Feline Cardiomyopathy – an update
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Introduction

Myocardial disease is an important cause of morbidity and mortality in domestic cats. Feline myocardial disease sometimes occurs in association with non-cardiac disease but when that is the case, it often is subclinical; idiopathic myocardial disease is more commonly responsible for clinical signs. Cardiomyopathy (CM) has been defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of other cardiovascular diseases sufficient to cause the observed myocardial abnormality.
Recently proposed schema for classification of human cardiomyopathies have emphasized the cause or molecular basis of myocardial disease. Although genetic etiologic factors are likely important, feline CM remains largely idiopathic. Accordingly, the use of morphopathologic/ functional designations remains valid. Specifically, hypertrophic cardiomyopathy (HCM) is defined by diffuse or regional hypertrophy of a nondilated ventricle in the absence of hemodynamic stimuli for hypertrophy. Dilated cardiomyopathy (DCM) is characterized by left or biventricular dilation associated with diminished systolic myocardial function. Restrictive cardiomyopathy (RCM) is functionally defined by diminished ventricular compliance; the ventricle may have a normal or nearly normal appearance but left or biatrial dilation are consistent features. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fatty or fibrofatty replacement of right and sometimes left ventricular myocardium and often, arrhythmias. During this session, the pathophysiology, diagnosis and therapy of hypertrophic cardiomyopathy (HCM), the most common feline myocardial disease, will be emphasized.

Etiopathogensis

It is accepted that that HCM in humans is primarily a genetic disease that is associated with numerous mutations of genes that encode sarcomeric proteins. HCM is inherited in Maine coon cats and Ragdoll cats, and in cats of these breeds is associated with distinct mutations of the myosin binding protein C (MYBPC) gene. Familial occurrence of HCM has been observed in other purebred lines and in mixbreed cats; it is therefore possible that feline HCM generally is a genetic disorder. The causes of the other forms of primary myocardial disease that are observed in the cat have not been established. It is possible that some examples of RCM represent the sequela of endomyocardial inflammation or perhaps, an alternate phenotypic expression of mutations that are associated with HCM. The prevalence of feline DCM decreased radically after the recognition of the association between this disorder and nutritional taurine deficiency, but idiopathic DCM is still sporadically observed.

Epidemiology

Several investigators have retrospectively evaluated the population characteristics of feline HCM. HCM is not exclusively a geriatric disease; patients of all ages can be affected and the median age at the time of detection in one report was 4.6 years. Males are more often affected than are females. A substantive proportion - between 33 and 55% - of cats with HCM are

subclinical (asymptomatic) when the disease is identified. The prevalence of HCM in apparently healthy cats is close to 15%. This prevalence is seemingly high but consistent with the current understanding of the HCM in humans; it is now accepted that HCM has a broad spectrum of phenotypic expression, often occurs in a subclinical form and is not inevitably associated with progression and poor outcome.

Pathophysiology

Diastolic dysfunction is thought to be the primary pathophysiologic mechanism responsible for clinical signs in HCM. Diastolic function refers to the ability of the ventricle to fill at low pressures. The primary determinants of diastolic function are the active process of myocardial relaxation and a mechanical property of the ventricle known as compliance. Diastolic dysfunction results in increased ventricular filling pressures when ventricular volumes are normal or small. High filling pressures are reflected “upstream” potentially resulting in atrial dilation and the development of pulmonary edema or pleural effusion. In feline CM, atrial dilation almost invariably precedes the development of congestive signs. Functional abnormalities in HCM are not limited to diastole. Although the clinical implications have been debated, most patients with HCM exhibit a valve motion abnormality – systolic anterior motion of the mitral valve or, SAM – that causes obstruction of left ventricular outflow. In affected cats, hydrodynamic forces, of which drag is most important, cause systolic movement of the mitral leaflets toward the interventricular septum. This abnormal valvular orientation causes dynamic, as opposed to fixed, obstruction of the left ventricular outflow and typically, concurrent mitral valve regurgitation. In addition, some patients, presumably those with long-standing HCM, develop systolic myocardial dysfunction resulting in a cardiac phenotype that has been referred to as “end-stage HCM” or “burnt-out HCM”.

Clinical Presentation / Diagnosis

Feline CM is identified when abnormalities are detected during physical examination of apparently healthy cats, when congestive heart failure (CHF) develops, or when CM is complicated by systemic thromboembolism. Many, but not all, cats with HCM have cardiac murmurs, but it is relevant that murmurs can develop in cats in which cardiac disease is absent. Furthermore, murmurs in cats, whether related to cardiac disease or not, are often labile, meaning that the intensity can change from moment to moment. Murmurs in cats can be provoked by increases in sympathetic activation, and an increase in murmur intensity documented during serial examinations does not indicate worsening of disease.
Retrospectively evaluated case series have identified an association between the administration of corticosteroids and the development of CHF in cats. Some affected cats may have had pre-existing, but clinically silent, HCM but this has not been established. The association is relevant because the long-term prognosis of corticosteroid associated CHF might be superior than for more typical presentations.
Patients with congestive heart failure typically are presented for evaluation of respiratory distress caused by pulmonary edema or pleural effusion. Cats with CHF rarely cough. Hypothermia is frequently recorded. Tachypnea is generally evident and pulmonary auscultation may disclose adventitious lungs sounds in patients with edema or attenuated sounds in those with pleural effusions. While tachycardia caused by sympathetic activation is commonly observed in canine patients with heart failure, heart rates of cats with CHF do not differ from those of healthy cats and fairly often, feline patients with heart failure are

bradycardic. Cardiac auscultation may reveal murmurs, gallop sounds and sometimes tachycarrhythmia, but these findings are not consistently present.
In the cat, radiographic patterns of specific chamber enlargement are not distinct. However, the chest film may reveal consequences of cardiac dysfunction; pleural effusion can be identified and the finding of pulmonary opacities together with cardiomegaly provides a non-invasive diagnosis of heart failure. Echocardiography is the only non-invasive method that can definitively characterize feline CM. Congestive heart failure is a clinical and/or radiographic diagnosis; the presence of heart failure cannot be determined based on echocardiographic data alone.
Blood concentrations of cardiac biomarkers including endothelin, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and troponin have been evaluated in veterinary patients. Circulating BNP concentration has a particular role in the diagnostic evaluation of patients suspected to have heart failure. This hormone is released by atrial and ventricular cardiomyocytes in response to increases in ventricular filling pressures; potentially, it is a blood-borne diagnostic marker of the heart failure state. The diagnostic accuracy of the quantitative NT-BNP assay, for identification of moderate or severe subclinical CM or identification of cardiac causes of respiratory distress is relatively high. However, the need to submit samples to a central laboratory is a disadvantage in the urgent/emergent setting. The point of care assay provides a binary – normal/abnormal – result and has a role when feline patients are presented for evaluation of respiratory distress, it is not possible to safely obtain diagnostic chest films and point of care echocardiographic examination is not available. Optimally, abnormal NT-BNP results are investigated echocardiographically.

Therapy
In order to facilitate the development of therapeutic guidelines, a modification of the AHA/ACVIM scheme for staging of heart disease can be applied to feline CM.

The role of drug therapy in patients with subclinical (asymptomatic) Stage B CM is uncertain. It is likely that most patients with HCM have slowly progressive or even non-progressive, disease. Furthermore, there is currently no published evidence that any agent can slow the progression of HCM. Based on this, periodic echocardiographic re-evaluation rather than therapy is appropriate when faced with patients that have Stage B1 disease; meaning, subclinical HCM with left atrial dimensions that are normal, or reflect only mild enlargement. In patients with stage B2 disease – those that have distinct left atrial enlargement – administration of clopidogrel is reasonable, in hopes of decreasing the probability of arterial thromboembolism [ATE]. It should be noted however, that evidence to support this approach is indirect and the incidence of ATE in patients with subclinical echocardiographically documented CM is not very high. Beta-blockade might also have a role in the management of subclinical HCM, particularly when SAM is evident. However, a recent open-label, non-randomized trial failed to show a benefit of atenolol in this scenario.

Heart failure is a clinical syndrome characterized by high venous pressures and/or low cardiac output that results from cardiac disease. CHF results in clinical signs related to tissue edema or body cavity effusions. Pulmonary edema is a consequence of left ventricular failure. In cats, pleural effusions may result from left ventricular or biventricular heart disease. For patients that have developed congestive signs, those with Stage C CM, general, supportive measures are indicated. Supplemental oxygen can be administered through use of an oxygen administration

cage or, if the patient is sufficiently tolerant, by mask, or nasal insufflation. Pleurocentesis should be performed when physical, radiographic or sonographic findings confirm that pleural effusion is responsible for respiratory distress.
In general, intravenous fluids should not be administered to patients with frank congestion. In the setting of CHF, infusion of fluid further increases venous pressures but does not improve cardiac performance. When cardiogenic pulmonary edema is present, diuretic administration is indicated. For acute decompensation, the intravenous route is preferred but intramuscular administration is appropriate when resistance to manual restraint or other factors make intravenous administration difficult or impossible. Preload reduction is used in the setting of heart failure because it may effectively eliminate clinical signs related to congestion. In general however, preload reduction does not improve cardiac performance. Indeed, aggressive reduction in filling pressures can decrease stroke volume potentially resulting in hypotension. Other than furosemide, for which efficacy is assumed, there are no medical interventions that have demonstrated efficacy in the management of feline heart failure. Because of this, the use of additional cardioactive agents in the management of acute decompensated heart failure is difficult to justify. Exceptions to this might be the use of antiarrhythmic agents for management of pathologic arrhythmias that contribute to the development of congestive signs, or perhaps the administration of pimbendan to patients with low output heart failure.

Evidence that supports administration of ancillary, medical therapy to patients with stage C is lacking. The results of a multicenter, randomized, placebo-controlled trial that had been designed to evaluate the relative efficacy of atenolol, diltiazem and enalapril in feline patients with diastolic heart failure have been reported but not published. The primary end-point of the trial was recurrence of congestive signs and none of the agents was superior to placebo in this regard, although atenolol was inferior. Administration of pimobendan to cats with CM has been retrospectively evaluated, and the drug is seemingly tolerated. The results of a prospective, double-blind placebo controlled trial have recently been reported. For patients enrolled in this exploratory trial, pimobendan administration did not lead to improved 180-day outcome.

Arterial thromboembolism is a serious and often unexpected complication of feline CM. It is unexpected because ATE is the first clinical manifestation of CM in the majority of patients in which it occurs. Emergent care of patients with ATE most importantly is supportive and includes analgesia. ATE is almost always associated with advanced CM that has resulted in left atrial enlargement and diagnostic evaluation to identify evidence of edema/effusion is important. Parenteral administration of anticoagulant therapy – unfractionated or low molecular weight heparin is reasonable in the short-term. The results of a clinical trial that compared aspirin to clopidogrel for secondary prevention of ATE provided strong evidence of the superiority of clopidogrel.

Prognosis
The results of a recent retrospective analysis of risk and mortality in HCM provide useful information regarding prognosis associated with subclinical [Stage B] disease. In general, the condition is benign but has important long-term clinical consequences. Over the course of follow-up, which for some patients extended 10 years, total cardiovascular mortality was 28%. Survival after the development of congestive heart failure or the occurrence of ATE was relatively brief with a median survival of less than one year.

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