PREVALENCE OF CARDIOMYOPATHY IN APPARENTLY HEALTHY CATS

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ABSTRACT

Subclinical cardiomyopathy (CM) sometimes is identified after abnormalities are detected during auscultation of apparently healthy cats. Little is known regarding the prevalence of CM in this population. Furthermore, the clinical importance of auscultatory abnormalities in apparently healthy cats is unclear. In order to estimate the prevalence of murmurs and CM, we prospectively evaluated a sample of apparently healthy cats. Cats with systemic hypertension or hyperthyroidism were excluded. 103 cats were subject to physical and echocardiographic examinations which were performed by two different investigators; the echocardiographer was unaware of the physical findings. Left ventricular wall thickness was determined by two-dimensional echocardiography in short- and long-axis planes. Left ventricular hypertrophy (LVH) was defined as an end-diastolic wall thickness ≥ 6 mm. Cats with LVH but without left ventricular dilation were considered to have hypertrophic CM (HCM). Cardiomyopathy was identified in 16 cats (15.5%; 95% CI: [9.2, 24.0]); 15 had HCM and one had arrythmogenic right ventricular cardiomyopathy. Murmurs were detected in 16 cats (15.5%; 95% CI: [9.2; 24.0]); of these cats, 5 had CM. Of 15 cats with HCM, 11 had segmental LVH, three cats had diffuse LVH, and one cat had borderline LVH and marked systolic anterior motion of the mitral valve. The sensitivity and specificity of murmurs for detection of a CM was 31% and 87%, respectively. The prevalence of feline subclinical CM in Southwest Virginia is near 16%; approximately a third of these cats had murmurs. In apparently healthy cats, a cardiac murmur is an insensitive marker of the presence of CM.

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DEDICATION

This thesis is dedicated to my wife, Christina R. Paige, for the many days she sacrificed to help support this project. I also dedicate this work to our pets for their unconditional friendship. Finally, to our unborn child, Sophia, we will meet you soon.

Sincerely,

Christopher F. Paige

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ATTRIBUTION

Dr. Jonathan Abbott is my graduate advisor. He contributed to the study design and data analysis. He is the investigator who performed the echocardiographic examinations.

Dr. R. Lee Pyle is a committee member. He is the investigator who performed the physical examinations.

Dr. François Elvinger is a committee member. He provided expertise in epidemiology and contributed to study design and data analysis.

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of a non-dilated ventricle in the absence of systemic disorders or structural cardiac diseases known to induce hypertrophy.[1] HCM in humans is sometimes inherited as a Mendelian autosomal dominant trait and numerous mutations in genes that encode sarcomeric proteins have been associated with this disease.[2] Sudden death, left heart failure and stroke are potential complications of this condition.[2] In people, HCM is the most common genetic cardiovascular disease; a prevalence of 0.2% has been reported.[2] Feline HCM, which is clinically, echocardiographically and histologically similar to the disorder observed in humans, has been proposed as a model for the human disease.[3] Studies have demonstrated that HCM in the Maine Coon cat is heritable and genomic clarification has recently been reported.[4,5] To date, feline HCM is defined only by echocardiographic or post-mortem criteria.[6] Feline HCM may be subclinical or result in clinical signs associated with left heart failure or aortic thromboembolism.[3] The spectrum of severity is wide and the rate of disease progression is variable, which makes it difficult to determine risk factors that predict outcome.

HCM is the most common disorder in cats with clinically evident cardiac disease. However, other forms of myocardial disease including dilated cardiomyopathy (DCM), arrhythmogenic right ventricular (ARVCM), restrictive (RCM) and unclassified cardiomyopathy (UCM) are also observed.[1, 6, 7] The obstructive form of HCM is typically associated with a cardiac murmur.[6] Because a cardiac murmur may prompt echocardiographic examination in the absence of clinical signs, patients with subclinical feline HCM are commonly identified. However, murmurs are inconsistently present in cats with all forms of cardiomyopathy. Therefore, the prevalence of feline cardiomyopathy including less common forms such as RCM and ARVCM might be greater than is generally thought.

The epidemiological characteristics of feline cardiomyopathy have been addressed, but those studies were limited by referral bias, misclassification bias and the shortcomings of retrospective analysis.[6-10] The earliest study to address occurrence of HCM was based on 4,933 necropsies, where 421 cats had acquired heart disease, and half

of those had characteristics of hypertrophic cardiomyopathy.[11] However, it is relevant that this study was carried out prior to the widespread recognition of systemic hypertension and also prior to the first description of feline hyperthyroidism. Both of these conditions can result in gross cardiac abnormalities that are indistinguishable from those of HCM, and therefore, misclassification may have biased the prevalence estimate. Other studies that followed were limited to retrospective analysis and restricted to referral populations, which may have inflated the prevalence measure.[6,7,9,10] Cote *et al* described a 21% (23 /103 cats) prevalence of heart murmurs among overtly healthy cats.[12] Because the cats were enrolled in a blood donor program, cats with a heart murmur or history of cardiac disease had been excluded prior to initiation of the study. A recent report detected 9 % (8 /94) prevalence of subclinical HCM among cats with a normal physical exam.[13] However, cats with murmurs were excluded from the study. In both studies, the exclusion of cats could have underestimated the prevalence estimates, because these cats may have had subclinical cardiac disease.

Our study is the first to provide unbiased estimates of the prevalence of both cardiomyopathy and murmurs in a sample of apparently healthy cats. To limit bias, physical and echocardiographic examinations were performed by independent investigators. Therefore, the echocardiographer was unaware of the physical findings. Unlike the previous studies, we minimized sampling time to more accurately represent the instantaneous occurrence of disease that is implicit in the definition of prevalence.[14] We also sought to clarify the clinical relevance of cardiac murmurs in apparently healthy cats by evaluating the diagnostic accuracy of this finding for detection of feline cardiomyopathy. To achieve these objectives we conducted a community-based population survey in which apparently healthy cats were subject to physical and echocardiographic examinations. We hope that our estimate of population prevalence and evaluation of cardiac murmurs will form the basis of future epidemiological investigation of feline cardiomyopathies.

CHAPTER 1

PREVALENCE OF CARDIOMYOPATHY IN APPARENTLY HEALTHY CATS.

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ABSTRACT

Objective—To determine the prevalence of murmurs and cardiomyopathy in apparently healthy cats, and to clarify the diagnostic utility of murmurs within this population.

Study Design—Cross-Sectional Study

Procedures—An electronic survey was used to identify apparently healthy cats. Enrolled cats were subject to physical and echocardiographic examinations which were performed by two independent investigators. Left ventricular wall thickness was determined by two-dimensional echocardiography in short- and long-axis planes. Left ventricular hypertrophy (LVH) was defined by an end-diastolic wall thickness ≥ 6 mm. Cats with LVH but without left ventricular dilation were considered to have hypertrophic cardiomyopathy (HCM). Murmurs and abnormal Doppler outflow tract velocities were compared.

Results— Cardiomyopathy (CM) was identified in 16 cats (15.5%; 95% CI: [9.2, 24.0]); 15 had HCM and one had arrythmogenic right ventricular cardiomyopathy. Murmurs were detected in 16 cats (15.5%; 95% CI: [9.2; 24.0]); of these cats, 5 had CM. Of 15 cats with HCM, 11 had segmental LVH, three cats had diffuse LVH, and one cat had borderline LVH with marked systolic anterior motion of the mitral valve. The sensitivity and specificity of murmurs for detecting a CM were 31% and 87%, respectively.

Conclusions— Prevalence of feline subclinical CM in a sample of apparently healthy cats in Southwest Virginia is near 16%. In apparently healthy cats, a cardiac murmur has low sensitivity as a marker of the presence of CM. Doppler echocardiographic evidence of dynamic right or left ventricular outflow tract obstruction was associated with the presence of a cardiac murmur. Cats in which Doppler echocardiographic evaluation disclosed abnormalities of ventricular ejection were more likely to have a cardiac murmur than those without this finding.

INTRODUCTION

Subclinical CM sometimes is identified after abnormalities are detected during auscultation of apparently healthy cats. However, little is known regarding the prevalence of CM in this population. Previous studies have addressed the prevalence of CM and murmurs in healthy cats, but these studies had limitations that relate to referral bias, retrospective analysis, and inclusion criteria.[7, 9,10,12,13] While many feline patients are referred for echocardiographic evaluation after detection of a murmur, the relationship between murmurs and cardiomyopathy in healthy cats remains unclear. We attempted to estimate the prevalence of cardiomyopathy and murmurs in apparently healthy cats and in so doing, clarify the clinical relevance and diagnostic utility of cardiac murmurs in this population. To achieve this objective we conducted a community-based population survey in which apparently healthy cats were subject to physical and echocardiographic examinations.

MATERIAL AND METHODS

We prospectively examined apparently healthy cats owned by veterinary students, staff and faculty at the Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM), Blacksburg, VA. This investigation was approved by the Animal Care and Use Committee and Institutional Review Board of Virginia Tech.

Enrollment— An email was sent to a distribution list that included students, technical staff and faculty of the VMRCVM. Pet-owners that were willing to enroll their cats were asked to complete an electronic, web-based survey which was used to identify cats that met inclusion criteria and also provide zoographic data. Apparently healthy cats were included if they had not previously been subject to echocardiographic examination, were not receiving treatment for cardiovascular disease and did not have a history of chronic illnesses such as inflammatory bowel disease, hyperthyroidism, renal disease, systemic hypertension or diabetes mellitus. Cats were excluded if the pet-owner had sought veterinary care for a systemic illness in the three months prior to recruitment. Cats that

had a history of a murmur, but had not been examined echocardiographically, were included.

Procedure—Physical examination, Doppler blood pressure estimation followed by electrocardiography, and then echocardiography were performed in that order in three different rooms. The physical and echocardiographic examinations were performed by two different board-certified veterinary cardiologists (RLP and JAA); the echocardiographer (JAA) was unaware of the physical findings. Echocardiographic images were digitally recorded for later quantitative and qualitative analysis. After digital echocardiographic records were randomized and patient identifiers concealed, echocardiographic measurements were obtained by a third investigator (CFP). The final echocardiographic diagnosis was the consensus opinion of the echocardiographer and the investigator (CFP) that performed the echocardiographic measurements and was determined without knowledge of the physical findings.

Physical Examination—All cats were subject to systematic, dynamic auscultatory examination. Auscultation was first performed when cats were at rest and then after provocation, defined for the purpose of this study as a maneuver in which the examiner quickly lifts the cat in the air at least two times. When identified, murmurs were described in terms of: intensity, which was graded on a six interval scale according to the recommendations of Levine, point of maximal intensity, and timing.[15] The presence or absence of a gallop sound was noted as was a description of the cardiac rhythm. Heart rate and respiratory rate were recorded for all cats.

Echocardiography—Examinations were performed without chemical restraint. Utilizing a Vingmed System FiVe sonograph[a] with a 7.5 MHz transducer, transthoracic echocardiography was performed as previously described.[16] Two-dimensional (2-D) short-axis and long-axis right parasternal images of the left ventricle were used to measure wall thickness. In the short-axis plane, end-diastole was defined as the maximal diastolic excursion of the ventricle or onset of the QRS. In the long-axis plane, end-

[a] General Electric Medical Systems, Waukesha, WI.

diastole was the first frame during which mitral valve closure was visible. The following dimensions were obtained from the short-axis image: end-diastolic left ventricular internal diameter (LVIDd), end-diastolic thickness of the interventricular septum (IVSd) and end-diastolic thickness of the left ventricular posterior wall (LVPWd). The end-diastolic thickness of the IVS was also measured in two additional sites. Specifically, the maximal thickness of the septum was measured in the two septal segments which extend from the papillary muscles to the central point of the septum (Figure 1). The line of measurement was parallel to a cord that extended through the centroid of the ventricular lumen (Figure 2). End-diastolic basilar septal thickness was measured in the long-axis plane and was the maximal dimension at a site between the aortic root and the point at which the anterior mitral valve leaflet most closely approaches the IVS during diastole (Figure 3). Septal measurements included left ventricular endocardial echoes but excluded echoes arising from the right ventricular endocardium.[17] Measurements of the LVPW included endocardial echoes but did not include the pericardium. Aortic (Ao): left atrial (LA) ratio was determined by M-mode. Left atrial enlargement was defined by a left atrial-aortic ratio in excess of 1.54. The subjects were also subject to conventional Doppler examination. Right and left ventricular outflow tract velocities were recorded. Color Doppler mapping and pulsed-wave spectral Doppler were used to screen for dynamic outflow tract obstruction. Echocardiographic dimensions and spectral Doppler measurements were the average of three, usually consecutive cardiac cycles.

Hypertrophic cardiomyopathy (HCM) was defined by an end-diastolic wall thickness $\geq$ 6 mm for more than 50% of any region of the interventricular septum or left ventricular posterior wall and the presence or absence of systolic anterior motion of the mitral valve was also noted.[3] Other forms of feline cardiomyopathy were classified as previously described.[7,18] Dynamic right ventricular outflow obstruction (DRVOT) was defined by a systolic jet that originated proximal to the infundibulum and had spectral Doppler characteristics that indicated late-systolic acceleration.[19] Dynamic left ventricular outflow tract obstruction was similarly defined by late-systolic acceleration.

Blood Pressure / Electrocardiography—Systemic blood pressure was estimated for all cats using the Doppler cuff-flowmeter method.[20] All estimates were obtained utilizing

either the left or right front limb. Cats were considered hypertensive if the average of three consecutive measurements was ≥ 180 mm Hg. After systemic blood pressure measurements, the subjects were restrained while in right lateral recumbence and a six-lead electrocardiogram was recorded. Average, electrocardiographic heart rate was reported only from the six-lead electrocardiogram. Arrhythmias were documented by either the six-lead electrocardiogram or the electrocardiogram that was recorded during echocardiography.

Thyroid Function—After completion of the cardiovascular examination, all cats that were ≥ 6 years old underwent jugular venipuncture, whole blood was obtained, and centrifuged. The serum supernatant was refrigerated, and the DRI Thyroxine (T4) assay[b] was performed utilizing an Olympus AV 400, Automated Chemistry Analyzer.[c] Those cats in which the T4 determination exceeded the upper limit of our laboratory reference range were considered hyperthyroid and excluded from further analysis.

Data analysis—Prevalence of cardiomyopathy and murmurs as well as the corresponding 95% confidence intervals (CI) were computed using the frequency procedure of SAS.[d] Associations between murmurs and the presence of dynamic outflow tract obstruction were assessed using the chi-square test. When statistically significant, the association was further assessed using the prevalence odds ratio. To determine the diagnostic utility of unprovoked murmurs for cardiomyopathy detection, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR) and respective 95% CI were derived using SISA.[e] Results associated with p-values that were less than 0.05 were considered statistically significant.

[b] Microgenics Corporation, 46360 Fremont Blvd., Fremont, CA
[c] Olympus America Inc., Two Corporate Center Drive, Melville, NY
[d] SAS, Version 8.02, SAS Institute Inc. Cary, NC
[e] Uitenbroek, Daan G."SISA-Binomial." 1997. <http://home.clara.net/sisa/binomial.htm>

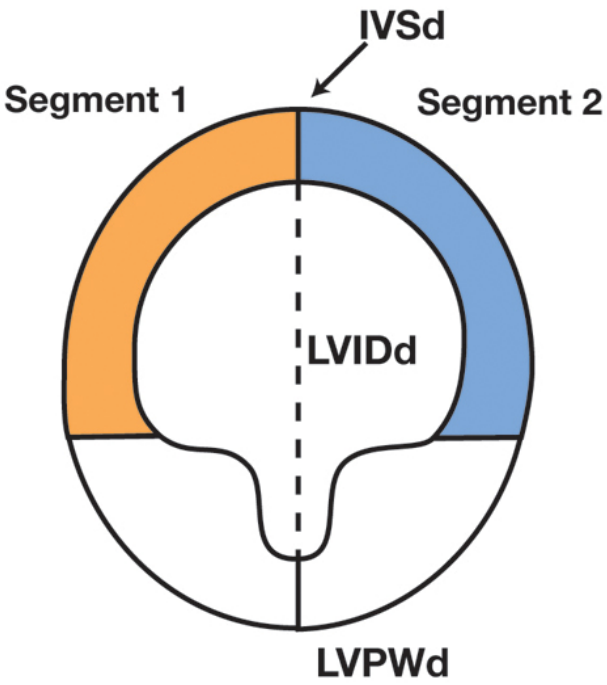

Figure 1. A schematic drawing showing regions measured during peak end-diastole. Segment 1 and 2 = a single linear dimension was obtained from each segment; this measurement represents the maximal thickness of each segment. IVSd=end-diastolic thickness of the interventricular septum, LVIDd=left ventricular internal diameter during diastole, LVPWd=end-diastolic thickness of the left ventricular posterior wall.

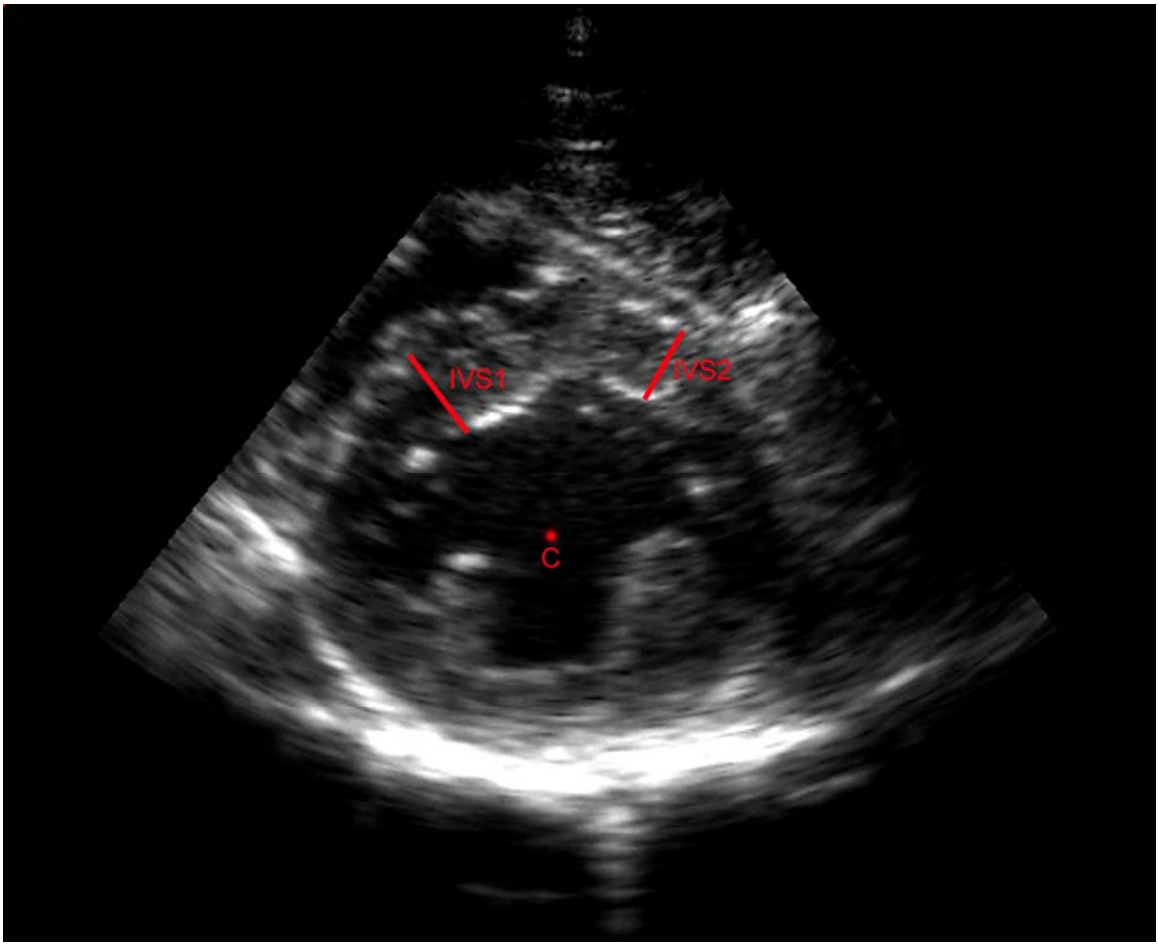

Figure 2. This is a 2-D short-axis image of the left ventricle of an echocardiographically normal cat. The measurements are perpendicular to the left ventricular endocardial border and directed towards the ventricular centroid (C). IVS1=interventricular septum segment 1, IVS2=interventricular septum segment 2.

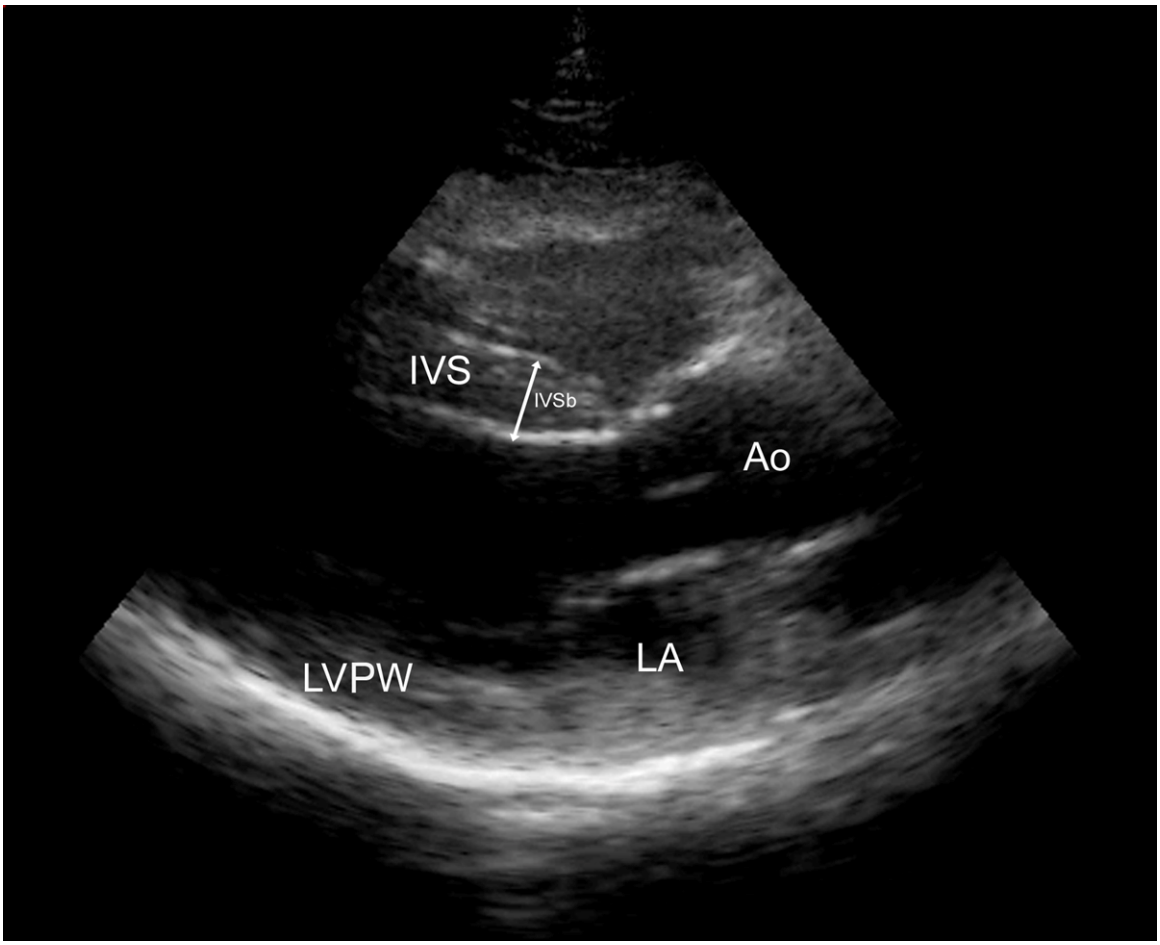

Figure 3. Right parasternal long-axis image of the left ventricle of an echocardiographically normal cat. IVS=interventricular septum, IVSb= measurement location of the basilar septum, LA=left atrium, Ao=aorta, and LVPW=left ventricular posterior wall.

RESULTS

Enrollment—There were 165 responses to our electronic survey and 145 cats met the initial inclusion criteria. We examined 132 cats over six non-consecutive days from late August 2005 to early November 2005. Twenty-nine of these cats were later excluded because they resisted manual restraint (22), were hyperthyroid (4), or had incomplete echocardiographic examinations (3). A total of a 103 apparently healthy cats were used for prevalence estimates. Forty-three cats were females. Mean body-weight ± standard deviation (SD) was 5.01 ± 1.13 kg. Precise ages were not always available so discrete age categories were constructed: < 1 yr (n=6), 1-5 yrs (n=62), 6-10 yrs (n=27), 11 to 15 yrs (n=7), and ≥ 16 yrs (n=1). The majority of cats were mixed breeds (domestic short hair n=75, domestic medium hair n=9, and domestic long hair n=10). Pure breeds included Himalayan (n=3), Siamese (n=3), Ocicat (n=2), and Maine Coon cat (n=1).

Physical Examination—Murmurs were detected in 16 cats (15.5%; 95% CI: [9.2; 24.0]). Murmur intensities were classified as follows: grade 1/6 (n=5), grade 2/6 (n=9), and grade 3/6 (n=2). A total of 28 cats had murmurs after the provocative maneuver; 13 out of the 28 did not have the murmur at rest. One cat had a murmur at rest, but not after the provocative maneuver. Based on auscultation, the mean heart rate of all cats was 173.7 beats per minute (bpm) ± 17.2 SD. The following additional abnormalities were identified through auscultation: gallop rhythm (n=2), bradycardia (n=1), and compensatory pause (n=1).

Doppler Blood Pressure / Electrocardiography—All cats were normotensive; average systolic blood pressure in 87 echocardiographically normal cats was 131.1 mm Hg ± 17.8 SD. In 15 cats with HCM, average systolic blood pressure was 136.4 mm Hg ± 19.6 SD. Based on electrocardiography, mean heart rate (HR) of 80 cats without CM was 189.4 bpm ± 23.8 SD; for cats with HCM, average HR was 188.7 bpm ± 27.2 SD. The following electrocardiographic abnormalities were identified during electrocardiography or echocardiography: two cats that did not have CM had ventricular pre-excitation, four cats without CM had ventricular premature complexes (VPC) and one cat without CM

had ventricular tachycardia (VT). Of the cats with CM, two with HCM had VPCs. Ventricular tachycardia was recorded from the cat with ARVC.

Echocardiography—Cardiomyopathy was identified in 16 cats (15.5%; 95% confidence interval (CI): [9.2, 24.0]); 15 had HCM and one had arrythmogenic right ventricular cardiomyopathy (ARVC). Of 15 cats with HCM, 11 had segmental LVH and in three of these cats, hypertrophy was localized to the basilar septum. In the cats with basilar septal hypertrophy, one cat was between 1 to 5 years of age while the remaining two were greater than 10 years of age. Three cats had diffuse LVH. One cat with marked systolic anterior motion of the mitral valve and maximal ventricular wall thickness of 5.9 mm was classified as HCM. The cat classified as ARVC had a prominent right ventricle, abnormal septal motion, tricuspid regurgitation, ventricular tachycardia, and an intermittent gallop sound.

Dynamic right ventricular outflow tract obstruction (DRVOT) with peak velocities ≥1.7 m/s was identified in 5 cats, and three other cats had lower velocities with evidence of late systolic acceleration. Left ventricular outflow tract obstruction (LVOT) was identified in 8 cats; two cats with HCM had SAM with supraphysiologic LVOT velocities (4.2 m/s and 2.1 m/s) and mitral regurgitation, 2 had mid-left ventricular obstruction and supraphysiologic velocities (1.8 m/s, 1.7 m/s), while the remaining 4 had late systolic acceleration with lower velocities (1.0 m/s (n=2), 1.1 m/s, 1.6 m/s). Of the 6 cats with dynamic LVOT obstruction in which SAM was not detected, two had HCM and four did not. Two cats, one with HCM and one without, had both right and left ventricular dynamic outflow tract obstruction.

Association of Murmurs and Dynamic Outflow Tract Obstruction—Of the 16 cats with murmurs, 5 had HCM. Six of 16 cats with unprovoked murmurs had a dynamic outflow tract obstruction: RVOT only (n=3; HCM=0), RVOT/LVOT (n=1; HCM=1), and LVOT/MR (n=2; HCM=2). Two cats with murmurs and HCM did not have an abnormal Doppler spectrogram. Ten of 28 cats with murmurs during the provocative maneuver had an Doppler evidence of dynamic outflow tract obstruction: RVOT only (n=5; HCM=0), LVOT only (n=2; HCM=1), RVOT/LVOT (n=1; HCM=1), and LVOT/MR (n=2;

HCM=2). The six cats which had a murmur at rest and dynamic outflow tract obstruction also developed a murmur during the provocative maneuver. A 2x2 table and calculated odds ratios defining the association between physical and echocardiographic findings are shown in Table 1. Statistically significant prevalence odds ratios describe the relationship between the echocardiographic finding of dynamic outflow tract obstruction and the physical finding of a murmur heard during rest and after provocation; cats in which Doppler characteristics of ventricular outflow were abnormal were more likely to have a cardiac murmur than those that did not.

Diagnostic Utility of Murmurs—To assess the diagnostic value of murmurs for detection of a cardiomyopathy, the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios (positive and negative) were calculated and are shown in Table 2.

Table 1. A 2X2 table and calculated odds ratio as the measure of association between cardiac murmurs and echocardiographic findings in apparently healthy.

	Outcome		
Diagnostic Test	Murmur +	Murmur –	Total
Abnormal Doppler Outflow +	6	10	16
Abnormal Doppler Outflow –	10	77	87
Total	16	87	103

	Determinant	Outcome	OR	95% CI	P-value
103	Abnormal Doppler Outflow	Murmur (unprovoked)	4.62	1.38, 15.5	<0.01
102	Abnormal Doppler Outflow	Murmur (after provocative maneuver)	6.30	2.02, 19.6	<0.001

OR = prevalence odds ratio, 95% CI = 95% confidence interval

Table 2. This 2X2 table provides raw prevalence data for unprovoked cardiac murmurs and cardiomyopathy (CM) in apparently healthy cats.

	Disease		
Diagnostic Test	CM +	CM –	Total
Murmur +	5	11	16
Murmur –	11	76	87
Total	16	87	103

	Value	95 % CI
Prevalence CM (%)	15.5	9.2, 24
Sensitivity (%)	31	9, 54
Specificity (%)	87	80, 94
PPV	0.31	0.09,0.54
NPV	0.87	0.80, 0.94
Positive LR	2.47	0.99, 6.16
Negative LR	0.79	0.56, 1.11

PPV, Positive Predictive Value; NPV, Negative Predictive Value; LR, Likelihood Ratio.

DISCUSSION

This study was the first prospective investigation of the relationship between auscultatory abnormalities and echocardiographic findings in a community-based population of apparently healthy cats. The prevalence of feline subclinical CM in Southwest Virginia is near 16%; approximately a third of these cats had murmurs. The majority of affected cats had HCM. Interestingly, only 5 out of the 16 cats with murmurs had a CM.

Previous veterinary investigations have addressed epidemiological characteristics of feline cardiomyopathy, but many of these studies evaluated referral-based populations or excluded cats with murmurs from the study population. Cote *et al* described a 21% (23 /103 cats) prevalence of heart murmurs among overtly healthy cats.[12] Because cats that had a heart murmur or history of cardiac disease had been excluded prior to initiation of that study, their prevalence estimate can not be directly compared to our findings. Because we included cats based on apparent health status, we believe we have achieved a better estimate of the true prevalence within our population. Importantly, our study design removed the echocardiographer's inherent bias to identify the source of a cardiac murmur. Each cat was examined systematically without knowledge of the physical findings which should further increase the validity of our prevalence estimate.

Based on our findings, feline HCM is more prevalent than is HCM in human beings.[21] The prevalence of HCM in our population sample seemingly was high but there are no similar published data with which to compare. However, it should be recognized that, relative to M-mode echocardiography which has been used in many studies of feline HCM, 2-D echocardiography is a sensitive method for detection of hypertrophy.[22] The majority (11/15) of cats with HCM had segmental left ventricular hypertrophy. The subjects with HCM that we identified were apparently mildly affected; hypertrophy was not marked, generally was segmental and none of the cats had echocardiographic evidence of atrial enlargement. The high prevalence of HCM in apparently healthy cats is consistent with the current understanding of the diversity of this disorder in human beings. In the past, the clinical impact of HCM in humans and perhaps in cats has been exaggerated because data typically have been obtained from referral populations. It is

currently accepted that the HCM in people is a genetic disorder that is associated with diverse phenotypic expression and a variable clinical course.[21,23] HCM in the Maine Coon cat is heritable and the genetic mutation associated with this disorder has recently been reported.[4,5] Familial HCM has been observed in other breeds of cats and based on this, it is possible that feline HCM generally is a genetic disorder.

Abnormal auscultatory findings often prompt an echocardiographic examination; it is the next logical diagnostic step when feline CM is suspected. However, previous retrospective studies have clearly demonstrated that cats without murmurs can also have a CM.[13,18] In this study, 11/16 cats with CM did not have murmurs. Within this study population, sensitivity and specificity describe the proportion of cats with CM and without CM that are identified by the presence or absence a murmur, respectively.[23] Interestingly, only 31% of cats with CM had murmurs, and 87% of cats without CM did not have murmurs. Because sensitivity is apparently low, the use of cardiac murmur as a diagnostic, screening test would yield a high number of false negative results. [24] The 95% confidence intervals (CI) for sensitivity and specificity were 0.085, 0.54 and 0.804, 0.943, respectively. The CI for sensitivity is wide because the sample size, though larger than previous investigations, was, in relative terms, small (Table 2).

To further explore the diagnostic accuracy of CM detection by murmurs, the positive predictive value (PPV) and negative predictive value (NPV) were calculated (Table 2). Because the number of cats with murmurs and CM were equal, PPV and NPV were numerically identical to our sensitivity and specificity estimates (Table 2). The PPV is the probability that a cat with a murmur has CM, while the NPV is the probability that a cat that does not have a murmur does not have CM.[25] Predictive values depend on population prevalence; our estimates are only relevant to the population of apparently healthy cats in our geographic region. Within this study population, our findings suggest that a murmur detects only 31 % of the cats with a murmur have CM, which means that 69% of cats with a murmur do not have CM. These predictive values suggest that auscultation does not reliably identify feline cardiomyopathy.

The calculation of likelihood ratios (LR) is another approach to the evaluation of diagnostic utility.[26] The positive LR is the proportional relationship between the probability of a positive test result in a subject that has disease and the probability of a

positive test result in a subject that does not have disease. For our data, the positive LR relates the probability that a subject with CM has a murmur with the probability that a subject that does not have CM has a murmur.[26] Based on our data, a cat with CM is 2.5 times more likely to have a murmur than a cat without CM. However, this was only a tendency of the data as the 95% CI included one; given our a priori specification of alpha=0.05, the result was not statistically significant. The negative likelihood ratio was 0.79; that is, cats with CM are less likely to be free of a murmur than are cats without CM. Again however, this result was not statistically significant. Taken together, these measures of diagnostic accuracy suggest that the presence or absence of cardiac murmurs in healthy cats does not usefully discriminate those with CM from those without.

In general, diagnostic tests that effectively screen populations for disease have high sensitivity. In this regard, the presence or absence of a cardiac murmur certainly has limitations. However, at present, physical examination likely remains the only practical means to select apparently healthy cats that may have CM. Furthermore, the specificity of auscultation is moderate.

The association between abnormal Doppler outflow tract velocities and murmurs was evaluated through the calculation of prevalence odds ratios. The odds ratio is an indirect measure of risk that is appropriate for use in the analysis of cross-sectional studies.[27] When statistically significant, it can be interpreted as the multiplicative relationship between an explanatory variable and the binary outcome. In our study, subjects with Doppler evidence of dynamic outflow tract obstruction were 5 times more likely to have a murmur at rest than did cats that did not have this finding, and 6.3 times more likely to have murmur after provocation (Table 1). The 95% CI of the odds ratio provides a measure of the precision of the estimate.[28]

Because this was a cross-sectional study, we cannot infer a causal association between echocardiographic findings and the presence of a murmur. However, we can conclude that cats with Doppler evidence of abnormal ventricular outflow are nearly 5 times more likely to have a murmur at rest, and those cats with Doppler evidence of abnormal ventricular outflow tract velocity are 6 times more likely to have murmur after provocation. Previous studies have addressed the labile nature of murmurs in cats, which can vary in intensity with heart rate.[19] Because auscultation was not performed during the

echocardiogram, it is plausible that some, if not all, of these cats with dynamic outflow tract obstruction, could develop a heart murmur during some circumstances.

These data must be interpreted in the context of the study limitations. The confidence intervals of our descriptive statistics were relatively broad and this of course is a reflection of sample size. It would have been better to examine larger number of cats but the sample size was determined by issues of practicality. The subjects enrolled in this investigation were pets and therefore it was not possible to confirm the diagnosis of HCM by post-mortem examination. We recognize that 22 of the cats resisted manual restraint, and inclusion of these cats may have influenced our prevalence results. A few cats had isolated basilar septal hypertrophy. It is recognized that a change in aorticoseptal angle – the development of a "sigmoid septum" – could possibly result in an artifactual appearance of septal hypertrophy.[29]

In summary, our epidemiologic study of feline cardiomyopathy has provided an unbiased prevalence estimate of murmurs and cardiomyopathy in apparently healthy cats. We have also clarified the clinical relevance of murmurs and the diagnostic role of auscultation for detection of CM. Our estimate of population prevalence and understanding of cardiac murmurs may form the basis of future epidemiological investigation of feline cardiomyopathies.

CONCLUSIONS

The prevalence of feline subclinical CM in Southwest Virginia is near 16%; approximately a third of these cats had murmurs. Hypertrophic CM is the most prevalent form of CM within our study population. Auscultation is not a sensitive diagnostic test for detection of feline CM. The presence of a cardiac murmur was associated with echocardiographic evidence of dynamic ventricular outflow tract obstruction.

FUTURE INVESTIGATIONS

Now we have identified the unbiased prevalence of cardiomyopathy and murmurs within this population of apparently healthy cats, future epidemiological studies can be directed towards longitudinal follow-up of our normal cats. This would allow the identification of incident cases, which can ultimately be used to calculate the incidence density, an epidemiological measure of disease occurrence.[24] Utilizing a cohort study design and the incidence density, a relative risk for various factors (i.e. identification of a murmur) could be determined between exposed and non-exposed groups of apparently healthy cats.[24] Any causal associations of these risk factors leading to an outcome of cardiomyopathy could then be determined. Based on this new understanding of disease progression and risk, therapeutic trials can be implemented, which currently remains the most clinically important, yet least understood, aspect of feline cardiomyopathy.

While hypertrophic cardiomyopathy remains the most common genetic cardiovascular disease in humans, this genetic association in Maine Coon cats has only recently been revealed.[2,5] Therefore, future investigations of this or other gene mutation in pure and mixed breed cats should be further pursued. Once identified, long-term follow-up of these cats would clarify the relationship of their genetic findings with the phenotypic expression of left ventricular hypertrophy.

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