Feline Cardiomyopathy – More than Genes! New Thoughts on Causes and Treatments

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Cats with heart disease often have a heart muscle disease called cardiomyopathy. Different forms of cardiomyopathy exist, including a thin-walled heart muscle with weak vigor of contraction (dilated cardiomyopathy), a thick walled heart muscle (hypertrophic cardiomyopathy), and a few other forms of heart muscle disease. These cardiomyopathies are fairly common in cats, with some surveys indicating that up to 10% of cats might have a form of heart disease. This heart disease is often clinically silent for many years, until there is a sudden onset of clinical sings. The most common issues are fluid accumulation in the heart (congestive heart failure), clot formation resulting in sudden onset lameness (arterial thromboembolism), fainting, or sudden death.

Hypertrophic cardiomyopathy (HCM) is the most common cause of cardiac disease in cats. In certain breeds of cats, especially Maine coon cats, there is a genetic test available to identify cats at risk of cardiomyopathy. Unfortunately, this is an acquired disease, and so while the genetic test is positive at birth, disease may not develop until 3 to 10 years of age, and some cats with the genetic mutation may never develop the disease. In our clinic, looking at Maine coon cats with HCM, there was a closer association between the size/weight of cats than there was between the presence or absence of the genetic mutation. Since some cats with the genetic mutation may never develop the disease, it seems that there must be other factors involved in development of the disease. This could be the presence of other genetic factors (e.g., other genetic mutations that bring on the disease) or it may be related to some environmental factor (e.g., diet, drugs, rate of growth, exposure to smoke, etc.).

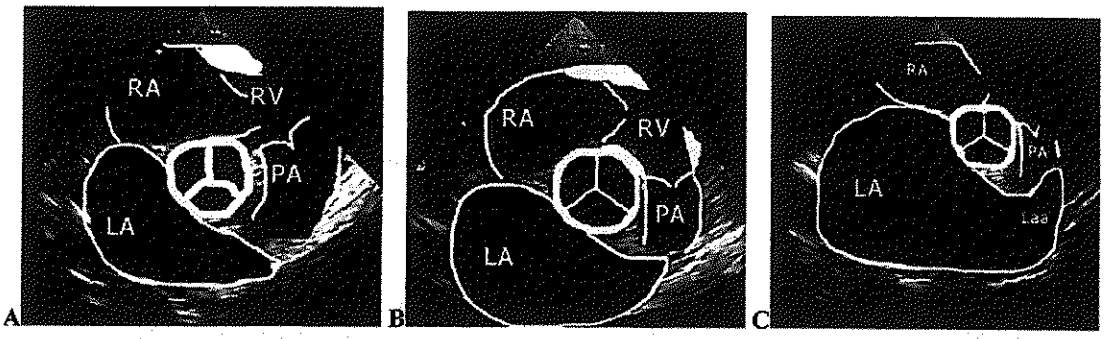
Many drugs are used to treat heart disease in cats, despite the fact that there has been very little research to help direct veterinarians on which drugs work best. Most drugs used in cats are also used in people, and many of the most effective drugs help to block some aspect of the body's compensatory response to reduced cardiac function. These drugs include ACE inhibitors (angiotensin-converting enzyme inhibitors such as enalapril or benazepril), beta-blockers (such as atenolol or carvedilol), and either feeding a reduced salt (sodium) diet or using diuretics. In addition, many drugs are used to try and prevent clot formation. Drugs like aspirin, clopidogrel, low molecular weight heparins, and coumadin (warfarin) have been used in cats to prevent clot formation. Which drugs work best? Unfortunately, we do not have adequate clinical trials to support a specific set of recommendations in cats.

Respiratory and cardiac abnormalities are common in cats, and identification of the specific underlying cause is important for both diagnostic and therapeutic success. Shortness of breath, cough and other respiratory signs may be due to upper airway obstruction (eg. laryngeal paralysis), pleural space disease (eg. pleural effusion or pneumothorax), pulmonary parenchymal disease (eg. pneumonia), cardiovascular disease or a combination of any of the above. A specific diagnosis is often established based on a combination of findings, including the results of history, physical examination, laboratory testing (including NT-proBNP and cardiac troponins), thoracic radiographs (chest x-rays), Electrocardiography (ECG) and echocardiography. Echocardiography is the best test to define cardiac function and structure, but the test is expensive and is not available for all cats. Measurement of cardiac biomarkers such as NT-proBNP can also play an important role in identifying cardiac disease, but the specific roles for these biomarkers are still being studied.

ECHOCARDIOGRAPHY

The growing availability and utility of ultrasonography is a vital aspect of improving patient care. The early identification of specific cardiac and non-cardiac illness is likely to improve outcome. Standard views can be learned with formal training, and advanced training is needed to become proficient in advanced echocardiographic skills. Echocardiography is especially helpful to determine the presence or absence of pleural or pericardial effusion. The degree of atrial enlargement in cats is correlated to the severity of disease, the prognosis, and the likelihood for developing arterial thromboembolism, so familiarity with this view can be very helpful.

Assessment of Left Atrial Size



CARDIAC BIOMARKERS

Natriuretic Peptides

The natriuretic peptides are a family of structurally similar proteins including atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP), C-type natriuretic peptide (CNP), and urodilatin. These proteins are regulators of salt and water homeostasis and blood pressure. These proteins are released in response to either dilation or thickening of the heart. When release to the blood stream they have a variety of actions, including causing loss of sodium (salt) and water via the kidneys – thus they help to prevent overdistension of the heart. Since they are release into the bloodstream when the heart enlarges, we can measure them, and they can give us an idea of the degree of heart disease that might be present. B-type natriuretic peptide (BNP; previously called Brain Natriuretic Peptide) has been well studied in cats.

NT-proBNP is the protein form of BNP that has been best characterized, and values of NT-proBNP are elevated in cats with congestive heart failure, and it also is elevated in many (most) cat with asymptomatic heart disease. Normal dogs and cats have very low levels of circulating ANP and BNP. The main clinical applications are 1) differentiation of respiratory signs (cough or shortness of breath) due to heart disease vs. lung disease in both dogs and cats and 2) in cats (predominantly) the determination of the presence or degree of underlying heart disease. They will not be useful to reliably differentiate between different types of heart disease. It appears that feline NT-proBNP could be useful as a screening tool for feline heart disease, especially to determine the presence of clinically significant heart disease.

HYPERTROPHIC CARDIOMYOPATHY

Atenolol - Beta blockade has gained favor as a therapeutic modality for cats with HCM, especially in those cats with HCM. The beta-blockers which have gained the greatest enthusiasm in cats are carvedilol and atenolol. Atenolol is the most commonly used drug in cats with hypertrophic cardiomyopathy that have not yet developed clinical signs. For many years there has been enthusiasm to use drugs that slow heart rate in cats with hypertrophic cardiomyopathy (HCM), a disease associated with abnormal filling of the heart. Additional effects which can be noted after administration of atenolol or other beta-blockers to cats with HCM include reduction or elimination of abnormal motion of the mitral valve (SAM), a reduction in the left ventricular outflow tract obstruction, and a reduction in leak at the mitral valve (mitral regurgitation). There has been one report of the use of a transdermal formulation of atenolol, which resulted in highly variable and mostly sub-therapeutic concentrations of atenolol, and so pending further study it can be presumed that the transdermal method of administration is best avoided in cats. One abstract of the results from a multicenter study evaluation of cats with congestive heart failure and diastolic dysfunction looked at 4 treatment regimens and found that domestic short hair cats treated with atenolol and furosemide survived for a shorter period of time than cats treated with the other 3 treatment options – As a result some cardiologists are less likely to give beta-blockers after the onset of congestive heart failure (fluid in the lungs).

Angiotensin-Converting Enzyme Inhibitors - Angiotensin-converting enzyme (ACE) inhibitors are commonly used in the management of CHF. By blocking this enzyme system in the body, these drugs reduce fluid retention and reduce blood pressure just a bit (acting as vasodilators). Angiotensin-converting enzyme inhibitors have proved to be useful in a variety of settings, including congestive heart failure, high blood pressure (systemic hypertension), and in certain kidney diseases associated with the loss of protein. In a large number of human and canine heart failure trials, ACE inhibitors have been proven to prolong survival. ACE inhibitors also result in improved clinical signs in dogs with heart failure. There are few well conducted clinical trials in cats with which to form solid guidelines regarding clinical use of ACE inhibitors either for hypertrophic cardiomyopathy or for congestive heart

failure, although most veterinary cardiologists would agree that ACE inhibitors are probably effective in cats with congestive heart failure. There is less agreement about the use of ACE inhibitors in cats with hypertrophic cardiomyopathy but many veterinary cardiologists will prescribe an ACE inhibitor in cats with HCM and marked left atrial enlargement, even if signs of CHF have not yet developed.

Furosemide (Lasix) – Furosemide is indicated once congestive heart failure (overt fluid retention in the lungs causing shortness of breath) is present. Most cardiologists would not recommend single agent use of furosemide for treatment of CHF. It can be difficult to define the exact dose of diuretic required by any individual cat with CHF. The dose required to clear significant edema accumulations and cause the animal to be minimally symptomatic (the desired dose) is often close to a dose that might result in side effects. We usually try to use the lowest possible dose of furosemide which will control signs of CHF. This often means a degree of experimentation must be performed to best evaluate an individual animal's needs. Giving an owner upper and lower limits for acceptable furosemide dose, and carefully explaining to them that they should "give more for difficulty breathing or rapid respirations, and give less if the animal seems weak, lethargic, anorexic, or depressed" has worked successfully for the author.

Pimobendan – Pimobendan is a calcium sensitizing drug that is useful as a positive inotrope to increase the vigor of contraction of the heart. In addition, pimobendan is a phosphodiesterase inhibitor with vasodilating effects , to make it a bit easier for the heart to pump blood forward. This combined action has been referred to as inodilation. Pimobendan has been well studied in dogs with valvular disease and in dogs with dilated cardiomyopathy. In dogs with dilated cardiomyopathy there seems to be both clinical benefit (dogs feel better) and evidence for improvement in well-being and survival time. As a result, in dogs, we routinely use pimobendan in addition to other historically helpful medications such as ACE inhibitors and diuretics. The drug has only been studied in dogs with active CHF, and the role for this drug in cats is unclear. There has been limited study regarding the use of this drug in cats with heart failure, there are some theoretical reasons why the drug might not be well tolerated in cats with hypertrophic cardiomyopathy, and at in those cats have thickening at the top of the interventricular septum causing obstruction to the outflow of blood from the left ventricular outflow tract. There are several abstracts describing the use of pimobendan in cats with advanced congestive heart failure. Because the drug has a positive inotropic effect, there has been a tendency for veterinarians to use pimobendan in cats after myocardial failure, evidenced by a reduced vigor of contraction on echocardiogram, is apparent. To date the preliminary reports and anecdotal evidence suggest that pimobendan can be used in cats with advanced heart failure and that it is well tolerated, even in many cats with hypertrophic cardiomyopathy, at least when obstruction is not present. Further studies are needed to better outline whether this drug has benefits in cats with CHF and which clinical situations are most appropriate for the use of the drug. The author currently is most likely to use pimobendan in cats under the following circumstances: 1) the cat has advanced heart disease and congestive heart failure 2) there is no left ventricular outflow tract obstruction and 3) the cat has signs of CHF that have not fully responded to twice a day furosemide and a solid dose of an ACE inhibitor or 4) the cat has combined heart and renal failure and/or there has been a deterioration in renal function following initiation of an ACE inhibitor.

PREVENTION OF ARTERIAL THROMBOEMBOLISM

Arterial thromboembolism (ATE) is a common complication of feline heart disease, occurring in 20-40% of cats with cardiomyopathy. The thrombus may develop in either the left ventricle or the left atrium, however, a left atrial origin is most common, and cats with cardiomyopathy that have dilatation of the left atrium are at increased risk for clot formation. Since the treatment of arterial thromboembolism is very difficult and often unsuccessful, prevention of this devastating event becomes very important.

Dalteparin and Enoxaparin – Regualr (unfractionated) heparin is a familiar drug to most veterinarians, but there are newer forms of heparin that have less side effects and can be used with twice a day dosing. These low molecular weight heparins (Dalteparin and Enoxaparin) have been recently used to prevent thrombus formation in cats at risk of ATE. We have used dalteparin (Fragmin; 160 U/kg) subcutaneously twice a day. One major action is to inactivate clotting factor Xa and is used as a preventative for arterial thromboembolism (clot to the leg). Recent research has suggested that the high dose administered at least twice a day might be desirable. Another low molecular weight heparin option is enoxaparin, which has been studied at 1 mg/kg subcutaneously q 12 hr. Both dalteparin and enoxaparin can be expensive to use on a long-term basis (several hundred dollars per month for twice a day treatment in most cats). The drug must be given by subcutaneous injections. Yet, many owners prefer injections to oral medications in cats, and the drug is currently the author's first choice for prevention of ATE in cats. There are

newer anticlotting drugs that are being approved for use in humans, drugs intended to replace Coumadin (warfarin), and one of these will likely play a role in the management of cats at some future date.

Clopidogrel and Aspirin – The antiplatelet drug, clopidogrel (Plavix), has been added to the armamentarium of drugs used to prevent thromboembolic disease. This drug reduces platelet activation and platelet degranulation. Clopidogrel seems to be well tolerated in many cats, although foaming at the mouth or vomiting has been seen in some cats, and an infrequent liver toxicity may occur. Compounding the drug may reduce this side effect for some cats, although the taste may still trigger this reaction in other cats. While chronic aspirin use can be associated with altered renal function, especially in animals that might get somewhat dehydrated while taking furosemide, renal insufficiency has not been recognized by the author with clopidogrel. Aspirin use also has been associated with reduced efficacy for furosemide, and this is another area where clipodogrel might have an advantage. There is no routine monitoring of clotting times or any other blood tests for this drug. Clopidogrel is supplied as 75 mg tablets and the proposed dose (pending further clinical experience) is ¼ of a tablet orally once a day. The dose and effectiveness of aspirin is unclear, although this is the least expensive anticlotting drug to use.

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