Cats with heart disease have been treated, at least in part, based on the morphologic appearance and presumed physiologic function of their ventricle. For example, cats with dilated cardiomyopathy and systolic dysfunction might be treated differently than cats with hypertrophic cardiomyopathy and diastolic dysfunction. However, most drugs associated with an improved survival in people with congestive heart failure have a mechanism of action that, at least in part, interferes with the neurohumoral stimulation that causes signs of CHF (e.g., angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone). There has been progressive support for use of therapies that interrupt these compensatory responses. Studies into the effects of neurohumoral activation at the cellular (myocardial) level have identified that progressive myocardial hypertrophy, cardiac remodeling, myocardial fibrosis, and progressive cardiac enlargement all are directly impacted by these seemingly exuberant compensatory reactions. However, in veterinary medicine, there are a few exceptions to these rules. Use of the beta-blocker atenolol in cats with congestive heart failure was associated with a reduced survival time in one abstract. Pimobendan in dogs with heart failure also seems to be an exception to this rule, and this newest cardiac drug both improves survival and improves quality of life in dogs with heart failure by reducing the clinical signs associated with heart disease. What is the best method to manage cats with heart disease? Unfortunately, we do not have adequate clinical trials to support a specific set of recommendations in cats. Currently, the practicing veterinarian must combine a strong knowledge of the mechanism of actions of various cardiac medications with the recommendations of and experiences of experts in the field.

**ASYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY**

**Atenolol** - Beta blockade has gained favor recently as a therapeutic modality for treatment of people with CHF. Several studies on the use of metoprolol and carvedilol have documented benefits that accrue from chronic treatment of these people with beta-blockers. These effects are often not seen for several months after initiation of beta blockade, and these benefits include up regulation of previously down regulated beta-receptors, improved cardiac performance (improved stroke volume), and improved survival. These clinical benefits appear to have sound theoretical basis, and are currently being evaluated in dogs with naturally occurring CHF as well as in earlier stages of heart disease. However, the beta-blocker which has gained the greatest enthusiasm in cats is atenolol, a beta-blocker that has not been demonstrated to be associated with improved survival in people with congestive heart failure. Atenolol is the most commonly used drug in cats with hypertrophic cardiomyopathy who 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 diastolic dysfunction, largely in an attempt to prolong diastole and improve cardiac filling. Both atenolol and sustained release formulations of diltiazem have been used to enhance diastolic dysfunction in cats with HCM, although some authors have reported adverse effects when using doses of diltiazem which are high enough to cause therapeutic drug concentrations of diltiazem for the entire 24 hours of the day. Additional effects which can be noted after administration of atenolol or other beta-blockers to cats with HCM include reduction or elimination of systolic anterior motion of the mitral valve, a reduction in the left ventricular outflow tract velocity, and a reduction in mitral regurgitation, and these changes are less frequently noted after administration of sustained release diltiazem. While elimination of these presumed offensive physiologic findings should reduce myocardial oxygen demand and improve myocardial ischemia, there have been no clinical trials which document improved outcome after initiation of atenolol. 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 furosemide alone, furosemide plus diltiazem, or furosemide plus enalapril. The furosemide plus enalapril treated cats lived the longest, however this did not reach statistical significance. Carvedilol has been used by some cardiologists with doses of 0.2 mg/kg BID and slow titration upwards towards a dose of 0.8 mg/kg BID, however many cats with CHF will not tolerate this upward titration, and the author, with albeit limited experience with carvedilol in cats, has not recognized clear clinical benefit of carvedilol over atenolol.
CAR DIOMYOPATHY AND CONGESTIVE HEART FAILURE

Angiotensin-Converting Enzyme Inhibitors - Angiotensin-converting enzyme (ACE) inhibitors are commonly used in the management of CHF. Interfering with the action of the renin angiotensin system leads to diminished plasma levels of angiotensin II and reduced stimulation of aldosterone. As a result, fluid retention and vasoconstriction are blunted. Newer information documents the benefit of ACE inhibition with respect to altering the progressive cardiac enlargement and remodeling known to attend most forms of heart failure. This effect on cardiac remodeling seems to be mediated (at least in part) via an increase in bradykinin. The beneficial effects of ACE inhibition likely result from both the vasodilation and the drug’s effects to reduce cardiac remodeling. If the progressive ventricular enlargement and progressive replacement of myocytes with non-distensible fibrous tissue can be avoided, survival might be prolonged, and symptoms of heart failure can be reduced.

Angiotensin-converting enzyme inhibitors have proved to be useful in a variety of settings. In a large number of human heart failure trials, ACE inhibitors have been proven to prolong survival. In addition, these drugs have been documented to slow the progressive cardiac enlargement, and delay the onset of CHF in humans with left ventricular dysfunction. In well designed canine heart failure trials, ACE inhibitors resulted in improved clinical signs and a prolonged the time until an animal dropped out of the study (equivalent to improved survival). 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. Which cats should be treated with ACE inhibitors? Most veterinary cardiologists would agree that ACE inhibitors are probably effective in cats with congestive heart failure due to a variety of underlying cardiac disorders including various forms of cardiomyopathy, congenital heart diseases associated with volume overload, and other forms of left-sided or biventricular congestive heart failure. There is also general agreement that ACE inhibitors are useful in the management of systemic hypertension, especially in cases where blood pressure remains elevated despite amloidipine and in cats with hypertension due to renal disease that is associated with even modest proteinuria. There is less agreement about the use of ACE inhibitors in cats with hypertrophic cardiomyopathy but there is increasing evidence that ACE inhibitors should be used in cats with HCM once CHF develops, and many veterinary cardiologists with prescribe an ACE inhibitor in cats with HCM and marked left atrial enlargement, even if signs of CHF have not yet developed. The role of ACE inhibitors in the treatment of animals with asymptomatic heart disease remains a hotly debated topic, and in the authors opinion the smaller the left atrium the less likely it is that and ACE inhibitor will result in clear clinical benefit.

Furosemide (Lasix) - It has been documented that asymptomatic heart disease is usually not associated with measurable activation of certain neuroendocrine systems, however, these neuroendocrine responses are stimulated following therapy with a diuretic. This stimulation of the neuroendocrine system is counterproductive, especially if one is to believe the prevailing attitudes regarding the progression of heart failure. Many cardiologists would now not recommend single agent use of furosemide for treatment of CHF. This does not mean that appropriate diuretics should not be used when congestion develops! Still, it is quite difficult to define the exact dose of diuretic required by any individual dog or 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 electrolyte disturbance, dehydration and the development of pre-renal azotemia. The combined use of ACE inhibitors and diuretics compromises one of the kidneys’ normal compensatory mechanisms (vasoconstriction of the efferent arteriole) and can lead to elevation of BUN and creatinine when 1) excessive diuretic dose is initiated or 2) significant pre-existing renal disease is present. Since most cardiologists now concurrently use ACE inhibitors and diuretics for animals with CHF, the risk of pre-renal azotemia with excessive doses of furosemide is quite real.

One approach is to use the lowest possible dose of furosemide which with 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. In most instances, canine patients are given less than 2 mg/kg q 12 h, and in most cats I initially try to use 6.25 mg/cat/day for chronic therapy. Some cats require higher doses of furosemide, but many cats that have experienced sudden onset pulmonary edema can be treated chronically with 6.25 mg/cat every other day. Cats with pleural effusion which was advanced enough to require thoracentesis often require more furosemide, and in most cases twice a day treatment will be required. When a dose of 2.2 mg/kg twice a day is exceeded during chronic therapy, the author usually thinks that diuretic resistance has been reached and may undertake one of several options to combat this complication. Many cats will not tolerate spironolactone alone or a combination hydrochlorothiazide
with spironolactone at doses that are usually recommended, but starting at 6.25 mg once a day for a week, and then increasing to twice a day can be tolerated by at least some cats. Alternatively, going to a higher dose of ACE inhibitor, reviewing dietary sodium intake, taking away the beta-blocker, or adding in pimobendan can be alternatives to going to higher and higher doses of furosemide.

**Pimobendan** – Pimobendan is a calcium sensitizing drug that is useful as a positive inotrope. In addition to this positive inotropic effect, pimobendan is a phosphodiesterase inhibitor with vasodilating effects. This combined action of positive inotropism and vasodilation has been referred to as inodilation. Pimobendan has been well studied in dogs with chronic valvular disease and in dogs with dilated cardiomyopathy. In dogs with dilated cardiomyopathy, especially in Doberman pinschers, there seems to be both anecdotal benefit and scientific evidence for improvement in clinical signs, improvement in well being, and an improved outcome after congestive heart failure has developed. Many authors indicate that there is a profound clinical benefit to addition of pimobendan to routinely used background therapies (ACE inhibitors and diuretics) for heart failure. In most veterinary studies of dogs with congestive heart failure that require diuretics, pimobendan treated dogs have fared as well or better than dogs treated with ACE inhibitors. Pimobendan also seems to be associated with a low side effect profile in dogs. The usual dose for pimobendan is 0.25 mg/kg q 12 hours in dogs. Several questions remain regarding pimobendan. Should it be used in dogs with or without an ACE inhibitor? A survey at a recent international meeting of veterinary cardiologists found that more than 50% used the 3 drug combination of pimobendan, furosemide, and an ACE inhibitor for management of congestive heart failure in dogs. Should pimobendan be used before the onset of congestive heart failure? The drug has only been studied in animals with active CHF, and the role for this drug in pre-CHF situations is unclear. Some reports in dogs with mitral regurgitation due to chronic valvular disease have indicated possible adverse effects of left ventricular hypertrophy an increasing mitral regurgitation at higher doses, and currently the author is withholding pimobendan until CHF is present or at least some signs of cardiac disease (eg, cough due to a markedly enlarged left atrium) are evident. For the purposes of this talk, one would be particularly interested in whether pimobendan has a role to play in the management of congestive heart failure in cats. This question has the least amount of information with which to form an answer. Many cats with congestive heart failure have hypertrophic cardiomyopathy, and at least a proportion of these cats have hypertrophy at the top of the interventricular septum which can obstruct the flow of blood through the left ventricular outflow tract (e.g., systolic anterior motion of the mitral valve and increased aortic outflow tract velocity). Most cardiologists have been concerned that drugs that increase inotropic state and drugs that act as vasodilators might worsen this physiologic problem, and therefore drugs like pimobendan might not be advisable. There is no evidence to support use of pimobendan in cats before the onset of congestive heart failure. There is at least one abstract 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 fractional shortening, 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. 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 there has been a deterioration in renal function (and creatinine > 2.5-3 mg/dl) following initiation of an ACE inhibitor.

**PREVENTION OF ARTERIAL THROMBOEMBOLISM**

Arterial thromboembolism (ATE) is a common complication of feline heart disease, occurring in 30-40% 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. Three factors are thought to contribute to thrombus formation: altered coagulability, altered blood flow, and endothelial damage. Cats with cardiomyopathy often have dilatation of the left atrium, and stasis of blood within the enlarged left atrium likely contributes to thrombus formation. Since the treatment of arterial thromboembolism is very difficult and often unsuccessful, prevention of this devastating event becomes very important.

**Dalteparin and Enoxaparin** – Unfractionated heparin is a very familiar drug to most veterinarians, and this drug is commonly used to prevent further enlargement of a thrombus in cats with active ATE. While several doses of heparin have been proposed in this setting, and the author's opinion is that heparin should be used at high doses (275-350 IU/kg q 6-8 hours) for active ATE. However, the long term use of unfractionated heparin is not usually advisable due to the need for frequent administration and the number of side effects that can
develop with chronic use. However, 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 once or (ideally) twice a day. One major action is to inactivate clotting factor Xa and is used as a preventative for ATE or PTE. Recent research has suggested that the high dose administered at least twice a day might be desirable when using surrogate endpoints to evaluate efficacy (rather than clinical endpoints). 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 authors first choice for prevention of ATE in cats.

**Clopidogrel** – A new antiplatelet drug, clopidogrel (Plavix), has been added to the armamentarium of drugs used to prevent thromboembolic disease. This drug reduces platelet activation, reduces platelet degranulation, and inhibits modification of glycoprotein IIb/IIIa receptor which leads to reduced aggregation. This is an antiplatelet drug from the thienopyridine family. Clopidogrel seems to be well tolerated in many cats, although foaming at the mouth or vomiting has been seen in some cats. Compounding the drug may reduce this side effect for some 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 clopidogrel 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 _ of a tablet orally once a day.

**References:**


