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Review article

Feline hypertrophic cardiomyopathy: genetics, current diagnosis and management

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart problem in cats, especially in Maine Coon, Ragdoll and Persian cats. Hypertrophy of interventricular septum and left ventricular wall lead to the impediment of the blood ejection. The adverse sequelae of left atrial enlargement contribute to the formation of thrombus and the progression of left side congestive heart failure. Medical management has been performed to manage HCM in cats. Several research studies have been proposed the possible assessments to seek an effective therapeutic for HCM. Furthermore, strategies for slowing the disease progression have been extensively studied to ameliorate the symptoms and prevent sudden cardiac death. This review summarizes the morphology, genetic information, clinical presentation, evaluation methods, management and prognosis indicators of HCM in cats. The genetic investigation may provide an important understanding of phenotypic variability of HCM and the treatment target to reduce morbidity and mortality of HCM in cats.

Keywords: Feline, Hypertrophic cardiomyopathy, Myocardial disease

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INTRODUCTION

Hypertrophic cardiomyopathy, or HCM, is a major cause of genetic heart problems in cats, HCM is a myocardial disease that affects the left ventricle of the heart in both humans and cats. (Ferasin et al., 2003). The well-known predisposed-breed cats are Maine coon, Ragdoll, British shorthair, domestic shorthair, Sphinx and Persian cats (Abbott, 2010; Ferasin et al., 2003; Granström et al., 2011). Research studies have been recently reported that HCM is more common in cats (14.7%) than in humans (0.2%) (Maron, 2004; Payne et al., 2015; Semsarian et al., 2015). Echocardiography is a diagnostic tool to evaluate and measure myocardial thickness in cats with HCM. A previous study of feline HCM demonstrated that the mean age of diagnosis was 7 years, with male cats being predominantly affected (64.86%). The characteristic of echocardiography variables are shown in Table 1. (Brizard et al., 2009).

Table 1 Characteristics and echocardiographic variables of 111 hypertrophic cardiomyopathy in cats; Values showed as mean ± SD or median and range in parentheses (Brizard et al., 2009).

Parameters	Mean ±SD	Normal range
Age in years	7 (1-18)	-
Male (number [%])	64.86 %	-
Heart rate (bpm)	188 (140-268)	140-240
LA/AO ratio	1.53 (1-4.1)	0.8 – 1.5
IVSDd (mm)	6.2 (7.8-22)	3-5
LVPWd (mm)	6.2 (4.2-16.2)	2.5-5.5
LVIDd (mm)	14.48 (7.8-22)	11-18
LVIDs (mm)	6.1 (2.1-16.4)	6.7-9.7
Fractional shortening (%)	57±11	36-55

LA = Left atrium, Ao = Aorta, IVSDd = Interventricular septum diameter at end diastole, LVPWd = Left ventricular proximal wall thickness at end diastole, LVIDd = Left ventricular internal diameter at end diastole, LVIDs = Left ventricular internal diameter at end systole

The Americal College of Veterinary Internal Medicine (ACVIM) recently published a consensus statement about guidelines for the classification, diagnosis, and management of cardiomyopathies in cats (Fuentes et al., 2020). However, the specific underlying cause of HCM cannot be identified and the pathogenesis is still unclear. HCM in humans is associated with more than 11 genetic variations in genes encoding sarcomeric mutations, and mutation in MYBPC3 were the mutations most frequently responsible for this disease (Elliott et al., 2014). Although our understanding of the diagnosis and treatment of HCM in humans has developed, feline HCM still remains undiagnosed until cats present clinical signs. The purpose of this review is to provide important information on the clinical presentation, diagnosis, and genes associated with feline HCM. The close similarity of the disease between cats and humans may provide a model for the future therapeutic strategies for HCM disease.

MORPHOLOGY AND THE CLASSIFICATION OF HYPERTROPHIC CARDIOMYOPATHY

HCM is a myocardial disease that affects cardiac muscle and leads to myocardial function impairment (Richardson, 1996). HCM can be characterized by an increase in left ventricular myocardial mass. However, secondary HCM, such as hyperthyroidism, systemic hypertension, aortic stenosis, and acromegaly, are the main differential diagnoses for this disease (Elliott et al., 2014; Häggström et al., 2015). In cats, cardiomyopathies have been classified into 5 forms: hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), nonspecific cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Fuentes et al., 2020).

GENETICS OF FELINE HYPERTROPHIC CARDIOMYOPATHY

Genes associated with HCM in cats are shown in Table 2. The prevalence of HCM in cats is approximately 34- 41.5%, and a myosin-binding protein-C gene (MYBPC3) mutation has been identified in association with HCM in Maine Coon and Ragdoll cats (Fries et al., 2008; Mary et al., 2010; Kittleson et al., 2015). The MYBPC3-A31P gene polymorphism has been detected in Maine Coon cats or cats crossbred with Maine Coon cats (Mary et al., 2010; Kittleson et al., 2015) Cat with homozygous mutations were found to be younger and have more severe HCM progression than cats with heterozygous gene mutations (Kittleson et al., 1999). MYBPC3-A74T region, another gene mutation in cardiac myosin binding protein C, has been investigated in Maine Coon cats and in cats with other breeds such as Persian cats and domestic shorthair cats. However, this gene polymorphism has low sensitivity (50%) for HCM detection and low association with clinical presentation (Longeri et al., 2013; Wess et al., 2010).

Table 2 Clinical studies of gene associated hypertrophic cardiomyopathy in cats.

Study type	Affected breed	Coding-protein	Gene	Gene prevalence	References
Clinical study (n = 3,310)	Maine Coon	cMyBPC	*MYBPC3*-A31P	34%	(Fries et al., 2008)
Clinical study (n = 151)	Maine Coon and other breeds	cMyBPC	*MYBPC3*-A31P *MYBPC3*-A74T	22% 48%	(Wess et al., 2010)
Clinical study (n = 151)	Maine Coon British Longhair	cMyBPC	*MYBPC3*-A31P	41.5%	(Mary et al., 2010)
Clinical study (n = 332)	Maine Coon	cMyBPC	*MYBPC3*-A31P	32%	(Godiksen et al., 2011)
Clinical study (n = 3,125)	Maine Coon Ragdoll	cMyBPC	*MYBPC3*-A31P *MYBPC3*-R820W	39.4% 27%	(Casamian-Sorrosal et al., 2014)
Clinical study (n = 251)	Ragdoll	cMyBPC	*MYBPC3*-R820W	34%	(Borgeat et al., 2014)
Clinical study (n = 282)	Ragdoll	cMyBPC	*MYBPC3*-R820W	44%	(Granström et al., 2015)

cMyBPC = Cardiac myosin binding protein-C

Other missense gene mutations in the different regions of myosin-binding protein C have been detected in a specific breeds of cats, such as the Ragdoll cat. Overall, 29-36 % of the MYBPC3-R820W mutations are heterozygous, and 2-5 % are homozygous; in addition, an association of MYBPC3-R820W homozygous gene mutations has been recognized in cats with left ventricular hypertrophy. Moreover, cardiac mortality and short median survival time (approximately 5.65 years) have been observed in cats with homozygous gene mutations (Borgeat et al., 2014; Borgeat et al., 2015; Kittleson et al., 2015). According to the recent ACVIM consensus statement in feline cardiomyopathies, genetic testing for MYBPC3-A31P and MYBPC3-R820W are recommended in Maine Coon and Ragdoll cats for breeding purposes.

The β-Myosin heavy chain (MYH7) gene is one of the most important genes encoding sarcomeric proteins. In humans, mutations in different regions of MYH7 gene may cause various cardiomyopathies, such as dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), noncompaction cardiomyopathy (NCC) and hypertrophic cardiomyopathy (HCM) (Walsh et al., 2010). Nevertheless, few studies have investigated MHY7 gene mutations in cats. An association of a heterozygous variant of the MYH7 gene has been reported in cats with skeletal myopathy, showing the similarity of phenotypic expression between cats and humans (Schipper et al., 2019).

CLINICAL PRESENTATION

Cats with HCM (53.5%) present clinical signs such as respiratory distress, pulmonary edema, pleural effusion and congestive heart failure (CHF). The most common clinical sign in cats with HCM is congestive heart failure (37%) (Payne et al., 2013; Payne et al., 2010). In addition, the formation of a blood clot or thromboembolism in the left atrium of the heart is the most common complication in cats with HCM, and thromboembolism commonly results in unilateral or bilateral hind limb paresis (Baty et al., 2001; Smith et al., 2003). However, cats in the early stages of HCM (46.4%) are usually asymptomatic (Payne et al., 2010).

HCM in cats is challenging to diagnose. Therefore, the detection of HCM in cats with a normal phenotype in the early stage may provide benefits for treatment strategies, prognosis and prevention. A heart murmur is a common clinical presentation in cats with HCM, and these murmurs are usually associated with dynamic left ventricular outflow tract obstruction (LVOTO), and dynamic right ventricular outflow tract obstruction (DRVOTO). Mechanical obstruction of the LV or RV outflow tract is attributed to vigorous systolic contraction and generates murmurs (Dirven et al., 2010; Nakamura et al., 2011; Paige et al., 2009; Payne et al., 2013; Rishniw and Thomas, 2002). Although murmurs auscultation has low sensitivity and low specificity in the detection of HCM, auscultation has been used for routine diagnostic screening in cats (Nakamura et al., 2011; Payne et al., 2013).

Hypertrophic cardiomyopathy biomarker examination

Cardiac biomarker measurement is another diagnostic tool for screening myocardial disease. Cardiac troponin-I (cTnI) is a cardiac biomarker used in the detection of myocardial injury. Previous studies have shown that cTnI increases in cats with HCM and can use as a useful diagnostic tool for predicting cardiac mortality in cats (Borgeat et al., 2014; Langhorn et al., 2014).

N-terminal pro-brain natriuretic peptide (NT-proBNP) is an inactive form of B-type natriuretic peptide (BNP) that is secreted from the cardiac myocytes. Elevated plasma NT-proBNP can indicate a severe stage of HCM, but screening cats in the stage of mild or moderate HCM is not recommended. The NT-proBNP value was only 58% sensitive and 86% specific in the detection of a moderate stage of HCM in cats (Hsu et al., 2009; Singh et al., 2010). However, plasma NT-proBNP concentration is useful for the differentiation of noncardiac respiratory distress from congestive heart failure. The results of a previous study showed significantly higher NT-proBNP levels in congestive heart failure with respiratory signs (Connolly et al., 2009; Fox et al., 2009; Ward et al., 2018).

Electrocardiographic examination and heart rate variability in hypertrophic cardiomyopathy

Many studies have suggested that sympathetic activation affects the heart rate and heart rate variability (HRV) in heart diseases. A cat with HCM may present with normal electrocardiography (ECG) or display increased R wave and S wave voltage or left axis deviation. Electrical disturbances such as atrial fibrillation and complex ventricular and supraventricular arrhythmia are usually found in cats with mild to moderate subclinical HCM (Jackson et al., 2014). In human medicine, heart rate variability has been used as an indicator to determine pathological conditions and heart failure (Butera et al., 2003). It is well known that the heart of an athlete in training appears to be enlarged and sudden cardiac death usually occurs in athletes with cardiac adaptation. HRV is probably the future predictive index for cardiovascular risk in the evaluation of sudden cardiac death in cats with HCM (Sessa et al., 2018).

Echocardiographic examination

The definitive diagnosis of HCM can be performed by echocardiographic examination. A history of syncope, weakness, murmur and a breed predisposed to HCM are indications for echocardiographic examination. Echocardiography images of cats with HCM clearly demonstrated ventricular hypertrophy (Figures 1; C and D). The upper limit of the left ventricular wall diameter at end diastole does not exceed 6 mm (Fox et al., 1995). Left atrial enlargement on echocardiography is useful to evaluate severity in cats with cardiomyopathy. It is recommended to evaluate the left ventricular outflow tract obstruction and the displacement of the mitral valve septum leaflet using 2D and M-mode echocardiography images. Dynamic obstruction of the left ventricular outflow tract and systolic anterior motion of the mitral valve (SAM) are common findings in cats with HCM, as shown in figure 2.

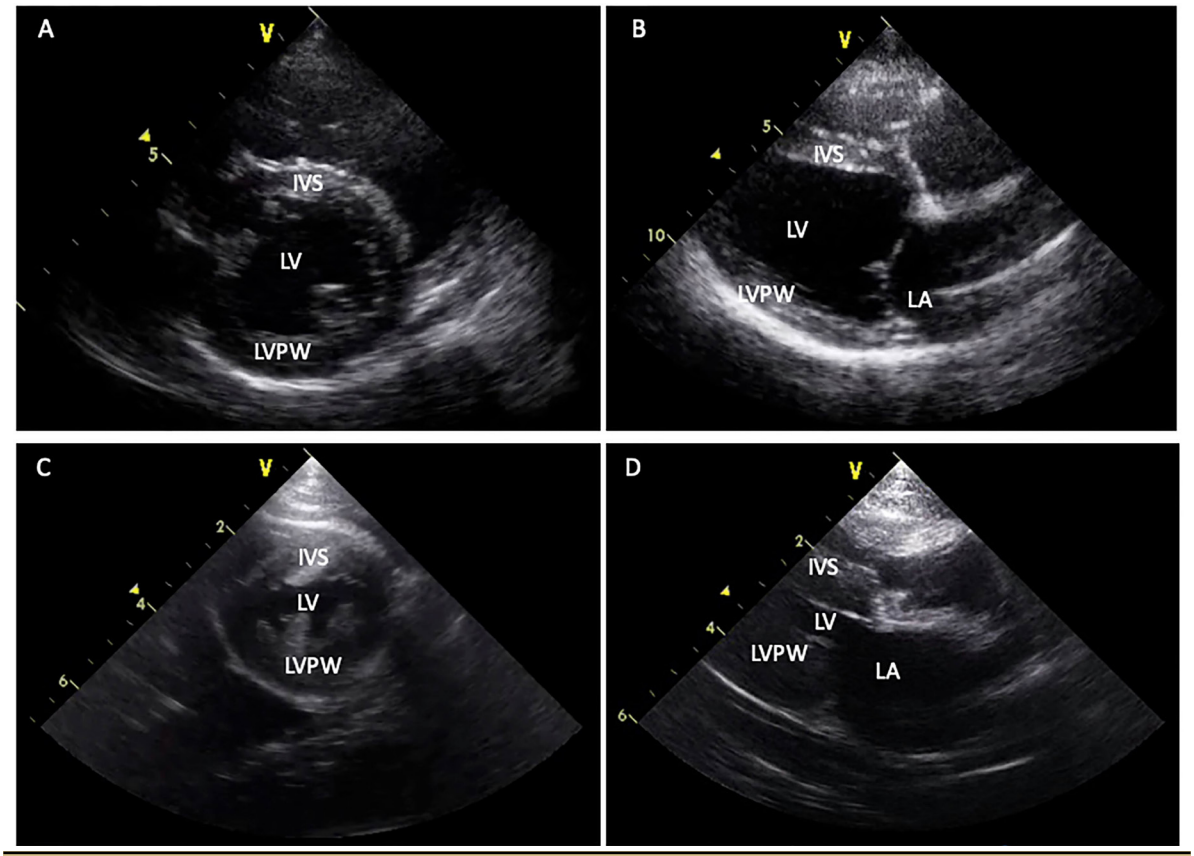

Figure 1 Left ventricular wall visualized by two dimensional echocardiography in the short and long axis view A and B represented a normal cat, C and D represented a cat with ventricular hypertrophy; IVS: interventricular septum; LVPW: left ventricular proximal wall; LV: left ventricle; LA: left atrium. (Petchdee, 2019; Unpublished data).

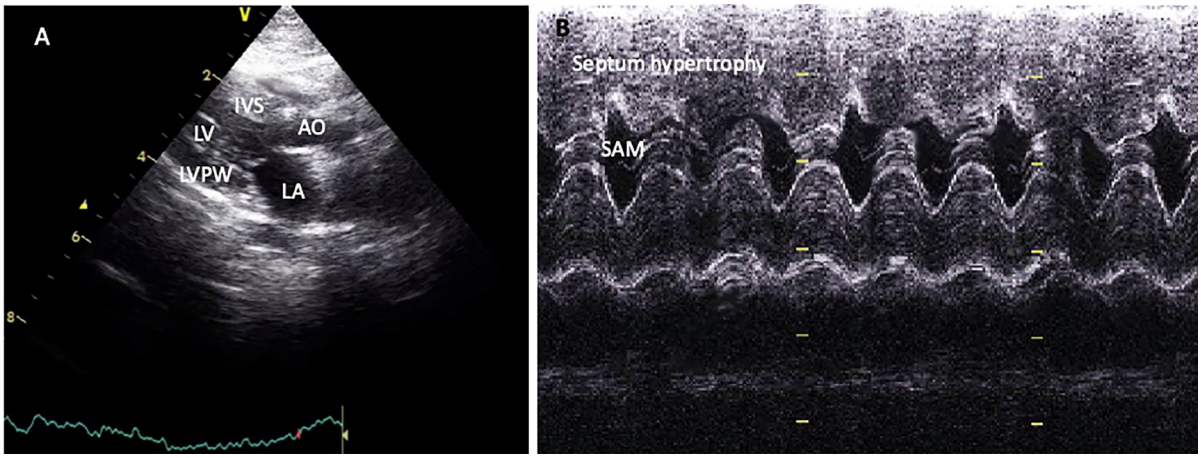

Figure 2 Two-dimensional echocardiographic image of a cat with HCM. (A) Right parasternal long axis view showed left ventricular outflow tract obstruction, (B) M mode view showed hypertrophy of ventricular septum and left ventricular wall and a systolic anterior motion (SAM); IVS: interventricular septum; LVPW: left ventricular proximal wall; LV: left ventricle; LA: left atrium and AO: Aorta. (Petchdee, 2019; Unpublished data).

MEDICAL MANAGEMENT

Medical management can be divided into preclinical and clinical stages. Medical treatment can improve the progression of left ventricular wall hypertrophy in affected cats, but medications are unable to ameliorate the myocardial function. Previous studies have demonstrated that the prevention of adverse effects is might be the ideal therapeutic approach for HCM in cats (Fuentes and Wilkie, 2017). The ACVIM consensus statement has provided guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. Treatment in cats with HCM consists of medications and management is based on stages of feline cardiomyopathy (Fuentes et al., 2020). A novel targeted therapy in symptomatic cats with HCM is a sarcomeric modulating drug (MYK-461) that directly acts on myosin and reduces contractility without affecting heart rate (Green et al., 2016; Stern et al., 2016). Medical treatments in cats with HCM are listed in Table 3.

PROGNOSTIC INDICATORS

Several studies have been shown that severe ventricular hypertrophy and left atrial enlargement are associated with a poor prognosis. However, the disease progression of HCM in cats is unpredictable, and congestive heart failure can progress rapidly over a few years. Cats can live only 2 to 13 years after the diagnosis of HCM. The survival time after diagnosis of congestive heart failure is 4,418 days (12 years) (Rush et al., 2002).

The progression of HCM in predisposed-breed cats, such as Maine coon and Ragdoll cats is usually severe. This might result from the contractile gene mutation in these two breeds of cats that increases susceptibility to the sarcomeric dysfunction. Cats with HCM can be effectively managed by pharmacological treatment. However, adjustments of the dose or the discontinuation of medical treatment should be based on patient clinical response.

Table 3 Management of cardiomyopathies in cats (Fuentes et al., 2020)

Staging	Definition	Treatment	Recommendation
Stage A (Predisposed)	Cats with risk to cardiomyopathy with no clinical sign and no structural heart change	No treatment is indicated	Echocardiographic re-evaluation every 1 year
Stage B1 (Low risk)	Cardiomyopathy with subclinical disease, normal or mild atrial enlargement	**Severe DVOTO** Atenolol 6.25-12.5 mg/cat q12-24h PO	Echocardiographic re-evaluation every 1 year
Stage B2 (High risk)	Cardiomyopathy with subclinical disease, moderate or severe atrial enlargement	**Prevent TE** Clopidogrel 18.75 mg/cat/day PO or Aspirin 5-81 mg/cat q3-5d PO **Complex ventricular ectopy** Atenolol 6.25 mg/cat q12h PO or Sotalol 10-20 mg/cat q12h PO **Atrial fibrillation** Diltiazem 1-3 mg/kg q8h or Atenolol 6.25 mg/cat q12h PO or Sotalol 10-20 mg/cat q12h PO	Monitoring for the progression of disease and the development of clinical signs
Stage C	Cats with previous or current clinical signs of CHF or TE	**Acute decompensated heart failure** Furosemide 1-2 mg/kg multiple bolus or CRI **Chronic heart failure** Furosemide 0.5-2 mg/kg q8-12h PO Benazepril 0.25 – 0.5 mg/kg q12-24h PO Clopidogrel 18.75 mg/cat/day PO Pimobendan 0.625–1.25 mg q12h PO	In chronic heart failure cats should be re-evaluate every 2-4 months, monitoring kidney function and maintaining the respiratory rate not exceed 30 breaths per minute
Stage D	Cats with refractory to medical treatment for CHF	Torsemide 0.1-0.2 mg/kg q24h PO Spironolactone 1-2 mg/kg q12-24h PO Pimobendan 0.625–1.25 mg q12h PO Taurine supplementation 250 mg q12h PO	Sodium dietary restriction and Taurine supplementation, monitoring serum potassium concentration

DVOTO = dynamic ventricular outflow tract obstruction, CRI = constant rate infusion, CHF = congestive heart failure, TE = thromboembolism, PO = per oral

CONCLUSION

Predisposed breed cats such as Maine Coon and Ragdoll usually contribute to the severe progression of HCM. It might have resulted from the contractile gene mutation in these two breed cats that increase susceptibility to the sarcomeric dysfunction. Cats with HCM can be effectively managed by pharmacological treatment. However, medical treatment could be considered to adjust in dose or discontinuation based on patient clinical response. Cats with clinical signs of congestive heart failure can be controlled and they can live longer with better life quality by the appropriate medical treatment. Recently, the application of a specific sarcomere inhibitor is being explored as a potential treatment to relieve left ventricular outflow tract obstruction in HCM cats. Further studies will be a valuable translational model for the myocardial disease, especially hypertrophic cardiomyopathy.

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