Management of Feline Cardiomyopathies

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Philip R. Fox, DVM, MSc, Diplomate ACVIM (Cardiology), Diplomate ECVIM (Cardiology), Diplomate ACVECC
Caspary Institute, The Animal Medical Center

Ideally, management of heart failure should be grounded in evidence from clinical trials designed to clarify efficacy, identify therapies that decrease morbidity, and determine strategies that prolong survival. Currently, such an evidence-based approach is limited owing to lack of clinical data. While most cardiologists are in general agreement with acute therapy for congestive heart failure, there is currently no consensus regarding chronic management or approach for asymptomatic patients. In cats, the clinical syndrome of heart failure is invariably associated with heart muscle disease (cardiomyopathy). Etiology, though occasionally detectable (e.g., thyrotoxicosis, taurine deficiency), is usually unknown.

Traditionally, treatment has been directed towards resolving clinical signs that are associated with abnormal fluid retention or organ congestion. Evidence from Doppler echocardiography has fostered increasing awareness that HF may also reflect the underlying functional myocardial derangement. That is, diastolic vs systolic dysfunction are important causes of CHF. Diastolic dysfunction can be considered to be associated with conditions impairing LV filling to the extent that pulmonary venous pressures become elevated in order to provide sufficient preload for adequate cardiac output. Diseases which alter diastolic function result in impaired LV distensibility or obstruction to LV filling and include hypertrophic and restrictive cardiomyopathies. As a general rule, diastolic heart failure is usually manifested by dyspnea associated with pulmonary congestion (edema). Treatment of diastolic HF can be directed at eliminating pulmonary congestion, improving diastolic function, and relieving myocardial ischemia. In contrast, systolic dysfunction is defined as impaired LV emptying (reduced pumping) due to diminished contractility. Cats with advanced LV systolic dysfunction are more likely to present with biventricular HF and some degree of forward output failure or cardiogenic shock. Treatment of systolic HF usually includes inotropic support.

THERAPIES FOR ASYMPTOMATIC BUT HIGH RISK CARDIOMYOPATHIES

Certain structural and functional abnormalities associated with diastolic heart disease (HCM, RCM) may increase morbidity and mortality. Based upon studies in affected humans and experimental animals (Note-not clinical feline clinical trials), certain conditions may warrant specific therapies.

Myocardial Infarction (MI) may be suspected from echocardiography (regional LV hypokinesis/dyskinesis, or segmental LV free wall thinning). Cause(s) remain unknown. **Beta-adrenergic Blockers** [propranolol, 2.5 to 5 mg q8-12h PO; atenolol 6.25-12.5 mg q12 to 24h PO] decrease mortality in people with acute MI and cardiac arrhythmias, and reduce long term mortality in chronic MI by antiarrhythmic effects and by preventing reinfarction. Sympathetic nervous system antagonists may indirectly improve ventricular compliance by reducing heart rate and myocardial ischemia. **Angiotensin-Converting Enzyme (ACE) Inhibitors** (Enalapril, 0.5 mg/kg q24h PO; benazepril (0.25-0.5 mg/kg q 24h PO: avoid use with hypotension) have

been advocated in human post myocardial infarction trials based upon their role in reducing cardiovascular remodeling, improving hemodynamics, reducing ischemic events, and increasing survival. These agents appear to be quite safe in cats with heart disease. **Calcium Channel Blockers** have not been efficacious (i.e., no reduction of subsequent cardiovascular events) in treating human MI, and diltiazem was harmful when MI and LV dysfunction were present,possibly by neuroendocrine activation.Whether these affects occur with MI in cats is undetermined.

Tachyarrhythmias diminish systolic and diastolic function, reduce diastolic filling (which can increase outflow gradients and reduce forward cardiac output), and thus increase myocardial oxygen utilization and ischemia. Beta-adrenergic blockers (propranolol, 5-10 mg q8 to 12h PO; atenolol, 6.25-12.5 mg q12-24h PO) antagonize the sympathetic nervous system, and may be useful for treating serious ventricular or supraventriculr tachycardias. While digoxin (0.031 mg [i.e., 1/4 of a 0.125 mg tablet] per 4.5 kg cat q 48h PO) or diltiazem may be administered for atrial tachyarrhythmias, heart rate control often requires the addition of a beta-blocker which is titrated to effect.

Massive LV Hypertrophy. Although the severity of hypertrophy is not a recognized risk factor for sudden death in human HCM, unfavorable prognosis may be associated with severe LV hypertrophy in some cats (LVd free wall or interventricular septal thickness > 8 mm). **Beta-blockers** may be used with the following rationale: 1) heart rate control (negative chronotropism) and associated indirect improvement of diastolic filling; 2) reduction of dynamic LV outflow tract obstruction; 3) reduction in myocardial oxygen utilization; 4) antiarrhythmic effects; and 5) ability to blunt sympathetic myocardial stimulation. Clinical reduction of resting heart rate to 120-160 beats/min is usually attainable with atenolol (6.25-12.5 mg q 12-24h PO) or propranolol (5-10 mg q 8 to12h PO) for an average size (4.5 kg) cat. **Calcium Channel blockers** are often advocated based upon their action to promote positive lusiotropy (i.e., to directly improve ventricular diastolic relaxation and filling). Diltiazem may slightly slow the heart rate in some cats but not in others, and heart rate reduction is much weaker compared with beta-blocker therapy**.** Several preparations of diltiazem are available. Diltiazem hydrochloride comes in 30 mg tablets and is dosed at 7.5 mg q 8 to 12h. Cardizem CD® capsules can be compounded and dosed at 10 mg/kg q24h. Dilacor XR is dosed initially at 30 mg per cat q12-24 h; some cats may tolerate 60 mg q12-24h though anorexia and vomiting may occur (note: Dilacor XR 240 mg capsule contains four controlled-released 60 mg tablets which can be broken in half to create a 30 mg dose). **ACE inhibitors** may blunt neuroendocrine activation and prevent deleterious cardiovascular remodeling. ACE inhibitors have been used safely, most commonly added to other therapies (Enalapril, 0.25 to 0.5 mg/kg q 24h PO).

Syncope. Recurrent syncope is a risk factor for sudden death in humans with HCM. In cats, syncope can be associated with tachyarrhythmias, dynamic LV outflow obstruction (LVOTO), and ischemia (infarction). Symptoms can often be managed successfully with beta-blockers to reduce or abolish LVOTO.

Spontaneous Echo Contrast ("Smoke") and Stasis. Associated with blood stasis, spontaneous echo contrast is considered to presage thrombosis and is associated with increased thromboembolic risk. It should warrant antiplatelet drugs (aspirin, 25 mg/kg q72hours) and perhaps more aggressive therapies.

"Malignant" Familial History (High Risk genotype). Pedigrees are occasionally identified with a documented heritable pattern of HCM with severe morbidity and mortality (e.g., Maine coon cats, others). Early intervention with calcium channel

blockers or beta-adrenergic blockers may be contemplated based on experimental considerations which hold that a pathway to the phenotypic expression of LV hypertrophy is influenced by triggers such as higher LV pressure and work load.

Myocardial Failure. In some HCM cats LV contractility is mildly to moderately reduced (e.g., fractional shortening, 23-29%; LV end-systolic dimension, 12-15 mm). This can result from acute or chronic myocardial infarction, myocarditis, and other causes of LV remodeling. Oral taurine supplementation (250 mg q 12-24h) is initiated whenever myocardial failure is detected. ACE inhibitors may be added to counteract neurohormonal activation and reduce remodeling. Judicious beta-blocker therapy might be beneficial if myocardial infarction is suspected, or with tachyarrhythmia.

TREATMENT OF SYMPTOMATIC CATS WITH DIASTOLIC HEART FAILURE

Acute Management of CHF

Pulmonary edema is rapidly progressive and life threatening. Furosemide inhibits renal tubular reabsorption of sodium or its accompanying anions, promotes brisk diuresis, and reduces vascular volume, thereby decreasing LV filling pressures (i.e., cardiac preload) and pulmonary congestion. Initially, furosemide is administered IV (1-2 mg/kg) every 1 to 2 hrs until the congestive state is substantially reduced. Then, the dosage frequency is reduced, typically to every 8 to 12 hours IM or SC. Peak diuresis usually occurs within 30 minutes of IV administration. Resolution of edema may be enhanced in the first 24 to 36 hours of therapy by adding the preload reducer, 2% nitroglycerin ointment (1/4 to ½ inch q 6hr cutaneously-alternate 12 hrs with and 12 hrs without nitroglycerine therapy to reduce tolerance). Supplemental oxygen (40 to 60% O_2-enriched inspired gas) may improve pulmonary gas exchange. Clinical resolution is indicated by reduced respiratory rate and work of breathing, resolved lung crackles, and radiographic clearing of alveolar infiltrates (usually complete by 24 to 36 hours). The endpoint of diuretic therapy is relief of clinical signs or progressive increase in BUN and creatinine. Dehydration and hypokalemia can result from overzealous diuresis.

Chronic Management of CHF

There are currently no data to indicate the most effective therapies, whether combined therapy is more advantageous than monotherapy, or whether therapy is significantly better than no therapy. Drugs are administered on an empirical basis, relying on clinical experiences, biases, and theoretical benefits.

Chronic therapy is individualized to eliminate congestion; prevent arterial thromboembolism; halt, slow, or reverse myocardial dysfunction (theoretically); promote enhanced quality of life; and prolong survival. Identifiable conditions (systemic hypertension, taurine deficiency, hyperthyroidism, anemia) are treated.

Diuretics. Furosemide is gradually decreased to the lowest effective dosage, typically, 6.25-12.5 mg q 12-24h). Some cats remain stable on 1-2 mg/kg PO given every other day while in others, diuretics may be used twice weekly or even discontinued. In contrast, upward titration is may be necessary with recurrent CHF. Because diuretic resistance may occur as heart failure progresses, cats with recurrent CHF are likely to benefit acutely from intravenous furosemide which has higher bioavailability, or to administration of two diuretics. (see Recurrent and Refractory Congestive Heart Failure, below). It is prudent to assess BUN, creatinine, electrolytes and blood pressure in anorectic cats.

ßeta-adrenergic Blockers. Prolonged activation of the sympathetic nervous system may lead to cardiovascular injury, disease progression, or arrhythmias. Since

LV diastolic function is very sensitive to increases in sympathetic tone, by decreasing heart rate with beta-blockers, diastole is prolonged and passive ventricular filling and compliance may improve. Prolonged diastolic filling also allows more time for coronary blood flow and reduces myocardial ischemia. Beta-blockers decrease myocardial oxygen requirements by reducing cardiac sympathetic stimulation,heart rate, LV contractility, systolic myocardial wall stress, and systemic blood pressure. Dynamic LV outflow tract obstruction and related pressure gradient is often reduced or abolished with beta-blocker therapy. Propranolol (5-10 mg q8-12h PO) or atenolol (6.25-12.5 mg q12-24h PO) are commonly used agents. Adverse reactions are uncommon but include lethargy or hypotension.

Calcium Channel Blockers. These agents are used to enhance diastolic performance, may reduce heart rate (verapamil much more so than diltiazem) and blood pressure; exert a mild negative inotropic effect (reducing myocardial oxygen consumption); and improve rapid diastolic ventricular filling. Diltiazem is generally ineffective to resolve dynamic LV outflow obstruction. For diltiazem hydrochloride (Cardizem, 1 mg/kg tid PO), the reported half life ($t_{1/2}$) is 113 ± 24 minutes; peak concentration following oral administration was achieved in 45 ± 36 minutes; and bioavailability 50 to 80%. Clinically, this drug is dosed at 7.5 mg tid PO. A long-acting diltiazem formulation is Cardizem CD, 10 mg/kg PO q 24h ($t_{1/2}$ 411 ± 59 minutes; peak concentration following oral administration achieved in 340 ± 140 minutes; bioavailability 22 to 59%). Another diltiazem preparation, Dilacor XR, is available in an extended release formulation. Each 240 mg capsules contains four controlled-released 60 mg tablets. Starting dose for a 5 kg cat is 30 mg q 24h and titration to 60 mg daily is tolerated in some patients, although vomiting is a side effect.

Angiotensin Converting Enzyme (ACE) Inhibitors. Neurohormonal activation plays an important role in heart failure. Thus, disruption of neurohormonal activation represents therapeutic rationale for using ACE inhibitors. The RAS plays a prominent role in human HCM patients by influencing or regulating the expression of myocardial hypertrophy. Inhibition of RAS has a beneficial effect on extracellular remodeling in CHF, and ACE inhibitors reduce ventricular remodeling by blocking the tropic effects of angiotensin II on myocytes. There is also survival value provided by early use of ACE inhibitors in acute human myocardial infarction. Many clinicians combine an ACE inhibitor (usually enalapril) with furosemide, with or without a beta-blocker or diltiazem, particularly with recurrent heart failure. Enalapril (0.25-0.5 mg/kg q24h PO) and benazepril (0.25-0.5 mg/kg q24h PO) are clinically well tolerated. Optimal timing for ACE inhibitor therapy and the effects of these agents on morbidity and mortality in feline cardiomyopathy is undetermined.

Reduction/Elimination of Dynamic LV Outflow Tract Obstruction. Negative inotropic drugs that reduce or eliminate LVOT obstruction have been widely used in humans with the obstructive form of HCM. In cats reduction of outflow gradient is usually best accomplished with beta-blocker therapy. Stimuli that provoke or intensify LV outflow tract gradients should theoretically be avoided including positive inotropes, reduction of LV volume, or decreased afterload. The clinical importance of decreasing obstruction, particularly in asymptomatic cats, has not been established. However, beta-blockers reduce or abolish syncope associated with dynamic LVOT obstruction.

Recurrent and Refractory CHF

When pulmonary edema or biventricular failure reoccurs, emergency treatment may be required (see above-Acute Pulmonary Edema). Therapy is then modified to either 1) increase the diuretic dose, 2) increase the "primary" drug dose (i.e., beta-

blocker, calcium channel blocker, or ACE inhibitor), 3) change to a different class of primary drugs, or 4) add a second or even third primary agent. When CHF recurs in spite of these manipulations, particularly with severe, chronic effusions, further upward dose titration of furosemide (e.g., 2-4 mg/kg q 8-12h PO) may be required. Probably more effective is selective nephron blockade-the addition of a second diuretic agent which acts at a different site in the nephron (and thus, act synergistically with furosemide). Hydrochlorothiazide (1-2 mg/kg PO q12-24h PO) and hydrochlorothiazide-spironolactone (Aldactazide, 2.2 mg/kg/day PO) have proven to be useful "second" diuretic agents. Close monitoring for dehydration, azotemia, hyponatremia, and hypokalemia is advised. Digitalization may be prescribed for unresponsive right-sided CHF, atrial fibrillation or myocardial (systolic) failure (see below).For continued refractory CHF: 1) ascertain that prescribed drugs are being administered as directed; 2) recalculate drug doses based on current body weight; 3) generate and re-evaluate a new data base (e.g., ECG, radiographs, echocardiogram, clinical pathology) to rule out systemic and metabolic disease, heartworms, neoplasia; 4) assess serum T_4 concentrations (cats > 6 years old); and 5) refer to a cardiologist.

SYSTOLIC (MYOCARDIAL) DYSFUNCTION

Initial Therapy

Treatment Goals. Initial therapy is directed to reduce or eliminate pulmonary and systemic venous congestion, promote increased forward cardiac output, control serious tachyarrhythmias or bradyarrhythmias, and improve myocardial contractility. General supportive measures such as thoracocentesis, external heating to combat hypothermia, oxygen administration, and minimization of stress are important and include the following considerations:

   Thoracocentesis. If breathing is compromised by severe pleural effusion (muffled heart and lung sounds, dull thoracic percussion note), thoracocentesis is advised, even before radiographs are taken.

   Acute Pulmonary Edema. Life threatening pulmonary edema is uncommon with myocardial failure. When edema is severe, therapy is similar as was discussed above (see Diastolic Failure).

   Inotropic Support. Synthetic sympathomimetic amines possess greater inotropic activity, provide quicker onset of action, and allow finer control than digoxin. Dobutamine (2-10 µg/kg/min constant rate infusion) is the preferred agent for hemodynamic support for severe myocardial failure. A common adverse side effect is seizures which are typically focal-facial, but occasionally become generalized. Often, they do not reoccur when the dose is reduced below 5 µg/kg/min.

   Taurine Supplementation. Although taurine deficiency is now a rare cause of DCM, taurine is inexpensive and safe, and is empirically administered (250 to 500 mg q12h PO) for 8 weeks (re-evaluate by echocardiography).

Chronic Maintenance Therapy

Diuretics. When congestion is controlled, furosemide is tapered to the lowest effective dose. To manage chronic effusions, upward dose titration (2.2 to 4.2 mg/kg q8-12h PO) or sequential nephron blockade (additional diuretic agents such as hydrochlorothiazide and spironolactone) may be effective. Refractory cases may require periodic thoracocentesis.

   ACE Inhibitors. These drugs may help blunt adverse neurohormonal alterations,

limit progressive cardiac chamber remodeling (dilation), and prevent or delaying clinical deterioration. Enalapril monotherapy (0.5 mg/kg PO daily) has been used to successfully manage some cases of mild idiopathic myocardial failure (%FS 23-29%; LVDs 12-14 mm). More severe systolic failure often require the addition of diuretics and digoxin.

Digitalis (Digoxin). While digitalis is the traditional agent for management of myocardial failure, there is little clinical data in cardiomyopathic cats, and digoxin's low therapeutic index makes its role controversial. Although higher plasma levels and more accurate dosing can be achieved with the elixir form, it is less palatable to cats than tablets. Renal insufficiency will reduce digoxin clearance and increase serum concentration. Digoxin can be given when a cat is hydrated and eating. Based upon a calculated dose of 0.005 to 0.01 mg/kg lean body weight and relatively normal BUN/creatinine, the following guidelines are suggested: for cats weighing 1.9 to 3.2 kg, ¼ of a 0.125-mg digoxin tablet (0.031 mg) every 2 to 3 days; for cats weighing 3.3 to 6.0 kg, ¼ tablet daily or every other day; and for cats weighing more than 6.0 kg, ¼ tablet daily (occasionally, q12h).Blood concentration should be evaluated 10 to 14 days after initiating therapy. When blood is drawn 10 to 12 hours post administration, a serum digoxin concentration of 1-2 ng/ml is presumed to be therapeutic. Anorexia and depression are early signs of toxicity.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Right-sided CHF is treated with furosemide, digoxin, and an ACE inhibitor. For atrial fibrillation or atrial tachycardia, digoxin combined with diltiazem or atenolol is used to maintain the resting heart rate between 140 to 160 beats/min. Symptomatic ventricular tachycardia has been successfully managed acutely with lidocaine (10-40 µg/kg/min CRI), and chronically with sotalol (2-4 mg/kg q12 hr PO).

THROMBOEMBOLISM

Treatment Goals. Therapy is directed toward 1) managing concomitant CHF or serious arrhythmias when present; 2) general patient support including nutritional supplementation, correction of hypothermia, and prevention of self mutilation; 3) adjunctive therapies to limit thrombus growth or formation; 4) close patient monitoring; and 5) thrombus prevention. Limb and/or organ viability is enhanced by rapid resolution of arterial occlusion. Acutely affected cats are a high surgical/anesthesia risk.

Supportive Therapies. Various medical treatments have been proposed, although most are empirical and efficacy is unsubstantiated. Pain relief is most critical during the first 24-36 hours. It is also important to maintain hydration, electrolyte balance, and nutritional support. Placement of a nasoesophageal feeding tube is advocated for anorectic cats. Self-mutilation is common following a saddle embolus and is characterized by excessive licking or chewing of the toes or lateral hock. Application of a loose-fitting bandage or stockinette is usually effective.

Thrombolytic Therapy. Streptokinase (loading dose [90,000 IU/cat over 20-30 minutes] followed by a constant rate infusion [45,000 IU/hr for 3 hours]) and urokinase generate the nonspecific proteolytic enzyme, plasmin, through conversion of the proen. Recombinant tissue-type plasminogen activator, t-pa (0.25 to 1.0 mg/kg/hr IV for a total dose of 1 to 10 mg/kg), has a lower affinity for circulating plasminogen and does not induce a systemic fibrinolytic state. It binds to fibrin within the thrombus and converts the entrapped plasminogen to plasmin. This initiates a local fibrinolysis with limited systemic proteolysis. Complications include bleeding and hyperkalemia (70%).

Anticoagulation Therapy. Heparin and warfarin (Coumadin®) have no effects on established thrombi. Their use has been based on the premise that by retarding clotting factor synthesis or accelerating their inactivation, thrombosis from activated blood clotting pathways can be prevented. Heparin binds to lysine sites on plasma antithrombin III, enhancing its ability to neutralize thrombin and activated factors XII, XI, X, IX; this prevents activation of the coagulation process. Efficacy in treating cats with thromboembolism has not been established and reported dosages vary widely. Low molecular weight heparins hold promise but doses have yet to be established. Warfarin impairs hepatic vitamin K metabolism, a vitamin necessary for synthesis of procoagulants (factors II or prothrombin, VII, IX, and X). Initial oral daily dosage (0.25 to 0.5 mg/cat) is adjusted to prolong the prothrombin time to twice the normal value, or it is adjusted by the international normalization ratio (INR) to maintain a value of 2.0 to 3.0. Hemorrhage is a potential complication.

Anti-Platelet Drugs. Exposure of blood to subendothelial connective tissue leads to rapid platelet activation, formation of platelet plugs and subsequent thrombus. Pharmacologic measures are directed to modify platelet aggregation. Aspirin induces a functional defect in platelets by irreversibly inactivating (through acetylation) cyclo-oxygenase. This enzyme is critical for converting arachidonic acid to thromboxane A_2,which in the vascular wall is responsible for converting arachidonic acid to prostacycline. Thromboxane A2 induces platelet activation (through release of platelet adenosine diphosphate) and vasoconstriction (as does serotonin), while prostacycline inhibits platelet aggregation and induces vasodilation. In cats, aspirin (25 mg/kg, or 1/4 of a 5-grain tablet q48-72h PO) inhibits platelet function for 3 to 5 days and is relatively safe. The optimal dose to inhibit thromboxane A_2 production but spare vascular endothelial prostacyclin synthesis is unknown for cats.

Prevention/Treatment of Hypercoagulable States. Hyperhomocysteinemia occurs in some cats with thromboembolism. Supplementation with B vitamins based upon this strategy for affected people has been advocated for cats.

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Philip R. Fox, DVM, MSc, DACVIM, DECVIM (Cardiology), DACVECC
Caspary Institute, The Animal Medical Center

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