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Echocardiographic Assessment of Right Ventricular Size and Function in Cats With Hypertrophic Cardiomyopathy

L.C. Visser, C.Q. Sloan, and J.A. Stern

Background: Studies evaluating right ventricular (RV) structural and functional abnormalities in feline hypertrophic cardiomyopathy (HCM) are limited.

Hypothesis: Right ventricular structural and functional abnormalities are present in cats with HCM and are associated with clinical severity.

Animals: Eighty-one client-owned cats.

Methods: Retrospective 2-dimensional (2D) echocardiographic study. Right atrial diameter (RAD), RV free wall thickness (RVFWd), RV internal dimension (RVIDd), RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE) were measured in control cats (n = 26), cats with subclinical HCM (subclinical HCM; n = 31), and cats with HCM and congestive heart failure (HCM + CHF; n = 24).

Results: Right heart size (RAD, RVFWd, and RVIDd) and RV function (FAC and TAPSE) significantly (all $P < .05$) increased and decreased, respectively, in the HCM + CHF group compared with controls. In the subclinical HCM group, only RVFWd was significantly ($P < .05$) higher than in controls. Compared with reference intervals derived from controls, 29% of cats with HCM had increased RVFWd. Increased left ventricular free wall thickness, increased RVIDd and decreased TAPSE independently correlated with increased left atrial size. Cats with HCM and pleural effusion were significantly more likely to have increased RVFWd and had increased RAD and decreased TAPSE compared with cats without pleural effusion.

Conclusions and Clinical Importance: Right ventricular remodeling and dysfunction occur in some cats with HCM and may be associated with clinical severity. Our results support involvement of RV in the pathophysiology of HCM in some cats and support echocardiographic assessment of the RV in cats with HCM.

Key words: Echocardiography; Feline; Right heart; Right ventricular hypertrophy.

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease defined by variable degrees of regional or global myocardial hypertrophy and is the most commonly diagnosed cardiac disease in cats.[1–3] In addition to left ventricular (LV) morphologic changes, LV functional abnormalities (systolic dysfunction) also have been reported in some cases and have been shown to be associated with worse outcome.[4,5] To date, it is unresolved if right ventricular (RV) functional abnormalities occur in cats with HCM, because echocardiographic studies of cats with HCM have almost exclusively focused on assessment of the left atrium (LA) and ventricle. One recent study[6] documented increased RV wall thickness in cats with HCM and found that RV hypertrophy was related to severity of LV hypertrophy and clinical severity. However, RV function was not evaluated in this study.

In humans, RV hypertrophy has been documented in 33–44% of cases of HCM.[7,8] Right ventricular

Abbreviations:

2D	2-dimensional
ACE	angiotensin-converting enzyme
Ao	aorta
CHF	congestive heart failure
CV	coefficient of variation
FAC	fractional area change
HCM	hypertrophic cardiomyopathy
IVSd	maximum interventricular septal wall thickness at end-diastole
LA	left atrium/atrial
LV FS	left ventricular fractional shortening
LVFWd	maximum left ventricular free wall thickness at end-diastole
LVIDd	left ventricular internal dimension at end-diastole
LVIDs	left ventricular internal dimension at end-systole
LV	left ventricle/ventricular
Lx	long axis
RAD	maximum right atrial diameter
RV FS	right ventricular fractional shortening
RVFWd	maximum right ventricular free wall thickness at end-diastole
RVIDd	right ventricular internal dimension at end-diastole
RVIDs	right ventricular internal dimension at end-systole
RV	right ventricle/ventricular
Sx	short axis
TAPSE	tricuspid annular plane systolic excursion

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hypertrophy is associated with increased risk of hospitalization for congestive heart failure (CHF), thromboembolic complications, ventricular tachyarrhythmias, and sudden death;[9,10] and, severe RV hypertrophy, albeit rare, is associated with worse prognosis in humans with HCM.[11] The impact of RV performance in the clinical status and outcome of humans affected with HCM also has been studied.[12–15] However, in cats, studies focusing on the assessment of RV size and function are limited, and it is unknown whether RV functional abnormalities occur in cats with HCM.

The primary purpose of our study was to echocardiographically compare RV wall thickness, chamber dimension, and function in cats with HCM (with and without CHF) to healthy cats. A secondary objective was to determine whether increased RV wall thickness, increased RV chamber size, or RV dysfunction is associated with clinical severity of HCM as determined by left atrial size and CHF status. We hypothesized that RV structural and functional abnormalities exist in cats with HCM and are associated with clinical severity.

Materials and Methods

Animals

Cats were eligible for inclusion in this retrospective study if they underwent a complete 2-dimensional (2D) echocardiographic study that included long axis (Lx) cine loops of the right heart and were diagnosed with HCM or were considered to be echocardiographically normal (controls) from June 2014 to February 2016. Cats were identified from the echocardiography database at the University of California, Davis Veterinary Medical Teaching Hospital, and clinical information was obtained from each cat's medical record. Cats were chosen on a consecutive basis provided the inclusion criteria and none of the exclusion criteria were met. Control cats had to be echocardiographically free of structural or functional abnormalities, free of clinical signs of systemic disease (i.e., apparently healthy), and could not be receiving medications known to affect the cardiovascular system. Exclusion criteria for cats diagnosed with HCM included any concurrent cardiac disease (including marked or severe right atrium [RA] and RV dilatation or an apical aneurysm suggestive of feline arrhythmogenic RV cardiomyopathy[16]) and any systemic disease including, clinical evidence of dehydration or hypovolemia, known pulmonary hypertension (estimated echocardiographically by a tricuspid regurgitation pressure gradient >36 mmHg), primary respiratory disease, hyperthyroidism, and systemic hypertension (systolic blood pressure, >170 mmHg). All cats (>6 years of age) diagnosed with HCM had serum thyroid hormone (T4) concentration and blood pressure measured. Cats with mitral valve regurgitation were included provided it was considered to be secondary to systolic anterior motion of the mitral valve. Cats were excluded if they were already receiving a beta-adrenergic receptor blocker, pimobendan, or sildenafil. Cats with a clinically relevant or sustained tachy- or brady-arrhythmia also were excluded. Cats with infrequent supraventricular or ventricular complexes were included. Cats were allocated into 1 of 3 groups: (1) control group consisting of echocardiographically normal, apparently healthy cats, (2) subclinical HCM group consisting of cats with HCM but without clinical evidence of CHF, and (3) HCM + CHF group consisting of cats with HCM and CHF. Congestive heart failure was diagnosed based on the presence of clinical signs, left atrial enlargement, and radiographic or ultrasonographic evidence of pleural effusion or radiographic evidence of pulmonary edema. Within the HCM + CHF group, cats that were considered to have more than mild pericardial effusion (by subjective assessment) were excluded because of the potential confounding effects of pericardial effusion on right heart size and function. For cats in all 3 groups, subjectively mild idiopathic tricuspid regurgitation was permitted but cats with more than subjectively mild tricuspid regurgitation were excluded.

Echocardiography

All echocardiographic studies[a] were performed by a board-certified veterinary cardiologist (L.C.V or J.A.S.) or a cardiology resident under the direct supervision of a board-certified veterinary cardiologist. The use of a sedative (butorphanol, 0.2 mg/kg IM or IV or buprenorphine, 0.01 mg/kg IM or IV) before echocardiography was permitted. All echocardiographic assessments, measurements, and calculations were performed by a single investigator (L.C.V.) at a digital off-cart workstation[b]. Values for each echocardiographic variable consisted of the average of 3 representative but not necessarily consecutive measurements. All echocardiographic variables for the study were measured using 2D echocardiography. All right heart size measurements were made from a right parasternal long-axis 4-chamber view (Fig 1).[6] Maximum right atrial diameter (RAD) was measured at end-systole from the mid-point of the interatrial septum to the right atrial lateral wall in a cranial-caudal plane and parallel to the tricuspid valve annulus. Right ventricular internal dimension (RVIDd) was measured at end-diastole and end-systole (RVIDs) at the level of the RV where the tips of the opened tricuspid valve leaflets contact the endomyocardium and parallel to the tricuspid valve annulus. Right ventricular fractional shortening (RV FS) was calculated as (RVIDd − RVIDs)/RVIDd × 100. The thickest portion of the RV free wall at end-diastole (RVFWd) was measured from the inner edge of the RV endomyocardium to the outer edge of the RV epimyocardium, excluding the pericardium. Maximum RV free wall thickness at end-diastole was indexed to body weight (iRVFWd) using the formula: RVFWd/(body weight [kg])$^{0.33}$.[17]

Right ventricular fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE) measurements were acquired from a left apical 4-chamber view (Fig 2). For FAC calculation, measurements of RV area were obtained by tracing the right ventricular endomyocardial border at end-diastole (RVAd) and end-systole (RVAs), excluding the papillary musculature. Percent FAC was derived from the following formula: (RVAd − RVAs)/RVAd × 100. The TAPSE measurement was obtained from 2D cine loops by drawing a line from the lateral tricuspid valve annulus to the RV apex at end-diastole. Without deleting the line, the cine loop was advanced to end-systole and a second line was drawn from the tricuspid valve's new location (tricuspid valve annulus now displaced apically relative to its starting point) back to the original starting point. The length of the second line quantifies the maximum longitudinal distance of the lateral tricuspid valve annulus during systole and represents TAPSE (as quantified by 2D echocardiography).[18]

The thickest portions of the interventricular septum (IVSd) and left ventricular free wall (LVFWd) were measured at end-diastole from both long- (Lx) and short-axis (Sx) images and, if ≥6 mm at any location, cats were diagnosed with HCM (provided no exclusion criteria were met).[3] Left ventricular internal dimension was measured at end-diastole (LVIDd) and end-systole (LVIDs) from right parasternal Sx views. Left ventricular fractional shortening (LV FS) was calculated as (LVIDd − LVIDs)/LVIDd × 100. Left atrial diameter was measured by the standard LA:Ao method from a right parasternal Sx imaging plane.[19] A LA:Ao >1.6 was used to determine LA enlargement.

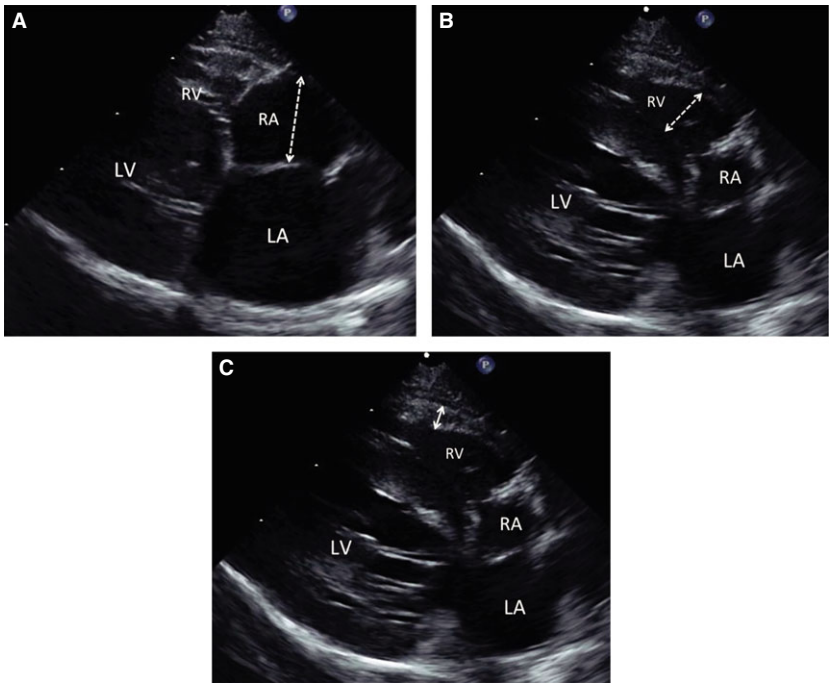

Fig 1. Representative measurement of the RA (dotted line [**A**]), right ventricular internal dimension (dotted line [**B**]), and maximum right ventricular wall thickness (solid white line [**C**]) acquired from the right parasternal Lx 4-chamber view. Maximum right atrial internal diameter was measured from the mid-point of the interatrial septum across to the right atrial lateral wall in a plane approximately parallel to the tricuspid valve annulus and just prior to tricuspid valve opening (end-systole). Right ventricular internal dimension was measured at end-diastole and end-systole (not shown) at the level of the right ventricle where the opened tricuspid leaflet tips contact the endomyocardium and approximately parallel to the tricuspid valve annulus. Right ventricular free wall thickness was measured at end-diastole at its maximum thickness from the inner edge of the endomyocardium to the outer edge of epimyocardium (and excluding the pericardium). RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; Lx, long axis.

Echocardiographic Measurement Variability

Echocardiographic measurement variability was determined from 9 randomly selected echocardiograms (3 per group). Intraobserver measurement variability was determined by measuring right heart indices (RAD, RVIDd, RVIDs, RV FS, RVFWd, FAC, and TAPSE) by a blinded investigator (LCV) on 3 separate occasions within 1 week but separated by at least 24 hours. To determine interobserver measurement variability, the same indices from the same 9 echocardiographic studies were measured once by a second trained investigator (CQS). This second investigator was blinded to the results of previous measurements and image and loops from which previous measurements were made.

Statistical Analysis

Statistical analyses were performed using commercial software packages.[c,d] Descriptive statistics were generated, and normality testing with the D'Agostino-Pearson test was performed for all continuous data. Data are reported as mean ± standard deviation (SD) unless otherwise stated. A value of $P < .05$ was considered statistically significant.

Differences in continuous data among the 3 groups were determined using 1-way analysis of variance (or Kruskal-Wallis test if non-Gaussian distribution) and, if significant, pair-wise comparisons were performed using Tukey's test (or Dunn's test if non-Gaussian distribution). Proportions were compared using a Chi-square test and, if significant, pair-wise comparisons were performed using multiple *z*-tests with Bonferroni corrections. Within the cats in the HCM + CHF group, an unpaired *t*-test was used to compare RVFWd and RVIDd in cats that received furosemide before echocardiography to those that did not. Within the HCM + CHF group, an unpaired *t*-test (or Mann-Whitney rank sum test) also was used to compare right heart size and function of cats with pulmonary edema (and without pleural effusion) to cats with pleural effusion.

From the cats in the control group, reference intervals for RVFWd were generated using the robust method as recommended by the Clinical and Laboratory Standards Institute when sample size is <120 subjects.[20] With the robust method, the upper (97.5%) and lower (2.5%) limits on the distribution are estimated with 90% confidence intervals (CI) of those limits by the bootstrap method using 5,000 replications.[21,22]

Simple (univariate) linear regression analyses were performed to determine the strength of association of selected clinical and echocardiographic indices to LA size (LA:Ao) as well as RVFWd versus LV wall thickness (LVFWd-Lx and IVSd-Lx). Multiple linear regression analysis was utilized to identify significant independent predictors of disease severity, as determined by LA size. Echocardiographic measurements performed in the current study in addition to age (years), body weight (kg), and sex (coded as female = 0, male = 1) were entered into a multiple linear regression model in a backward stepwise manner if P was <.2 based on univariate linear regression analysis. For all linear regression models, assumptions of linearity, homoscedasticity, normality of residuals, and little or no multicollinearity (for multiple linear regression) were met.

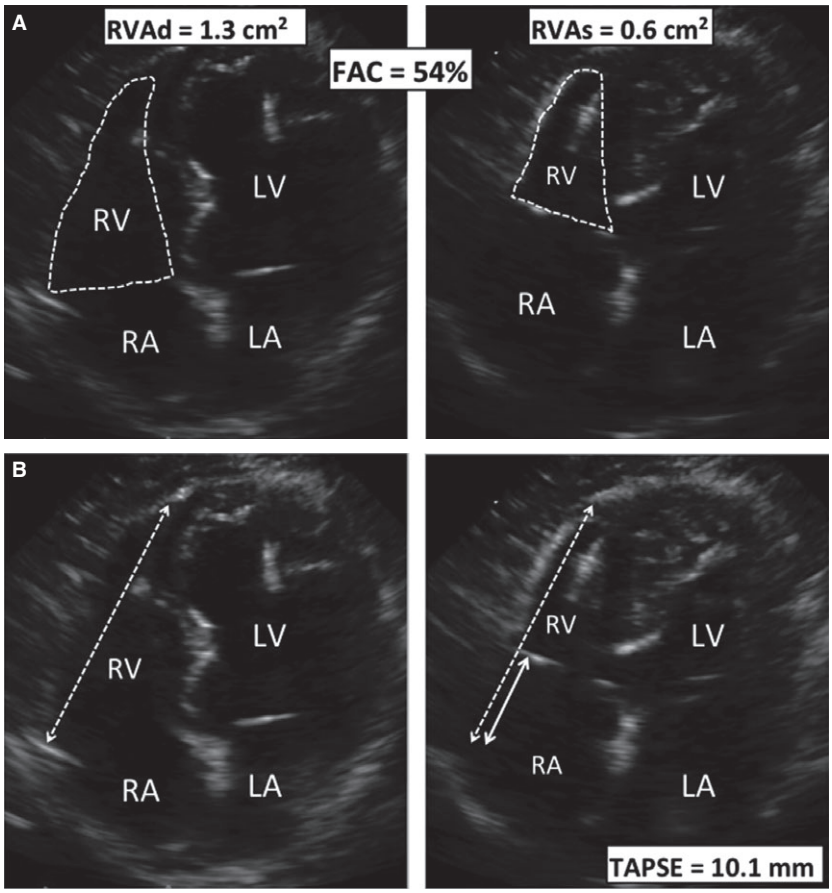

Fig 2. Representative measurement of fractional area change (FAC [**A**]) and tricuspid annular plane systolic excursion (TAPSE [**B**]) acquired from a left apical 4-chamber view. For FAC, right ventricular area measurements were obtained at end-diastole (RVAd) and end-systole (RVAs) by tracing the endomyocardial border (dotted lines). Percent FAC is calculated as ([RVAd − RVAs]/RVAd) × 100. For TAPSE, a digital caliper was used to draw a line (dotted line) from the lateral tricuspid valve annulus to right ventricular apex at end-diastole. The cine loop was then advanced to end-systole without deleting the line and a second line (solid line) was drawn from the new location of the tricuspid valve annulus back to its original starting point as shown and represents TAPSE as quantified by 2D echocardiography. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; 2D, 2-dimensional.

Two-way single-measure intraclass correlation coefficient (ICC) for absolute agreement and average percent coefficient of variation (CV) were used to quantify echocardiographic measurement agreement and variability. Percent CV = (standard deviation of the measurements/average of the measurements) × 100. For the purposes of this study, an ICC value >0.75 denoted high echocardiographic measurement agreement and CV <10% represented low measurement variability.

Results

Clinical and Echocardiographic Data

A summary of clinical data is presented in Table 1. The study consisted of 81 cats: 26 in the control group, 31 in the subclinical HCM group, and 24 cats in the HCM + CHF group. No statistically significant differences for body weight, age, sex, purebred status, heart rate, or sedation status (yes or no; butorphanol or buprenorphine) were identified among the groups (all $P \geq .07$). In the control group, purebred cats included 1 Scottish fold, 1 British shorthair, and 1 Siamese. In the subclinical HCM group, purebred cats included 2 Maine coons, 2 Ragdolls, 2 Persians, 1 Devon rex, 1 Sphinx, 1 Bengal, and 1 Siamese. In the HCM + CHF group, purebred cats included, 2 Maine coons, 2 Ragdolls, 1 Sphinx, and 1 Siamese. Significantly ($P < .05$) more cats in the HCM + CHF group had received furosemide (n = 9 [38%]) or an angiotensin-converting enzyme inhibitor (ACE) (n = 4 [17%]) before their echocardiographic examination compared to those in the subclinical HCM (furosemide n = 0 [0%]; ACE inhibitor [ACE-i] n = 1 [3%]) and control groups (furosemide n = 0 [0%]; ACE-i *n* = 0 [0%]).

A summary of the echocardiographic data is presented in Table 2. All right heart size indices (RAD, RVIDd, and RVFWd) for the cats in CHF (HCM + CHF) group were significantly ($P < .05$) higher than those of cats not in CHF (control and subclinical HCM groups). Right ventricular function (RVIDs, RV FS, FAC, and TAPSE) was significantly (all $P < .05$) decreased in the cats in the HCM + CHF group compared with cats not in CHF (control and subclinical HCM) groups. When cats with subclinical HCM were compared with the control group, RVFWd was the only significantly ($P < .05$) different

Table 1. Clinical data of all study cats (n = 81).

	Control (n = 26)	Subclinical HCM (n = 31)	HCM + CHF (n = 24)	P Value
Body weight (kg)	4.8 ± 0.8	5.3 ± 1.0	5.5 ± 1.7	.07
Age (years)*	6 (3–10)	10 (4–11)	11 (4–13)	.18
Male: number (%)	12 (46)	23 (74)	15 (63)	.09
Purebred: number (%)	3 (12)	10 (32)	6 (25)	.18
Heart rate (min^{-1})	190 ± 26	191 ± 24	201 ± 34	.32
Received sedation: number (%)	7 (27)	7 (23)	12 (50)	.08
Furosemide: number (%)	0 (0)	0 (0)	9 (38)[a,b]	**< .0001**
ACE-inhibitor: number (%)	0 (0)	1 (3)	4 (17)[a,b]	**.03**

HCM, hypertrophic cardiomyopathy; HCM + CHF, hypertrophy cardiomyopathy and congestive heart failure; ACE, angiotensin-converting enzyme. Bolded values denote statistical significance.

*Median (interquartile range) presented as a result of non-Gaussian distribution.

[a]$P < .05$ as compared to control group.

[b]$P < .05$ as compared to subclinical HCM group.

Table 2. Echocardiographic data of all study cats (n = 81).

	Control (n = 26)	Subclinical HCM (n = 31)	HCM + CHF (n = 24)	P Value
Right heart				
RAD (mm)*	11.1 (10.1–12.3)	10.9 (10.1–12.2)	13.2 (12.1–14.1)[a,b]	**< .0001**
RVIDd (mm)	6.7 ± 1.4	6.5 ± 1.3	8.0 ± 1.5[a,b]	**.0003**
RVFWd (mm)	2.4 ± 0.4	3.1 ± 0.6[a]	3.6 ± 0.9[a,b]	**< .0001**
iRVFWd	1.4 ± 0.3	1.8 ± 0.3[a]	2.1 ± 0.4[a,b]	**< .0001**
RVIDs (mm)	3.4 ± 1.1	3.3 ± 0.8	4.8 ± 1.7[a,b]	**< .0001**
RV FS (%)	50.0 ± 8.8	48.9 ± 11.2	40.8 ± 13.2[a,b]	**.01**
FAC (%)†	63.9 ± 6.6	63.5 ± 10.4	51.4 ± 14.4[a,b]	**.0004**
TAPSE (mm)	9.1 ± 1.4	8.5 ± 1.1	6.5 ± 1.7[a,b]	**< .0001**
Left heart				
LA:Ao	1.4 ± 0.1	1.4 ± 0.2	2.1 ± 0.4[a,b]	**< .0001**
LVIDd (mm)	14.2 ± 1.8	13.4 ± 1.7	14.1 ± 2.6	.22
LVIDs (mm)	6.7 ± 1.5	5.7 ± 1.4	7.6 ± 2.1[b]	**.0004**
LV FS (%)	53.1 ± 7.2	57.1 ± 8.5	45.7 ± 11.9[a,b]	**.0001**

RAD, maximum right atrial diameter; RVIDd, right ventricular internal dimension at end-diastole; RVFWd, maximum right ventricular free wall thickness at end-diastole; iRVFWd, RVFWd indexed to body weight; RVIDs, right ventricular internal dimension at end-systole; RV FS, right ventricular fractional shortening; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; LA:Ao, left atrium to aorta ratio; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; LV FS, left ventricular fractional shortening; HCM, hypertrophic cardiomyopathy; HCM + CHF, hypertrophic cardiomyopathy and congestive heart failure.

Bolded values denote statistical significance.

*Median (interquartile range) presented as a result of non-Gaussian distribution.

†Could not be measured in 3 in the control group, 10 cats in the subclinical HCM group, and 4 cats in the HCM + CHF group.

[a]$P < .05$ as compared to control group.

[b]$P < .05$ as compared to subclinical HCM group.

(increased) right heart index (Table 2; Fig 3). When RVFWd was indexed to body weight (iRVFWd) to rule out an effect of body size on RVFWd, the statistically significant difference ($P < .05$) persisted among the 3 groups.

Left atrial size (LA:Ao) was significantly ($P < .05$) larger in the cats with CHF (HCM + CHF) group compared with cats not in CHF (control and subclinical HCM) groups. Left ventricular internal dimension at end-diastole (LVIDd) did not differ significantly among any of the groups. Left ventricular shortening fraction was significantly decreased in the HCM + CHF group compared with that in the subclinical HCM group and control group ($P < .05$ for both). LVIDs was significantly ($P < .05$) larger in the HCM + CHF group compared with that in the subclinical HCM group, but there was no significant difference between HCM + CHF and the control groups.

Within the HCM + CHF group, the RVFWd and RVIDd of cats (n = 9) that received furosemide before echocardiography (RVFWd = 3.9 ± 0.9 mm; RVIDd = 8.5 ± 1.3 mm) were not significantly different (P = .19 and P = .20, respectively) compared with cats (n = 15) that did not receive furosemide (RVFWd = 3.4 ± 0.8 mm; RVIDd = 7.7 ± 1.6 mm).

The reference interval for RVFWd that was derived from the 26 control cats was 1.2–3.5 mm. Of the cats diagnosed with HCM (subclinical HCM and HCM + CHF groups), 16 (29%) had RVFWd of >3.5 mm, 7 (23%) in the subclinical HCM group and 9 (38%) in the HCM + CHF group (Fig 3).

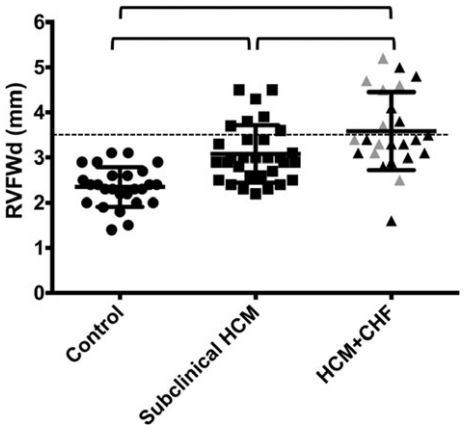

Fig 3. Scatter dot plots of maximum right ventricular free wall thickness at end-diastole (RVFWd) for all cats in each group. For each group, bars and error bars represent mean and standard deviation. Brackets (above the groups) denote statistically significant ($P < .05$) differences among the groups. The dotted line represents the upper reference interval for RVFWd as determined from the control group. Gray triangles represent cats that received furosemide prior to echocardiography. HCM, hypertrophic cardiomyopathy; HCM + CHF, hypertrophic cardiomyopathy with congestive heart failure; RVFWd, maximum right ventricular free wall thickness at end-diastole.

For all study cats, RVFWd was significantly and positively correlated with LVFWd ($r^2 = 0.3$; $P < .001$) and IVSd ($r^2 = 0.25$; $r < 0.001$).

Correlation of Echocardiographic Indices to LA Size

Correlation of echocardiographic indices to LA size (LA:Ao) is presented in Table 3. Some echocardiographic indices (RVIDs, IVSd-Sx & LVFWd-Sx, and LVIDs) were not entered into the multiple linear regression model because of a multicollinearity violation (with RV FS, IVSd-Lx, LVFWd-Lx, and LV FS, respectively), and FAC was removed from the model because of numerous missing data points (low measurement feasibility). Based on the univariate analysis, indices of right heart size (RAD, RVIDd, RVFWd) and RV function (TAPSE, RV FS, FAC) as well as indices of LV wall thickness (IVSd-Lx, LVFWd-Lx) and function (LV FS) exhibited significant (all $P \leq .02$) linear correlations to LA:Ao. However, only decreased TAPSE and increased LVFWd-Lx and RVIDd maintained significant (all $P \leq .04$) and independent linear correlations with increased LA:Ao based on the multiple linear regression analysis (Table 3).

Cats with Pleural Effusion versus Pulmonary Edema

A subanalysis of cats within the HCM + CHF group comparing those with pulmonary edema (and without pleural effusion) to those with pleural effusion is presented in Table 4. Right atrial diameter was significantly ($P = .049$) higher and TAPSE was significantly ($P = .03$) decreased in cats with pleural effusion compared to cats with pulmonary edema. The percentage of cats with RVFWd >3.5 mm was significantly higher ($P = .04$) in cats with pleural effusion (58%) compared to cats with pulmonary edema (17%).

Table 3. Results of linear regression analyses for the prediction of disease severity as assessed via LA size (LA:Ao).

	Univariate Regression		Multiple Regression
Variable	R^2	*P* value	*P* value
Age	0.005	.52	–
Gender (M/F)	<0.0001	.95	–
Body weight	0.33	.10	–
Heart rate	0.01	.36	–
RAD	0.22	<.0001	0.19
RVIDd	0.15	.0003	**0.04**
RVFWd	0.23	<.0001	–
RV FS	0.07	.02	–
FAC*	0.13	.003	–
TAPSE	0.33	<.0001	**< 0.0001**
LVIDd	0.01	.33	–
IVSd − Lx	0.24	<.0001	0.23
LVFWd − Lx	0.31	<.0001	**0.004**
LV FS	0.13	.001	–

RAD, maximum right atrial diameter; RVIDd, right ventricular internal dimension at end-diastole; RVFWd, maximum right ventricular free wall thickness at end-diastole; RV FS, right ventricular fractional shortening; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; LVIDd, left ventricular internal dimension at end-diastole; IVSd, maximum interventricular septal wall thickness at end-diastole; LVFWd, maximum left ventricular free wall thickness at end-diastole; LV FS, left ventricular fractional shortening; Lx, long axis; R^2, coefficient of determination.

Overall multiple linear regression model fit was $R^2 = 0.59$; $P < .0001$. "–" denotes variable not included in the final model. Bolded values denote statistical significance.

*Not entered into the multiple regression model as a result of numerous missing data points.

Right Heart Echocardiographic Measurement Feasibility and Variability

All right heart size and function indices could be measured in all 81 cats with the exception of FAC, which could not be measured in 17 cats (21%); 3 (12%) in the control group, 10 (32%) in the subclinical HCM group, and 4 (17%) in the HCM + CHF group. All ICC and CV values for each right heart echocardiographic index from 9 randomly selected cats (3 per group) are presented in Table 5. For intraobserver variability, RAD, RVFWd, RVIDs, FAC, and TAPSE had high measurement agreement (ICC, >0.75) and RAD, RVIDd, RVFWd, and TAPSE had low measurement variability (CV < 10%). For interobserver variability, RAD, RVFWd, TAPSE exhibited high measurement agreement, and RAD, RVIDd, and TAPSE exhibited low measurement variability.

Table 4. Right heart size and function in cats with HCM and pulmonary edema (and without pleural effusion) compared to cats with HCM and pleural effusion.

Variable	Pulmonary Edema (n = 12)	Pleural Effusion (n = 12)	P Value
RAD (mm)*	12.4 (11.7–13.7)	13.9 (12.6–15.2)	**.049**
RVIDd (mm)	7.6 ± 1.5	8.5 ± 1.4	.12
RVFWd (mm)	3.3 ± 0.8	3.9 ± 0.8	.10
RV FS (%)	44.2 ± 14.1	37.4 ± 11.9	.22
FAC (%)†	58.2 ± 13.2	46.5 ± 15.0	.17
TAPSE (mm)	7.3 ± 1.8	5.7 ± 1.3	**.03**
RVFWd >3.5 mm: number (%)	2 (17)	7 (58)	**.04**

RAD, maximum right atrial diameter; RVIDd, right ventricular internal dimension at end-diastole; RVFWd, maximum right ventricular free wall thickness at end-diastole; RV FS, right ventricular fractional shortening; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion.

Bolded values denote statistical significance.

*Median (interquartile range) presented as a result of non-Gaussian distribution.

†Could not be measured in 3 cats with pulmonary edema and 1 cat with pleural effusion.

Table 5. Echocardiographic measurement variability data of right heart size and function indices from 9 randomly selected studies (3 per group).

Right Heart Echocardiographic Indices	Intraobserver Variability		Interobserver Variability	
	ICC	CV (%)	ICC	CV (%)
RAD	0.93	3.6	0.92	5.4
RVIDd	0.72	8.9	0.58	8.9
RVFWd	0.91	7.5	0.88	10.3
RVIDs	0.83	11.9	0.70	14.6
RV FS	0.49	18.2	0.47	13.8
FAC	0.84	11.4	0.53	21.6
TAPSE	0.95	4.9	0.83	9.9

RAD, maximum right atrial diameter; RVIDd, right ventricular internal dimension at end-diastole; RVFWd, maximum right ventricular free wall thickness at end-diastole; RVIDs, right ventricular internal dimension at end-systole; RV FS, right ventricular fractional shortening; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; ICC, intraclass correlation coefficient; CV, coefficient of variation.

Discussion

Our results support the hypothesis that RV remodeling and dysfunction occur in some cats with HCM. Specifically, increased RVFWd (RV hypertrophy) was identified in some cats with HCM (with and without CHF) when compared to healthy cats, and cats with HCM and CHF exhibited increased RV wall thickness compared to cats with subclinical HCM, which suggests that increased RV wall thickness may be associated with the clinical status or severity of HCM in some cats. Cats with CHF secondary to HCM also exhibited RA and RV chamber dilatation and RV dysfunction compared to cats without CHF (control and subclinical HCM groups). Our results also showed that RV size (RVIDd) and function (TAPSE) as well as LV wall thickness (LVFWd-Lx), independently correlated with LA size, a surrogate marker of LV hemodynamic burden and clinical morbidity. This suggests that the RV may be involved in feline HCM and as LV hemodynamic burden worsens (i.e., as LA size increases), RV remodeling and dysfunction may also occur. Of the cats diagnosed with CHF, cats with pleural effusion exhibited increased RA size and decreased RV function (assessed by TAPSE), and were more likely to have increased RV wall thickness compared to cats with pulmonary edema, which suggests that RV hypertrophy may be involved in the pathophysiology of pleural effusion in cats with HCM. Lastly, we found that the majority of the right heart measurements, with the exception of RV FS and FAC, had clinically acceptable measurement variability.

To the authors' knowledge, ours is the first study to objectively assess right heart size and function in cats with HCM. In humans, right heart assessment has been shown to have a clinically relevant impact on predicting clinical status and outcome in a variety of cardiovascular diseases, including diseases conventionally viewed as left heart-specific, such as mitral valve disease and HCM.[12,23–26] Recently, RV function has also been shown to have prognostic value in dogs with arrhythmogenic RV cardiomyopathy and myxomatous mitral valve disease.[27,28] Right ventricular dysfunction and dilatation in individuals with LV dysfunction can be explained by multiple independent or composite mechanisms including (1) pulmonary venous hypertension with subsequent "reactive" or "protective" pulmonary arterial hypertension; (2) the cardiomyopathic process simultaneously affecting both ventricles; (3) ischemic damage to both ventricles; (4) LV dysfunction that may affect RV coronary perfusion pressure, an important determinant of RV function; (5) ventricular interdependence caused by septal dysfunction; and (6) LV dilatation in a finite pericardial compartment that may hinder RV diastolic function.[29,30] Any one or some combination of these mechanisms may explain the changes in RV (and RA) size and function noted in our study. Unfortunately, the retrospective nature of our investigation prohibited determining the cause of the observed right heart changes. For example, because pulmonary arterial pressures could not be reliably estimated (and

were not assessed invasively) in our cats, it is impossible to determine whether the RV hypertrophy noted in the cats with HCM (with and without CHF) was secondary to pulmonary hypertension or was an effect of the hypertrophic cardiomyopathic process involving the RV.

Using reference intervals generated from our control cats, 29% of the cats with HCM (with and without CHF) had RV hypertrophy (increased RVFWd). A recent study[6] also documented a similar prevalence (35%) of increased RV free wall thickness in cats with HCM when utilizing the same echocardiographic imaging plane as used in our current study. Similar to humans where prevalence ranges from 33 to 44%,[7,8] this suggests a substantial proportion of cats with HCM are affected with RV hypertrophy. However, caution is advised in interpreting the reference values generated in our study given the relatively few number of control cats. This range was created to give a rough estimate of normal RV wall thickness in healthy cats. New reference values should be generated in a prospective manner from a much larger sample of the population to generate more precise reference intervals. It is apparent from our study and another[6] that not all cats with HCM have increased RV free wall thickness (the majority did not exhibit RV hypertrophy in this study). There are several possible explanations for this finding, including echocardiography lacking precision or sensitivity to detect RV hypertrophy, RV hypertrophy developing only at certain stages of the disease (e.g., severe disease), or the RV only being thickened in some cats with HCM (i.e., phenotypic diversity).

The clinical and prognostic value of LA size (determined echocardiographically) in cats with HCM has been repeatedly demonstrated, and thus is often used as a clinical surrogate of clinical severity and hemodynamic burden.[5,19,31–34] In our study, LV free wall thickness, RV chamber size, and RV function (as assessed by 2D TAPSE) were independently correlated with LA size. These results suggest that RV size (RVIDd) and wall thickness (RVFWd), in addition to increased LV wall thickness (LVFWd), may be associated with clinical severity in cats with HCM. Furthermore, a cardiac magnetic resonance study of RV involvement in humans with HCM found a similar weak-to-moderate positive correlation of RV wall thickness to LV wall thickness.[7] This finding can also be interpreted to suggest that the presence of RV hypertrophy (increased RVFWd) is associated with more severe disease in cats with HCM (as assessed by LV wall thickness), as suggested previously in humans[8] and cats with[6] HCM. The increased RVFWd identified in cats with HCM and CHF compared to cats with subclinical HCM also suggests that RV hypertrophy may be associated with clinical severity of HCM. A recent study[6] of cats with HCM also documented that increased RV free wall thickness was associated with clinical severity in a similar comparison of RVFWd in cats with HCM with and without CHF.

To date, echocardiographic assessment of RA and RV size and function is underutilized in feline cardiology. Indices of RV size and function are notoriously difficult to acquire and measure given the chamber's relatively complex shape. With the exception of RV FS and FAC, the right heart measurements utilized in our study were easy to measure with acceptable measurement variability. In particular, TAPSE acquired by 2D echocardiography was a simple, quick, and easily obtained measurement of RV function. This is likely because it was much easier to consistently visualize (and track) the tricuspid valve annulus throughout the cardiac cycle compared with visualizing the RV endomyocardium. Ultimately, prospective validation and within-day and day-to-day repeatability studies of these RV size and function indices are warranted to further assess their accuracy and reproducibility in cats.

Our study indicated that of the cats with HCM and CHF, cats with pleural effusion were more likely to have increased RV free wall thickness, had increased right atrial size, and had decreased RV function compared to cats with CHF but without pleural effusion. An additional study has also identified RV hypertrophy in significantly more cats with HCM and CHF with pleural effusion compared to cats with HCM and CHF without pleural effusion.[6] These findings suggest that RV hypertrophy and dysfunction may have pathophysiological relevance in cats with HCM, as it is reasonable to speculate that RV hypertrophy may lead to RV dysfunction and subsequent RA dilatation and CHF secondary to pleural effusion. However, these results are preliminary and should not be over interpreted. A cause-and-effect relationship cannot be determined from our study. Prospective longitudinal studies are needed to clarify this hypothesis.

Our study has several limitations. First, our study population was comprised of cats solely affected with HCM, and cats with additional abnormalities (e.g., hyperthyroidism, systemic hypertension) were excluded. As such, our results apply only to similar cases. Also, ours was a retrospective study in which echocardiographic studies were not uniformly optimized for right-sided heart assessment. Most cardiologists conventionally optimize the majority of their images for the left side of the heart. Therefore, we were forced to acquire certain measurements from limited imaging planes. For example, RV size measurements (chamber dimension and wall thickness) could only be reliably measured in the RV inflow tract region imaged from right parasternal Lx views. Furthermore, in dogs[35] and humans,[36] most of RV function indices are measured from the left apical longitudinal 4-chamber imaging plane. In dogs, this view often is optimized for the right heart by placing the transducer slightly more cranial to the standard left apical 4-chamber view with varying degrees of caudal angulation.[35] Fortunately, in our experience, in cats, the natural tendency when obtaining a standard left apical 4-chamber view is to inadvertently move cranially, thus assisting with viewing of the right heart. We acknowledge that prospective studies designed with the intent to optimize right heart imaging a priori are needed to corroborate our findings.

An additional limitation was that the investigator performing echocardiographic measurements was not blinded to the clinical diagnosis of the cats, thus potentially biasing our results. However, we assert that true blinding would be nearly impossible, as morphologic changes of HCM in cats are easily observed when performing echocardiographic measurements.

Recently, allometric scaling exponents of echocardiographic left-sided cardiac measurements derived from a large number of cats were reported to range from 0.2 to 0.3.[37] This finding is slightly less than that reported for dogs and the theoretical value used in the current study (0.33) when indexing RV free wall thickness to body weight. Given that echocardiographic variables in cats may scale differently,[37] we acknowledge that this may affect the precision of our results for iRVFWd.

Lastly, we recognize the potential confounding effects of the drugs (particularly sedatives and furosemide) that many cats with CHF received before echocardiography. However, the proportion of cats that received a sedative (butorphanol or buprenorphine) in each of the 3 groups was not statistically different, and a recent report suggested that sedatives do not significantly alter echocardiographic measurements in cats.[38] Also, furosemide may alter right heart chamber dimensions, because hydration status has been shown to produce changes in normal cats that may lead to an erroneous diagnosis of HCM.[39] However, in the HCM + CHF group, the RVFWd and RVIDd of cats that received furosemide before echocardiography were not statistically different compared to the cats that did not receive furosemide. We also acknowledge that furosemide may affect RV function (by a reduction in preload), and this was not controlled for in this study.

In conclusion, the results of our study identified increased RV free wall thickness in some cats with HCM, and suggest that increased RV free wall thickness may be associated with the clinical severity of HCM. Increased RV chamber size and RV dysfunction were associated with LV hemodynamic burden and clinical morbidity as determined by LA size. Our results also suggest that increased RV chamber size, RV hypertrophy (increased RV wall thickness), and RV dysfunction may be involved in the pathophysiology of pleural effusion in cats with HCM. Based on these findings, we conclude that the RV may be involved in the pathophysiology of HCM in cats. Thus, we encourage the echocardiographic assessment of the RV in cats with HCM. Future prospective longitudinal studies are necessary to confirm these findings and help characterize the clinical and prognostic value of RV remodeling and dysfunction in cats with HCM.

Footnotes

[a] Philips IE33, Philips Healthcare, Andover, MA

[b] Syngo® Dynamic Workplace, Version 10.0.01_HF04_Rev5 (Build 2884), Siemens Medical Solutions, USA, Inc, Malvern, PA

[c] Prism 6 for Mac OS X, Version 6.0 g, GraphPad Software, Inc, La Jolla, CA

[d] MedCalc Statistical Software for Windows 10, Version 16.4.3, MedCalc Software bvba, Ostend, Belgium

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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