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Original Article

Spontaneously occurring restrictive nonhypertrophied cardiomyopathy in domestic cats: a new animal model of human disease

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ABSTRACT

Background: Spontaneously occurring small animal models of myocardial disease, closely resembling the human condition, have been reported for hypertrophic cardiomyopathy (in cats) and arrhythmogenic right ventricular cardiomyopathy (in cats and boxer dogs). Nonhypertrophied restrictive cardiomyopathy (RCM) is a well-recognized but relatively uncommon primary heart muscle disease causing substantial morbidity in humans. We describe RCM occurring in felines here as a potential model of human disease.
Methods: We used two-dimensional and Doppler echocardiography to define morphologic and functional features of RCM in 35 domestic cats (25 male; 10±4 years old) presenting to a subspecialty veterinary clinic. Ten underwent complete necropsy examination. Echocardiographic parameters of diastolic filling were compared to those in 41 normal controls.
Results: The 35 cats presented with congestive heart failure (n=32), lethargy (n=2), or syncope (n=1), associated with thromboembolism in 5 and supraventricular tachyarrhythmias in 8. During an average 4.4-year follow-up period, 18 died or were euthanized due to profound heart failure, and 3 died suddenly; survival from clinical presentation to death was 0.1 to 52 months. Echocardiographic and necropsy examination showed biatrial enlargement, nondilated ventricular chambers, and normal wall thicknesses and atrioventricular valves. Histopathology demonstrated disorganized myocyte architecture and patchy replacement myocardial fibrosis. Pulsed Doppler demonstrated restrictive physiology with increased early (E) mitral filling velocity (1.1±0.3 m/s) and peak E to peak late (A) flow ratios (4.3±1.2), reduced A filling velocity (0.3±0.1 m/s), and shortened mitral deceleration time (40.7±9.3 ms; all P<.001 vs. controls), with preserved left ventricular systolic function.
Conclusions: A primary myocardial disease occurring spontaneously in domestic cats is remarkably similar to restrictive nondilated and nonhypertrophied cardiomyopathy in man and represents another potential animal model for human disease.

1. Introduction

Recent reports have described distinctive clinical and pathologic features of spontaneously occurring cardiomyopathies in small animals, notably hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) [1–6]. Clinical and morphologic profiles in these cats and dogs resemble (if not replicate) their respective conditions in humans and potentially represent spontaneously occurring animal models of human disease.

Another myocardial disease occurring in man is characterized by impaired ventricular filling and restrictive physiology, associated with the phenotype of enlarged atria in the presence of normal ventricular thickness and chamber size, and normal atrioventricular valves [7]. The natural history of this condition (known as primary restrictive cardiomyopathy [RCM]) in patients is usually adverse due to congestive heart failure and sudden death [8–16], but without definitive treatment strategies other than heart transplant [12], and with an incompletely understood pathogenesis. In the present study, we report the first comprehensive description of the clinical, echocardiographic, and pathologic features of RCM occurring spontaneously in domestic cats and closely resembling the same disease in humans.

2. Methods

2.1. Study population

This protocol was approved by investigator Institutional Animal Use and Care Committee, with owner consent to participate. Between June 2002 and January 2006, clinical and echocardiographic records of

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The Animal Medical Center (Caspary Research Institute and Bobst Hospital) in New York City were reviewed for feline patients presenting to the Cardiology Specialty Clinic for evaluation of acute dyspnea and/or weakness, or congestive heart failure with radiographic evidence of pulmonary congestion or pleural effusion (n=1125). Cats with severe anemia, systemic hypertension, or thyrotoxicosis were excluded.

Over this period of time, 54 cases (4.8%) met our criteria for RCM on the basis of a distinctive phenotype by echocardiography or at autopsy, and with signs of heart failure: (a) marked biatrial enlargement, (b) normal left ventricular (LV) wall thickness and ventricular chamber size, (c) normal LV systolic function, and (d) restrictive LV filling pattern with pulsed Doppler echocardiography. Nineteen animals with technically suboptimal mitral inflow velocities were excluded, and the remaining 35 cats constitute the study group.

RCM cats were 1.5 to 17.1 years old (mean 10±4); 25 (71%) were males. Body weight was 2.4 to 8.8 kg (mean, 4.9±1.5) (Table 1). Breeds included domestic short hair (n=25), Siamese (n=2), and one each American short hair, domestic long hair, Manx, Birman, Singapura, Burmese, Himalayan, and Maine Coon. None of these cats were known to be related.

At initial diagnosis, 32 of the 35 RCM cats had clinical signs consistent with congestive heart failure including tachypnea, dyspnea, ascites, or jugular venous distention; 2 presented with lethargy, and 1 presented with syncope and transient paresis. Of 34 animals that died, 10 were available for gross and histologic postmortem examination.

2.2. Controls

Forty-one healthy cats without clinical evidence of cardiovascular disease and with normal echocardiographic and Doppler studies were selected during the same study period for comparison with RCM cats: 1.0 to 17.7 years old (mean, 10.1±4.6) and 2.5 to 10.6 kg in weight (mean, 4.8±1.8); 23 (56%) were neutered males (Table 1). Breeds included domestic short hair (n=24), domestic long hair (n=3), Maine coon cat (n=2), Himalayan (n=2), Persian (n=2), Siamese (n=2), and one each of Scottish fold, Angora, Siamese, Burmese, Abyssinian, and American short hair breeds. Control cats did not differ from RCM cats with regard to age (P=.9), gender (P=.2), or body weight (P=.6).

In addition, 6 other normal cats that died from trauma without evidence of cardiovascular disease were selected as controls for comparison with the 10 RCM cats that underwent autopsy examination. Controls were 2 to 11 years old (mean, 6.5±3.4 years); weight was 2.9 to 5.9 kg (mean, 4.5±1.1); four were male. None of the 41 control cats studied with echocardiography was assessed postmortem.

2.3. Echocardiographic methods

Standard M-mode, two-dimensional, and Doppler echocardiographic examinations were performed in conscious, unsedated, manually restrained cats as previously described [1,4,17] using commercially available cardiovascular ultrasound systems equipped with 7 and 7.5-mHz, phased-array transducers. M-mode echocardiograms were derived from two-dimensional images under direct anatomic visualization with simultaneous electrocardiographic (ECG) recording [1] to achieve as closely as possible the standard imaging planes described in man [18]. Measurements were reported after averaging three to five consecutive cycles. Left ventricular end-diastolic (LVIDd) and end-systolic (LVIDs) diameters were measured, and LV short axis shortening fraction (% FS) was calculated by the following formula: LVIDd−LVIDs/LVIDd×100.

Ventricular septum and LV posterior free wall thicknesses were measured at end-diastole at the right parasternal short-axis view at the level of chordae tendineae. Left atrial (LA) dimension at end-systole and aortic root (Ao) dimensions at end-diastole were measured from the left basal short-axis view. Right atrium was judged to be dilated if comparable in size to the enlarged left atrium in two echocardiographic views. Pulsed-wave Doppler echocardiography measured transmitral early (E) and atrial (A) filling velocities, ratio of peak early to peak late flow (E/A), and E-wave deceleration time [19,20] from the left apical four-chamber view with the sample volume in the LV inflow tract at the tips of the mitral leaflets.

2.4. Radiographic and ECG methods

Thoracic radiographs were obtained in each RCM cat. Pulmonary edema was judged to be present by LA enlargement with alveolar or interstitial lung patterns [21]. ECG was recorded from a right lateral recumbent position [1,4,22] in 20 RCM cats, and simultaneous lead II ECG was recorded during echocardiographic examination in all RCM cats.

Table 1
Demographic, echocardiographic, and morphological comparison of cats with RCM and normal controls[a]

Parameter	RCM	Controls	P value
No. of animals	35	41	
Age, years	10±4.0 (1.5–17.1)	10.1.±4.6 (1–17.7)	.88
Male, n (%)	25 (71)	23 (56)	.23
Body weight, kg.	4.9±1.5 (2.4–8.8)	4.8±1.8 (2.5–10.6)	.6
Max. LV wall thickness, mm			
VS	4.4±0.8 (3.0–5.8)	4.1±0.6 (3.1–5.0)	.03
LVPW	4.5±0.8 (3.0–5.8)	3.9±0.5 (3.0–5.0)	<.001
LV cavity, mm			
End-diastole	15.6±2.0 (9.5–18.9)	14.9±2.1 (10–18.2)	.12
End-systole	8.4±1.3 (5.3–10.2)	7.1±1.4 (4.5–10.2)	<.001
Fractional shortening, %	45.2±8.6 (35.2–60.2)	52.2±5.8 (38.1–60.1)	<.001
LA dimension, mm	20.5±2.4 (16.3–27.6)	11.9±1.0 (10–13.5)	<.001
LA:Ao ratio	2.3±0.3 (1.8–3.4)	1.2±0.1 (1.1–1.3)	<.001
E-wave, m/s	1.1±0.27 (0.7–1.8)	0.69±0.12 (0.5– 0.9)	<.001
A-wave, m/s	0.27±0.1 (0.12–0.47)	0.68±0.12 (0.5–1.0)	<.001
E/A ratio	4.3±1.2 (2.8–7.6)	1.0±0.3 (0.6–1.5)	<.001
E-wave deceleration (ms)	40.7±9.3 (21.9–62.2)	86.5±20.6 (53.5–191.6)	<.001

Abbreviations: A-wave=transmitral atrial (A) filling velocity; E-wave=transmitral early (E) filling velocity; LVPW=left ventricular posterior free wall; m/s=meters/second; ms=millisecond; max=maximum; VS=ventricular septum.
[a] Expressed as mean±S.D. (range).