AN APPROACH TO ASYMPTOMATIC ACQUIRED HEART DISEASE IN DOGS AND CATS

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Cardiovascular diseases in dogs and cats produce devastating consequences in those severely affected. Newer diagnostic methods allow earlier and more comprehensive evaluations of patients with heart disease. Frequently the diagnosis is made before clinical signs are evident—obviously the best time for medical or surgical intervention, when possible. Acquired diseases for which early intervention has been proven or would seem likely to be beneficial include dirofilariasis, mitral regurgitation (MMVD, MR, endocardiosis), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), hypertension, endocarditis, and some cases of pericardial effusion. This brief manuscript will include a discussion of only the most commonly encountered canine and feline diseases, MMVD, DCM and HCM.

This author does not generally employ diuretics and salt-restriction prior to the onset of (CHF). Potential exceptions to this stance might include diuretics in the management of coexistent hypertension and the use of spironolactone as an aldosterone receptor blocker. Similarly, salt restriction, which is useful after the onset of CHF, is not employed prior to its appearance. Again, an exception is in the hypertensive patient. In addition, mild salt restriction, in the form of avoidance of salty treats is probably never contraindicated and the pet’s palate may likewise be retrained by mild restriction in anticipation of the need for future sodium restriction. With the exception of patients in atrial fibrillation, digoxin is likewise reserved for patients in heart failure. The role of exercise restriction is not well established. It is known that controlled exercise improves muscle strength and cardiac function in humans in CHF, but may also induce or aggravate arrhythmias. I do not restrict exercise in heart patients prior to the advent of CHF unless the precipitation of life-threatening arrhythmias or syncope is of concern.

Mitral Regurgitation

Mitral regurgitation, often recognized during mid-life, affords the veterinarian with the somewhat unique opportunity of a long symptom-free window for potential intervention. Since the ideal treatment, surgical correction, is available to a limited number of clients, medical intervention remains the only hope for most clients with dogs suffering from MMVD. Potential and readily available interventions include angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, afterload reducing agents, inodilators and spironolactone.

There are not data on beta-blockers in experimental MMVD indicating hemodynamic and remodeling benefit. Additionally, there are clear data indicating quality of life and survival benefit in humans with CHF, treated with beta-blockers. Unfortunately, dosing these agents is somewhat difficult in small dogs and this author has yet to routinely embrace this group of agents (carvedilol, atenolol, and metoprolol) in this setting, either before or after the onset of CHF. This stance was strengthened by the failure of bisoprolol to slow progression of MMVD in asymptomatic dogs in an (unpublished) placebo-controlled, double-blind trial.

ACE inhibitors have received the majority of attention in asymptomatic MMVD. There are studies which support and refute the activation of the RAAS prior to CHF in MMVD, leaving the question to be answered by clinical trials. Two studies have prospectively evaluated enalapril in dogs with
MMVD, prior to the onset of heart failure. The first (SVEP) was carried out in Northern Europe in Cavalier King Charles Spaniels. This well-designed double-blind, placebo-controlled (DBPC) study was unable to demonstrate a benefit in time to onset of CHF when the drug was compared to placebo in mildly to moderately affected Cavalier King Charles Spaniels. The second (VETPROOF), a DBPC trial carried out in the U.S., has recently been completed (to both CHF and death as end-points). This study showed benefits in time remaining in study, number of dogs CHF-free at 500 days and study termination. The Kaplan-Meier “Survival” Curves demonstrate a strong, but not statistically significant, trend toward a modest increase in time to onset of heart failure. Both studies demonstrated the safety of enalapril in aged dogs with compensated heart disease. A recent survey of 100 ACVIM-board-certified cardiologists showed that 70% believed that ACE-Inhibitors were useful in asymptomatic MMVD and while the ACVIM Consensus Panel on MMVD failed to reach 100% consensus on its use in this arena, the majority of panelists believed it to be useful.

This author offers ACE-I therapy to dogs with asymptomatic MMVD and radiographic and/or echocardiographic evidence of remodeling (VHS > 11; LA:Ao > 1.6). Reasons for this approach include the proven hemodynamic improvement in human MMVD, the results of the VETPROOF, the strong safety record, and potential for benefit in reducing mitral regurgitation and in blunting remodeling initiated by the RAAS. Careful scrutiny of renal function, blood pressure, and serum potassium concentration is provided initially and periodically during therapy. In addition, the owner is advised as to cost, the potential for lifetime administration, the risk of hypotension, and the varied results of clinical trials.

Aldosterone-receptor-blockers, such as spironolactone and eplerinone have revolutionized the treatment of heart failure in man (RALES, EPHESUS, & EMPHASIS studies), as an adjunct to ACE inhibition as “aldosterone breakthrough” (ABT) has been recognized in humans receiving chronic ACE inhibition. This has been shown in the authors' laboratory in dogs challenged with furosemide and receiving ACE inhibitors (ACEI) very early in the course of the experiment. In addition, using urine aldosterone measurements, 30-40% of clinical cases receiving either enalapril or benazepril experienced ABT, regardless of clinical status (pre-, acute, or chronic heart failure). Interestingly, 2 publications have failed to show diuretic efficacy with spironolactone alone and in conjunction with furosemide in normal dogs. However, a relatively recent publication of a placebo-controlled, double-blind trial of standard therapy with either placebo or spironolactone demonstrated survival benefit in dogs with heart failure due to MMVD, using 2 mg/kg daily. This author now begins spironolactone whenever an ACEI is initiated.

Conventional vasodilator therapy has been largely replaced with the advent of ACE inhibitors but venodilators play a role in emergency management of CHF and afterload-reducing arteriolar dilators agents are often employed to unload the heart, reducing mitral regurgitation. There is certainly evidence to show that arteriolar vasodilators, such as hydralazine and amlodipine, can reduce mitral regurgitation. Unfortunately, these drugs activate the RAAS and may increase resting heart rate as well. If used chronically prior to the onset of CHF, their use should be accompanied by concurrent ACE inhibition or angiotensin receptor blockade.

While pimobendan, the inodilator, has been proven to be useful in the treatment of dogs with CHF due to MMVD, there has been controversy regarding its use prior to the onset of heart failure. However, the very recently published EPIC, a double-blind, placebo-controlled trial, showed significant improvement in the time to development of heart failure or sudden death in dogs with ACVIM Stage B2 MMVD. This will likely become standard of care for asymptomatic MMVD.

In summary, while each of these drug groups has theoretical utility in this setting, heretofore, there has not been strong evidence for any. While a combination of 2 or even 3 of these drugs has appeal, the risk is hypotension and its attendant undesirable sequelae. The use of pimobendan not only adds its primary benefit in delaying onset of heart failure, but also will lessen the incidence of hypotension in polypharmacy by its inotropic action. In most cases, however, I begin an ACE-inhibitor.
and pimobendan after there is radiographic or echocardiographic evidence of remodeling. The owner is involved in the decision and is educated as to the variable proof of efficacy, cost, risks, and that the drugs will likely be given for life. Enalapril is initiated at .25-.5 mg/kg after renal function, blood pressure, and serum electrolytes are evaluated. In approximately one week the dosage is increased to the target dosage of .5-1 mg/kg either QD or divided BID. Renal parameters, serum electrolytes, and ideally systemic blood pressure are rechecked in 2-3 weeks and then as often as clinically indicated thereafter. In addition, I now add spironolactone at 2 mg/kg sid. In Europe there is now a combination product with benazepril and spironolactone which has proven to improve compliance and is certainly more convenient. The exact role for pimobendan is still being determined. It is safe and data show it to be effective in this setting. Ideally, all 3 compounds are started approximately together, but pimobendan is sometimes delayed if financial concerns exist.

**Dilated Cardiomyopathy**

DCM in dogs is a much more devastating disease than MMVD and is more often diagnosed after the onset of CHF. Nevertheless, DCM may be diagnosed prior to CHF, via echocardiography, after detection of a cardiac gallop or murmur or through routine screening in certain breeds. It seems clear that beta-blockers, administered early, are beneficial in this disease in humans; anecdotal reports suggest a similar benefit in dogs. ACE-inhibitors have been shown to provide benefit in humans with DCM or ischemic cardiomyopathy prior to heart failure. O’Grady, in a retrospective study, showed that Doberman pinschers with occult DCM lived longer (substantially so) when they received ACE-I, as compared to the control population which did not. Aldosterone-receptor-blockers, such as spironolactone (0.5 mg/kg bid) or eplerinone have the same theoretical benefit in DCM as in MMVD. Pimobendan has improved survival and quality of life in Doberman pinschers with DCM and CHF and may have a future role prior to CHF. Carnitine and taurine have potential benefits in dogs deficient in these nutrients and may be instituted either alone or together, with or without having measured serum concentrations. Carnitine is provided as a treatment option for asymptomatic DCM, particularly in boxers, while taurine and carnitine are administered to all American cocker spaniels with DCM. Pimobendan, the inodilator, has been proven to be useful in the treatment of Doberman pinschers CHF due to DCM, and more recently, in the PROTECT, a double-blind, placebo-controlled trial, asymptomatic Doberman pinschers with DCM received benefit.

In the clinic at NCSU, asymptomatic DCM would most typically be treated with avoidance of heavily-salted foods, possibly taurine and/or carnitine (depending on the breed and input from the owner), an ACE-Inhibitor (Enalapril at .5-1 mg/kg daily, starting at .25-.5 and increasing to the target dosage in 1 week), pimobendan (0.25 mg/kg bid), and spironolactone (2mg/kg sid). If atrial fibrillation is present, digoxin (and diltiazem, if needed) are added, to control the ventricular response (<120 bpm, ideally) within 72-96 hours. After approximately 2 weeks carvedilol or atenolol is added (for a large-breed dog, 3.125 mg QD x 2 weeks, then bid x 2 weeks, then 6.25/3.125 mg x 2 weeks, etc) until a full dose of 25-50 mg daily, divided BID, is achieved or the patient shows signs of intolerance. If intolerance develops (usually lassitude, inappetance, and hypotension), the dosage is dropped to the last tolerated dosage for 2-4 weeks and then an attempt is made to increase as previously described. If the patient cannot tolerate increases in carvedilol, the last tolerated dosage is accepted as maximum. Human studies indicate that, though lessened, sub-optimal dosages still provide benefit. Pimobendan is helpful in instances of beta-blocker intolerance through inotropic and vasodilatory support.
**Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy typically affects cats of middle age (6.5 years on average). Most are affected with a murmur or gallop, but a significant number (22% of 260 cats) with heart failure, described by Rush, et al. had neither. This suggests that clinical indicators, prior to onset of signs, are often absent, minimizing the chance of intervention.

Drugs that enhance ventricular relaxation and slow the heart include the beta adrenergic (atenolol), and calcium channel (diltiazem) blockers are indicated in treatment of the diastolic dysfunction of HCM. Beta blockers improve diastolic performance only indirectly, enhancing ventricular filling by reducing heart rate and improving myocardial perfusion. Traditionally, beta-blockers have been administered orally to reduce and prevent elevations in LVEDP, to lower systolic pressure gradients and myocardial oxygen requirements, to prevent stress-induced tachycardia and reduce resting heart rate, and for their antiarrhythmic effects. When arrhythmias are present, this drug may be initiated earlier in the disease course. This is the author’s treatment of choice for asymptomatic HCM, for cats with documented outflow obstruction (HOCM), and when tachycardia is noted.

Calcium channel blocking agents have been effective in human HCM by reducing heart rate, myocardial oxygen consumption, and diastolic dysfunction. In addition to directly enhancing myocardial relaxation, these drugs dilate peripheral and coronary arteries. Bright has demonstrated the utility of diltiazem (3-7.5 mg po tid) in the treatment of symptomatic feline HCM, including those cases refractory to the beta-blocker, propranolol. Unfortunately, current packaging for human use, makes accurate feline dosing of diltiazem difficult. Long-acting diltiazem may be substituted and includes Cardizem CD (45 PO qd; requires disassembling capsules) or Dilacor (30 mg PO bid; requires disassembling capsules). Combining a calcium channel blocker and a beta blocker has theoretical advantages and is often done, using a long-acting form of each drug, one in the morning and one in the evening. There is no role for amlodipine in the normotensive cat with HCM as it has no theoretical or proven benefit and it may precipitate hypotension. This author does not use diltiazem in HCM prior to the onset of heart failure.

A report by Rush, et al. demonstrated a reduction in wall thickness with the administration of enalapril to cats with HCM. This suggests a potential role for ACE-inhibitors in the treatment of HCM. These drugs are generally safe and do play a role in some symptomatic cats. While it is logical that the renin-angiotensin-aldosterone system is not pathologically activated in asymptomatic patients, and hence ACE-inhibitors might not be useful, Rush’s data argue otherwise. In a double-blind, placebo-controlled study, MacDonald, et al. evaluated the role of the ACE-inhibitor, ramipril (12 months therapy), in asymptomatic HCM in Maine Coon cats and found no benefits in terms of diastolic function, myocardial mass, or suppression of aldosterone or BNP levels. This author does not use ACE-Inhibitors in asymptomatic HCM unless there is evidence of myocardial damage (infarctions) for which this drug group has shown to be efficacious in man.

Other therapies, including, aspirin or low molecular weight heparin, home confinement, and moderate salt restriction should be instituted as needed. Taurine supplementation is not indicated in the treatment of HCM. In asymptomatic cats with HCM, the author advises home confinement, moderate salt restriction, Beta- and/or calcium channel blockade, and aspirin (with left atrial enlargement) indefinitely. If left atrial enlargement is severe (>2.4 cm), if clots or spontaneous left atrial echo (“smoke”) are noted, or with a history of systemic thromboemboli, low molecular weight heparin (dalteparin, Fragmin) is administered at 100 units/kg SQ qd.

**Additional Reading – Dog**


Additional Reading – Cat