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Cardiovascular Indicators and Mitral Valve Disease in Dogs with Spontaneous Hypercortisolism - Prospective Evaluation

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ABSTRACT

***Background*:** Canine hypercortisolism (HC) is the most prevalent endocrinopathy in dogs in southern Brazil. The prognosis depends on several factors including the general health status, owners´ commitment, and the development of disease complications and comorbidities occurrence, such as cardiovascular complications including mitral valve disease (MVD), systemic arterial hypertension, and left ventricular hypertrophy. The main objective of the present study was to assess cardiovascular parameters in canine HC, based on investigating survival-related variables. The study also aimed to evaluate the influence of concurrent preclinical (MVD) on dogs` survival and the impact of HC on MVD progression.
***Materials, Methods & Results*:** A total of 25 dogs with spontaneous HC were enrolled and divided into 2 subgroups accordingly to their echocardiographic findings: group HC (normal echocardiography at first evaluation, n = 16); and group HC + MVD (concurrent presence of stages B1 and B2 MVD diagnosed at the first evaluation, n = 9). The patients were evaluated at diagnosis (T0); 6 months after treatment begging (T1); and after 12 months of treatment (T2). The owners were further contacted by phone or e-mail for 1 more year after T2 regarding survival information. A control group (CG, n = 20) was also evaluated at T0 and T1. At each evaluation, dogs were submitted to a complete clinical evaluation and physical exam, associated with a minimum database (CBC, serum biochemistry, and urine analysis) and cardiovascular evaluation composed of systolic blood pressure determination, electrocardiogram (ECG), and echodopplercardiography. In the HC group, 11/16 dogs underwent the evaluation at T2, while 4/9 dogs from the HC + MVD group and 17/20 dogs from the CG underwent the evaluation at T2. Five dogs (31.25%) from the HC group and 4 dogs (44.44%) from the HC + MVD group died before the end of the follow-up period. In the control group, only 1 dog (5.26%) died before the end of the study. Despite the higher mortality in the HC + MVD group during the follow-up period, there was no significant difference ($P = 0.632$) in survival when compared with the HC group. The MVD of 4 dogs included in the HC + MVD group was classified as stage B1, while the other 5 dogs were classified as stage B2. Only 1 dog from the CG developed stage B1 MVD in the period studied; however, progression of the MVD stage was documented in 1/4 of dogs in the HC + MVD group and MVD development was documented in 3/11 of dogs from the HC group from T0 to T2. The odds ratio (OR) and respective 95% confidence interval (95%CI) for HC as a risk factor for MVD progression were 4.267 (0.4268 - 42.65; $P = 0.342$). Exercise intolerance (12/16 dogs) and dyspnea (6/16 dogs) were the cardiorespiratory clinical signs with the highest incidence in the HC group at T0. When compared to the control group, both exercise intolerance ($P < 0.001$) and dyspnea ($P = 0.03$) occurrence were significantly higher in the HC group. The age ($P = 0.001$) and the occurrence of dyspnea ($P = 0.036$) at diagnosis were significantly higher in dogs with HC that died during the follow-up than those that remained alive. Regarding the occurrence of cardiac arrhythmias verified by ECG, no statistically significant differences were observed among groups.
***Discussion*:** The study suggests that systemic hypertension and altered echocardiographic measurements did not interfere with dogs' survival; however, dyspnea was associated with a worse prognosis. Finally, it is possible to conclude that mitral valve degeneration is a common comorbidity in dogs with HC, however, it was not evidenced their interference in the survival of dogs with this endocrine disease or even a role of the HC in the progression of the MVD.

Keywords: Cushing's syndrome, hyperadrenocorticism, dyspnea, echocardiography, prognosis.

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INTRODUCTION

Canine hypercortisolism (HC) is an important disease in small animal medicine and is the most prevalent endocrinopathy in dogs in southern Brazil [35]. HC is characterized by a myriad of clinical signs with systemic impact, including cardiovascular complications such as systemic arterial hypertension [18,21,30,32] and left ventricular hypertrophy [11,23,42]. The main risk group for HC is characterized by middle to advanced-age small-breed dogs [10,27,31], similar to that observed for mitral valve degeneration (MVD) [28].

Prognosis and survival in canine HC depend on the general health status, owners´ commitment, and disease complications. In addition, it is not clear how comorbidities presence may influence the survival of dogs with HC. Median survival time in dogs with spontaneous HC undergoing drug treatment ranges from 102 to 852 days accordingly to cortisol production imbalance origin (pituitary-dependent HC - PDH or adrenal-dependent HC - ADH) [2,5,15,19]. Furthermore, drug choice (mitotane or trilostane) does not seem to affect survival [5,15,19].

The present study aimed to assess cardiovascular parameters in dogs with spontaneous HC on diagnosis and during medical treatment, investigating possible survival-related cardiocirculatory factors. The study also aimed to assess concurrent MVD influence in survival and MVD progression in dogs with HC.

MATERIALS AND METHODS

Patient selection

This was a prospective cohort study that included dogs with HC selected from the Endocrinology Service of the Veterinary Teaching Hospital (HCV) of the Universidade Federal do Rio Grande do Sul (UFRGS). HC diagnosis was based on the presence of compatible medical history, clinical signs, physical examination, clinical pathology, abdominal ultrasonography, and a positive result in at least one dynamic endocrine test (low dose dexamethasone suppression test and/or ACTH stimulation test), according to the criteria of the American College of Veterinary Internal Medicine (ACVIM) consensus statement [6].

All dogs performed a minimum database composed of complete blood count, urinalysis, and serum biochemical profile (albumin, alanine aminotransferase, total calcium, total cholesterol, creatinine, alkaline phosphatase, phosphorus, fructosamine, glucose, urea, and triglycerides) at each clinical reevaluation. Chronic kidney disease (IRIS stage 2 or greater), diabetes mellitus, previously diagnosed heart diseases (myocardiopathies, valvopathies stage B2 or greater), a recent history of diseases with systemic impact (pancreatitis, inflammatory, or infectious diseases), and/or recent use of drugs which could interfere with the evaluated parameters (anti-hypertensive drugs, diuretics, pimobendan) were adopted as exclusion criteria.

A total of 25 patients with HC were enrolled and divided into 2 subgroups accordingly to their echocardiographic findings: HC (normal echocardiography at first evaluation, n = 16); and HC + MVD (concurrent presence of stages B1 and B2 MVD diagnosed at the first evaluation, n = 9). The diagnosis of MVD was based on the echocardiographic evaluation through changes such as thickening and the presence of valvular leaflets and small nodules [16-18]. The patients of both HC groups were evaluated at 3 different time points: at diagnosis (T0); 6 months after treatment begging (T1); and after 12 months of treatment (T2). In addition, owners were contacted via phone and/or e-mail for further information during a period of up to 1 year after the last evaluation (24 mo total follow-up time). The survival time was considered the interval between the first evaluation of the patient (T0) and his death, regardless of the cause.

A control group (CG, n = 20) of healthy dogs (through medical history, physical examination, and minimum database) with a demographic profile similar to that of the HC patients, was selected for convenience and submitted to the same evaluation of HC dogs at 2-time points with an interval of 6 months (T0 and T1).

Cardiovascular examination

Doppler echocardiography (Micromaxx[1], sector transducers 1-5 and 4-8 MHz) was performed by the same examiner (F.A.C.S). The dogs were placed in the left lateral position for the right and left parasternal short axis and long axis. Two-dimensional, M-Mode, and Doppler imaging (colored and spectral) were used [12,41]. Each examination included the following evaluations: right atrium; left atrium (LA); aortic root diameter (Ao); LA/Ao ratio; interventricular septum thickness in diastole (IVSd); left-ventricular free-wall thickness in diastole (LVFWd); left-ventricular internal diameter in systole (LVIDs) and diastole (LVIDd); right ventricular internal diameter in diastole (RVIDd);

fractional shortening (FS); ejection fraction (EF); and blood flow through the mitral, tricuspid, aortic, and pulmonary valves. The left-ventricular filling pattern was used to assess diastolic function by measuring the transmitral early (E) and late (A) diastolic flow wave velocities (E/A ratio), and isovolumetric relaxation time (IVRT) [12,41].

Systolic blood pressure was measured using Doppler ultrasonography with a portable vascular Doppler (DV610[2]) accordingly to the standardized rules previously established by the Consensus of the American College of Veterinary Internal Medicine [9]. The mean value of 5 consistent measurements was used for statistical analysis.

Electrocardiogram (ECG) was recorded for 2 min in leads I, II, III, aVR, aVL, and aVF, and the precordial leads (rV2, V2, V4, and V10) using a computerized electrocardiogram device (ECG-PC[3]). The dogs were positioned in the right lateral recumbency, without pharmacological restraint, according to standardization [43]. Cardiac rhythm, heart rate, P wave duration, and amplitude, PR interval, QRS complex duration, R wave amplitude, T wave amplitude, QT interval, ST segment, and electric axis were evaluated for interpretation of each exam. Cardiac rhythm was considered for descriptive statistical evaluation.

In addition to cardiovascular tests, the animals were evaluated for the occurrence of cardiorespiratory clinical signs, through anamnesis. Information regarding dyspnea, exercise intolerance, cough, cyanosis, syncope, and sleep quality was graded and registered.

Statistical analysis

Statistical analysis was performed using SPSS[4] software version 20.0. Categorical variables were expressed as frequencies and percentages and compared among the groups by Fisher's exact test, while the McNemar test was used for time points (i.e., T0, T1, and T2) comparison. Quantitative variables were expressed as mean and standard deviation (for symmetrically distributed data) and median, minimum, and maximum (for asymmetrically distributed data). The symmetrical distribution of data was assessed by the Shapiro-Wilk test. Quantitative variables with symmetrical distribution were compared using the Student's *t*-test, while variables with asymmetrical distribution were compared among time points by the Wilcoxon test, and among groups by the Mann-Whitney test. The influence of HC on MVD progression was assessed by Fisher´s exact test. Survival time analysis was performed using a Kaplan-Meier curve. A significance level of 5% was adopted for the comparisons.

RESULTS

The demographic characteristics of the 45 animals divided into the groups HC, HC + MVD, and CD included in the study are summarized in Table 1. In the HC group, there were 15 dogs with PDH and 1 with ADH, while in the HC + MVD group, all dogs were classified as PDH.

In the HC group, 9 of 16 dogs underwent the evaluation at T1 (4 dogs died, the owners of 2 dogs were unable to return to the hospital at this time point, and 1 dog was lost to follow-up because of owner withdrawal from the study). Eleven of 16 dogs underwent the evaluation at T2, 1 of which died between T2 and the end of follow-up (up to 1 year after). During follow-up, dogs with HC were submitted to clinical treatment with oral twice daily trilostane[5], and dose adjustments were defined by the endocrinology team responsible for the cases. Initial treatment doses ranged from 0.41 to 0.99 mg/kg (0.67 ± 0.21 mg/kg), while T1 doses were ranging from 0.7 to 3.23 mg/kg (1.34 ± 0.8 mg/kg), and at T2, doses were ranging from 0.6 to 3.43 mg/kg (1.9 ± 0.96 mg/kg). Trilostane doses were significantly increased over the study ($P < 0.05$).

According to the classification system of heart failure proposed for dogs with MVD [24], all dogs from the groups HC and CG were considered at risk of MVD (stage A) at T0 due to their demographic characteristics (age, size, and/or breed). Four dogs included in the HC + MVD group were classified in stage B1, and 5 dogs were classified in stage B2. Only 4 dogs from this group completed reevaluations at T1 and T2. One owner decided to withdraw his dog from the study, and another 4 dogs died between T0 and T1. The dogs of the HC + MVD group were submitted to clinical treatment with twice daily trilostane, following the same therapeutic criteria of the HC group. In addition, for the patients staged in B2, additional cardiovascular therapy was recommended following the MVD consensus criteria [24]. In CG, 17 of 20 dogs underwent the evaluation at T1. One dog died and the owners of 2 dogs were unable to return to the hospital at this time point.

A comparison of cardiovascular indicators among the HC groups and the control group at T0 is presented in Table 2. There were no significant differ-

ences among cardiovascular parameters in the different time points studied in the 3 groups ($P > 0.05$, data not shown). Data regarding MVD evolution in each group are shown in Figure 1 and further detailed in Table 3. Based on the MVD incidence and evolution observed in each group, the odds ratio (OR) and respective 95% confidence interval (95% CI) for HC as a risk factor for MVD progression over time was defined as 4.267 (0.4268 – 42.65, $P = 0.342$). Exercise intolerance (12/16 dogs, 75%) and dyspnea (6/16 dogs, 37.5%) were the cardiorespiratory clinical signs with the highest incidence in the HC group at T0. When compared to the control group, both exercise intolerance ($P < 0.001$) and dyspnea ($P = 0.03$) occurrence were significantly higher in the HC group.

Five dogs of the HC group died (survival time from 54 to 373 days) and 11 dogs remained alive at the end of the study (follow-up between 465 and 766 days). There was no significant difference ($P = 0.064$) in weight between patients who died (17.4 ± 12.0 kg) and those who remained alive (8.6 ± 5.9 kg) until the end of follow-up. However, the age of dogs who died (13.4 ± 1.1 years) was significantly higher ($P = 0.001$) when compared to dogs alive (8.7 ± 2.4 years) at the end of follow-up. Cardiovascular parameters at diagnosis were compared between alive and deceased patients at the end of the follow-up (Table 4).

When comparing the occurrence of clinical signs at T0, significant differences were not observed in cough, exercise intolerance, cyanosis, syncope, and sleep quality between dogs alive at the end of the follow-up and those who died. However, there was a significantly higher occurrence of dyspnea ($P = 0.036$) in the animals that died (80%) than in those that remained alive (18.2%). According to the information provided by the owners and the medical records, the causes of death in HC dogs were as follows: hepatic neoplasia (2), abdominal neoplasia (1), chronic kidney disease (1), and euthanasia due to HC complications (1). Only 1 of these patients was submitted for necropsy, being confirmed the rupture of a hepatic hemangiosarcoma was the cause of death.

Four dogs of the HC + MVD group died (survival from 47 to 115 days) and 5 remained alive at the end of the study (follow-up from 387 to 654 days). According to the information provided by the owners and the medical records, the causes of death in the HC + MVD group were pulmonary edema (2), complications due to mucocele rupture (1), and an undetermined cause (1). Figure 2 shows the survival curve comparing dogs from the HC and HC + MVD groups over the follow-up. There was no statistical difference between survival in both groups ($P = 0.632$). In the control group, 1 dog died due to complications of hepatic insufficiency of unclear origin (survival of 198 days) and 19 patients remained alive at the end of the study (follow-up between 302 and 570 days).

The 3 groups exhibited a similar percentage of cardiac arrhythmias occurrence verified by ECG. In the HC group, 5/16 (31.3%) dogs exhibited cardiac rhythm disturbances: sinus arrest (2), sinus tachycardia (1), left anterior fascicular block (1), and isolated ventricular premature complexes (1). In the HC + MVD group, 3/9 (33.3%) dogs exhibited sinus arrest. In the control group, 8/20 (40%) dogs exhibited cardiac rhythm disturbances: sinus tachycardia (6), sinus arrest (1), and isolated ventricular premature complexes (1).

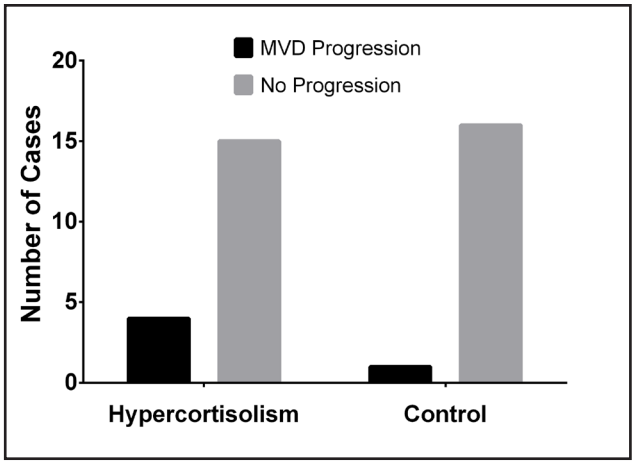

Figure 1. Frequency of mitral valve disease progression over the time points studied in dogs with HC and the Control group.

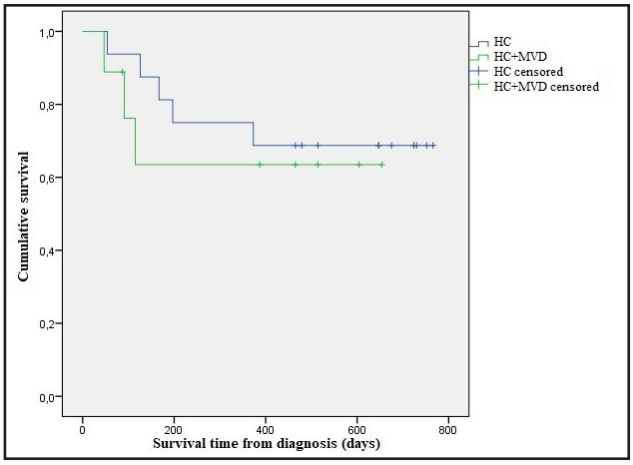

Figure 2. Survival curve comparing dogs with HC and dogs with concurrent HC and MVD.

Table 1. Demographic characteristics of the dogs included in the study in each group.

Demographic characteristics	HC group (n = 16)	HC + MVD group (n = 9)	Control group (n = 20)
Male			
Intact	2	2	1
Neutered	1	3	10
Female			
Intact	-	-	-
Spayed	13	4	9
Age (years)*	10.2 ± 3.0 [5-15]	12.2 ± 2.9 [6-16]	10.2 ± 2.8 [6-15]
Weight (kg)*	11.4 ± 8.9 [2.6-33.2]	8.4 ± 6.3 [1.6-17.5]	8.5 ± 5.5 [2.1-23]
BCS (9-pt)	6.7 ± 1.2	6.6 ± 1.2	5.6 ± 1.0
Breed			
Yorkshire Terrier	4	2	5
Lhasa Apso	3	-	2
Australian Cattle Dog	1	-	-
Boxer	1	-	-
Cocker	-	1	-
Maltese	1	1	1
Miniature Schnauzer	1	-	1
Pinscher	1	-	-
Poodle	-	-	2
Dachshund	1	2	2
Shih Tzu	1	-	1
Mixed breed	2	3	6

*Age and weight are reported as mean ± standard deviation [range]. BCS: Body Condition Score.

Table 2. Cardiovascular parameters (mean ± standard deviation) of dogs with hypercortisolism at diagnosis (HC and HC + MVD groups), and dogs of the Control group.

Parameter (unit)	HC group (n = 16)	HC + MVD group (n = 9)	Control group (n = 20)
HR (bpm)	115.94 ± 20.63	117.11 ± 29.94	135.58 ± 34.57
SBP (mmHg)	183.94 ± 44.05	181.78 ± 47.73	164.68 ± 27.8
LA (cm)	2.52 ± 0.6	2.75 ± 0.27[a]	2.31 ± 0.48
Ao (cm)	1.9 ± 0.55	1.86 ± 0.35	1.82 ± 0.38
LA/Ao ratio	1.35 ± 0.15	1.51 ± 0.21[a,b]	1.28 ± 0.11
RVIDd (cm)	1.09 ± 0.33	1.10 ± 0.33	1.09 ± 0.35
IVSd (cm)	0.69 ± 0.2	0.66 ± 0.15	0.62 ± 0.16
LVFWd (cm)	0.60 ± 0.19	0.57 ± 0.11	0.54 ± 0.16
LVIDd (cm)	2.85 ± 0.63	3.16 ± 0.4[a]	2.65 ± 0.41
LVIDs (cm)	1.69 ± 0.43	1.95 ± 0.3[a]	1.60 ± 0.26
Fractional shortening (%)	40.7 ± 5.4	38.56 ± 3.4	39.7 ± 4.6
Ejection fraction (%)	73.0 ± 6.2	70.33 ± 4.3	72.11 ± 5.16
AoFV (cm/s)	110.9 ± 22.8[a]	111.7 ± 19.04[a]	95.7 ± 11.5
AoFG (mmHg)	5.11 ± 2.21[a]	5.12 ± 1.68[a]	3.71 ± 0.9
PFV (cm/s)	93.4 ± 15.12	86.63 ± 15.7	94.72 ± 26.33
PFG (mmHg)	3.58 ± 1.14	3.09 ± 1.09	3.84 ± 2.49
E wave (cm/s)	69.49 ± 12.47	68.88 ± 17.91	70.9 ± 14.91
A wave (cm/s)	69.2 ± 12.64	73.6 ± 21.97	72.88 ± 13.64
E/A ratio	1.04 ± 0.3	0.99 ± 0.34	0.98 ± 0.23
IVRT (ms)	62.5 ± 9.13	65.56 ± 15.9	58.68 ± 14.89

HC: hypercortisolim; MVD: mitral valve disease; HR: heart rate; SBP: systolic blood pressure; LA: left atrium; Ao: aortic root diameter; RVIDd: right ventricular internal diameter in diastole; IVSd: interventricular septum thickness in diastole; LVFWd: left-ventricular free-wall thickness in diastole; LVIDd: left-ventricular internal diameter in diastole; LVIDs: left-ventricular internal diameter in systole; AoFV: aortic flow peak velocity; AoFG: aortic flow gradient; PFV: pulmonary flow peak velocity; PFG: pulmonary flow gradient; IVRT: isovolumetric relaxation time. [a]Significantly different ($P < 0.05$) from the values of control group. [b]Significantly different ($P < 0.05$) from the values of HC group.

Table 3. Mitral valve disease progression in each group accordingly with the number of dogs that completed the reevaluations at 6 and 12 months in the HC and HC + MVD groups, and at six months in the Control group.

Mitral valve disease progression	HC group (n = 11)	HC + MVD group (n = 4)	Control group (n = 17)
No progression from stage A	8 (72.7%)	-	16 (94.1%)
Progression from A to B1 (T0-T1)	2 (18.2%)	-	1 (5.9%)
Progression from A to B1 (T1-T2)	1 (9.1%)	-	-
No progression from stage B1 (T0-T2)	-	3 (75%)	-
Progression from B1 to B2 (T1-T2)	0 (0%)	0 (0%)	-
Progression from B2 to C (T1-T2)	-	1 (25%)	-

HC: hypercortisolism; MVD: mitral valve disease; T0: at diagnosis; T1: 6 months after beginning treatment; T2: 12 months after beginning treatment.

Table 4. Cardiovascular parameters (mean ± standard deviation) comparison of dogs with HC alive or deceased at the end of the follow-up.

Parameter (unit)	HC group Dogs alive at the end of the follow-up (n = 11)	HC group Dogs that died during the follow-up (n = 5)	*P*-value
HR (bpm)	116.82 ± 24.53	114.0 ± 9.19	0.810
SBP (mmHg)	192.09 ± 47.77	166.0 ± 31.41	0.287
LA (cm)	2.3 ± 0.4	3.0 ± 0.74	0.025*
Ao (cm)	1.71 ± 0.39	2.32 ± 0.66	0.036*
LA/Ao ratio	1.36 ± 0.14	1.32 ± 0.18	0.666
RVIDd (cm)	1.02 ± 0.32	1.24 ± 0.36	0.242
IVSd (cm)	0.62 ± 0.13	0.83 ± 0.25	0.038*
LVFWd (cm)	0.54 ± 0.15	0.74 ± 0.22	0.058
LVIDd (cm)	2.75 ± 0.61	3.07 ± 0.69	0.366
LVIDs (cm)	1.63 ± 0.41	1.81 ± 0.51	0.472
Fractional shortening (%)	40.6 ± 5.83	41.0 ± 4.74	0.905
Ejection fraction (%)	72.91 ± 6.55	74.4 ± 5.86	0.888
AoFV (cm/s)	112.49 ± 12.83	107.36 ± 39.0	0.787
AoFG (mmHg)	5.12 ± 1.16	5.1 ± 3.86	0.992
PFV (cm/s)	97.53 ± 13.17	84.3 ± 16.52	0.106
PFG (mmHg)	3.87 ± 1.04	2.93 ± 1.18	0.129
E wave (cm/s)	73.24 ± 10.93	61.24 ± 12.67	0.073
A wave (cm/s)	67.04 ± 14.2	73.96 ± 7.36	0.327
E/A ratio	1.13 ± 0.3	0.84 ± 0.21	0.068
IVRT (ms)	60.91 ± 7.0	66.0 ± 12.94	0.318

HR: heart rate; SBP: systolic blood pressure; LA: left atrium; Ao: aortic root diameter; RVIDd: right ventricular internal diameter in diastole; IVSd: interventricular septum thickness in diastole; LVFWd: left-ventricular free-wall thickness in diastole; LVIDd: left-ventricular internal diameter in diastole; LVIDs: left-ventricular internal diameter in systole; AoFV: aortic flow peak velocity; AoFG: aortic flow gradient; PFV: pulmonary flow peak velocity; PFG: pulmonary flow gradient; IVRT: isovolumetric relaxation time. *Indicates a significant difference between groups ($P < 0.05$).

DISCUSSION

To the authors' knowledge, this is the first study that investigated the influence of MVD as a comorbidity in survival time in dogs diagnosed with HC, and the influence of HC and its treatment with trilostane in MVD progression. Despite the higher percentage of mortality in the HC + MVD group during the follow-up, there was no significant difference in the survival curve when compared with the HC group. The same was observed regarding MVD progression among dogs of the groups HC and HC + MVD when compared with the Control group. Despite a higher MVD progression rate in dogs with HC, with or without stage B MVD at diagnosis, no statistically significant influence of the HC on MVD was demonstrated. The pathophysiology of heart failure involves a variety of mechanisms, including aldosterone-induced cardiac remodeling [34]. The

decreasing aldosterone secretory reserve in dogs receiving trilostane is common [37], therefore is a factor that could be associated with a reduction of cardiac remodeling in dogs treating HC with this drug. The beneficial effect of pharmacological inhibition of aldosterone synthesis has already been suggested in rats with heart failure [16]. To further investigate this hypothesis, it would be interesting to evaluate a group of dogs with MVD and without HC; however, this was beyond the aim of this study. Also, to better assess HC impact on MVD progression, ideally, a group of dogs with HC without trilostane treatment should be monitored; however, this rises ethical questions. The small number of dogs that finished the evaluation at T2 negatively impacts statistical analysis power; however, the larger 95%CI (OR = 4.267, 95%CI = 0.4268 – 42.65) observed for HC as a predisposing factor for MVD progression suggests there may exist an influence and warrants further investigation.

The present study evidenced the importance of MVD as a comorbidity in dogs with HC since 9/25 (36%) of the dogs presented heart disease as a comorbidity at the time of HC diagnosis. A limitation of the present study was the inclusion of dogs with different MVD staging in the HC + MVD group. Studies dividing patients with distinct stages into separate groups would be an alternative for a more comprehensive analysis, which was not possible in the present study due to the sparse number of dogs enrolled in the HC + MVD group. However, the objective was to include the data of these patients to compare the influence of the preclinical heart disease discovered during the screening of patients at the time of diagnosis of HC.

The present study's survival rates were similar to data from a recent study [15], reinforcing a good response to clinical treatment with trilostane. A retrospective study reported that the lack of treatment of dogs with HC is associated with a higher risk of death when compared to patients treated with trilostane [29].

As in the present study, advanced age at diagnosis has been reported as a factor in shorter survival time in canine HC [14,15]. The causes of death in canine HC are diverse and in many cases are not related to the disease. Retrospective studies attributed 25.9 to 38.2% of deaths to HC in dogs with the syndrome [15,20]. Among the causes related to death by HC are metastases and vena cava invasion in the cases of ADH, neurological signs in PDH cases, as well as progressive physical deterioration and pulmonary thromboembolism that can occur in any form of HC [2,15,19]. In the HC group of the present study, 2 dogs had cancer-related death without necropsy confirmation (the possibility of tumor association to HC cannot be disregarded) and 1 dog was euthanized due to progressive physical deterioration associated with the disease. Cardiorespiratory involvement is often cited among the causes of death in canine HC. Although a study cites the occurrence of mitral endocardiosis in 2 patients [15], in most studies, cardiorespiratory diagnosis is not defined, being mentioned only as cardiac disease and respiratory disease [15,38], heart failure and pulmonary edema [2], and dyspnea [15,29].

Although patients with cardiac comorbidity have been discarded in the HC group, the occurrence of exercise intolerance and dyspnea is justified by the endocrine disease itself, since HC can impair eupnea due to overall muscle weakness, including respiratory muscles, body weight gain with centripetal fat deposition, hepatomegaly, lethargy, pulmonary mineralization, and eventually pulmonary thromboembolism [6].

Dyspnea is a sign associated with an increased risk of death in dogs with MVD [25]. However, it may also be present in the canine HC by several factors above mentioned [6,7]. In the HC group of the present study, dyspnea was a clinical sign with a significantly higher occurrence in dogs that died during the follow-up. Thus, the involvement of these complications in dogs with dyspnea in the present study cannot be ruled out, since the diagnosis of thromboembolism and pulmonary mineralization depends on advanced imaging techniques [4,7,17] that were not performed.

Despite larger echocardiographic dimensions evidenced in dogs that died during the follow-up, these are alterations that may be related to the higher mean weight of these dogs, once the reference values vary according to the size of the animal [8]. The increased thickness of the interventricular septum may be related to cardiac remodeling caused by HC [11,23,33], a hypothesis that would require studies associating survival, imaging, and histopathology of the heart for further investigation.

Systemic arterial hypertension is common in canine HC, affecting 59-86% of patients [15,18,21,30,32]. In the present study, 12/16 (75%) of the dogs in the HC group exhibited systolic blood pressures above 160 mmHg at diagnosis, which is considered hypertension with a moderate risk of damage to the target organs [1]. Despite all care taken with standards for SBP measurements, one factor that may be associated with the elevated SBP in some control dogs is the anxiety or excitement of the patients at the time of the examination, which can lead to falsely elevated values in the hospital environment [40]. Also, sinus tachycardia evidenced on ECG by 30% of control dogs, is another finding that may be related to anxiety or excitement. The excitement hypothesis may be further supported because no dog had ventricular concentric hypertrophy or proteinuria (which could suggest cardiac and renal secondary damage, respectively). Moreover, these dogs were further investigated at home, and all of them showed SBP values below 160 mmHg; however, these values were not considered for statistical analysis.

Recent studies reported the presence of left ventricular concentric hypertrophy (characterized by an increased interventricular septum and left ventricular free-wall thickness) as an important consequence of HC in humans [37,38] and dogs [6,7,34]. In the present study, despite higher mean interventricular septum and left ventricular free-wall measurements in the HC group when compared to the control group, there was no significant difference between the groups. Hypertension probably is not the only factor causing left ventricular hypertrophy in HC since associations or positive correlations between such parameters were not documented in 2 studies [11,42]. A theory suggesting a direct effect of cortisol on cardiomyocytes is currently discussed [3]. None of the studies with echocardiographic evaluation suggested increases in aortic flow velocity and pressure gradient, however, the focus of many of these was the evaluation of cardiac structure. One hypothesis that may be related to this finding is the fact HC causes endothelial dysfunction [22,36], which may increase arterial vascular stiffness [13,26] and, consequently, such resistance may increase the left ventricular outflow tract.

There were no significant differences in the cardiovascular parameters of the HC group during the follow-up of the present study. The mean values of all parameters were similar to the reference for canine species during the study, except SBP, despite reducing throughout the treatment, was always above the reference value. Studies in humans report that control of HC as the underlying cause is not effective in controlling SBP in 25 to 56% of hypertensive patients [6,14]. In addition, as in the present study, other studies in dogs with HC did not report a significant decrease in SBP after treatment [18,38,39].

Finally, despite hypercortisolism can interfere with the heterogeneity of ventricular repolarization parameters in dogs and is also associated with higher arrhythmogenic risk and atrial fibrillation in humans [44], no particular difference in ECG abnormalities could be documented among dogs with HC with or without MVD in comparison with controls.

CONCLUSION

The present study suggests that systemic arterial hypertension and echocardiographic measurements did not interfere with the survival time of patients with HC, however, dyspnea at the time of diagnosis was a clinical sign associated with a worse prognosis. Finally, it is possible to conclude that mitral valve degeneration is a common comorbidity in dogs with HC, however, it was not evidenced their interference in the survival of dogs with this endocrine disease or even a role of the HC in the progression of the MVD.

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***Ethical approval*.** The study was approved by the Universidade Federal do Rio Grande do Sul Ethics Committee on Animal Use (CEUA, under protocol n. 31830), and a consent form was signed by the owners authorizing their dogs' participation in the study.

***Declaration of interest*.** The authors declare no competing interests concerning the research, authorship, and/or publication of this article. The authors alone are responsible for the content and writing of the paper.

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