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REVIEW

Management of asymptomatic (occult) feline cardiomyopathy: challenges and realities

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Abstract *Background:* Cardiomyopathy distinguishes a heterogeneous group of myocardial disorders that represent the most prevalent cause of feline heart disease. Etiology is uncertain and the natural history is presently unresolved. Hypertrophic cardiomyopathy is the most common of these conditions, and while the majority of affected cats are asymptomatic, a proportion is at risk to develop serious morbidities — the most devastating of which include congestive heart failure, arterial thromboembolism, and cardiac death. Predicting when or whether an asymptomatic cat might develop morbidity is hindered by lack of evidence-based clinical trials. Superimposed, these issues create an irresolvable predicament that presently confounds medical decision-making.
Methods: Review of current perspectives for managing asymptomatic (occult) feline cardiomyopathy.
Results: Complex pathophysiology and (likely) sarcomeric mutations give rise to heterogeneous cardiac phenotypes and variable clinical findings. Echocardiography remains the gold standard to clarify cardiac morphology. Frequently, however, detection of echocardiographic alterations — though often of unproven clinical significance — extrapolates by inference or implication a specter of disease, and with this, leads to a path of long-term treatment and testing. Presently, there is no proof that any particular therapy reduces morbidity or prolongs survival of cats affected with occult cardiomyopathy. Recently, however, evidence has accumulated to support the belief that certain prognostic indicators suggest risk for poor outcome. Accordingly, and in absence of evidence-based clinical trials, current practice has shifted to view therapy with the intent to target pathophysiology underlying

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documented or perceived clinical markers, whose presence portends high risk in certain patients. Affected animals and potentially siblings should be monitored using clinical testing that also takes into account age-related comorbidities.

Conclusions: Asymptomatic (occult) feline cardiomyopathy includes complex and heterogeneous diseases whose outcomes are challenging to predict. Review of available evidence-based treatment data leaves no uncertainties regarding drugs with established efficacy. There presently are none. Current management focuses upon identification of documented risk factors, individualized and tailored therapy, and cogent monitoring. Drugs most commonly considered in this paradigm include those that might reduce thromboembolic risk in cases with substantial left atrial enlargement or dysfunction, agents to counteract left ventricular remodeling, or medications that ameliorate systolic or diastolic dysfunction. Discovering reliable prognostic indicators may further improve stratification to identify patients at highest risk, or detect subsets that respond favorably. These issues shape the challenge to identify sensible preventative management and cost-effective, long-term monitoring strategies.

Abbreviations

ARVC	arrhythmogenic right ventricular cardiomyopathy
CHF	congestive heart failure
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
HOCM	hypertrophic obstructive cardiomyopathy
RCM	restrictive cardiomyopathy
SAM	systolic anterior motion of the septal mitral valve leaflet

Although medical therapy for congestive heart failure (CHF) is plainly indicated to restore normal breathing and promote survival, the benefit of treating cats with asymptomatic (occult) cardiomyopathy remains unsubstantiated and controversial. The natural history of occult disease is variable and difficult to predict with certainty. Whereas the majority of affected cats appear to remain asymptomatic throughout life, cardiomyopathy can produce considerable morbidity in others, leading to CHF, arterial thromboembolism, and death.

Feline myocardial disease (cardiomyopathy) constitutes the leading cause of cardiac morbidity and mortality,[1−5] and hypertrophic cardiomyopathy (HCM) is the most prevalent of these disorders.[1−10] The cat is also affected less commonly by other forms of primary myocardial disease including restrictive cardiomyopathy (RCM),[11] endomyocardial fibrosis,[12] arrhythmogenic right ventricular cardiomyopathy (also termed arrhythmogenic right ventricular dysplasia, or arrhythmic cardiomyopathy) (ARVC),[13] and dilated cardiomyopathy (DCM). Some cats have myocardial disease whose echocardiographic, radiographic, and clinical characteristics do not closely conform to contemporary classification. Taxing, such cases have been referred to as 'unclassified' forms of cardiomyopathy, a generally equivocal and elusive descriptor.

Several obstacles have hampered the development of cost-effective and clinically successful management strategies. By and large, occult cardiomyopathy is challenging to diagnose and characterize. Physical examination, electrocardiography, and thoracic radiography have limited sensitivity and specificity.[14,15] Cardiac biomarkers such as NT-proBNP offer additional information when measured in populations at risk for heart disease,[7] but are less reliable when applied by themselves for purposes of generic screening and monitoring.[16] Echocardiography, the gold standard for cardiac diagnosis, is expensive, has a steep learning curve, and is unavailable in many locals.[7] Furthermore, myocardial diseases are complex and heterogeneous disorders and the natural history and mechanisms responsible for disease progression are poorly understood. Structural features can remain static, change over time, or take on characteristics that resemble morphologies or mimic dysfunction that characterize other disease forms. Frequently, some hearts will display more than one phenotype. Additionally, comorbidities including anemia, systemic hypertension, and thyrotoxicosis that are often detected during advanced age can affect the heart. These issues, coupled with limitations inherent in diagnostic classification schemes, may make it difficult to accurately characterize underlying

pathologies in all cases, and leave uncertainties with respect to the degree of structural or functional impediment.[1] Finally, investigations of drugs intended to improve diastolic function in the cat have been generally hindered by lack of prospective multicenter trials, small study cohorts, suboptimal drug pharmacology, and lack of proven efficacy. Subgroups of cats within disease categories that may respond more favorably to early interventions compared to others, remain to be defined.

Evidence-based treatment

Preferably, therapy should be directed by guidelines developed by consensus panels, whose basis is supported by evidence-based data. Accordingly, treatment recommendation guidelines have been developed for human patients and are periodically updated in accordance with prevailing levels of scientific evidence. Their goal is to eliminate unsound, excessively risky, or unnecessary practices in favor of those that have better outcomes and are associated with fewer side effects. To this purpose, the American College of Cardiology and American Heart Association Task Force issue consensus recommendations communicate three clinical classes of disease based upon levels of scientific evidence[17]: class I refers to conditions where there is evidence or general agreement, that a given treatment is useful and effective, while class III refers to conditions where evidence or general agreement shows that treatment is not effective or may be harmful. Class II recommendations are labeled for conditions with conflicting evidence or opinion about treatment efficacy with sub-classifications that further qualify the weight of evidence in this category. These recommendations rely upon scientific data which itself are graded according to its strength. Portrayed in their simplest form, levels of evidence (ranked as A, B, C) denote categories of 'proof' derived by amalgamation of available published evidence that supports treatment recommendations. The strongest weight of evidence (A) is designated to derive from multiple randomized trials with large numbers of subjects. An intermediate weight of evidence (B) denotes limited randomized trials with small numbers of study subjects, well conducted non-randomized studies, or observational registries. Rank C signifies the lowest grade of evidence which is represented when the basis for recommendation falls to expert consensus.

In veterinary medicine level A evidence is rarely obtainable. Level B evidence comprised of clinical trials is occasionally available. Most often, however, therapies are based upon level C evidence and frequently, non-consensus opinions constitute the basis for treatment recommendations. Evidence-based clinical trials are required to identify effective treatment strategies for cats diagnosed with asymptomatic cardiomyopathy. Importantly, it remains to be demonstrated that a particular treatment is superior to another, or for that matter, compared with no therapy at all; and that any specific therapy provides a benefit to reduce morbidity, improve quality of life, prevent catastrophic events, and prolong survival.

Diagnosing asymptomatic (occult) cardiomyopathy

Cats with asymptomatic heart disease may present with incidental findings of a heart murmur, gallop heart sounds, or arrhythmia. Others may have complete absence of detectable abnormalities on physical examination. Because heart murmurs are prevalent in cats,[18] can result from cardiomyopathy, non-cardiac diseases, and may even be considered "physiologic" in some cats with flow murmurs, affected animals should be further evaluated to determine etiology. An ECG should be performed following a detailed history and physical examination if heart rate or rhythm abnormalities are detected. Clinical pathology may be informative and reveal systemic and metabolic diseases and comorbidities. Anemia can cause or contribute to heart murmurs. Hyperthyroidism is relatively common in geriatric cats and serum thyroid hormone concentrations should be measured in cats seven years of age or older. Systolic blood pressure should be checked to identify systemic hypertension. Measurement of blood NT-proBNP concentration can detect occult cardiomyopathy in some cases[7] and other biomarkers such as troponin I may be complementary. Thoracic radiographs may help rule out non-cardiac diseases, but are generally insensitive for detecting occult cardiomyopathy.[14,15] A comprehensive 2-dimensional (2D) imaging and Doppler examination may be required to assess cardiac chamber and wall dimensions, evaluate systolic and diastolic function, detect cardiac valve incompetency, identify dynamic outflow tract obstruction, and assess known echocardiographic risk factors. The indication and frequency of

repeat testing should depend upon results of these findings.

'Medicalization' of normal variation, equivocal, or mild conditions: the hazards of over classification of disease

Echocardiography provides a noninvasive, safe and reliable method to assess cardiac structure and function and as such, is the current gold standard for diagnosing feline heart disease. Optimal image acquisition and interpretation, however, requires substantial training and experience to spot artifacts, recognize age-related cardiac changes, identify systemic and metabolic effects of noncardiac disease, and accurately distinguish and comprehend the difference between equivocal lesions, variations that are not medically relevant, and findings that signal concern. The unfettered use of echocardiography, coupled with absence of consensus guidelines that could provide direction and rationale for diagnosing and managing occult cardiomyopathy, exposes pitfalls associated with dependence on a modality that generates reports laden by copious measurements. Indeed, there is a tendency to view patients whose echocardiographic parameters fall even slightly outside of the reference range, as being affected with a malady or disorder, and to label them as having a 'disease.' Accordingly, treatment is often blandished by echocardiographic detection of real or subjective structural abnormalities, based upon the mistaken notion that the presence of any alteration confers risk for adverse outcome. Since society generally treats diseases with drugs, labeling a patient as "diseased" plays into the logic that it must be good to treat this "disease", and implicitly, that prescribed medications are effective. Furthermore, categorizing a patient as having heart disease can negatively impact future health care decisions, as may follow upraised concerns of falsely elevated anesthetic risk, and reflexively triggering extra or unnecessary tests. As follows, this bias often inadvertently if not mechanically, activates recommendations for life-long administration of medication with no proven merit, and holds little appeal for pet owners or their cats owing to cost and quality of life considerations. Additionally, as pet insurance gains popularity, medicalization of normal variation may disqualify animals for future insurance benefits, adding unnecessary financial burden to the pet owning public. On the whole, this upbraids reasonable considerations for more focused strategies impelled by proof of benefit.

Feline cardiovascular risk markers

Many affected cats remain symptom-free for long periods of time and often for life, while others develop morbidities that include syncope, CHF, arterial thromboembolism, or sudden death. The processes responsible for initiating progression from the occult state to symptomatic are poorly understood, but involve genetic factors, as yet unknown pathophysiology associated with the natural history of myocardial disease, as well as known triggers that include systemic and metabolic disorders, stress, concurrent diseases, parenteral fluid administration, and anesthesia. The long-term prognosis is generally poor for RCM, DCM, and ARVC. In contrast, a high proportion of cats with asymptomatic HCM have been documented to have five-year survival or greater.[19]

Two retrospective HCM studies based upon data combining both occult cardiomyopathy and heart failure patients have reported population characteristics and outcomes that assist with risk stratification. In one study of 127 cats comprising 54% symptomatic and 46% asymptomatic animals, multivariate analysis revealed that left atrial size, age, and breed were significantly associated with survival time.[8] More recently, data from 282 cats comprising 33% symptomatic and 67% asymptomatic animals reported that prognostic indicators of risk for cardiac death (based upon multivariate analysis) included echocardiographic variables of left atrial dysfunction, low left ventricular systolic function (left ventricular shortening fraction $\leq$30%), and extreme left ventricular hypertrophy (left ventricular end-diastolic wall thickness $\geq$9.0 mm).[9] The importance of dynamic right ventricular outflow tract obstruction in cats is currently undetermined. While refinement of risk stratification will require further study, current information permits a level of risk assessment that may be considered during the treatment decision-making process.[20]

Rationale for treating asymptomatic feline cardiomyopathy

Recommendations for cardiac therapy must be directed by medical evidence and modulated by clinical expertise, owners' values and expectations,

and financial considerations. Justification for treatments should be based upon evidence that they reduce morbidity, improve quality of life, prolong survival, and ideally, are cost-effective. Presently, recommendations to treat and monitor asymptomatic cats that have high-risk markers appear rational, but these putative strategies will require prospective clinical trials to prove that they have merit.

Factors associated with cardiac morbidity

Diastolic dysfunction

This abnormality characterizes the principal pathophysiologic consequence of a wide range of phenotypically heterogeneous myocardial disorders. Cardiomyopathies are affected by complex intrinsic and extrinsic factors that compromise left ventricular diastolic performance, including increased myocardial mass (hypertrophy), increased calcium sensitivity and altered calcium handling of contractile elements, myocardial injury (inflammation, myocytolysis, apoptosis, and necrosis) and repair (fibrosis, matrix changes), myocyte disorganization, and ischemia. Such alterations impede diastolic function and promote ventricular stiffness and reduction of chamber compliance. Diastolic dysfunction is a poorly understood but prevalent condition in humans with a variety of cardiac disorders, and can progress to heart failure.[21—24]

Preclinical diastolic dysfunction appears to be prevalent in most cats with occult cardiomyopathy, in particular in RCM[11] and HCM.[25] Altered diastolic function ultimately results in increased left ventricular end-diastolic pressure and mean left atrial pressure and can lead to development of pulmonary edema (CHF) in some cases. Cardiogenic pulmonary edema that develops in the setting of abnormal diastolic function but preserved ejection fraction is termed diastolic heart failure[21,22] and is the most common cause of feline cardiac-related hospital visits.

Restrictive diastolic filling generally represents an advanced and severe stage of diastolic dysfunction, most commonly with RCM and HCM. Additionally, most cats with DCM demonstrate this pattern, although it is typically intercepted in affected cats that present with cardiac decompensation. Diastolic dysfunction and in particular, restrictive filling pattern is associated with decreased survival in cats.[11] Similarly, diastolic dysfunction has prognostic importance in human patients with both preserved and depressed left ventricular systolic function.[23] Comprehensive Doppler echocardiography can provide information regarding diastolic function and filling pressures.[24,26] In patients with ischemic cardiomyopathy, Doppler-based diagnosis of diastolic dysfunction provides strong prediction for adverse outcome when evaluating transmitral Doppler flow patterns including isovolumic relaxation time, early peak (E wave), and late (A wave) phases of diastole; deceleration time; and mitral annular velocities using tissue Doppler imaging.[24] However, the prognostic value of these variables for risk assessment in cats with asymptomatic (occult) cardiomyopathy remains to be demonstrated. Myocardial infarction is a common necropsy finding in cats with cardiomyopathy,[3] and echocardiography can readily identify depressed global and segmental myocardial function. Regional left ventricular wall hypokinesis and systolic dysfunction are poor prognostic indicators in feline HCM.[9] The presence of restrictive filling pattern in patients with myocardial infarction was associated with worse survival, regardless the left ventricular ejection fraction.[27]

Left atrial enlargement and dysfunction

Substantial left atrial enlargement and dysfunction can be associated with shortened survival in cats with HCM.[4,9,28,29] In many cases it is an indicator of chronic atrial pressure overload, and this echocardiographic finding may complement evidence derived from Doppler echocardiography that indicates flow patterns suggestive of impaired left ventricular relaxation and pseudonormal or restrictive left ventricular filling.[21,22] Furthermore, impaired left atrial systolic function and left atrial appendage flow velocities are associated with cardiovascular morbidity in the cat.[9,29] Left atrial dimension is an independent predictor of sudden death in humans.[30] Left atrial mechanical dysfunction and left ventricular diastolic abnormalities are interconnected. They are associated with decreased left atrial appendage flow velocities, predictive of spontaneous echocardiographic contrast in cats with cardiomyopathy.[29] In human patients left atrial spontaneous echo contrast is a significant predictor of thrombus formation and thromboembolic events,[31] and this association is believed to be similarly important in cats with myocardial disease.

Left ventricular remodeling and systolic dysfunction

Additional risk factors have been reported for cats with HCM. These include extreme left ventricular hypertrophy (end-diastolic left ventricular posterior wall or interventricular septum thickness >9.0 mm), regional left ventricular wall motion abnormality and thinning, and reduced (≤30%) left ventricular fractional shortening. In humans with HCM, left ventricular hypertrophy is related to the severity of diastolic dysfunction, and extreme left ventricular hypertrophy (>30 mm) is an important risk factor for cardiac morbidity and in particular, for sudden cardiac death.[32] Furthermore, cardiac remodeling is a well-recognized sequela to feline[33] and human[34] myocardial disease, especially HCM. Segmental wall motion abnormalities occur with feline[35] and human[36] cardiomyopathies, accompany myocardial infarction,[37] and are an independent predictor of arrhythmic events in humans with nonischemic DCM.[38]

"Malignant" family history of sudden death (high risk genotype)

Pedigrees may be encountered that have heritable patterns of sudden or unexpected death. This is detected most often in the Main coon cat breed with HCM[39] although other breeds may also be at risk. Asymptomatic siblings should be screened regularly by echocardiography to determine whether they have a phenotype similar to affected individuals.

Advanced structural lesions

Asymptomatic cats with arrhythmic right ventricular cardiomyopathy can be identified largely on the basis of severe right ventricular dilation and ventricular arrhythmia,[1,13] and be at risk for developing CHF. Cats with end-stage HCM are at high risk for adverse outcomes. This phenotype is characterized by progressive left ventricular systolic dysfunction, dilation (which often involves the apical to mid left ventricle), regional or global wall thinning of previously concentrically hypertrophied ventricles, severe left atrial enlargement, restrictive left ventricular filling, and myocyte injury with interstitial fibrosis and replacement fibrosis.[3,33]

Endomyocardial fibrosis is a heterogeneous and poorly understood condition. In advanced cases it may be characterized by prominent and often diffuse scaring that can be seen to bridge ventricular septum and left ventricular posterior wall; left ventricular remodeling and myocardial dysfunction; and extreme left atrial dilation.[12] Affected cats are at risk for CHF and arterial thromboembolism.

Dynamic obstruction of the left ventricular outflow tract

Until recently, the obstructive form of feline HCM (i.e., hypertrophic obstructive cardiomyopathy) was assumed to denote increased cardiac risk. This perception was largely based upon extrapolated reports from humans with HCM that demonstrated systolic anterior motion of the anterior mitral valve leaflet (SAM) as an independent predictor of disease progression, heart failure status, exercise intolerance, stroke, and cardiac death.[40] Conflicting findings from small retrospective studies of feline HCM did not dispel this assumption.[2,4,5,8,18] However, recent studies in cats have failed to support the notion that SAM (i.e., HOCM) increases cardiac morbidity or mortality.[9,19] While asymptomatic cats are occasionally detected with loud systolic, apical murmurs associated with SAM — but without evidence of left ventricular hypertrophy, the long-term consequences of this dynamic condition are unknown. Whether or not these cases merit therapy or should simply be monitored remains unresolved.

Therapeutic implications

Drugs should be considered on the basis of their theoretical benefit to mitigate pathophysiology associated with cardiovascular risk factors and coexisting medical conditions (Table 1). Long term, individualized patient monitoring should be planned in order to best determine if a disease regresses, remains static, or progresses to a point that provokes contemplation for modifying therapy. Central to accomplishing these strategies are effective client—veterinarian relationships, which explore and take into consideration the owner's philosophic and economic concerns, and their willingness as well as their ability to administer medication.

Presently, there is no data that establishes a treatment benefit for cats with mild to moderate asymptomatic (occult) cardiomyopathy. Whether therapy reduces disease progression, forestalls morbidity, or improves outcome compared with cats that are not treated at all, lingers as a promise unfulfilled that awaits authentication

Table 1 Medical therapies considered for asymptomatic cats with risk markers for cardiac morbidity and mortality.

Drug class	Example	Main action	Theoretical benefit	Main indication	Clinical benefit demonstrated in cats	Used by authors	Relevant feline citations
ACEI	Enalapril	RAAS inhibition	↓ neuroendocrine activation; Myocardial protection	Moderate/severe LA enlargement	No	Yes	41,42
Beta-blocker	Atenolol	Negative inotropic and chronotropic; Antiischemic; Antiarrhythmic	Relief of outflow tract obstruction; Heart rate control; Antiarrhythmic	Moderate/severe LV dynamic outflow tract obstruction	No	Yes	43
Antiplatelet	Clopidogrel Aspirin	Platelet inhibition	Antithrombotic	Moderate/severe LA enlargement, SEC, ↓ LAA flow	No	Yes	44,45
Calcium channel blocker	Diltiazem	Antiarrhythmic Positive lusitropic	Heart rate control; Improved LV relaxation	Atrial fibrillation; Abnormal LV relaxation	No No	Yes No	—
Digitalis	Digoxin	Antiarrhythmic	Heart rate control	Atrial fibrillation	No	No	—
Potassium channel blocker	Sotalol	Antiarrhythmic	Antiarrhythmic	Ventricular/ supraventricular ectopy	No	Yes	—
Antifibrotic	Spironolactone	Antifibrotic	↓ myocardial fibrosis	Moderate/severe LV hypertrophy	No	No	46
Nutraceutical	Taurine	Essential for normal myocardial calcium kinetics	Restoring myocardial function	Taurine-deficient cardiomyopathy	Yes	Yes	47

from evidence-based clinical trials. Currently considered cardiac drugs include antiplatelet agents, beta-adrenergic blockers, and angiotensin converting enzyme inhibitors (Table 1). Calcium channel blockers have by and large been abandoned as first line agents owing to lack of validation for efficacy. Platelet inhibitors have been considered in cases where ventricular remodeling and moderate to severe left atrial dilation and dysfunction are present. Potassium channel antagonists (sotalol) or calcium channel blockers (diltiazem) and digoxin have been used selectively in cases where ventricular or supraventricular ectopy, respectively, is judged to impose increased risk for sudden death or arrhythmia-induced cardiomyopathy. Sparse and anecdotal observations related to administering selective beta-1 receptor blocker (atenolol) to cats with HOCM suggest that left ventricular hypertrophy regresses in a very limited number of cases. All in all, initiation of any treatment at the stage of occult heart disease is based largely upon data derived from extrapolated human trials, experimental research models, or personal opinion. As such, drug therapy remains controversial until benefit can be established from clinical trials.

Conflicts of interest

None.

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