, requiring long training and very careful image collection and analysis – features that may not be attainable in situations such as stressed or even fractious patients.

Electrocardiography (ECG) is a non-invasive, easily reproducible, and low-cost exam that is often used in human medicine and telemedicine as a preliminary method for heart disease detection (Liu *et al.*, 2023). Specific ECG measurements have been investigated as indirect signs of LV hypertrophy or overload (Veiga; Santos; Sousa, 2019; Liu *et al.*, 2023). CHF from MMVD may promote LV hypertrophy (Keene *et al.*, 2019), leading to ECG signs of disease. R-peak time (RPT), also named intrinsicoid deflection, defined as the time between QRS onset and the peak of the R wave (Romhilt; Estes; Durham, 1968; Veiga; Santos; Sousa, 2019), represents the time from electrical activation to spread from the endocardium to epicardium. Few studies have investigated RPT in dogs (Mateos Pañero *et al.*, 2021; Battaia *et al.*, 2022) and only one (Veiga; Santos; Sousa, 2019) addressed its use in MMVD diagnosis, showing preliminary but promising results.

Thus, the current study aimed to describe RPT distribution in a population of dogs with diagnosed MMVD. In addition, we investigated the correlations of RPT with MMVD stage and LV end-diastolic diameter and its performance as a stage predictor.

MATERIAL AND METHODS

This study collected data from medical records between January and September 2023 from a private cardiology service in Cachoeira Paulista, SP, Brazil. Authorization was received from the Animal Ethics Committee of the Universidade de Vassouras (003/2023 and 0018/2024). Effect size was calculated in GPower 3.1.9.7®, based on previously published data (Veiga; Santos; Souza, 2019), by inputting the number of individuals and means of each group (A, B1, B2, C, and D), and adopting a conservative standard deviation of 8ms, returning an effect size of 0.457 for the mean difference between groups. The sample size was then calculated for a one-way ANOVA fixed effects (f=0.457; α=0.05, and power = 0.8), giving a number of 70 dogs (14 in each group). A loss of 10% in each group was estimated, so the total number of dogs was defined as a minimum of 15 in each group.

All dogs included in the study were examined by the same veterinarian (R.B.S.S) and received an MMVD diagnosis and staging according to the ACVIM consensus, based on clinical and echocardiographic data (Keene *et al.*, 2019). Data were collected on age, sex, breed, weight, and MMVD stage (A, B1, B2, C, and D). Echocardiographic measurements (LA/Ao, LV end diastolic diameter normalized by weight – LVEDdn, calculated as LVIDd (cm)/weight (kg)$^{0.294}$, SF% – shortening fraction, and EM/IVRT – E mitral wave velocity/isovolumetric relaxation time) were all performed by the same veterinarian (R.B.S.S) using the same equipment (Infinity X lite – Ultramedic) and according to recommended guidelines (Keene *et al.*, 2019). All ECG exams were collected by the same veterinarian (R.B.S.S) with the same equipment (InCardio Duo 2.9.0 - InPulse – Animal Health) in right lateral recumbence. Parameters were measured by the same experienced (F.S.F) veterinarian, blinded to any patient data (exams were randomized and anonymized). RPT values were measured in lead D2 throughout five QRS complexes in sequence, from QRS onset to the peak of the R wave and the mean value was used.

Statistics were performed in Jamovi v2.4.11. Graphics for RPT and echocardiographic measurements were made in GraphPad Prism v.9. Normally distributed data (tested by Shapiro-Wilk) are presented as mean ± standard deviation (SD) and nonparametric data as median (interquartile range, IQR) and minimum-maximum. Homogeneity of variances were tested by the Levene's test. Comparisons of age and shortening fraction (SF%) between groups were performed using one-way ANOVA with Tukey *post-hoc* and Em/IVRT using one-way ANOVA with Welch's correction and Games-Howell *post-hoc*. Comparisons between sexes for all groups were performed by the binomial test, with a difference of 50% for both groups. RPT, LA/Ao, and LVEDdn were compared between groups using Kruskal-Wallis with Dwass-Steel-Crtichlow-Fligner pairwise comparisons (α=0.05 for all tests). Correlations were performed by Spearman's correlation (nonparametric data). Receiver operating characteristic (ROC) curves were investigated for establishing RPT cut-points to differentiate stage A from B1, B2, C, and D (i.e., diagnosed

MMVD) and to differentiate stages A and B1 (grouped) from B2, C, and D (i.e., dogs that would benefit from treatment according to the ACVIM consensus statement (Keene *et al.*, 2019). Youden's index was calculated by the formula: 1 – (sensitivity + specificity).

RESULTS

A total of 81 dogs were included, from 11 breeds, ranging from 1 and 17 years of age, and with a median weight of 5.8 (IQR 4.0) kg. A difference in age was observed between groups (p=0.001), but restricted to group A *vs.* B1, B2, C, and D (p<0.01 for all comparisons). There was no statistically significant difference between males and females in any populations (p=0.824) or among the stages. The most prevalent breeds with MMVD (stages B1, B2, C, and D) were Poodle (29.6%), Shih Tzu (13.6%), mongrel dogs (12.3%), and Pinscher and Spitz (6.2% each). Table 1 summarizes the demographic information of the study.

The echocardiographic data showed an effect of MMVD stage on the LA/Ao ratio (p<0.001; ε^2=0.765), with the *post-hoc* revealing differences between A *vs.* B2, C, and D; B1 *vs.* B2, C, and D; B2 *vs.* D; and C *vs.* D (p<0.05 for all pairwise comparisons). The LVEDdn was also affected by stages (p<0.001; ε^2=0.654), with the *post-hoc* revealing differences between A *vs.* C and D; B1 *vs.* C and D; and C *vs.* D (p<0.05 for all pairwise comparisons). The SF% also differed between stages (p=0.007) with the *post-hoc* revealing differences between B1 *vs.* C and D (respectively, p=0.049 and p=0.036). MMVD stage also had an effect on Em/IVRT (p<0.001), revealing differences between A *vs.* C and D; B1 *vs.* C and D; B2 *vs.* D; and C *vs.* D (p<0.05 for all comparisons). Table 2 and figure 1 summarize the aforementioned findings.

All groups presented non-normal distribution of RPT. Groups A, B1, and B2 showed a negatively skewed distribution, while groups C and D showed a positive skew. As shown in table 3, RPT was different among groups (p<0.001; ε^2=0.725). Pairwise comparisons revealed significant differences between: A *vs.* C and D; B1 *vs.* C and D; B2 *vs.* C and D (p<0.05 for all results). Figure 2 summarizes the RPT distributions.

Table 1. Study's population characteristics. Source: made by the authors.

MMVD stage	*n*	*Sex*	*Age (years)*		*Weight (kg)*	
			Mean (±SD)	*Min - Max*	*Mean (±SD)*	*Min - Max*
A	16	F – 8 (50%) M – 8 (50%)	7.48±3.96*1,2,3,4	1-16	5.07±2.36	2.3-9.7
B1	20	F - 12 (60%) M – 8 (40%)	11.15±1.9*1	8-15	6.78±2.24	3.8-12.2
B2	6	F - 5 (83.3%) M – 1 (16.7%)	12±1.79*2	10-14	6.15±2.02	4-9.5
C	24	F - 12 (50%) M – 12 (50%)	13.08±2.67*3	7-17	6.52±3.18	2-13.3
D	15	F - 5 (33,3%) M – 10 (66,7%)	11.13±3.31*4	4-17	5.94±3.09	2.8-12.5

Breeds and MMVD prevalence

Chihuahua (B1 – 2.5%); Dachshund (C – 2.5%; D – 1.2%); Fox Paulistinha (C – 2.5%); Jack Russel Terrier (B2 – 1.2%); Lhasa Apso (B1 – 2.5%); Maltese (A – 1.2%); *Mongrel* (A – 1.2%; B1 – 1.2%; B2 – 1.2%; C – 6.2%; D – 3.7%); Pinscher (A – 1.2%; B1 – 1.2%); *Poodle* (A – 4.9%; B1 – 8.6%; B2 – 3.7%; C – 12.3%; D – 6.2%); Shih Tzu (A – 3.7%; B1 – 7.4%; B2 – 1.2%; C1.2%; D – 3.7%); Spitz *(A – 3.7%; D – 1.2%);* Yorkshire (A – 3.7%; B1 – 1.2%; C – 1.2%; D – 1.2%)

*F – female; M – male; Min – minimum; Max – maximum; MMVD – myxomatous mitral valve disease; SD – standard deviation. * - statistically significant difference (p<0.05).*

Table 2. Echocardiographic measurements (mean±SD) of 81 dogs in different stages of myxomatous mitral valve disease (MMVD). Source: made by the authors.

MMVD stage	*n*	*LA/Ao*	*LVEDdn*	*Em/IVRT*	*SF%*
A	16	1.32±0.16*1,2,3	1.32±0.15ψ1,2	1.39±0.51 Φ1,2	43.10±7.19
B1	20	1.39±0.15*4,5,6	1.33±0.17 ψ3,4	1.18±0.36 Φ3,4	42.94±6.11 λ1,2
B2	6	1.67±0.04*1,4,7	1.68±0.36	1.90±0.72 Φ5	45.95±7.28
C	24	1.93±0.32*2,5,8	1.73±0.24 ψ1,3,5	2.22±1.00 Φ1,3,6	49.18±8.21 λ1
D	15	2.36±0.48*3,6,7,8	2.09±0.30† ψ2,4,5	3.62±0.99 Φ2,4,5,6	50.27±7.59 λ2

LA/Ao – left atrium to aorta size ration; LVEDdn – left ventricle end diastolic diameter normalized by weight$^{0.294}$; EM/IVRT – E mitral wave velocity/isovolumetric relaxation time; SF – shortening fraction; † - non-normally distributed (median 2.01, IQR 0.23); *, ψ,Φ, λ - p<0.05 for *post-hoc* comparison in the same column.

The RPT showed a very strong positive correlation with MMVD stage (ρ=0.830), LVEDdn (ρ=0.719), and LA/Ao (ρ=0.760). There was only a moderate correlation between RPT and age (ρ=0.379) and age and MMVD stage (ρ=0.376) p<0.001 for all.

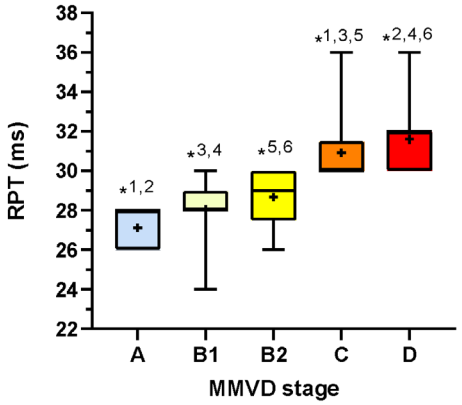
Table 4 presents the sensitivity and specificity for different RPT cut-points when aiming to differentiate stage A patients (without MMVD) from B1, B2, C, and D (with MMVD). The highest Youden's index was achieved with a RPT cut-point of 29 ms, yielding a sensitivity of 73.85% and a specificity of 100%.

To differentiate patients in stages A and B1 (patients at risk or with mild disease, that don't need medication) from patients in groups B2, C, and D (patients that would benefit from medication, according to the ACVIM consensus), a RPT cut-point of 30 ms yielded the highest Youden's index (0.850), with a 93.33% sensitivity and 91.67% specificity, as shown in table 5.

The area under the curve (AUC) for the RPT ROC curve was 0.892 (differentiating A *vs*. B1, B2, C, and D, grouped) and 0.935 (differentiating A and B1 *vs*. B2, C, and D). Figure 3 presents the ROC curves for the RPT diagnostic performance in both cases.

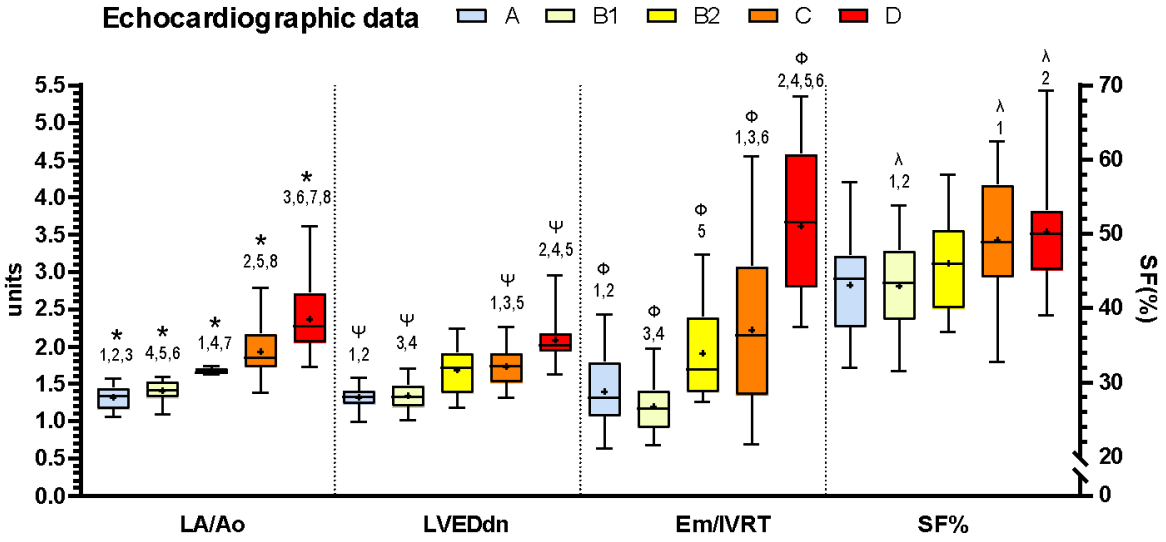
DISCUSSION

The current study investigated 81dogs with a wide age range (from 1 to 17 years). The only difference in age was found when comparing stage A with other stages. There were no age differences between the groups with MMVD, and small dogs were overrepresented in the study (median weight of 5.8



Boxplot representation of R-peak time (RPT) in different myxomatous mitral valve disease (MMVD) groups. * - p<0.05 for *post-hoc* comparison between groups.

Figure 2. R-peak time (RPT) in different myxomatous mitral valve disease (MMVD) stages. Source: compiled by the authors.



Boxplot representation of echocardiographic measurements in MMVD stages. LA/Ao – left atrium to aorta size ratio; LVEDdn – left ventricle end diastolic diameter normalized by weight$^{0.294}$; EM/IVRT – E mitral wave velocity/isovolumic relaxation time; SF – shortening fraction (right Y axis); † - non-normally distributed (median 2.01, IQR 0.23); *, ψ,Φ, λ - p<0.05 for *post-hoc* comparison for each parameter between MMVD stages.

Figure 1. Echocardiographic measurements in different myxomatous mitral valve disease (MMVD) stages. Source: compiled by the authors.

Table 3. RPT in different myxomatous mitral valve disease (MMVD) stages. Source: compiled by the authors.

MMVD stage	*n*	*Median (IQR) ms*	*Min – Max (ms)*	*Skewness*
A*1, *2	16	28 (2)	26 – 28	-0.279
B1*3, *4	20	28 (1)	24 – 30	-1.172
B2*5, *6	6	29 (2)	26 - 30	-0.857
C*1, *3, *5	24	30 (0.5)	30 – 36	1.787
D*2, *4, *6	15	32 (2)	30 - 36	1.403

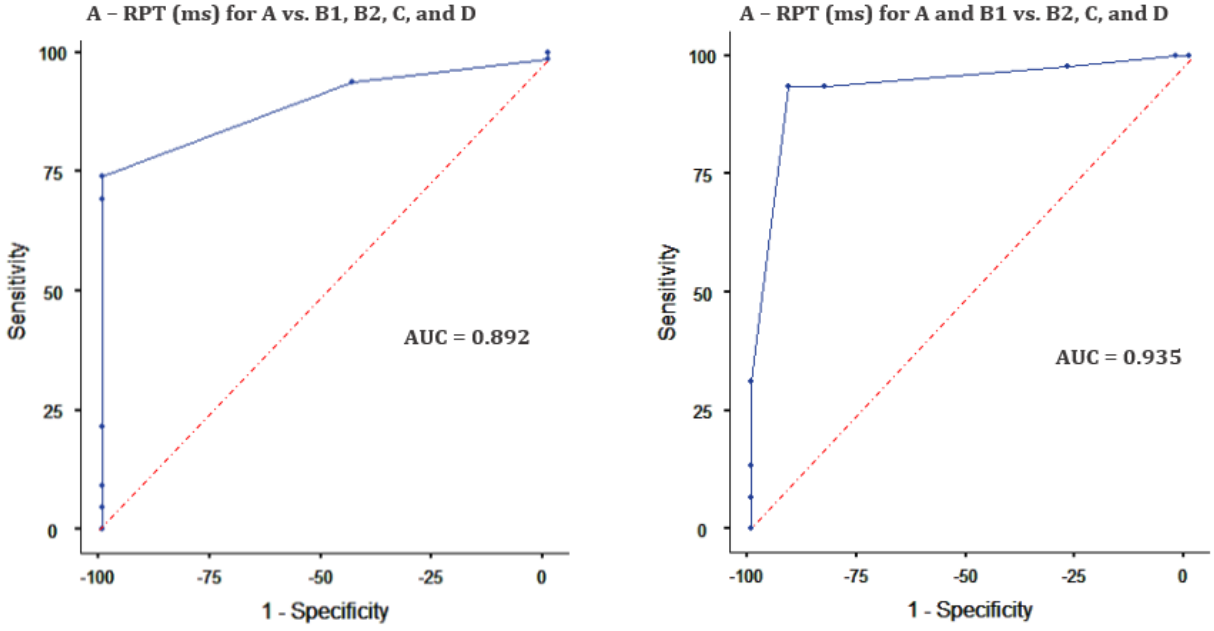
kg, positively skewed distribution, with 29.6% of Poodles). These results agree with the description that this is a chronic age-related disease and has a higher prevalence in small breed dogs (Borgarelli; Buchanan, 2012; Sargent *et al.*, 2015; Keene *et al.*, 2019). Despite the documented higher prevalence in males, there was no overall sex difference; group B2 included

Table 4. RPT cut-points for differentiating dogs with (B1, B2, C, and D) and without (A) myxomatous mitral valve disease (MMVD). Source: compiled by the authors.

RPT cutpoint (ms)	*Sensitivity (%)*	*Specificity (%)*	*PPV / NPV (%)*	*Youden's index*
24	100%	0%	80.25% / -	0
26	98.46%	0%	80% - 0%	-0.015
28	93.85%	43.75%	87.14% - 63.64%	0.376
29	73.85%	100%	100% - 48.48%	0.739
30	69.23%	100%	100% - 44.44%	0.692
32	21.54%	100%	100% - 23.88%	0.215
34	9.23%	100%	100% - 21.33%	0.092
36	4.62%	100%	100% - 20.51%	0.046

Table 5. RPT cutpoints for differentiating dogs in stages A and B1 of myxomatous mitral valve disease (MMVD) from dogs in stages B2, C, and D. Source: made by the authors.

RPT cutpoint (ms)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%) / NPV(%)*	*Youden's index*
24	100%	0%	55.56% / -	0
26	100%	2.78%	56.25% / 100%	0.028
28	97.78%	27.78%	62.86% / 90.91%	0.256
29	93.33%	83.33%	87.5% / 90.91%	0.767
30	93.33%	91.67%	93.33% / 91.67%	0.850
32	31.11%	100%	100% / 53.73%	0.311
34	13.33%	100%	100% / 48%	0.133
36	6.67%	100%	100% / 46.15%	0.067



Curve A for RPT to differentiate dogs with (stages B1, B2, C, and D) and without (stage A) MMVD. Curve B for RPT to differentiate patients in stages A and B from patients in stages B1, C, and D.

Figure 3. Receiver operating characteristic (ROC) curves for RPT for myxomatous mitral valve disease (MMVD) stage identification. Source: compiled by the authors.

more females, but this was probably due to the small sample size obtained.

The MMVD stage effect on echocardiographic data (mainly on LA/Ao and LVEDdn) was not surprising, insofar as MMVD staging is largely based on these parameters, as recommended by the ACVIM consensus (Keene *et al.*, 2019). Figure 1 shows a clear upward tendency of LA/Ao, LVEDdn, and Em/IVRT throughout the progressive MMVD stages.

The RPT distribution was different throughout MMVD stages (negatively skewed in A, B1, and B2 and positively skewed in C and D). The non-normal distribution of RPT in lead D2 agrees with the results found in a study that investigated RPT in 60 dogs with different thoracic conformations (Mateos Pañero *et al.*, 2021), although it is different from another study that reported normally distributed RPT values in 45 dogs with MMVD (Veiga; Santos; Souza, 2019). Larger samples are needed in order to investigate the true population distribution of this parameter in MMVD dogs.

Herein, we found consistently lower RPT values (in ms) than those reported in the only other study investigating RPT in MMVD (control – 36.7±2.9; B1 - 34.6±4.7; B2 -36±4.2; C – 42.9±6.8; and D - 39±5.5) (Veiga; Santos; Souza, 2019). Researchers found a stage effect in RPT, with *post-hoc* analysis showing differences between B1 and C and B2 and C. Our study found further differences (A *vs*. C and D; B1 *vs*. C and D; B2 *vs*. C and D). Importantly, there was an overlap in RPT values between classes (except for A, with a maximum value of 28ms, compared to C and D, in both cases the minimum value was 30ms). Despite the necessity of analyzing this variable with a nonparametric test, we also found a strong positive correlation between RPT and: MMVD stage (ρ=0.830), LVEDdn (ρ=0.719), and LA/Ao (ρ=0.760), highlighting that RPT may become wider as MMVD, and its characteristic cardiac remodeling, progresses. The differences found here are important to support the investigation of RPT as a screening tool in MMVD and will be further discussed below.

Two analyses were performed to investigate RPT performance in MMVD diagnosis and staging. First, RPT cut-points were tested for differentiating dogs with (B1, B2, C, and D) and without MMVD (stage A). The AUC for the ROC curve was 0.892 and the best combination of sensitivity - 73.85%, and specificity – 100% (represented as a high Youden's index – 0.739) was for an RPT of 29ms in D2. In table 4, it can be highlighted that when setting the cut-point at 30ms, there was only a low drop in sensitivity, but when the next value was tested (32ms), it fell to 21.54%, suggesting that this could lead to a high number of false negatives.

The second analysis performed was aimed at differentiating patients that would benefit from treatment (B2, C, and D) from those that would not, based on the ACVIM consensus (Keene *et al.*, 2019). In this case, RPT performance improved, yielding an AUC for the ROC curve of 0.935 and with an optimal cut-point of 30ms (93.33% sensitivity, 91.67% specificity, and 0.850 Youden's index).

To our knowledge, this is the first study to investigate RPT performance in MMVD staging. However, this study is not sufficient to set RPT cut-points for diagnosing and staging canine MMVD, or to recommend it as a disease progression marker. The main finding here is that, if further investigated in larger and prospective studies, it may be possible in the future to use RPT, together with clinical signs, as a practical screening tool in MMVD diagnosis and staging.

The current study presents some important limitations. First, the minimum sample size for one group (B2) was not achieved, leading to an underpowered sample and making it necessary to perform a nonparametric analysis of the main outcome. Second, we chose to investigate RPT solely in the D2 lead as this is the most commonly used lead in ECG analysis and because precordial leads are not always performed by some veterinarians. Furthermore, we investigated only this lead with a robust blind analysis (mean between five QRS complexes). Third, it is noteworthy that a wide range of RPT values in D2 was demonstrated in dogs with different thoracic conformations (Mateos Pañero *et al.*, 2021) and this aspect was not investigated here, suggesting that the thoracic index could be used in future studies as a covariate to improve the predictive value of RPT modeling.

Despite having been described a long time ago – 1915 - in dog hearts (Lewis; Rothschild; Starling, 1915), RPT is still an unexplored terrain in veterinary cardiology and, more specifically, in MMVD. Future studies should aim to describe RPT distribution in larger populations, and different ECG leads. Notwithstanding, insofar as echocardiography presents some major practical limitations, studies could focus not on naively trying to substitute echocardiography, but instead on finding a low-cost screening tool for diagnosing and staging MMVD. The diagnostic performance of this measure could be improved when used together with clinical or radiographic data (such as the presence and intensity of heart murmurs and vertebral heart scale scoring, for example).

CONCLUSIONS

RPT differed among MMVD stages, demonstrating a strong positive correlation with clinical staging and echocardiographic measurements of cardiac remodeling, and showed good performance in a preliminary investigation for predicting MMVD diagnosis and stage. Despite some major limitations, the current study reports promising results that indicate the need for larger studies investigating RPT as a tool – possibly associated with clinical and radiographic data - to aid clinicians in diagnosing and staging MMVD when echocardiography is not possible.

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