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Vasovagal tonus index in dog with myxomatous mitral valve disease[1]

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ABSTRACT.- Brüler B.C., Giannico A.T., Dittrich G. & Sousa M.G. 2017. **Vasovagal tonus index in dog with myxomatous mitral valve disease.** *Pesquisa Veterinária Brasileira 37(10):1181-1186*. Departamento de Medicina Veterinária, Universidade Federal do Paraná, Campus Agrárias, Juvevê, Rua dos Funcionários 1540, Curitiba, PR 80035-050, Brazil. E-mail: bbruler@gmail.com

The vasovagal tonus index (VVTI) is a useful and assessable index, obtained from standard ECG recordings, that is used to estimate heart rate variability (HRV), and may provide valuable information regarding the likelihood of progression into congestive heart failure (CHF). In this paperwork, we investigated how the vasovagal tonus index (VVTI) behaves in dogs with naturally-occurring myxomatous mitral valve disease (MMVD) Electrocardiographic (ECG) recordings and echocardiographic data of 120 patients diagnosed with MMVD were reviewed. The VVTI was calculated from twenty consecutive RR intervals for each dog enrolled in the study. Lower VVTI values were found in MMVD patients in American College of Veterinary Internal Medicine (ACVIM) stage C compared with stages B1 and B2. Values were also lower in patients with severe cardiac remodeling. When a cut-off value of 6.66 is used, VVTI was able to discriminate MMVD patients in stage C from B1 and B2 dogs with a sensitivity of 70 per cent and a specificity of 77 per cent. MMVD dogs in which VVTI is lower than 6.66 are 30% more likely to develop congestive heart failure (CHF).

INDEX TERMS: Vasovagal tonus index, dog, mitral valve disease, heart rate variability, prognosis, autonomic nervous system, electrocardiography, congestive heart failure.

RESUMO.- [**Índice de tônus vasovagal em cães com doença mixomatosa da valva mitral.**] O índice de tônus vasovagal (ITVV) é uma ferramenta útil e acessível, obtida por meio de traçados eletrocardiográficos convencionais (ECG), utilizada para calcular a variabilidade da frequência cardíaca (VFC), podendo também fornecer informações valiosas referentes à probabilidade de desenvolvimento de insuficiência cardíaca congestiva (ICC). Neste trabalho, foi investigado como o ITVV se comporta em cães com degeneração mixomatosa da valva mitral (DMVM) de ocorrência natural, ECGs e exames ecocardiográficos de 120 pacientes diagnosticados com DMVM foram avaliados. O ITVV foi calculado a partir de 20 intervalos RR consecutivos para cada cão envolvido. Valores menores de ITVV foram encontrados em pacientes em estágio C de doença mitral pela classificação do American College of Veterinary Internal Medicine (ACVIM), comparado com pacientes em estágio B1 e B2. Valores também foram menores em pacientes com remodelamento cardíaco importante. Quando um valor de corte de 6,66 foi usado, o ITVV foi capaz de distinguir pacientes em estágio C de B1 e B2 com uma sensibilidade de 70 por cento e uma especificidade de 77 por cento. Cães com DMVM cujo ITVV é menor que 6,66 são 30% mais propensos a evoluírem para ICC.

TERMOS DE INDEXAÇÃO: Tônus vasovagal, cães, doença mixomatosa da valva mitral, frequência cardíaca, prognóstico, sistema nervoso autônomo, eletrocardiografia, insuficiência cardíaca congestiva.

INTRODUCTION

The ability of the heart to adapt to various conditions by means of change in heart rate (HR) is mediated by cardiac autonomic tone (Pomeranz et al. 1985). Patterns of increased and decreased HR are a signal of good adaptation and efficient autonomic mechanisms, and reflect a healthy heart (Saul et al. 1988). This physiological phenomenon can be assessed by a measure of autonomic function known as

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heart rate variability (HRV) (Stein et al. 1994). Therefore, an increase in sympathetic tone is followed by a decrease in HRV, while an increase in parasympathetic tone results in increased HRV (Montano et al. 2001).

Analyses of beat-to-beat changes in HR provide sensitive and early information of impaired cardiac function. Decreased HRV values are a common finding in initial stages of congestive heart failure (CHF) even before clinical signs become overt (Task Force 1996), and numerous medical and veterinary studies have acknowledged that certain measures of autonomic function may act as a prognostic surrogate in various structural cardiovascular conditions (Stein et al. 1994, Calvert et al. 1998, Nolan et al. 1998, Lahiri et al. 2008). HRV indexes can be obtained by linear methods of either time or frequency domain analysis, with a few unconventional nonlinear methods also described in people (Vanderlei et al. 2009). In most cases, values of HRV are preferably obtained by 24-hour Holter monitoring, which is time-consuming and may be laborious to apply in daily clinical practice. In this scenario, the vasovagal tonus index (VVTI) stands out as an useful time domain indicator of HRV obtained from the standard electrocardiographic data, which does not require any specific equipment for its calculation, besides a conventional ECG recorder. It is mainly influenced by the parasympathetic tone, whose applicability has been recognized in previous studies (Häggström et al. 1996, Doxey & Boswood 2004).

In this prospective cross-sectional observational study, we sought to investigate if VVTI is able to identify remodeling, as well as CHF, in dogs with naturally occurring mitral valve disease.

MATERIALS AND METHODS

Dogs were recruited for this study among patients attending routine cardiological evaluation in a veterinary hospital. All procedures were conducted in accordance with the institutional Animal Use Committee guidelines, under the protocol 039/2015. Three--minute ECG tracings were acquired using a computer-based ECG recorder (ECGP V6, TEB - Brazilian Electronic Technology Ltda, São Paulo, SP, Brazil) and echocardiography was carried out using an ultrasonography system (MyLab 30 - Esaote, Genova, Italy) equipped with a 5.0 MHz and a 7.5 MHz phased array transducers (P240 and P023 reference - Esaote, Genova, Italy).

In order to be included in the study, dogs needed to be diagnosed with MMVD at any stage, based on echocardiographic criteria of impaired valvar anatomy and function (Chetboul & Tissier 2012). Dogs with evidence of any congenital or acquired cardiac disease other than degenerative mitral valve disease were excluded from the study, along with patients with relevant systemic conditions or undergoing chronic medical therapy. After a positive diagnosis, three-minute ECG tracings were acquired for each patient. Bad quality recordings and ECG tracings where arrhythmias prevented a continuous run of 20 R-R intervals of sinus rhythm were excluded from the study, along with ECG tracings of patients being given any antiarrhythmic drug when the recording was obtained. Finally, dogs visibly frightened and agitated, along with dogs that would not allow stress-free mechanical contentions were also excluded from the study.

ECG recordings were reviewed and the first 20 consecutive R-R intervals in which cardiac rhythm was of sinus origin were used to calculate VVTI for each patient. The index was obtained by calculating the natural logarithm of the variance of the 20 measured R-R intervals, as described by the equation VVTI=NL [VAR (R-R1 - R-R20)], where NL: natural logarithm, VAR: variance. Indexes of congestion and function obtained by echocardiographic examination, such as left atrium to aorta ratio (LA/Ao), body weight-indexed left ventricular internal diameter in diastole and systole (BW-indexed LVd and BW-indexed LVs), wall stress index in diastole and systole (WSId and WSId), fractional shortening (FS), mitral E wave velocity (mitral E), mitral E-to-A ratio (mitral E/A), isovolumic relaxation time (IVRT) and mitral E-to-IVRT ratio (E/IVRT) were also documented for each dog on the study. All indexes were measured by the same investigator, as to avoid interinvestigator discrepancy.

For statistical purposes, the dogs were divided into three groups based on left atrial remodeling, according to Ljungvall et al. (2011). LA/Ao<1.4, 1.4<LA/Ao<1.8; LA/Ao>1.8). LA and Ao diameters were measured at right parasternal window using short axis images at the very last frame before aortic valve opening, and left ventricular volumes and diameters in systole and diastole were assessed by M-mode, also in short axis images. (Chetboul & Tissier 2012). Also, another classification was based on the stage of mitral valve disease (B1, B2 and C) proposed by the American College of Veterinary Internal Medicine (Atkins et al. 2009), which depended on the animal history concerning clinical signs attributable to CHF, as well as the echocardiographic proof of left atrial overload.

All data underwent the Shapiro-Wilk normality test. Either an analysis of variance followed by Tukey´s multiple comparison test or the Kruskal-Wallis test followed by Dunn's test was used to investigate differences in VVTI in the studied population. Either Pearson's or Spearman's test was used to assess whether correlations existed between VVTI and heart rate (HR), age and body-weight, as well as between VVTI and the echocardiographic parameters. Also, receiver operating characteristic (ROC) curves were constructed to investigate sensitivity and specificity of VVTI to differentiate MMVD dogs with remodeled hearts from those without remodeling, as well as those with overt clinical signs from the asymptomatic animals. All analyses were performed using the software GraphPad Prism (Version 5.0 - San Diego, CA, USA) using default settings. For all analyses, the level of significance was defined as $P<0.05$.

RESULTS

One hundred and twenty client-owned dogs diagnosed with MMVD were recruited at the end of the study. Several breeds were represented, and the age and body-weight of the animals varied from 6-18 years and 2.3-15.5 kg, respectively. Poodles (33/120) and Miniature Pinschers (17/120) were overrepresented in the study population.

No correlation was found between VVTI and body-weight ($P=0.1113$), but a significant negative correlation was documented between VVTI and HR ($P<0.0001$), as well as between VVTI and age ($P=0.0491$).

The three groups of dogs divided according to left atrial size held 40 animals each, and differences regarding age ($P=0.0598$) and body-weight ($P=0.2232$) did not exist between groups. VVTI values based on LA/Ao size are shown in Table 1. A significant difference between group LA/Ao>1.8 and the two groups in which LA/Ao was lower than 1.8 was documented ($P<0.05$). The lowest VVTI values were found in dogs with LA/Ao>1.8 whereas the highest values corresponded to the animals with LA/Ao<1.4 (Fig.1A).

Table 1. Descriptive statistics of vasovagal tonus index (VVTI) calculated for dogs with myxomatous mitral valve disease (MMVD) and divided into groups in accordance with left atrial size

	LA/Ao			P
	<1.4 (n=40)	1.4-1.8 (n=40)	>1.8 (n=40)	(Kruskal-Wallis)
Minimum	5.710	1.370	2.250	
25% Percentile	6.798	6.898	5.250	
Median	8.560[a]	7.880 a	6.330[b]	<0.0001
75% Percentile	9.285	8.888	7.358	
Maximum	10.51	10.82	9.900	
Coefficient of variation	16.99%	22.51%	25.43%	

When the dogs were divided in accordance with the ACVIM consensus statement, 40, 60 and 20 animals were assigned into groups B1, B2 and C, respectively. Again, no difference was found regarding age (P=0.1532) or body-weight (P=0.6307) between these three groups. Table 2 brings VVTI values distributed within the groups. When VVTI values of patients in groups B1, B2 and C were compared, a significant difference between group C and groups B1 and B2 was identified (P<0.05). The lowest VVTI values were found in group C, while the highest values corresponded to group B1 (Fig.1B).

The relationship between VVTI and cardiac rhythms during ECG recording was also investigated. The identification of the rhythms was done according to heart rate and

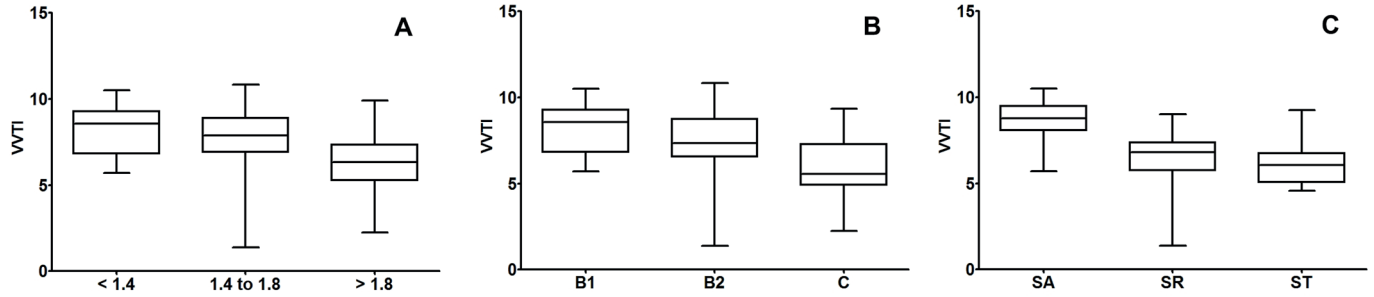

Fig.1. Box plot depicting the medians, interquartile ranges and amplitude of vasovagal tonus index in dogs with myxomatous mitral valve disease, subdivided in accordance with (**A**) left atrial remodeling, (**B**) the American Colege of Veterinary Internal Medicine's mitral valve disease classification, and (**C**) cardiac rhythm during electrocardiographic recording. SA = sinus arrhythmia, SR = sinus rhythm, ST = sinus tachycardia.

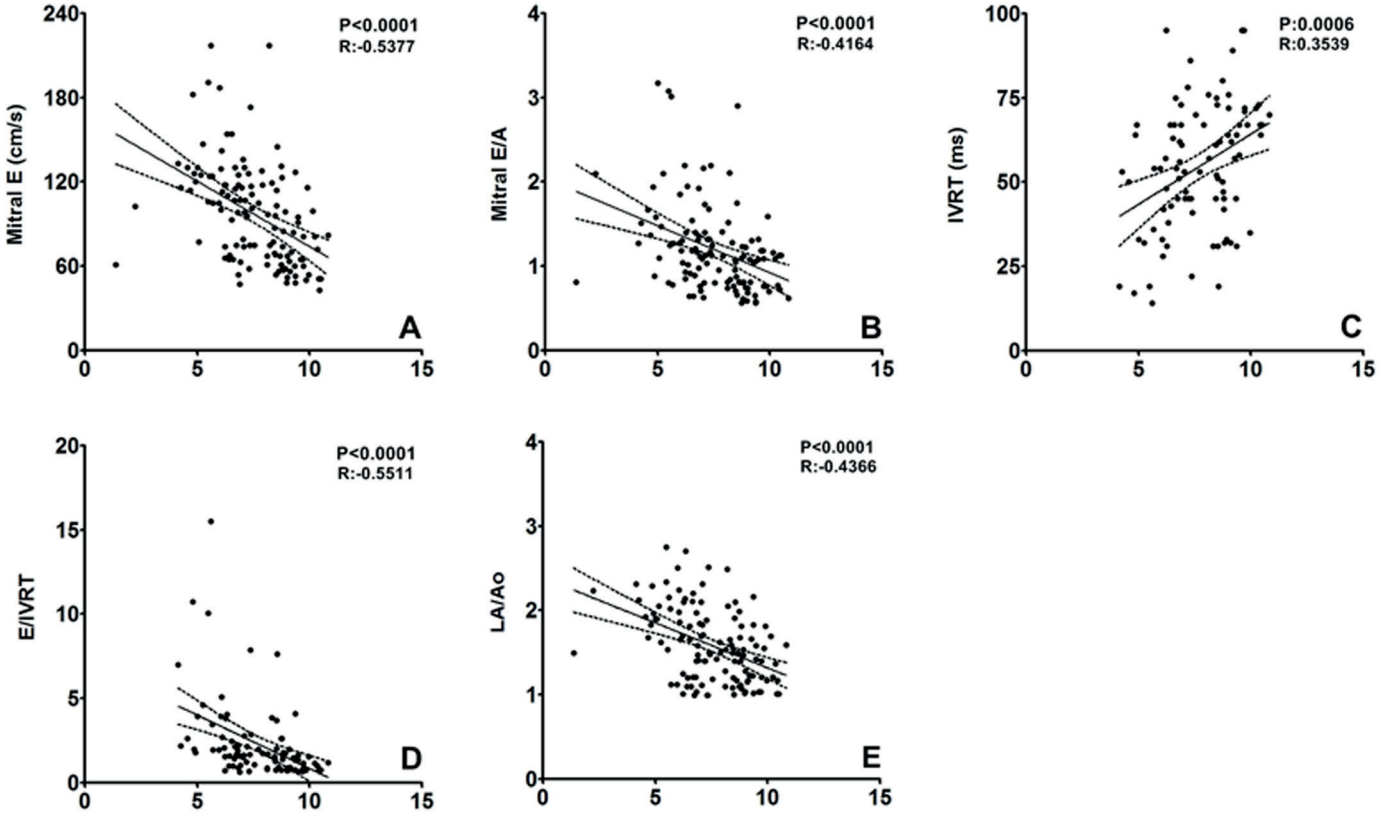

Fig.2. Scatter plots depicting significant correlations between vasovagal tonus index and mitral E peak velocity (**A**), mitral E-to-A ratio (**B**), isovolumic relaxation time (**C**), E-to-IVRT ratio (**D**) and left atrium-to-aorta ratio (**E**). Best-fit lines and 95% confidence band are shown.

Table 2. Descriptive statistics of vasovagal tonus index (VVTI) calculated for dogs with myxomatous mitral valve disease (MMVD) and divided into stages in accordance with the consensus statement proposed by the American College of Veterinary Internal Medicine (ACVIM)

	B1 (n=40)	B2 (n=60)	C (n=20)	P (Kruskal-Wallis)
Minimum	5.710	1.370	2.250	
25% Percentile	6.798	6.533	4.890	
Median	8.560[a]	7.340[a]	5.555[b]	<0.0001
75% Percentile	9.285	8.735	7.293	
Maximum	10.51	10.82	9.350	
Coefficient of variation	16.99%	22.51%	29.28%	

regularity of the QRS complexes. A sequence of sinus beats, with regular intervals and rate within normal for age and breed was classified as sinus rhythm (SR). Sinus beats where R-R intervals presented a variation of 10% or higher between consecutive beats was classified as sinus arrhythmia (SA). Finally, a sequence of sinus beats with increased heart rate regarding age and breed was classified as sinus tachycardia (ST) (Tilley 1992). VVTI calculated for dogs with SA was significantly different from that calculated for animals presenting either SR or ST. The lowest VVTI values were found in the ST group and the highest values corresponded to the SA group (Fig.1C).

When it comes to echocardiographic indices of congestion and function, no correlation was found between VVTI and BW-indexed LVd (R: -0.0919; P=0.3440), BW-indexed LVs (R: -0.0634; P=0.5144), WSIs (R: -0.0362; P=0.6943) and FS (R: -0.1043; P=0.2570). On the contrary, a significant correlation was observed between VVTI and mitral E wave (R:-0.5377; P<0.0001), mitral E/A (R:-0.4164; P<0.0001), IVRT (R:0.3539; P=0.0006), E/IVRT ratio (R:-0.5511; P<0.0001), WSId (R:-0.1931; P=0.0346), and LA/Ao (R:-0.4366; P<0.0001) (Fig.2).

The ROC curve constructed to investigate sensitivity and specificity to differentiate dogs with remodeled hearts from those without remodeling found an AUC of 0.6802 (95% CI: 0.5815 to 0.7789; P=0.0013) (Fig.3-A). To differentiate asymptomatic dogs from those with CHF, an AUC of 0.7778 (95% CI: 0.6574 to 0.8981; P<0.0001) was observed (Fig.3B). VVTI cut-off values and its respective sensitivity, specificity, and positive likelihood ratio were calculated and are shown in Table 3.

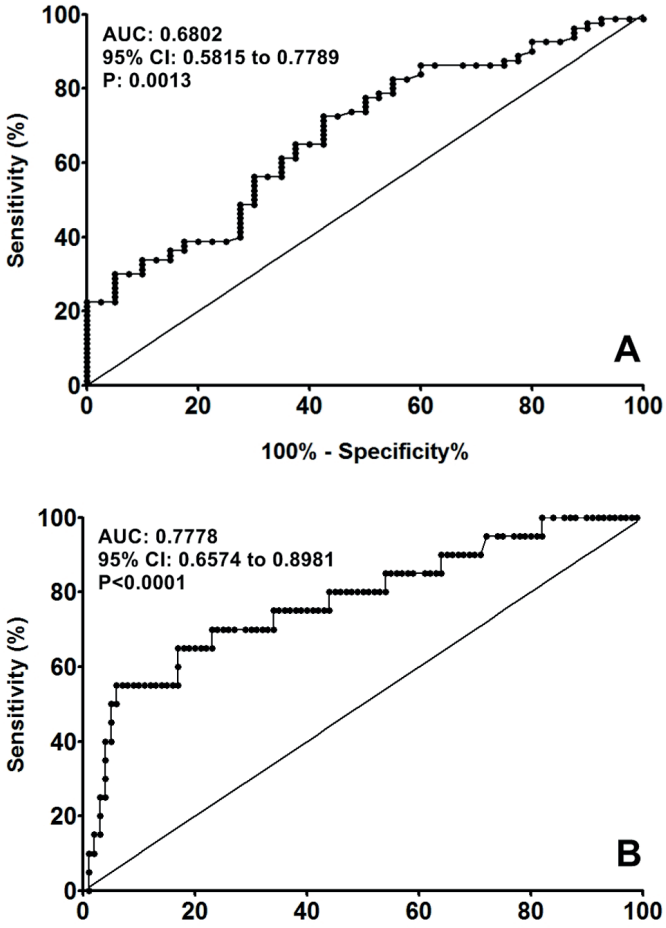

Fig.3. Receiver operating characteristic curves constructed to investigate sensitivity and specificity of vasovagal tonus index to differentiate myxomatous mitral valve disease dogs with remodeled hearts from those without remodeling (**A**), as well as those with overt clinical signs from the asymptomatic animals (**B**).

DISCUSSION

In this prospective study, lower VVTI values were found in MMVD dogs in stage C as compared to patients in stages B1 and B2. Values <7.385, <6.660 or <5.525 are associated with a positive likelihood ratio of 1.82, 3.04 or 10.0, respectively, which translates into a dog having a slight (0-15%), moderate (15-30%) or large (45%) increase in the proba-

Table 3. Cut-off values and their corresponding sensitivity and specificity indices when using vasovagal tonus index (VVTI) to differentiate dogs with remodeled and normal hearts, and asymptomatic dogs from those presenting overt clinical signs

	VVTI cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio (+)
Normal vs.	< 5.830	22.50 (13.91 to 33.21)	97.50 (86.84 to 99.94)	9.00
Remodeled	< 6.220	30.00 (20.26 to 41.28)	95.00 (83.08 to 99.39)	6.00
Hearts	< 6.860	41.25 (30.35 to 52.82)	72.50 (56.11 to 85.40)	1.50
	< 7.095	50.00 (38.61 to 61.39)	70.00 (53.47 to 83.44)	1.67
	< 7.425	60.00 (48.44 to 70.80)	65.00 (48.32 to 79.37)	1.71
Asymptomatic vs.	< 5.525	50.00 (27.20 to 72.80)	95.00 (88.72 to 98.36)	10.00
Symptomatic	< 6.220	55.00 (31.53 to 76.94)	85.00 (76.47 to 91.35)	3.67
Dogs	< 6.660	70.00 (45.72 to 88.11)	77.00 (67.51 to 84.83)	3.04
	< 7.035	75.00 (50.90 to 91.34)	66.00 (55.85 to 75.18)	2.21
	< 7.385	80.00 (56.34 to 94.27)	56.00 (45.72 to 65.92)	1.82

bility of being symptomatic (stage C) than asymptomatic (either stage B1 or B2). Therefore, the lower the VVTI becomes, the more suggestive that an asymptomatic MMVD patient may evolve into CHF. This finding is extremely valuable for clinical decision making, and is in accordance with previously reported data that suggests parasympathetic withdrawal in CHF syndrome (Eckberg et al. 1971, Oliveira et al. 2012). Left atrial enlargement is associated with the progression of MMVD, and the degree of dilation is recognized as a prognostic surrogate (Borgarelli et al. 2008, Reynolds et al. 2012). Because this study documented the lower VVTI values in patients with LA/Ao >1.8 as compared to dogs with smaller left atriums, VVTI might also be considered a surrogate for CHF. This finding is supported by the results of a retrospective study regarding multiple cardiac conditions, where the referred index has proven to be the most useful discriminatory parameter for detection of heart failure among a variety of selected laboratory and electrocardiographic parameters (Boswood et al. 2006).

Conventional HRV measures have been studied in people with heart disease, and were found to be an excellent predictor of adverse outcome (Saul et al. 1988, Nolan et al. 1998, Lahiri et al. 2008). Time-domain heart rate variability parameters have also shown to have prognostic potential for determining the severity of MMVD in dogs (Rasmussen et al. 2012, Oliveira et al. 2012). These measures, however, usually hold the disadvantage of requiring a 24 hour Holter monitoring.

In our study, we sought to investigate if an unconventional and straightforward measure of HRV, obtained by the analyses of only 20 consecutive RR intervals, might be reliable in differentiating MMVD dogs in stages B1, B2, and C. Our results suggest that VVTI can discriminate MMVD patients in stage C from B1 and B2 dogs with a sensitivity of 70 per cent and a specificity of 77 per cent when a cut-off value of 6.66 is to be used.

Previous studies have acknowledged the feasibility of the VVTI as a measure of HRV in dogs with cardiac disease. Doxey and Boswood (2004) analyzed its diagnostic potential for CHF in 92 dogs of several breeds and different heart conditions. In that study, VVTI was shown to be a good diagnostic tool for CHF with a sensitivity of 100 per cent and a specificity of 83.6 per cent when a cut-off value of 6.75 was used. Boswood et al. 2006 analyzed the effects of heart disease, heart failure and diuresis on nine selected laboratory and echocardiographic parameters in dogs with multiple heart conditions, and observed that the VVTI decreased with the onset of CHF, proving to be the most useful discriminatory parameter for this syndrome among the tested. Also, Pereira et al. (2008) studied the index's applicability in dogs with dilated cardiomyopathy (DCM) and found the index to be a moderately accurate diagnostic tool for the assessment of severity of heart failure in DCM patients. When using a cut-off value of 7.59, a good sensitivity of 88.7 per cent was calculated, but the specificity of 62.5 per cent was considered low. When it comes to MMVD, Häggström et al. (1996) investigated the index in Cavalier King Charles spaniels, which are known for the rapid progression of MMVD into CHF. In their study, VVTI was similar in healthy and early staged subjects, but the index became significantly lower in CHF patients. Interestingly, our study is the first one to evaluate VVTI applicability in the general population of dogs with MMVD, exclusively.

Also, this investigation documented significant correlations between VVTI and some of the studied echocardiographic parameters. A moderate negative relationship was found between the VVTI and mitral E (R:-0.54) and between VVTI and E/IRVT (R:-0.55). A weak negative relationship was found between the VVTI and mitral E/A (R:-0.42), and VVTI and LA/Ao (R:-0.44). A weak positive relationship was documented between VVTI and IVRT (R: 0.35). As reported before, decreased HRV values are commonly observed during the initial stages of CHF even before clinical signs become evident (Task Force 1996). In severe cases of mitral valve regurgitation, volume overload leads to left atrial and ventricular remodeling, both associated with clinical onset (Reynolds et al. 2012). Many echocardiographic indices tend to become altered when a still asymptomatic MMVD dog progresses into symptomatic CHF. In this study, the significant correlation found regarding the echo indices of congestion and function is supportive of VVTI being lower as CHF becomes more severe.

The negative correlation between VVTI and heart rate is likely ascribed to the role played by the parasympathetic tone in VVTI, therefore producing higher values when slower rates and irregular rhythms are present. VVTI is a time-domain method of analysis and, being acquired over a short period of time, provides information about high-frequency variations in heart rate, which are predominantly a result of vagal influences (Doxey & Boswood 2004). This also explains the higher values of VVTI in patients presenting sinus arrhythmia when compared to dogs presented with sinus rhythm and sinus tachycardia. The influence of the autonomic nervous system on the heart is dependent on information from baroreceptors, chemoreceptors, atrial and ventricular receptors, among others. Therefore, several factors can interfere with HRV, including exercise and physical and mental stress, respiration, blood pressure regulation, thermoregulation, and influence of the renin-angiotensin system (Stein et al. 1994). Even though these uncontrolled conditions during ECG recording may increase HR, the lower VVTI found in animals exhibiting sinus tachycardia may reflect high sympathetic and low parasympathetic outflows, commonly found in severe cases of MMVD (Häggström et al. 1996). As for the negative correlation documented between VVTI and age, this is mostly likely due to the late onset and progressive nature of MMVD, usually becoming clinically relevant in animals of higher ages.

An important limitation involving the use of VVTI is the impossibility of calculation when a consecutive 20-beat recording of sinus rhythm is lacking. In severe stages of cardiac remodeling, atrial fibrillation and ventricular premature complexes are a common finding during ECG recordings, which invalidate the index (Verheule et al. 2003). In our study, arrhythmias did not preclude the calculation of the index in the population of dogs, but we do recognize that it might be a limitation in the clinical setting. Also, being the

VVTI an index influenced mainly by the parasympathetic tone, external influences in heart rate, including stress, fear and agitation, may result in low values in healthy animals. For this reason, it is encouraged that ECG recordings be acquired in a quiet and stress-free environment. Finally, the lack of attention in this study regarding possible effects of treatment over the index, as documented by Boswood et al. 2006, may need to be taken in consideration.

CONCLUSIONS

This study supports the use of VVTI as a nonconventional index of HRV that may provide valuable information when assessing the severity of MMVD and the likelihood of a patient progressing into CHF.

Dogs with VVTI <7.425 are slightly more likely to have remodeled hearts (around 15% increase in probability) as compared to those in which VVTI is higher, while those with VVTI <5.830 are moderately more likely to have dilated cardiac chambers (35-45% increase in probability).

Also MMVD dogs in which VVTI is lower than 6.66 have a moderate increase of 30% in the probability of evolving into CHF. Knowing how this index behaves in this particular canine heart disease may also be useful in studies aimed at predicting CHF in human beings with MVP.

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