DIASTOLIC FUNCTION IS IMPAIRED IN DOGS WITH MYXOMATOUS MITRAL VALVE DISEASE

DISFUNÇÃO DIASTÓLICA EM CÃES COM DOENÇA MIXOMATOSA DA VALVA MITRAL

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SUMMARY

Myxomatous mitral valve disease (MMVD) is the most common cardiac disease in dogs, and the echocardiogram is required to investigate the degree of remodeling and the intensity of cardiac dysfunction. Therefore, the aim of this study was to assess diastolic function in dogs with MMVD in different stages, and to compare them with healthy animals. This study enrolled 12 mature dogs with MMVD, which were subdivided in two groups: stage B2 (n=7) and stage C (n=5). Also, 9 healthy adult dogs were recruited to serve as controls. Several echocardiographic data were obtained for the assessment of diastolic function, as well as some parameters intended to evaluate the cardiac structure and systolic function, which were used to search for correlations with the diastolic parameters. Concerning diastolic function, a significant difference was found to exist between groups for the peak velocity of left ventricular slow filling, the isovolumic relaxation time, and the mitral annular velocities at early and late diastole. These findings are associated with the structural and hemodynamic changes ascribed to the progression of MMVD and the intensification of congestive heart failure. The indices calculated from the peak velocity of left ventricular rapid filling and the mitral annular velocities obtained at early and late diastole also differed between healthy and diseased dogs. Because some of these indices are surrogates for left ventricular filling pressure and the congestive status of the patient, the results of this study are supportive of the relationship between the progression of MMVD and diastolic impairment, besides the eccentric structural remodeling attributable to this cardiac disease.

KEY-WORDS: Cardiac disease. Valve disease. Animals. Echocardiography. Cardiac function.

RESUMO

A degeneração mixomatosa da valva mitral (DMVM) é a cardiopatia de maior prevalência em cães e a ecocardiografia é necessária para avaliar o grau de remodelamento e a intensidade da disfunção cardíaca. Assim, o escopo desta pesquisa foi avaliar a função diastólica em cães com DMVM em diferentes estágios, comparando-os com cães saudáveis. Foram arrolados 12 cães adultos portadores de DMVM, os quais foram subdivididos em dois grupos: estágio B2 (n=7) e estágio C (n=5). Além disso, foi constituído um grupo controle com 9 cães adultos clinicamente saudáveis. Foram obtidos parâmetros ecocardiográficos para avaliação da função diastólica, assim como algumas variáveis para avaliação estrutural do coração e da função sistólica, as quais foram empregadas para investigar correlações com os parâmetros diastólicos. No tocante à função diastólica, houve diferença significativa entre grupos na avaliação da velocidade máxima do enchimento ventricular esquerdo lento, do tempo de relaxamento isovolumétrico e das velocidades anulares da mitral em início e final da diástole. Tais resultados refletem modificações estruturais e hemodinâmicas que acompanham a progressão da enfermidade mitral e a intensificação da insuficiência cardíaca congestiva. Os índices calculados a partir das relações entre a velocidade máxima do enchimento ventricular esquerdo rápido e as velocidades anulares da mitral, bem como entre as velocidades anulares da mitral obtidas no início e final da diástole, também foram diferentes entre cães saudáveis e enfermos. Como alguns desses parâmetros refletem a pressão de enchimento do ventrículo esquerdo e o estado congestivo do paciente, os resultados desta pesquisa apontam para a relação existente entre a progressão da DMVM e o prejuízo diastólico, além do remodelamento estrutural excêntrico que acompanha essa enfermidade.

PALAVRAS-CHAVE: Cardiopatias. Endocardiose. Animais. Ecocardiografia. Função cardíaca.

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INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common cardiac disease in dogs. Although the pathophysiology of MMVD is still not completely understood, a hereditary genetic basis was already demonstrated to be responsible for the valve degeneration in Cavalier King Charles Spaniel dogs (THRUSFIELD et al.,1985; HAGGSTROM et al.,1992; BEARDOW e BUCHANAN, 1993; WARE, 2007).

This degeneration is characterized by mitral valve structural disarray, which eventually progress up to impair the ability of the valve to avoid the backflow of blood from the left ventricle towards the left atrium during ventricular systole. Blood regurgitation results in left atrial dilation and is responsible for the development of clinical signs over time (MUCHA, 2001; ATIKINS et al. 2007; BORGARELLI et al. 2008).

Reducing the stroke volume activates the renin-angiotensin-aldosterone system to increase preload, but the vasoconstrictive effect of angiotensin II also interferes with afterload. The upregulated activity of angiotensin II results in myocyte hypertrophy and remodeling of the extracellular matrix, which is characterized by the augmented synthesis of collagen III, interstitial fibrosis, myocyte atrophy and apoptosis. Also, because aldosterone is involved with fibroblasts [mRNA] transcription, causing its proliferation and the deposition of collagen within the heart tissue, it does play an important role in cardiac remodeling. All these alterations are responsible for the passive stiffness of the ventricles and arterial bed, therefore interfering with ventricular filling and arterial compliance (SERRO AZUL et al., 1977).

Diastolic function is related with the capacity of the heart to overwhelm the altered preload, therefore maintaining intracardiac pressures within the physiological range and a normal stroke volume. With this in mind, diastolic dysfunction is likely to represent a key surrogate for congestive heart failure. In dogs, it is well known that the progression of MMVD is associated with myocardial remodeling and the deterioration of contractile function (BONAGURA & SCHOBER, 2009). However, little is known concerning the impairment of relaxation and compliance in these patients in accordance with the intensification of congestion. In this study, the authors hypothesized that congestion plays a major role in diastolic dysfunction. Therefore, the aim of this study was twofold: to investigate diastolic function in dogs with MMVD and varying degrees of congestive heart failure, and to assess the relation between diastolic parameters, systolic data, and cardiac remodeling assessed by echocardiography.

MATERIAL E METHODS

Dogs with MMVD and remodeled hearts, either asymptomatic or presenting overt clinical signs attributable to CHF, were enrolled into a prospective cross-sectional observational study. The diagnosis of MMVD was based on physical examination and ancillary techniques, including a complete transthoracic echocardiogram. Altered laboratory analysis, including CBC and biochemistry, were considered exclusion criteria, as were the absence of cardiac remodeling and other pulmonary diseases documented on chest radiographs. Once included in the study, MMVD dogs were categorized in groups in accordance with the ACVIM consensus statement on canine valvular disease (ATKINS et al, 2009). Also, normal age-matched dogs were recruited from the university experimental kennel to serve as healthy controls.

The echocardiogram was performed with the dogs restrained in right and left lateral recumbencies, using a 5.0-7.5 MHz transducer. Images were acquired and stored for offline measurements, which included parameter of diastolic function, systolic function, and cardiac morphology. Diastolic data included the peak velocity of left ventricular rapid filling (mitral E wave: E_m), the peak velocity of left ventricular slow filling (mitral A wave: A_m), and the isovolumic relaxation time (IVRT), which were obtained using pulsed-wave Doppler. These parameters required either an apical 4- or 5-chamber image obtained from the left parasternal window. Also, tissue Doppler imaging was used to acquire mitral annular velocity at early and late diastole, which was obtained at both the septal and lateral and averaged to produce the mean annular velocities (E_{TDI}, A_{TDI}) sites. Several indices were calculated from these parameters, including the E_m-to-A_m ratio (E_m/A_m), E_{TDI}-to-A_{TDI} ratio (E_{TDI}/A_{TDI}), E_m-to-E_{TDI} ratio (E_m/E_{TDI}), and A_m-to-A_{TDI} ratio (A_m/A_{TDI}). The echocardiographic parameters aimed at assessing systolic function and cardiac morphology included the left ventricular end-diastolic (LV_d) and end-systolic (LV_s) diameters, left atrium-to-aorta ratio (LA/Ao), fractional shortening (FS), ejection fraction (EF), and the mitral annular systolic velocity at both the septal and lateral sites, whose average value was considered as the mean annular systolic velocity (S_{TDI}). All echocardiographic information represented the mean of at least three consecutive cardiac cycles, and were obtained in accordance with the guidelines described elsewhere (BOON, 2011).

All data underwent the Shapiro-Wilk normality test. Whenever a normal distribution was attained, an analysis of variance followed by the post-hoc Tukey test was used to compare MMVD groups with the controls. When data was not normally distributed, we used Kruskal-Wallis test followed by Dunn's multiple comparisons test instead. Also, significant correlations between diastolic parameters and the echocardiographic surrogates of systolic function and cardiac remodeling were investigated using either the Pearson or Spearman correlation coefficients. All analyses were performed with the software Graphpad Prism® v.3.00, and significance was set at $P<0.05$.

RESULTS

Twelve adult dogs (3.0-17.3 kg) with MMVD and dilated hearts were included into this investigation. Cardiac remodeling was determined based on the increased LA/Ao ratio (>1.4) and VHS (>10.5). Seven

mature animals (10.2-14.0 kg) had no clinical signs at all, and were included in stage B2 group, while five adult dogs (3.0-14.0 kg) already exhibited clinical signs ascribed to heart failure and were categorized into stage C. Finally, nine mature dogs (10.2-17.3 kg) that presented no murmur on auscultation nor exhibited any clinical signs were recruited to serve as healthy controls. Body weight was not considered statistically different (P=0.4049) between groups.

While the peak velocity of left ventricular slow filling (A_m) and the mean late diastolic annular velocity (A_{TDI}) increased significantly with the progression of MMVD, a reduction was observed for IVRT and the early diastolic annular velocity (Table 1). Although E_m and E_{TDI} remained unchanged between groups, the variation documented for A_m and A_{TDI} resulted in significant differences for E_m/A_m and E_{TDI}/A_{TDI} between healthy and MMVD dogs (Table 2). Changes in cardiac morphology ascribed to the progression of MMVD were demonstrated by the increase in LA/Ao ratio and the left ventricular end-diastolic diameter (LV_d). However, cardiac systolic function was apparently preserved as the comparison of systolic surrogates in MMVD dogs were similar to those recorded in healthy subjects (Table 3).

Significant correlations were documented between LA/Ao and A_m (R=0.5714; P=0.0068), IVRT (R=-0.4810; P=0.0273), A_{TDI} (R=0.5992; P=0.0273), E_m/A_m (R=-0.4698; P=0.0316), E_{TDI}/A_{TDI} (R=-0.5700; P=0.0070), E_m/E_{TDI} (R=0.4704; P=0.0314); between $LV_{d\text{-index}}$ and E_m/E_{TDI} (R=-0.4614; P=0.0205); between FS and A_{TDI} (R=0.5106; P=0.0180), E_{TDI}/A_{TDI} (R=-0.5359; P=0.0123), A_m/A_{TDI} (R=-0.4999; P=0.0210); between EF and A_{TDI} (R=0.5010; P=0.0207), E_{TDI}/A_{TDI} (R=-0.5488; P=0.0100), A_m/A_{TDI} (R=-0.5995; P=0.0070); and finally, between S_{TDI} and E_m/E_{TDI} (R=0.4354; P=0.0485) (Figures 1 and 2).

Table 1 - Means (SD) or medians (IQR) of the diastolic parameters obtained by transthoracic echocardiography from healthy (n=9) and MMVD dogs (n=12).

	Groups			*P*
	Healthy	Stage B2	Stage C	
E_m (cm/s) *	80.5 (63.5-84.3)	80.7 (77.4-86.9)	72.7 (63.0-110.7)	0.2887
A_m (cm/s)	49.8 (14.2)^{A}	79.8 (20.2)^{B}	66.7 (22.5)^{AB}	0.0172
IVRT (ms) *	102.0 (81.0-105.0)^{A}	95.0 (57.0-108.0)^{A}	51.0 (38.0-60.5)^{B}	0.0083
E_{TDI} (cm/s)	12.5 (1.5)^{A}	12.4 (0.9)^{A}	8.5 (2.1)^{B}	0.0002
A_{TDI} (cm/s) *	7.6 (7.1-8.9)^{A}	9.4 (7.2-9.6)^{AB}	13.4 (11.6-15.9)^{B}	0.0037

* Nonparametric data (Medians and IQR are shown)

Table 2 - Means (SD) or medians (IQR) of the calculated echocardiographic indices used to assess diastolic function in healthy (n=9) and MMVD dogs (n=12).

	Groups			*P*
	Healthy	Stage B2	Stage C	
E_m/A_m	1.5 (0.3)^{A}	1.1 (0.3)^{B}	1.2 (0.1)^{AB}	0.0243
E_{TDI}/A_{TDI}	1.6 (0.2)^{A}	1.4 (0.4)^{A}	0.6 (0.1)^{B}	<0.0001
E_m/E_{TDI} *	5.8 (5.3-7.0)	6.7 (6.2-7.5)	10.1 (6.0-14.9)	0.0748
A_m/A_{TDI}	6.5 (2.3)^{AB}	9.1 (3.2)^{B}	5.1 (2.3)^{A}	0.0470

* Nonparametric data (Medians and IQR are shown)

Table 3 - Means (SD) or medians (IQR) of the echocardiographic data used to assess either cardiac morphology or systolic function in healthy (n=9) and MMVD dogs (n=12).

	Groups			*P*
	Healthy	Stage B2	Stage C	
LA/Ao*	1.2 (1.1-1.2)^{A}	1.7 (1.5-2.1)^{B}	1.8 (1.6-3.0)^{B}	0.0004
LV_d (mm/m^2)	49.3 (7.4)^{A}	62.2 (11.4)^{AB}	71.3 (18.4)^{B}	0.0110
LV_s (mm/m^2)	36.3 (11.6)	39.3 (8.7)	41.0 (6.5)	0.6746
FS (%)	37.4 (5.6)	37.1 (9.5)	45.4 (6.4)	0.1251
EF (%)	68.9 (6.6)	67.1 (10.9)	77.6 (6.1)	0.1008
S_{TDI} (cm/s)	13.7 (2.4)	14.4 (2.6)	14.9 (2.3)	0.6689

* Nonparametric data (Medians and IQR are shown)

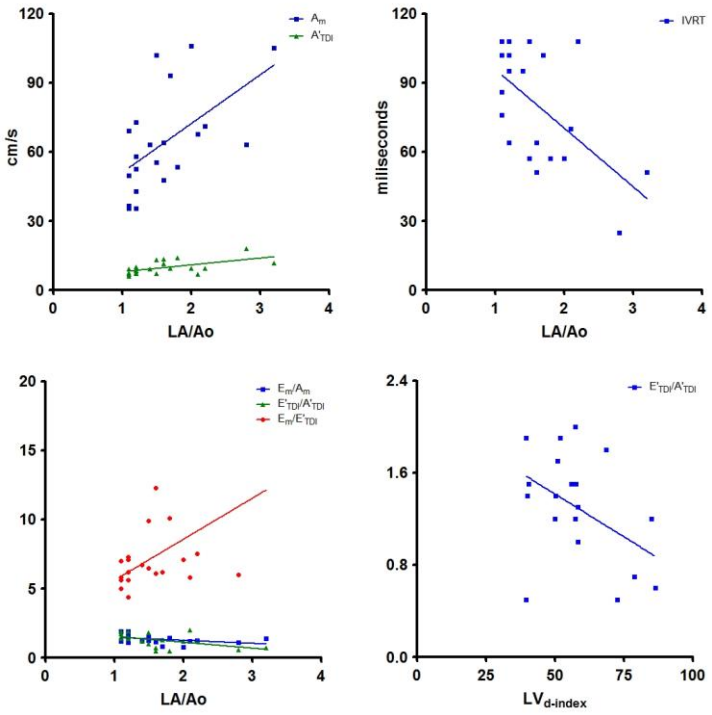

Figure 1 - Scatterplots showing the mild-to-moderate correlations between the echocardiographic surrogates for cardiac structural remodeling (LA/Ao, LV_d) and the parameters used to assess diastolic function. Best-fit lines are shown.

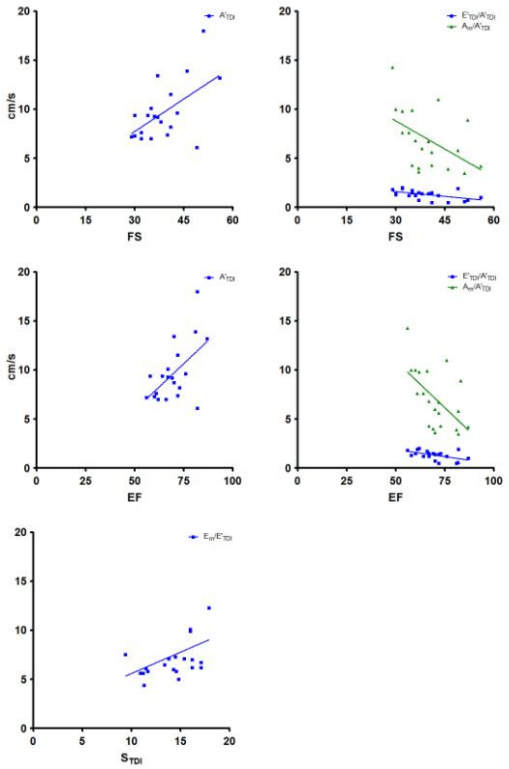

Figure 2 - Scatterplots showing the mild-to-moderate correlations between the echocardiographic surrogates for systolic function (FS, EF, S_{TDI}) and the parameters used to assess diastolic function. Best-fit lines are shown.

DISCUSSION

The echocardiogram was performed following the guidelines reported by Kienle and Thomas (2004) and Boon (2011), with the aim of obtaining images that were suitable for measurement of all parameters included in this investigation.

The changes documented in LV_d in MMVD as compared to the healthy dogs are related to the morphological change attributable to the activation of the renin-angiotensin-aldosterone system, therefore resulting in increased preload. The eccentric hypertrophy is a consequence of chronic volume overload, which becomes more evident with the progression of the valvular disease. A similar remodeling was previously reported by Pedersen (2000) and Mucha (2001), who studied dogs with MMVD and chronic congestive heart failure. In another study, Firm and Petric (2002) reported that the left ventricular end-diastolic diameter may be a prognostic surrogate concerning the progression of the cardiac disease.

The LA-to-Ao ratio was significantly different between MMVD and healthy dogs, reflecting the volume overload that accompanies the progression of MMVD, therefore resulting in increased left-ventricular filling pressure (Borgenhagen, 1977). This condition is clearly responsible for the congestion heart failure and the consequent cardiac remodeling that follows the natural progression of MMVD in dogs.

Concerning systolic function, no differences were observed between the parameter obtained in MMVD and healthy dogs. However, in spite of the absence of difference in FS and EF between groups, a clear trend of increase was observed when stage C MMVD dogs were compared with the healthy controls. This finding is likely attributable to volume overload and the Frank-Starling principle (Kittleson, 2006; Boon, 2011), which plays an important role in MMVD once remodeling exists.

Even though the peak velocity of left ventricular rapid filling (E_m) was not different between groups, a significant difference existed for A_m between healthy and stage B2 MMVD dogs, which points towards an increased preload and a major role played by the late ventricular filling in end-diastolic volume (KIENLE & THOMAS, 2004). This finding might indicate an increased left ventricular filling pressure and a consequent diastolic dysfunction, (BOON, 2011). Interestingly, no differences existed for A_m between healthy and stage C dogs, but this finding is likely related to the progression of diastolic dysfunction to pseudonormalization, which results in a normal E_m-to-A_m ratio. All these findings possibly reflect the structural and hemodynamic modifications that develop with the intensification of congestive heart failure ascribed to MMVD (CAMACHO, 1996; MUCHA, 2001).

The tissue Doppler assessment showed a lower E_{TDI} and a higher A_{TDI} for MMVD stage C dogs as compared with both healthy and MMVD stage B2 dogs. The average E_{TDI}/A_{TDI} remained below 1 for the majority of stage C dogs, which contrasted with the healthy animals and pointed to diastolic dysfunction (OYAMA, 2004). This finding is probably ascribed to the augmented left ventricular filling pressure, therefore resulting in a minor role played by the rapid component of ventricular filling and the intensification of congestion. Also, the inversed E_{TDI}-to-A_{TDI} ratio is supportive of the cardiac remodeling reported by Bonagura (2009), who described an impaired relaxation in dogs with MMVD, as well as the deterioration of diastolic function with the progression of congestive heart failure. On the other hand, the systolic myocardial velocity (S_{TDI}) attained no difference between healthy and diseased dogs, which is in agreement with the absence of an overt compromise in systolic function already shown by other echocardiographic indicators of contractility (Boon, 2011).

In our study, the intensification of MMVD was clearly associated with an elevation in the E_m-to-E_{TDI} ratio, even though no significant differences between groups could be documented. This parameter was previously shown to be an useful surrogate for left ventricular filling pressure, therefore permitting the echocardiographic assessment of congestion. Omnem (2000) and Schober (2008) reported that changes in ventricular diastole are responsible for alterations in the E_m-to-E_{TDI} ratio, which might be associated with a worse prognosis. In general, the average E_m/E_{TDI} increased with from 5.8 in healthy dogs to 6.7 and 10.1 in stages B2 and C MMVD dogs, showing that filling pressure and congestion was more intense in dogs with valve degeneration as compared with the normal subjects.

Even though this investigation found interesting results regarding diastolic dysfunction in dogs with MMVD, we do acknowledge its several limitations, which include the small number of animals enrolled, the absence of MMVD dogs in stages B1 and D, the absence of further assessment of diastolic function, including speckle tracking analysis, and, last but not least, the absence of follow-up assessment to evaluate the progression of MMVD and how the echocardiographic surrogated of diastolic function change over time.

CONCLUSION

This study documented morphological remodeling associated with the progression of MMVD in dogs. Also, we identified several echocardiographic parameters that are supportive of diastolic impairment, especially in stage C dogs. Further studies are warranted to investigate how diastolic dysfunction interferes with survival times and the animal's tendency to evolve into overt congestion heart failure.

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