

Comparative study of the clinical and echodopplercardiographic aspects of left ventricular hypertrophy and hypertrophic cardiomyopathy in cats (*Felis catus*)

Estudo comparativo dos aspectos clínicos e ecodopplercardiográficos da hipertrofia ventricular esquerda e da cardiomiopatia hipertrófica em felinos (*Felis catus*)

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Abstract

The aim of the present study was to differentiate hypertrophic cardiomyopathy (HCM) from concentric left ventricular hypertrophy (CLVH) and to compare their echodopplercardiography measurements in random bred domestic cats. After owners consent 135 cats of any sex or age with no history of heart disease were randomly submitted to physical examination and echocardiogram. When left ventricular hypertrophy was present on the echocardiogram, cats were further examined by chest X-rays, abdominal ultrasonography and laboratory work. Those presenting cardiac hypertrophy with the diagnosis of any disease that could cause left ventricular hypertrophy were allocated into one group (CLVH) and those presenting hypertrophy without any concomitant detectable disease were allocated to another group (HCM). Cats with ventricular hypertrophy cats were included (n = 10), among which five were classified as secondary CLVH, with hyperthyroidism being the main cause and five characterized as HCM. Considering the diagnosis of concentric ventricular hypertrophy, other diseases should be investigated and ruled out, such as hyperthyroidism. It is also necessary to consider and monitor cardiac changes more closely, since their phenotypic manifestation was more severe than those observed in the animals with HCM. However, to determine whether disease progression in these animals is faster severer than in others, further epidemiological studies are necessary.

Keywords: feline, echocardiogram, heart disease, hyperthyroidism.

Resumo

O objetivo do presente estudo foi diferenciar a cardiomiopatia hipertrófica (CMH) da hipertrofia ventricular concêntrica (HVC) e comparar suas medidas ecodopplercardiográficas em gatos domésticos criados aleatoriamente. Após o consentimento dos proprietários, 135 gatos de qualquer sexo ou idade sem história de doença cardíaca foram submetidos aleatoriamente ao exame físico e ao ecocardiograma. Quando a hipertrofia ventricular esquerda estava presente no ecocardiograma, os gatos foram examinados posteriormente por radiografias de tórax, ultrassonografia abdominal e exames laboratoriais. Aqueles que apresentavam hipertrofia cardíaca com o diagnóstico de qualquer doença que pudesse causar hipertrofia ventricular esquerda foram alocados em um grupo (HVC) e aqueles que apresentavam hipertrofia sem qualquer doença detectável concomitante foram alocados em outro grupo (CMH). Gatos com hipertrofia ventricular foram incluídos (n = 10), dos quais cinco foram classificados como HVC secundários, sendo o hipertireoidismo a principal causa e cinco caracterizados como CMH. Considerando o diagnóstico de hipertrofia ventricular concêntrica, outras doenças devem ser investigadas e descartadas, como o hipertireoidismo. Também é necessário considerar e monitorar as alterações cardíacas mais de perto,



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uma vez que sua manifestação fenotípica foi mais severa do que aquelas observadas nos animais com CMH. No entanto, para determinar se a progressão da doença nesses animais é mais rápida do que em outros, mais estudos epidemiológicos são necessários.

Palavras-chave: felino, ecocardiograma, doença cardíaca, hipertireoidismo.

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by a concentric hypertrophy of the left ventricle without volume enlargement (Côté et al., 2011b). This hereditary disease of incomplete penetrance has been well described for purebred cats like Maine Coon, Ragdoll, American Short Hair, English Short Hair (Meurs et al., 2005, 2007), Sphynx (Chetboul et al., 2012) and Persian (Trehou-Sechi et al., 2012). Cardiomyocyte hypertrophy can be present in different cardiopathies, although the myofibrillar disorder is characteristic of HCM (Maron et al., 1982).

Both HCM and concentric left ventricle hypertrophy (CLVH) present similar phenotype although different etiology. HCM is genetically determined and CLVH is secondary to different diseases and conditions such as aortic stenosis, arterial hypertension, chronic kidney disease, hyperthyroidism and hyperaldosteronism (Côté et al., 2011a; Marino et al., 2014). Most of the studies on feline cardiopathies, due to their genetic origin, are concentrated in purebred cats, therefore, the aim of the present study was to differentiate HCM from CLVH and to compare their echodopplercardiography measurements in random bred domestic cats.

Material and methods

This study was approved by the animal use committee CEUA-FAPUR protocol number 01-05-13.

After owners consent 135 cats of any sex or age presented to UFRRJ or IEMEV with no history of heart disease were randomly submitted to physical examination and echocardiogram. The echocardiographic evaluation was always performed by the same operator, using m-mode, two-dimensional mode and spectral Doppler evaluation to identify those with left ventricular hypertrophy.

All procedures were performed with the cats manually restrained by their owners, under no sedation. All cats presenting left ventricular wall or ventricular septum in diastole over 5 mm (Ware, 2011; Häggström et al., 2016) were included in the study and further evaluated by Doppler blood pressure measurement, as suggested by Acierno et al. (2018) after acclimatized; physical exam; chest x-rays; abdominal ultrasound and laboratory work. The physical exam was always performed by the same veterinarian, as well as the radiographic and ultrasonographic evaluation.

Urine was collected by cystocentesis for urinalysis and urinary protein/ creatinine ratio determination. Blood samples were collected after 8 hours fasting for blood urea nitrogen (BUN), creatinine, sodium, potassium, ionic calcium, phosphorus and total T4 (radioimmunoassay). Azotemic cats repeated BUN, creatine and blood pressure measurement exams after 7 days to ensure the result (International Renal Interest Society, 2017).

Cats not presenting clinical signs of the disease that could induce CLVH were classified as HCM and cats with those clinical signs, especially considering laboratory work, blood pressure and image results were classified as CLVH. When chronic kidney disease (CKD) was detected, it was only considered as causing ventricular hypertrophy when the cat presented persistent azotemia and blood hypertension associated with ultrasound detected kidney morphology change.

Regarding chronic kidney disease (CKD), only animals with left ventricular hypertrophy were staged according to the International Renal Interest Society (2017).

A descriptive and comparative statistical analysis of the age group was performed using Fisher's exact test. Doppler echocardiographic variables were analyzed by mean and standard deviation and a variation of data using the coefficient of variation. The comparison of Doppler echocardiographic variables between groups (HCM and CLVH) was performed using the Mann Whitney test. The significance level adopted for all samples was $p \leq 0.05$. BioEstat, version 5.3®.

Results

Ten left ventricular hypertrophy cats were identified and out of those, five were classified as HCM and five as CLVH. Among the CLVH cats, hypertiroidism was the cause for hypertrophy for four cats and for one cat blood hypertension secondary to chronic kidney disease (stage II) was the cause (Table 1).

CLVH cats were older than HCM cats ($U = 2; p = 0.0141$). The mean age for CLVH was 14.8 ± 4.9 years and for HCM cats 5.8 ± 2.8 years.

Although the majority of the cats with left ventricular hypertrophy were females (4/5 CLVH and 3/5 HCM), there was no statistic difference by sex ($p = 0.3957$).

Abdominal ultrasound revealed abnormalities in renal morphology of cats of both groups with similar frequency ($p = 0.5000$) between cats with CLVH ($n = 4$) and those with HCM ($n = 3$).

Chest x-rays of the HCM cats suggested bilateral enlargement of the heart in 2 animals and right atrium enlargement in 3. In CLVH cats the radiographic exam suggested right atrium enlargement in 3 animals; bilateral enlargement in 1 and another one with no cardiac silhouette change.

Most HCM and CLVH cats echocardiography measurements were similar. Differences were: HCM cats presented larger measurements of Left atrium (LA) ($U = 3.5; p = 0.0301$), left ventricle in diastole (LVd) ($U = 1.5; p = 0.0108$) and left ventricle in systole (LVs) ($U = 4.5; p = 0.0473$) while: left ventricular wall in diastole (LVWd) measurement was largest for CLVH cats (Table 2).

Besides those variations, one HCM cat presented systolic anterior movement of the mitral valve (SAM) and another cat presented dynamic obstruction of the left ventricular outflow tract (LVOT). Two of the CLVH cats presented both SAM and LVOT and in one of them mitral valve insufficiency was also observed.

Discussion

The percentage of HCM cats among the left ventricle concentric hypertrophic cats (3.7%) was lower than the expected 10 - 15% (Côté et al., 2011b; Fox, 1999; Paige et al., 2009; Abbott, 2010; Branquinho et al., 2010) what might have been influenced by the number of females included, once males are known to be more predisposed to HCM than females (Fox, 1999; Rush et al., 2002).

Table 1. Laboratory tests results, measurement of systolic blood pressure and ultrasonography exam of random bred cats with hypertrophic cardiomyopathy and secondary concentric ventricular hypertrophy.

Animal	Age (Years)	BUN1	BUN2	Cr1	Cr2	U.D	PU:CU	Na	K	Cai	P	T4t	BP1	BP2	USG	Stagin of CKD
Hypertrophic cardiomyopathy																
1	5	53	48	1.3	1.3	1030	0.3	140	4.1	1.4	3.8	24.3	139	--	N	At Risk
2	2	28	30	1.3	1.3	1050	1.69	148	4.3	1.3	3.6	22.6	140	--	N	At Risk
3	5	105	102	1.9	1.9	1028	0.28	139	3.8	1.13	5.6	28.8	139	--	Ch	II
4	8	97	80	2.0	2.0	1026	0.1	137	4.8	1.23	8.2	26.7	140	--	Ch	II
5	9	45	56	1.5	1.6	1050	0.17	143	4.4	1.25	7.9	22.6	161	138	Ch	I
Concentric Hypertrophy of the Left Ventricle																
6	19	89	106	2.6	2.1	1012	0.3	137	4	1.1	17	28.8	223	220	Ch	II
7	7	52	48	1.5	1.3	1030	0.2	140	4.9	1.26	6.6	36.4	123	--	N	At Risk
8	17	89	*	2.3	*	*	*	150	3.9	0.87	7	34.5	161	*	Ch	II
9	13	90	75	0.9	1	1046	0.53	146	3.2	1.1	4	89.3	138	--	Ch	I
10	18	88	98	1.4	1.5	1025	0.7	144	2.6	1.2	3.6	78	122	--	Ch	I

BUN1 = first measurement of blood urea nitrogen; BUN2 = second measurement of blood urea nitrogen; Cr1 = first measurement of creatinine; Cr2 = Second measurement of creatinine; U.D = urinary density; PU:CU = urinary creatinine protein ratio; Na = sodium; K = potassium; Cai = ionic calcium; P = phosphorus; T4t = total tetraiodothyronine; *unrealized; - there was no need for repetition; BP1 = systolic systemic blood pressure; BP2 = systolic systemic blood pressure; USG = abdominal ultrasonography; N = normal; Ch = changed in renal morphology; CKD = Chronic Kidney Disease.

Table 2. Doppler echocardiography (in cm) in the M-mode of random bred cats, with hypertrophic cardiomyopathy and secondary concentric ventricular hypertrophy.

Animal	LA	LA/AO	VSd	VSs	LVWd	LVWs	LVd	LVs	AoVmax	AoGrP	SF	EF
Hypertrophic cardiomyopathy												
1	1.25	0.98	0.52	0.6	0.52	0.8	1.25	0.71	0.88	3.1	43	78
2	1.27	1.4	0.57	0.91	0.39	0.44	1.37	0.75	0.86	2.9	45	80
3	1.8	1.63	0.55	0.97	0.52	0.93	1.93	0.97	0.98	3.9	50	84
4	1.49	1.16	0.46	1.04	0.55	1.07	1.66	0.41	1.09	4.7	75	98
5	1.62	1.42	0.66	0.83	0.41	0.69	1.38	0.66	0.88	3.1	53	87
Mean	1.49 ^a ±0.23	1.32±0.25	0.55±0.07	0.87±0.17	0.48 ^a ±0.07	0.79±0.24	1.52 ^a ±0.28	0.7 ^a ±0.20	0.94±0.10	3.54±0.75	53.2±12.81	85.4±7.86
C.V	0.16	0.19	0.13	0.19	0.15	0.31	0.18	0.29	0.10	0.21	0.24	0.09
Concentric Hypertrophy of the Left Ventricle												
6	1.06	1.16	0.56	0.8	0.5	0.8	1.14	0.62	0.97	3.8	55	89
7	1.16	1.15	0.52	1.01	0.67	0.79	1.34	0.61	0.92	3.4	55	88
8	1.16	1.29	0.56	0.78	0.54	0.78	1.25	0.6	0.88	3.1	52	86
9	1.28	1.35	0.59	0.86	0.59	0.97	1.24	0.41	1.2	5.7	67	95
10	1.27	1.23	0.52	0.8	0.62	0.75	1.24	0.6	0.88	3.1	52	87
Mean	1.19 ^b ±0.1	1.24±0.1	0.55±0.03	0.85±0.1	0.58 ^b ±0.1	0.82±0.1	1.24 ^b ±0.1	0.57 ^b ±0.1	0.97±0.5	3.82±0.3	56.2±6.2	89.0±3.5
C.V	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.9	0.1	0.1	0.04

Different letters in the column mean difference at the 5% level. LA = Left atrium; LA/AO = left atrium/aorta ratio; VSd = ventricular septum in diastole; VSs = ventricular septum in systole; LVWd = left ventricular wall in diastole; LVWs = left ventricular wall in systole; LVd = left ventricle in diastole; LVs = left ventricle in systole; AoVmax = Aortic peak velocity; AoGrP = aortic flow pressure gradient; SF = shortening fraction; EF = ejection fraction; CV = coefficient of variation.

Hyperthyroidism was the main cause of CLVH among the included cats and their age range matches the expected range for the occurrence of hyperthyroidism (Peterson, 2012; Vaske et al., 2016), reinforcing that monitoring hyperthyroidism cats heart is a requirement for good veterinary procedures. Furthermore, young adult cats were the most HCM affected (5.8 ± 2.8 years) what, although does not contradicts previous reports (8,19), when analysed along with the age range detected for CLVH cats (14.8 ± 4.9 years) suggests that hyperthyroidism CLVH cats could have been hypertrophic before developing the thyroid dysfunction. Therefore, longitudinal cohort studies are needed to establish cause and effect.

Once the previous clinical history of the chronic kidney disease cat was unavailable, the same rational can be extrapolated; the cat could have presented primary hypertension previously, what could have induced either left ventricle wall hypertrophy or the kidney disease (Acierno et al., 2018). Among the cats that were characterized as hypertensive, one presented CKD (sustained azotemia, low urinary density and altered renal morphology). It can be inferred that CKD has caused the blood hypertension and consequently secondary ventricular hypertrophy (International Renal Interest Society, 2017; Brown et al., 2007), but it is impossible to rule out primary hypertension as cause of the renal injury and ventricular hypertrophy in consequence (Acierno et al., 2018; Pouchelon et al., 2015). There were no previous exams as well as BP measurements prior to evaluation. No cat was diagnosed with primary hypertension although it has been reported in 13 to 20% of the feline population (Maggio et al., 2000; Elliott et al., 2001; Jepson et al., 2007).

One animal died (N.8) and had BP measured only once. However, in addition to hypertension, it had increased levels of total T4, azotemia, low urinary density, altered renal morphology and blood hypertension, alterations that allow to consider that ventricular hypertrophy diagnosed at echocardiographic examination was related to secondary disease, although it was impossible to determine which one was responsible for cardiac changes (hyperthyroidism, chronic kidney disease and hypertension), or even though if they were associated in this condition (Acierno et al., 2018; Brown et al., 2007).

In CKD stage II cats (2 HCM cats and 1 CLVH due to hyperthyroidism) (showing discrete renal azotemia and absence of clinical signs) (International Renal Interest Society, 2017) without hypertension, concentric ventricular hypertrophy was not considered to be a consequence of the renal disease. One CKD stage II animal (N.6) presented sustained azotemia, low urinary density and blood hypertension, therefore, CKD was considered to be the cause of the CLVH. It is important to consider that CKD as the cause of ventricular hypertrophy is not fully elucidated among domestic animals, therefore hypertension along with laboratory findings (Table 1) was considered to be determinant of the chronic pressure overload (Brown et al., 2007; Pouchelon et al., 2015; Maggio et al., 2000; Maciel, 2001; Ronco & Di Lullo, 2014).

Hyperphosphatemia was present in all stage II CKD animals (Table 1), therefore it is important to mention that it could have stimulated the production of parathormone (Kogica et al., 2015), which could lead to cardiovascular disorders such as hypertrophy, as described in humans (Neves et al., 2008). Since there is no scientific evidence associating hyperparathyroidism with concentric ventricular hypertrophy in small animals medicine it was impossible to include hyperphosphatemia as an etiologic factor ventricular hypertrophy.

The biatrial increase in the evaluation of the cardiac silhouette is a radiographic alteration that in the past was highly related to the presence of feline hypertrophic cardiomyopathy, however, Winter et al. (2015), in his study, found a low correlation between this radiographic finding and the disease in question, considering that the biatrial increase may be present in different feline cardiomyopathies.

Since the right atrial enlargement observed in chest x-rays of 6 cats (60%) was not concomitant with left atrial remodeling, it was considered to be an independent finding (Oura et al., 2015).

When the mean values of left ventricular cavity diameter measurements in systole and diastole were compared, the animals with CLVH had a smaller diameter at both moments, suggesting that the hypertrophy in these animals causes reduction of ventricular relaxation, reflected in a lower final diastolic volume, besides greater ejection fraction, resulting in a lower final systolic volume. These findings suggest that diseases that occur in CLVH, generate more pronounced hypertrophy. This evidence is reinforced when analyzing the means of both the shortening fraction and the ejection fraction of the CLVH animals, which are larger than those of the HCM cats. Although there was no statistical difference, these findings, together with the results of aortic flow velocity and pressure gradient, which also had their mean measurements greater in CLVH cats, suggest that in these animals a higher ventricular and hemodynamic response on account of hypertrophy is occurring.

On the echocardiographic examination the size of the left atrium of HCM cats was greater than the size of the left atrium CLVH animals, which may suggest that cats with HCM present a tendency to volume overload of the left atrium greater than the CLVH cats. However, the CLVH animals, although presenting a hypertrophic process more pronounced than the animals with HCM, presented no atrial overload. As the ventricular hypertrophies were differently distributed between the two groups of cats, it may be suggested that the magnitude of the atrial overload has more to do with the form the hypertrophy is presented than to its intensity in itself, at least in the initial stages of disease (Côté et al., 2011b; Sampedrano et al., 2006; Ferasin, 2009a).

LA enlargement was increased in one HCM animal (N.3). This same animal presented hypertrophy of the interventricular septum and of the left ventricular wall in both systole and diastole. It is believed that LA enlargement may be an initial reflection of the difficulty of this chamber in pumping blood into the left ventricle, due to a greater resistance generated by hypertrophy. The finding of both septum and left ventricular wall hypertrophy in diastole without reducing the final diastolic and systolic volume may lead to the diagnosis of unclassified feline cardiomyopathy, although it may also be a stage of evolution of HCM (Sampedrano et al., 2006; Ferasin, 2009a, 2009b).

Conclusion

Considering the diagnosis of concentric ventricular hypertrophy, other diseases should be investigated and ruled out, such as hyperthyroidism, which was the main cause of secondary concentric hypertrophy in the present study. Although sensitive in the detection of concentric hypertrophy, echocardiographic findings are similar regardless of the cause of hypertrophy, as

well as clinical and epidemiological aspects it is also necessary to monitor cardiac changes of CLVH closely, since their phenotypic manifestation was more severe than those observed in the animals with HCM. However, to determine whether disease progression in CLVH animals is faster than in HCM, further epidemiological studies are necessary.

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