Title

Survival and prognostic factors in cats with restrictive cardiomyopathy: a review of 90 cases

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Objectives

Large studies focusing on restrictive cardiomyopathy in the cat are scant. The aims of this retrospective study were to describe epidemiological characteristics and to analyze prognostic factors affecting survival in cats with restrictive cardiomyopathy.

Methods

The clinical archives of the Clinica Veterinaria Gran Sasso (Italy) and of the cardiology unit of the Department of Veterinary Medicine (University of Milan, Italy) from 1997 to 2015 were reviewed for all cats diagnosed with restrictive cardiomyopathy based on an echocardiographic exam (left atrial/biatrial enlargement, normal left ventricle wall thickness, normal or mildly decreased systolic function and restrictive left ventricle filling pattern with pulsed Doppler echocardiography)

Results

The study population comprised 90 cats (53 male and 37 female) with an echocardiographic diagnosis of restrictive cardiomyopathy. Most were domestic shorthair (n=60) with a mean age of 10.0±4.3 years and a median weight of 3.8 kg (IQR 3.2-5 kg). Most cats were symptomatic (n=87). The most common clinical sign was respiratory distress (n= 75). Follow-up was available on 60 cats and the median survival time (MST) was 69 days (95% CI 0-175 days). Cardiac-related death occurred in 50 cats. In the multivariate Cox analysis only respiratory distress showed a statistically significant effect on survival. The cats without respiratory distress showed a MST of 466 days (95%CI 0-1208); cats with respiratory distress showing a MST of 64 days (95%CI 8-120, p=0.011).

Conclusions and relevance

RCM can be considered an end stage condition associated with a poor prognosis, with few cats not showing clinical signs and surviving longer than a year: most cats died for cardiac disease in a very short time.

Introduction

Restrictive cardiomyopathy (RCM) is a myocardial disorder characterized by myocardial stiffness, severe diastolic dysfunction (restrictive physiology) and an overall poor prognosis.[1-4] It is not clear if some of the RCM cases may be considered the end result of other forms of cardiomyopathy (CM), mainly hypertrophic cardiomyopathy (HCM) and myocarditis.[2,5-10] As serial echocardiographic exams are seldom available for review to substantiate changes in the echocardiographic appearance, it is difficult to quantify or identify if different separate etiologies contribute to a common end-stage pattern. RCM is often morphologically sub-classified into two forms: myocardial and endomyocardial.[1] Echocardiography allows classification and is at the moment the most common tool for diagnosis. Both forms of RCM are characterized by atrial enlargement, normal left ventricular (LV) wall thickness, normal or mildly decreased systolic function. and restrictive LV filling pattern with pulsed Doppler echocardiography; in the endomyocardial form, thick hyperechoic tissues bridge the LV lumen.[1-4,8] Large studies focusing on RCM in the cat are scant.[2,3] The aims of this retrospective study were to describe epidemiological characteristics and to analyze prognostic factors affecting survival in cats with RCM.

Materials and methods

The clinical archives of the Clinica Veterinaria Gran Sasso (Italy) and of the cardiology unit of the Department of Veterinary Medicine (University of Milan, Italy) were reviewed to identify cats diagnosed with RCM based on an echocardiographic exam from 1997 to 2015. Inclusion criteria were any patient with a complete case record (owner data, patient signalment and anamnesis, complete clinical findings and cardiac investigation) and an echocardiographic diagnosis of RCM.

The diagnosis was based in both institutions on the echocardiographic presence of: left atrial/biatrial enlargement, normal LV wall thickness (m-mode LV wall thickness in diastole < 6mm measured by the leading edge to leading edge method), normal or mildly decreased systolic function and restrictive LV

filling pattern with pulsed wave Doppler echocardiography (E wave/A wave ratio [E/A] >2).[2,4,8] The latter criteria was not strictly considered for inclusion in cases where E and A waves were summated (for tachycardia) or A wave was absent (due to supraventricular arrhythmia) and all previously mentioned echocardiographic characteristics were present. In case of focal hypertrophy (> 6 mm in M-mode or B mode measurements) the case was excluded from the study.

Left atrial enlargement was defined by a left atrium to aortic root ratio (LA/Ao) greater than 1.5 on B-mode.[11] Left atrial enlargement was subsequently classified as mild to moderate if the LA/Ao ratio was 1.5-2.0, while cats with a LA/Ao ratio >2.0 were considered to have severe LA enlargement.[11] Echocardiographic signs of increased risk for arterial thromboembolism (ATE) included the presence of spontaneous echocardiographic contrast ('smoke effect') or the direct visualization of intracardiac thrombi in the left atrium or auricle.

Cats diagnosed with a CM other than RCM, congenital heart disease, systemic hypertension, hyperthyroidism or those with incomplete case records were excluded from the analysis.

Systemic systolic blood pressure was assessed non-invasively using a Doppler-based technique in all patients as recommended by the American College of Veterinary Internal Medicine Guidelines.[12] When BP was >150 mmHg on serial repeated measurements, the cat was classified as affected by systemic hypertension and excluded from the study.[13] All cats older than 10 years of age had their T4 levels tested.[14] If the patient presented with a clinical history or with clinical findings related to the presence of hyperthyroidism (polyphagia, progressive weight loss), T4 levels, haematology and biochemistry were performed regardless of the patient's age. Thoracic radiograph were performed in all cats with respiratory distress.

Respiratory distress was defined by the presence of increased respiratory rate associated with an increase in effort and/or open mouth breathing and/ or orthopnea. Increased respiratory rate (tachypnoea) alone was not considered sufficient due to the possibility of tachypnoea being identified in normal cats in the hospital environment.[15]

Follow-up status and cause of death was determined by reviewing the medical records and/or phone interviews with the owners by investigators or trained senior veterinary students, when more information was required. If the cats had died, an attempt was made to classify the events as cardiac related or not. Cardiac-related death was defined as death occurring because of progression of clinical signs of heart failure (HF)/ATE. Euthanasia because of refractory HF/ATE was scored as cardiac-related death. Sudden death was regarded as cardiac-related if no other cause of death was obvious. Cats still alive or that had died or were euthanized for reason unrelated to cardiac disease were censored in the statistical analysis. Subjects lost to follow-up were included in the survival analysis up until the last time point at which they were known to be alive and then were thereafter censored in the analysis.

Statistical analysis

Basic descriptive statistical analyses were performed using Microsoft Excel. Data were analyzed using a commercially available software (SPSS Statistics for Windows v23). In all cases a *P value* <0.05 was described as significant. The Shapiro-Wilk test was used to verify variables normal's distribution. Normally distributed data were reporter as mean ± SD and non-normally distributed data as median and interquartile range (IQR).

Survival time was calculated from the time of diagnosis to the date of death or last telephone contact. The Kaplan-Meier method was used to estimate the survival function and plot time to event curves in

the different group. A log-rank test with right-censoring was used to determine whether a significant difference existed between groups.

Schoenfeld residuals and time dependent covariates were used to test the assumption of proportional hazards. Univariate and multivariate Cox proportional hazard analysis were performed in order to determine the effect of any variable on survival. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated.

Variables were added to the multivariable model in a manual stepwise manner, including first all variables statistically significant in the univariate analysis, and then excluding those not reaching statistical significance one by one, until all the variables included were statistically significant (backwards regression analysis).

Variables assessed for their effect on outcome were breed (longhair vs shorthair), sex, age at presentation, presence of clinical signs (respiratory distress, syncopal episode, limbs paresis/paralysis) presence of pleural/pericardial effusion, pulmonary edema and abdominal distension,and echocardiographic variables (left atrium/aortic ratio, mild-moderate or severe left atrial enlargement, LV FS, LV dimensions in systole/diastole and presence of echocardiographic signs of increased risk for ATE)..

Results

From January 1997 to December 2015, 767 cats were diagnosed with a CM; most cats had HCM (594 cats, 77.5%), 115 cats (15%) were classified as RCM, 34 cats (4%) as dilated CM (DCM), 22 cats (3%) as unclassified CM (UCM) and 4 cats (0.5%) as arrhythmogenic right ventricular cardiomyopathy. Twenty-five cats with RCM were thereafter excluded because they didn't meet the inclusion criteria (12 incomplete case records and 13 incomplete echocardiographic reports). The final study population comprised 90 cats with an echocardiographic diagnosis of RCM.

Male cats were predominant in the population (58.9% were male and 41.1% were female). Forty-three male and 34 female were neutered. Breed population included mostly domestic shorthair cats (n=60, 67%), followed by Persians (n=15, 17%), longhair cats (n=11, 12%; four Norwegian Forest Cats, four Birman and three Maine Coons), three Siamese cats and one Chartreux. At presentation the mean age was 10.0 ± 4.3 years and the median weight was 3.8 kg (IQR 3.2-5 kg). The majority (n=87; 97%) of cats had clinical signs at presentation, with only three cats asymptomatic. Only the minority of cats had a murmur (n=9; 10%). Twelve cats (13%) presented supraventricular arrhythmias.

Presenting complaints are listed in table 1.

Thoracic radiographs were performed in the 75 cats (83%) presenting with respiratory distress. Pleural effusion was observed in 44 cases (58.7%), pulmonary edema in 19 (25.3%) and both in 12 cases (16%).

All cats received a therapy with furosemide and ACE inhibitors. Diltiazem was administered in all cats that presented with supraventricular arrhythmias. Anti-thrombotic treatment (aspirin low dose before January 2013 or clopidogrel after) was administered in all cats with clinical and/or echocardiographic signs of increased risk of ATE (presence of thrombus, smooke effect) and/or moderate atrial dilatation, (LA/Ao>1.8).

All cats included in the study were conscious, unsedated, manually restrained during the echocardiographic examination. Echocardiographic parameters in cats with RCM are showed in Table 2. All cases had a restrictive pattern with the exception of 18 cats: 6 cats had the E wave summated to the A wave for tachycardia and 12 cats had supraventricular arrhythmia and the A wave absent. Most cats had severe left atrial enlargement (n=72, 80%) and 25 cats (27.8%) presented echocardiographic signs for increased risk of ATE (smoke effect or mural thrombi). Patchy or extensive areas of increased echogenicity of the endocardium were observed in only 2 cases. During the echocardiographic examination pericardial effusion was observed in 6 cats.

153 Follow-up was available on 60 cats and the median survival time (MST) was 69 days (95% CI 0-175 days).
154 Cardiac-related death occurred in 50 cats (83%), 5 cats were still alive at last follow-up and 5 cats had
155 died from unrelated cardiac causes (3 neoplasia and 2 chronic kidney disease).
156 In the univariate Cox analysis respiratory distress, pleural effusion and left atrial enlargement (mild-
157 moderate versus severe) showed a statistically significant effect on survival with a HR (95% CI)
158 respectively of 3.54 (1.25-9.99; p=0.017), 2.34 (1.16-4.71; p=0.017) and 2.32 (1.08-4.99; p=0.031). In the
159 multivariate Cox regression backward analysis only respiratory distress showed a statistically significant
160 effect on survival. Cats presenting without respiratory distress showed a MST of 466 days (95%CI 0-
161 1208), in contrast with cats that presented with respiratory distress showing a shorter (p=0.011) MST of
162 64 days (95%CI 8-120) (Figure 1).

163 **Discussion**

164 The present results showed that RCM is almost exclusively diagnosed at late stage when the patients are
165 referred after the development of clinical signs. Additionally, long term prognosis is poor. Almost all cats
166 in our study showed signs of congestive HF alongside with cardiogenic thromboembolism and this is
167 similar to what has previously been reported in literature.[2,3,16]
168 Prognosis is poor as shown by the short survival time after the diagnosis: the MST in our study
169 population is slightly shorter (2 months) than the MST reported by Fox (3 months) and Ferasin (4
170 months) and longer that the MST reported by Kimura (1 month).[2,3,16] Survival seemed better in those
171 cats not presenting with respiratory distress, however they were only a minority.
172 In our study respiratory distress is the only factor affecting the survival in the multivariate analysis
173 (stronger than pleural effusion and atrial enlargement): this fact emphasizes how in a population of cat
174 with RCM the presence of respiratory distress is the most useful variable in order to distinguish cats with
175 poor prognosis.

In our study population, RCM was the second most commonly diagnosed CM in cats with a 10-year prevalence of 15 % in all cats with CM referred to our two centres. DCM and UCM were otherwise less common, with a prevalence of 4% and 3%. In our institutions diagnosis of DCM was based on the echocardiographic observation of LV end systolic diameter >14 mm and a fractional shortening (FS) <28% in M-mode and diagnosis of *UCM* was made by exclusion, on the basis of evidence of myocardial abnormality that did not fit to any of the recognized disease classification.[3] A variable prevalence in RCM has been reported in cats, with Schober reporting the lowest prevalence of RCM, at 2.4% of all cases of primary feline CM (n = 450) diagnosed between 2007 and 2015 (91.5% were HCM, 2.4% DCM, 2.7% UCM, and 1.1% were ARVC); also in a study performed by Fox (2014), the prevalence of cats with RCM was low (5%).[2,17] In another report from Japan the RCM prevalence (endomyocardial form) was slightly higher with a prevalence of 13% (327 autopsies from cats with heart disease in 10-year).[16] In contrast in a retrospective study from the UK including 105 cats with primary CM the prevalence of RCM was 21%.[3] These differences on RCM prevalence probably are related to different diagnostic criteria used. Both inter- and intraobserver agreement for myocardial disease classification in cats has also been reported to be poor.[18] Most authors would agree that there is marked overlap between CM categories and there is a possibility, yet infrequently observed, of a change in CM (eg: an end stage HCM with LV wall thinning may result phenotypically more a RCM/DCM than HCM); there are examples of families of cats (Norwegian forest) that include individuals with HCM and RCM, or a mixed HCM/RCM phenotype.[8,9] Moreover restrictive ventricular physiology is not RCM-specific but rather occurs over a wide range of myocardial pathologies, end-stage in particular. In general, definitive qualitative and quantitative echocardiographic criteria and diagnostic cutoffs in the diagnosis of feline RCM are poorly defined and remain controversial with only 1 study reporting objective data.[2,17] Challenge is the diagnosis not only by echocardiography, but also by pathology because accepted objective histopathology criteria in the

199 diagnosis of feline RCM are lacking.[17] Therefore, the prevalence may have been influenced by the
200 different diagnostic criteria and classification in different studies. Geographical distribution may also be
201 another source of prevalence variation between the studies.
202 None of the cats in this study showed transition into a different CM.
203 Several previous RCM studies have shown a female predisposition or equal predisposition. [2,3,19] Similar
204 to Kimura in our study cats with RCM were predominantly male.[16] The most represented breed was
205 domestic shorthair cat, that is the most common cat breed in Italy.[19]
206 The mean age at presentation reflects the adult-onset of the disease as reported by literature.[2,3,16] The
207 wide range of the age at diagnosis may reflect a wide disease onset, as is the case for HCM, or it could
208 indicate the presence of different underlying pathogenesis leading to a common final echocardiographic
209 appearance,, as could be the case for acute myocardial damage, myocarditis, end stage HCM or
210 neoplasia.[8]
211 A heart murmur was rarely identified in cats with RCM in our study, which is similar to what has been
212 previously reported; the lack of a heart murmur is in line with the current observations that the
213 presence or absence of a heart murmur is not a useful screening tool in cats.[20]
214 Endomyocardial fibrosis was identified only in 2 cats. It is possible that this type of RCM might have
215 been underdiagnosed during echocardiographic examination due to their location and size, the quality
216 of the ultrasonographic equipment, the skill of the operator and the lack of cooperation of some
217 patients.
218 Limitations of this study were mainly related to its retrospective nature. Diagnosis was based only on
219 echocardiography and post-mortem was available only in few cases; no cardiac biomarkers were
220 available. B-mode measurements of LV wall thickness was not available in all cases, but those were a
221 minority. The authors chose a value of ≥ 6 mm for the definition of LV hypertrophy based on previously

published studies and no allometric scaling was used in order to control the effect of the body weitgh.[2,4,21] No other diastolic information were available in cats with summated E and A waves for tachycardia or A wave absent for arrhythmia. The distribution of CMs might be biased by the echocardiographic criteria used in both referral centers where the study was carried, however no consensus in cardiomyopathy classification is currently available in veterinary cardiology for uniform classification of feline cardiomyopathies.[18] No cat included in the study was previously diagnosed with HCM based on a previous echo; the authors excluded cases in which focal hypertrophy was present in an attempt to exclude end stage HCM, nevertheless the authors cannot completely rule out that some cats with HCM could have been included. Treatment in the current population was not standardized but consisted mainly of loop diuretics, ace inhibitors and anti-thrombotic treatment. Finally, owner related information could have biased the results due to misinterpretation of clinical signs or failure to recognize cardiac-related death.

Conclusion

RCM can be considered an end stage condition associated with a poor prognosis, with few cats not showing clinical signs and surviving longer than a year: most cats died for cardiac disease in a very short time.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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