

HCM IN CATS – UPDATE ON DIAGNOSIS AND MANAGEMENT

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INTRODUCTION

Myocardial disease is the most frequently diagnosed type of heart disease in the cat. Until recently, the two most common forms of cardiomyopathy in the cat were idiopathic dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). The discovery in 1987 that most cases of DCM in cats resulted from inadequate amounts of available dietary taurine caused most cat food manufacturers to increase the taurine content in their cat diets. Since then, the prevalence of DCM in cats has drastically declined.

In the past, all cats with concentrically hypertrophied ventricles were considered to have HCM. It is now obvious that many of these cats suffer from hyperthyroidism or from systemic hypertension, and that their myocardial disease is secondary to these conditions. The term hypertrophic cardiomyopathy should be reserved for those patients with idiopathic left ventricular hypertrophy. Cats with HCM may range from one to 16 years of age, with a large percentage ranging from 4 to 7 years. Neutered male cats were found to be at increased risk for HCM compared to neutered female cats, but significant breed predilections are more difficult to identify. A colony of Maine Coon cats has been identified that display a severe and rapidly progressive form of HCM.

PATHOLOGY

Hypertrophic cardiomyopathy is characterized by concentric hypertrophy of the left ventricle. In recent years there has been interest in the variable distribution of left ventricular hypertrophy in cats with HCM. Some patterns of LV hypertrophy undoubtedly have functional correlates, such as dynamic subaortic or midventricular LV obstruction, but the precise relationship of structure to function in feline HCM is poorly understood. In some cats, LV hypertrophy is symmetrical, affecting all wall segments proportionally. In other cases, particular segments of the interventricular septum or LV free wall and papillary muscles are hypertrophied, while other regions are either less severely affected or normal. The most common form of disproportionate hypertrophy is asymmetric septal hypertrophy. However, morphologic variability exists even within this group, as hypertrophy may be confined to the base or middle region of the septum or may be distributed along its entire length. Other gross pathologic changes observed in feline HCM include left atrial dilation, narrowing of the LV outflow tract, thickening and fibrosis of the mitral valve, variable amounts of endocardial and myocardial fibrosis, right ventricular hypertrophy, and intracardiac thrombi. Histopathology reveals hypertrophy of muscle cells and, in some cases, myocardial fiber disarray. Some hypertrophied cells show degenerative changes such as myofibrillar lysis, sarcoplasmic vacuolization, clumping of Z band material, and abundant lipofuscin granules. Interstitial fibrosis is usually present, and, in some cases, fibromuscular hyperplasia of intramural coronary arteries is observed.

Systemic thromboembolism is recognized as a common complication of all forms of cardiomyopathy and may occur in as many as 1/3 of symptomatically affected cats. Most commonly, thromboemboli are found lodged in the terminal aorta ("saddle thrombi"), but any systemic artery is a potential site for obstruction.

Meurs KM, Sanchez X, David RM, et al. A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy. *Hum Mol Genet* 14(23):3587-93 (2005). Hypertrophic cardiomyopathy (HCM) is one of the most common causes of sudden cardiac death in young adults and is a familial disease in at least 60% of cases. Causative mutations have been identified in several sarcomeric genes, including the myosin binding protein C (MYBPC3) gene. Although numerous causative mutations have been identified, the pathogenetic process is still poorly understood. A large animal model of familial HCM in the cat has been identified and may be used for additional study. As the first spontaneous large animal model of this familial disease, feline familial HCM provides a valuable model for investigators to evaluate pathophysiologic processes and therapeutic (pharmacologic or genetic) manipulations. The MYBPC3 gene was chosen as a candidate gene in this model after identifying a reduction in the protein in myocardium from affected cats in comparison to control cats ($P < 0.001$). DNA sequencing was performed and sequence alterations were evaluated for evidence that they changed the amino acid produced, that the amino acid was conserved and that the protein structure was altered. We identified a single base pair change (G to C) in the feline MYBPC3 gene in affected cats that computationally alters the protein conformation of this gene and results in sarcomeric disorganization. We have identified a causative mutation in the feline MYBPC3 gene that results in the development of familial HCM. This is the first report of a spontaneous mutation causing HCM in a non-human species. It should provide a valuable model for evaluating pathophysiologic processes and therapeutic manipulations.

HISTORY AND CLINICAL SIGNS

Labored respiration (tachypnea, open-mouthed breathing) is the most common owner complaint, developing either as a consequence of pleural effusion or pulmonary edema. Other common clinical signs include lethargy and anorexia. Some cats present for sudden paralysis, usually of the hindleg, due to arterial thromboembolism. Syncope and sudden death are uncommon signs and are most frequent in cats with HCM. Sudden death is likely the consequence of terminal ventricular arrhythmias that have developed subsequent to myocardial ischemia.

PHYSICAL EXAMINATION

Systolic murmurs are common in all types of feline cardiomyopathy. They usually result from systolic anterior motion of the mitral valve/mitral insufficiency or from dynamic right ventricular outflow tract obstruction. Audible disturbances of rhythm and

pulse deficits are also common. Gallop heart sounds are audible in most cases where ventricular gallops, S3 sounds, are most common in DCM and atrial gallops, S4 sounds, are more common in HCM. Rapid heart rates make precise identification of these sounds impossible by auscultation and difficult by phonocardiography. Summation gallops may also be auscultated. Rales, dyspnea, and open mouth breathing are common in cats with left-sided heart failure, but coughing is very uncommon. Heart sounds and lung sounds may be muffled due to pleural effusion. Jugular distension and jugular venous pulses are frequently noted in cats with pleural effusion. Hypothermia, weak arterial pulses, and other signs of cardiogenic shock may be present with advanced heart failure. Physical evidence of systemic thromboembolism includes posterior paresis or paralysis with cool, stiff, and usually painful hindlimbs. The gastrocnemius muscles are very hard, and femoral pulses are absent or unequal. Nonpigmented pads may be obviously cyanotic. Evidence of embolism to other systemic sites, such as a foreleg, may also be noted.

Cote E, Manning AM, Emerson D, et al. Assessment of the prevalence of heart murmurs in overtly healthy cats. JAVMA 225(3):384-8 (2004). OBJECTIVE: To assess the frequency of heart murmurs in overtly healthy cats. DESIGN: Prospective study. SAMPLE POPULATION: 103 healthy domestic cats. PROCEDURE: Background information and physical characteristics were assessed in cats that were candidates for blood donation during an 8-month period. For cats with heart murmurs, additional information collected included murmur timing, grade, point of maximal intensity, and presence of additional heart sounds. RESULTS: Heart murmurs were detected in 22 of the 103 (21%) cats. Echocardiography was performed in 7 of those 22 cats. The echocardiogram was considered normal in 1 cat; in the other 6 cats, diagnoses included hypertrophic cardiomyopathy (interventricular septal hypertrophic form [IVSH]; n = 4), left ventricular concentric hypertrophy with valvular disease (1), and equivocal IVSH (1). Thirteen cats had more than 1 examination during the study; 3 of them developed heart murmurs. There were no significant differences in age, sex, breed, coat color, eye color, or heart rate between cats with and without murmurs. Among the 103 cats, there were 6 pairs of siblings from 6 multiple-cat households and 16 cats from 7 multiple-cat households in which the cats were not related; the proportion of cats with murmurs was higher in the related cats (5/12) than in the unrelated cats (3/16), but the difference was not significant. CONCLUSIONS AND CLINICAL RELEVANCE: Results indicated that heart murmurs are detectable in a large proportion of overtly healthy cats and that many murmurs appear to be caused by structural heart disease that is in a clinically latent state.

FELINE HEART MURMURS

Heart murmurs in cats are almost dynamic in nature, meaning that rather than organic valvular insufficiencies or valvular stenoses, their heart murmurs arise from two structures encroaching on one another. This encroachment decreases the diameter through which blood can flow, resulting in turbulence and the development of an audible murmur. Unfortunately physical examination, electrocardiography, and thoracic radiography cannot differentiate between these two types of heart murmurs. Only Doppler echocardiography can identify where the murmur originates.

ELECTROCARDIOGRAPHIC ASSOCIATIONS

Frequent ECG abnormalities in cats with HCM include increased QRS amplitude and duration, indicating left ventricular enlargement, and widened P waves, indicating left atrial enlargement. Arrhythmias are common in cats with HCM and include VPCs, ventricular tachycardia, APCs, atrial tachycardia, and, more rarely, atrial fibrillation. Conduction disturbances resulting in marked left axis deviation (0 to -60°) are common, and complete bundle branch blocks, second or third degree heart block, and other complex disturbances have been reported on occasion.

Cote E, Harpster NK, Laste NJ, et al. Atrial fibrillation in cats: 50 cases (1979-2002). JAVMA 225(2):256-60 (2004). OBJECTIVE: To determine signalment, clinical signs, diagnostic findings, treatment, and outcome for cats with atrial fibrillation (AF). DESIGN: Retrospective study. ANIMALS: 50 cats. PROCEDURE: Medical records of cats that met criteria for a diagnosis of AF (ECG consisting of at least 2 leads, clear absence of P waves, supraventricular rhythm, and convincingly irregularly irregular rhythm) and had undergone echocardiography were reviewed. RESULTS: There were 41 males (37 castrated) and 9 females (7 spayed). Forty-one were of mixed breeding; 9 were purebred. Mean +/- SD age was 10.2 +/- 3.7 years. The most common chief complaints were dyspnea, aortic thromboembolism, and lethargy. In 11 cats, AF was an incidental finding. Mean +/- SD ventricular rate was 223 +/- 36 beats/min. The most common echocardiographic abnormalities were restrictive or unclassified cardiomyopathy (n = 19), concentric left ventricular hypertrophy (18), and dilated cardiomyopathy (6). Mean +/- SD left atrial-to-aortic diameter ratio (n = 39) was 2.55 +/- 0.80. The most common thoracic radiographic findings were cardiomegaly, pleural effusion, and pulmonary edema. Median survival time (n = 24) was 165 days (range, 0 to 1,095 days). Eight of 24 cats lived for > or = 1 year after a diagnosis of AF was made. CONCLUSIONS AND CLINICAL RELEVANCE: Results suggest that AF occurs primarily in older adult male cats with structural heart disease severe enough to lead to atrial enlargement. Atrial fibrillation in these cats was most commonly first detected when signs of decompensated cardiac disease were evident, but also was commonly identified as an incidental finding.

THORACIC RADIOGRAPHY

The "classic" patterns described herein are rarely, if ever, sufficiently suggestive to allow differentiation of the various cardiomyopathies. In addition, the heart is often obscured by pleural effusion. Hypertrophic cardiomyopathy is typically characterized by left atrial dilation and concentric left ventricular hypertrophy, giving the heart a "valentine" shape on the DV radiograph. Mild to marked pulmonary edema is common in cats with HCM, and typically occurs with a patchy distribution throughout the lungs rather than in the perihilar pattern seen in dogs.

ECHOCARDIOGRAPHY

Echocardiographic findings in HCM include left atrial enlargement, increased left ventricular and septal diastolic wall thickness, reduced end-systolic left ventricular dimensions, normal or increased indices of contractility (fractional shortening), and, in those cases with dynamic LV outflow tract obstruction, systolic anterior motion of the mitral valve (SAM). M-mode echocardiography measurements in cats with HCM have been reported by several investigators. While such measures are useful, careful examination of the entire heart in both long-axis and short-axis planes by two-dimensional echocardiography is required to demonstrate the true extent of the diverse patterns of ventricular hypertrophy observed in cats with HCM. Increased diastolic wall thickness (usually defined at >6 mm) is observed globally throughout the interventricular septum and LV wall of some cats, but in others hypertrophy is confined to a focal segment of the interventricular septum or LV wall. One of the most consistent echocardiographic findings in cats with clinical HCM is a dilated left atrium. An isolated finding of slightly increased septal or LV wall thickness in a cat without left atrial dilation or other clinical findings is insufficient to make this diagnosis. Doppler and color flow mapping studies are useful for demonstrating the presence and severity of LV outflow obstruction, mitral regurgitation, and dynamic right ventricular outflow tract obstruction.

DIAGNOSIS

Diagnosis of the various types of cardiomyopathy is often impossible without echocardiography. As already discussed, certain clinical features may preferentially suggest the underlying disorder. In addition, it is important to rule out other disorders. Differential diagnoses include hyperthyroidism, congenital heart defects (aortic stenosis, VSD, mitral dysplasia), degenerative or infective valvular disease, systemic hypertension, heartworms (uncommon in cats), respiratory disorders, and other disorders causing pleural effusion such as pyothorax, chylothorax, FIP, diaphragmatic hernia, and thymic lymphosarcoma.

SYSTEMIC ARTERIAL THROMBOEMBOLISM

Systemic arterial thromboembolism is a common sequela to feline cardiomyopathies. Some necropsy reports have identified thromboembolism in 48% of cats with hypertrophic cardiomyopathy, 29% with restrictive cardiomyopathy, and 25% with dilated cardiomyopathy. Thrombosis is clot formation within a cardiac chamber or vessel while embolization is when the clot or foreign material, i.e. bacteria, lodge within the blood vessel. Thrombosis requires at least one of three essential conditions to be present. These conditions have been identified in Virchow's triad and include 1) local vessel or tissue injury, 2) circulatory stasis, and 3) altered blood coagulability. All forms of feline cardiomyopathy commonly display endothelial fibrosis within the left atrium. It is believed these injuries present reactive substrates to circulating blood and trigger platelet adhesion and aggregation with activation of the intrinsic clotting cascade. Circulatory stasis frequently occurs with chamber dilation and reduced cardiac contractility. Importantly blood stasis is not only a common requirement for platelet adhesion, but decreased blood flow decreases clearance of activated clotting factors. It is also believed that in the face of feline cardiomyopathic processes feline platelets have an increased responsiveness to collagen resulting in hypercoagulable states. Over 90% of feline systemic arterial thromboembolism occurs within the distal aortic bifurcation and is termed a "saddle thrombus". Infrequently thrombosis may occur within the right brachial artery (but rarely the left). Clinical manifestations include acute hindlimb pain and lateralized paresis. Clinical indicators of a favorable prognosis include 1) resolution of congestive heart failure with therapy, 2) lack of left atrial or left ventricular thrombi, 3) re-establishment of appetite, 4) maintenance of normal BUN, creatinine and electrolytes, 5) return of limb viability and function, 6) return of femoral arterial pulses, 7) lack of self-mutilation, and 8) a committed owner. Clinical indicators of a poor prognosis include 1) refractory congestive heart failure, 2) acute hyperkalemia from reperfusion injury, 3) declining limb viability, 4) clinical evidence of multi-organ involvement, 5) presence of left atrial or left ventricular thrombi, 6) rising BUN and creatinine levels, 7) DIC, 8) unresponsive hypothermia, 9) severe left atrial enlargement and arrhythmias, 10) uncommitted owner with limited financial resources. Major complications following thromboembolism include reperfusion hyperkalemia, self-mutilation and re-embolization.

Reports have documented that approximately 37% of cats survived an initial bout of thromboembolism with an average survival time of 11.5 months. Unfortunately the likelihood of another thrombotic event is high because the inciting conditions (Virchow's triad) continue to be present. Newer platelet antagonists and low molecular weight heparin are in the process of evaluation and may prove to decrease the incidence of re-embolization.

TREATMENT

Objectives of therapy are (1) to treat the underlying cause, if one can be established, (2) to medically manage congestive heart failure, (3) to control arrhythmias, and (4) to treat or prevent thromboembolic complications.

Treatment of cats with HCM

Since the primary abnormality is reduced diastolic compliance, medical management is designed to control existing tachycardia (to increase diastolic filling period) and to increase the ability of the heart to relax. In patients with dynamic obstruction, use of a negative inotrope may lessen the degree of obstruction (and positive inotropes may worsen the obstruction). 1) Furosemide is used to control edema. 2) Atenolol is commonly used to slow the heart rate and to reduce or eliminate dynamic obstruction. 3) Alternatively, diltiazem has been suggested to improve filling (positive lusitropic effect) and to decrease the heart rate. 4) ACE inhibitors are used to blunt the activation of the renin-angiotensin-aldosterone system. 5) Anticoagulant therapy is administered by some to prevent thromboembolism.

Treatment of cats with aortic thromboembolism

Many approaches to this difficult problem have been suggested and none is very satisfactory. With all methods of treatment, therapy is often unsuccessful and the recurrence rate is high. The site of thrombosis and duration of the event is critical in determining the clinical outcome. Cats with thrombi occluding the renal arteries or with gastrointestinal infarction have an extremely poor prognosis. Treatment may be surgical or medical. Surgical removal of aortic thromboemboli should only be attempted within the first 12 hours of occurrence, if at all. Many cats die when surgery is attempted because of underlying heart disease, from anesthetic depression of the heart, or during the washout phase (of toxins, potassium, etc.) if perfusion is reestablished. Alternatively, removal of thromboemboli may be attempted using embolectomy catheters, but this is very difficult in cats. Medical therapy consists of two arms: anti-coagulation and thrombolytic therapy. Anti-coagulation is initiated in an effort to prevent further thrombosis and may be accomplished with aspirin, heparin or coumarin. Aspirin induces a functional defect in platelets by irreversibly inactivating cyclo-oxygenase. Cyclo-oxygenase is required for conversion of arachidonic acid to thromboxane A₂, which induces platelet activation and vasoconstriction. Heparin binds to sites on anti-thrombin III thereby enhancing its ability to neutralize thrombin and activated factors XII, XI, X and IX. Coumarin impairs hepatic vitamin K metabolism, which is necessary for synthesis of procoagulants (factors II, VII, IX, and X). Thrombolytic therapy may be accomplished with streptokinase or recombinant tissue plasminogen activator (TPA). Streptokinase acts by generating the nonspecific proteolytic enzyme plasmin. Generation of plasmin results in a generalized lytic state with the hazard of bleeding complications. Tissue plasminogen activator has a lower affinity for circulating plasminogen and instead preferentially binds with fibrin within the thrombus. The entrapped plasminogen is converted to plasmin and thereby initiates a local fibrinolysis with limited systemic fibrinolysis. With TPA the likelihood of bleeding complications is reduced, but cost is often prohibitive (\$1200 per 50 mg vial). Aggressive attempts to dissolve emboli using thrombolytic drugs should also be reserved for cats with more serious thromboembolic events. Pion, et. al. reported successful thrombolysis, defined as evidence of reperfusion within 36 hours of TPA (Activase, Genentech) treatment, in 50 per cent of cats with spontaneous aortic thromboembolism that were treated with tissue plasminogen activator. Forty-three percent of the cats walked within 48 hours of presentation. However, 50 per cent of the cats died from either reperfusion syndrome (70 per cent), heart failure (15 per cent), or suddenly (15 per cent). Bleeding into and around the kidney was also observed in several cats.

Many cats with saddle thrombi will regain function of the hind limbs, albeit slowly, with conservative therapy. Recovery takes several weeks to months and residual deficits (peripheral neuropathy, muscle contracture) are common. Conservative management consists of pain management, anticoagulant therapy to prevent additional clot formation and therapies aimed at resolving concurrent heart failure. Pain management is one of the most important goals of treating cats with systemic thromboembolism. Butorphanol is used frequently but more aggressive measures, i.e. morphine epidurals, may be required in some cases.

Prevention of thromboembolism

Low dose aspirin every three days is the most widely employed prophylactic measure. While aspirin is known to exert antithrombotic and anti-ischemic effects in some circumstances, there is no objective evidence of its efficacy for the treatment or prophylaxis of systemic aortic thromboembolism in cats. Recurrence of thromboembolic events in aspirin treated cats, as high as 75 per cent in one study, has fueled renewed interest in warfarin as a prophylactic anticoagulant in cats considered at high risk (prior embolic episode). Preliminary dosage recommendations have been developed but there is inadequate data to determine if this approach has an acceptable risk to benefit ratio. Due to the possibility of serious bleeding complications, this alternative should only be considered for indoor cats that can be monitored frequently using appropriate measures of the coagulation system. Owners willing to administer subcutaneous injections may utilize heparin for its anticoagulant purposes. The development of low molecular weight heparin, with more predictable anticoagulant properties, may start to replace traditional unfractionated heparin. Similar to warfarin and aspirin, the benefits of heparin are still uncertain

PROGNOSIS

The prognosis for cats with asymptomatic HCM is fair while that for symptomatic cats with HCM is guarded. That finding highlights that the best time to evaluate cats with heart disease is after the detection of a heart murmur, gallop sound or arrhythmia rather than waiting until clinical signs develop. Cats with asymptomatic HCM often live many years and ultimately die of non-cardiac disease. In symptomatic cats heart failure appears to be more common than arterial embolism as a cause of death, and sudden death is probably the least common. Some cats respond favorably to drug administration and may live several years while others continue to display refractory congestive heart failure.

Rush JE, Freeman LM, Fenollosa NK, et al. Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases (1990-1999). JAVMA 220(2):202-7 (2002). OBJECTIVE: To determine current population characteristics of, clinical findings in, and survival times for cats with hypertrophic cardiomyopathy (HCM). DESIGN: Retrospective study. ANIMALS: 260 cats with HCM. PROCEDURE: Information was obtained from the medical records. Cats were classified into 1 of 4 clinical groups (congestive heart failure [CHF] group, arterial thromboembolism [ATE] group, syncope group, or cats without clinical signs [subclinical group]) on the basis of the primary clinical signs at the initial examination. RESULTS: 120 cats were classified in the CHF group, 43 in the ATE group, 10 in the syncope group, and 87 in the subclinical group. Antecedent events that may have precipitated CHF included i.v. fluid administration, anesthesia, surgery, and recent corticosteroid administration. Median survival time was 709 days (range, 2 to 4,418 days) for cats that survived > 24 hours. Cats in the subclinical group lived the longest (median survival time, 1,129 days; range, 2 to 3,778 days), followed by cats in the syncope group (654 days; range, 28 to 1,505 days), cats in the CHF group (563 days; range, 2 to 4,418 days), and cats in the ATE group (184 days; range, 2 to 2,278 days). Causes of death included ATE (n = 56), CHF (49),

