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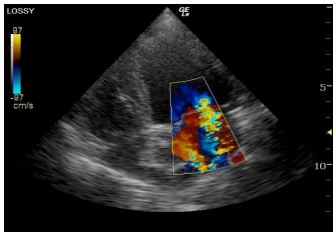
APRIL 2013

VALVULAR DISEASE & CONSENSUS - 5 PAGES



Mitral valve disease (MVD): Myxomatous valvular degeneration refers to sterile degenerative disease that affects middle-aged and older dogs. Mitral valve apparatus includes left ventricular papillary muscles, chordae tendinae, valvular annulus, and anterior and posterior leaflets. The anterior leaflet is continuous with the aortic outflow tract.

Accumulation of mucopolyssacharides within the spongiosa and fibrosa layers of the leaflets creates a vegetative nodular appearance. This vegetative pathology may also have bacteremia as a contributing cause due to dental disease or any other source of bacterial pervasion. Lengthening of chordae tendinae occurs secondarily to excessive turbulent forces that occur. Chondrodystrophic breeds are over represented and concurrently have collapsing trachea and intervertebral disc disease. The Cavalier King Charles Spaniel is the prototype for this phenomenon developing MVD (mitral valve disease) at an early age. MVD prevalence can be as high as 33% in toy breeds >10 years of age and is the most common cardiac disease (75-80%) in the dog. Recently, Borgarelli et.al. (ACVIM 2005/2006) reported MVD in a large population of German shepherd dogs that demonstrated a more rapid progression of the disease compared to other breeds

Distortion of the mitral valve leaflets prevents normal cooptation resulting in regurgitive flow of the stroke volume into the left atrium. Lengthening and rupture of the chordae can lead to leaflet **prolapse** (impingement into the atrium), eventual **flail** leaflet (inversion into the atrium) and further progression of this phenomenon. Often chordae rupture occurs suddenly leading to rapid onset of congestive heart failure (CHF) not allowing the myocardium adequate time to hypertrophy and compensate for the defect. Small defects, on the other hand, can be well tolerated if progressive in time. The result is volume overload of the left atrium and left ventricle leading to eccentric hypertrophy (hypertrophy + dilation). Eccentric hypertrophy leads to dilation of the mitral annulus further complicating the myocardial LA and LV stretch. Myocardial oxygen deprivation due to poor coronary perfusion (stretch and catecholamine stimulation) leads to myocardial cell death, replacement fibrosis, and myocardial dysfunction. This pathological progression is known as “overload cardiomyopathy.”

Progressive cough is the most common **sign** due to left sided volume overload, consequent pulmonary edema and LA bulge at the left main stem bronchus. *Respiratory distress* ensues gradually in chronic cases or rapidly in cases of primary chordae rupture. ***Exercise intolerance, syncope, ascites, weight loss, and anorexia*** are also commonly observed. Physical exam reveals audible turbulent flow (murmur) best heard over the left cardiac apex. The murmur audibility and length into systole typically corresponds to the degree of mitral regurgitation but not necessarily to the severity of the cardiac status. Concurrent

systemic hypertension may induce progression of the disease necessitating systemic blood pressure measurements during medical management.

A challenging situation occurs when the practitioner must distinguish the origin of a cough to be **respiratory** (tracheal collapse, chronic bronchitis, COPD) **or cardiac** (pulm. edema, mainstem bronchus pressure). A cough history of months or years, normal to high body scores, and normal heart rates with sinus arrhythmia tend to support chronic airway disease. While MVD tends to be progressive in nature, body scores tend to be low and heart rates tend to elevate with possible pathological arrhythmias present. However, both diseases can be present simultaneously and advanced diagnostics such as **ultrasound** examination will be necessary to distinguish the culprit of the clinical symptoms.

NT-proBNP levels (Idexx labs) may aid in differentiating causes of dyspnea as being respiratory or cardiac in origin. B- type natriuretic peptide is released from the heart when ventricular filling pressure is increased. ProBNP is cleaved into NT-proBNP (inactive molecule) and BNP in a 1:1 ratio. NT-proBNP is a cardiac biomarker which can aid in the differentiation of heart disease and respiratory disease in dyspneic patients and can also provide added information for early detection of cardiac disease in subclinical patients (especially high risk breeds such as Cavalier King Charles Spaniels, Cocker Spaniels, Dobermans, Boxers). In the future, we may be able to use it to monitor therapy or determine prognosis but this has not yet been fully determined or at least reported in the current literature.

Blood is collected into a lavender top tube (EDTA) and the sample is spun immediately. Plasma is separated into a special pink top tube obtained from Idexx which contains a protein stabilizer and submitted to the laboratory.

Values (from Idexx website):

<900 pmol/L– normal, significant heart disease is unlikely

900-1800 pmol/L– elevated – heart disease and/or CHF may be present – consider work up if clinically applicable

1800-2700 pmol/L – elevated and consistent with cardiac disease and/or CHF. Recommend cardiac work up.

>2700 pmol/L – significantly elevated. CHF is likely. If dyspneic – would be consistent with CHF rather than primary respiratory disease. Advise thorough cardiac work up.

Radiographic findings may reveal a vertical or bulging caudal cardiac waist, hilar edema, general cardiomegaly, elevation of the left mainstem bronchus, and right-sided enlargement in advanced cases with pulmonary hypertension or tricuspid disease.

Echocardiograhic findings allow the practioner to precisely assess cardiac function under the weight of the pathology in order to assess the myocardial response at the time of exam and quantify that response as precise therapy is utilized over time.

General treatment options: A consensus panel comprised of many respected cardiologists have presented at ACVIM several times with future plans to publish a consensus statement in JVIM. The following is a summary from the panel discussion at ACVIM June 2009 Montreal, QC Canada.

Stage A – high risk of cardiac disease – no clinical signs

No medical therapy (consensus achieved), no dietary therapy

Stage B – heart disease is present

B1 –murmur no chamber enlargement

B2 – murmur with left atrial and left ventricular enlargement but asymptomatic

Treatment for B1 – no medical therapy, recheck radiographs and echocardiogram in one year (earlier if in large breed dog which may progress faster) (consensus achieved)

Treatment for B2 – no consensus achieved: some advise starting ACEI such as **enalapril** at 0.5 mg/kg SID/BID or **benazepril** 0.25-0.5 mg/kg SID (more renal friendly and a true Sid ace inhibitor) as an afterload reducer in cases with marked left heart enlargement or for those with progressive disease. A minority of cardiologists did not advise any medical treatment. No consensus on usage of beta-blockers at this stage (used by some but clinical studies are still underway, thus not being advised at this point). No consensus but can consider mild sodium restriction

Stage C – Past or current clinical signs of heart failure

Treatment Acute CHF (consensus achieved)

1) Lasix 2 mg/kg IV or IM hourly until the RR decreases or a total of 8 mg/kg total dose or constant rate infusion 1 mg/kg/hr for life threatening pulmonary edema.

2) Pimobendan 0.25-0.3 mg/kg PO BID (use in acute phase as well as chronic therapy)

3) Oxygen

4) ACEI – used by majority of panelists – enalapril 0.5 mg /kg PO BID

Stage D – end stage disease refractory to standard therapy of diuretics, ACEI and pimobendan

5) Abdominocentesis when applicable to decrease discomfort if causing respiratory distress

6) Sedation – anti-anxiety

7) Sodium nitroprusside/ dobutamine (in critical care facilities)

8) Nitroglycerin no consensus – ½ inch 12 hours on and 12 hours off

Stage C Chronic therapy (consensus achieved)

1) Lasix 2 mg/kg PO BID – can increase incrementally as needed
2) ACEI enalapril 0.5 mg /kg PO BID (measure creatinine and electrolytes in 3-7 days)
3) Pimobendan 0.25-0.3 mg/kg PO BID
4) Spironolactone 0.25-2 mg/kg PO BID – no consensus but used by majority
5) No consensus on beta blockers (some animals will have been on previously and may continue at lower dose, do not start beta blockers at this phase), digoxin, theophylline, cough suppressants which may be needed in specific cases
6) No consensus on sodium restriction – it's more important that the dog eat.

We also advise monitoring BUN, creatinine, electrolytes and urine specific gravity +/- blood pressure measurement are necessary at 5-7 days. A repeat ECG is warranted if arrhythmia was present at the original exam (anti-arrhythmicc may be necessary), as well as a general cardiac exam (heart rate <170 small breeds; < 140 medium breeds; < 120 large breeds) with attention paid toward possible onset of hypotension. **Hycodan** syrup at 0.2-0.3 mg/kg sedated is recommended for cough control particularly 1 hour before bedtime at a high-end dose to allow for optimal sleep patterns both for the patient and the client. A mildly restricted salt, optimized **high quality protein diet** (4gm/100kcal) should be considered to avoid wasting and minimize the onset of sodium induced volume overloads. **Fatty acid supplementation** has been suggested for cell membrane stabilization and to combat low blood levels I CHF dogs (40 mg/kg/day EPA). **Digoxin** may be necessary if supraventricular tachycardia or atrial fibrillation is present. Suggested dose in dogs is 0.005-0.008 mg/kg bid (0.125 mg/0.25mg tabs; 0.05 mg/ml and 0.15mg/ml elixir). Target serum of 1-1.4 ng/ml 8-10 hrs post pill > 5 days post therapy. ***Avoid in cases of liver disease***. The inotropic property of this drug is considered relatively weak compared to Pimobendan. Diltiazem is an alternative anti-arrhythmic used for supraventricular tachycardia or atrial fibrillation at a target dose of 2 mg/kg PO TID – using an up titrating regime starting at 0.5 mg/kg PO TID and gradually weaning the dose upwards to the target dose. Often digoxin and diltiazem are used together if necessary to achieve control of the arrhythmia.

Morphine: In dogs 0.025-0.05 mg/kg IV decreases anxiety and improves respiratory efficiency and O2 consumption. Morphine also dilates splanchnic vasculature/venous capacitance and, hence, reduces pulmonary edema.

Supporting studies:

Atkins et al. has demonstrated a delay in CHF onset of 3-4 months in the **VETPROOF enalapril** trial for mitral insufficiency cases with left atrial enlargement. ***Average elapsed time to CHF*** *(defined as radiographic evidence of pulmonary edema)* ***was 474 days*** from the time of MVI + LAE diagnosis by ultrasound assessment. The utilized dose was 0.5 mg/kg as opposed to the SVEP trial at 0.34 mg/kg that had previously discounted enalopril's effectiveness in this regard. Enalapril was initiated when the echo parameter of la/ao > 1.6 whether or not the patient presented with signs. Strongest indicator of a poor outcome in this study was severe left atrial enlargement on radiographs and echo assessment. The median time of survival from entry into the study (and enalapril treatment) and progression to heart failure was 2.5 years.. Median time from heart failure to death was approximately 10 months. Pimobendan was not utilized in these cases.

European colleagues and American cardiologists have been utilizing **Pimobendan** (**PB**) for treatment of DCM at echo diagnosis and MVI +LAE cases over the last 4-5 years (Europe) with dramatic success. O'grady and Gordon et al. have demonstrated dramatic results as a "rescue" drug when traditional CHF treatment (diuretics, enacard, digoxin) begins to fail. European colleagues have been starting directly on Pimobendan at DCM diagnosis via ultrasound or with MVI + LAE. Pimobendan is a phosphodiesterase (PDE) III inhibitor with calcium sensitizing properties. It therefore is a vasodilator and a positive inotrope replacing or as a synergist with traditional enalapril/digoxin therapy. The calcium sensitizing activity increases contractility without myocardial energy expenditure. Profound improvements have been noted in nearly every case with respect to attitude and activity levels within 24 hrs. Reports of atrial fibrillation have been reported. A recent study (Rosenthal et. al

ACVIM 2006) demonstrated an increased ventricular arrhythmogenic activity associated with Pimobendan as well. Therefore, baseline ECG and initial post therapy ECGs should be performed until further track record can be established.

At **ACVIM 2004** results from the **PiTCH** study revealed Pimobendan to be a "cleaner" inotrope than digoxin as a calcium sensitizer that also functions regardless of degree of myocardial remodeling. It simply renders the functional myocardium more efficient. PB reduces heart rate and therefore improves the rate/pressure product. Moreover, PB reduces regurgitant fraction and chamber-dilating after load. It was also noted that the PCV often improves in patients with chronic anemia due to cardiac disease given the increased bone marrow perfusion. ***PB is best absorbed on an empty stomach*** and, therefore is useful in anorexic patients in hospital. This enables rapid clinical improvement including indirectly reestablishing appetite due to better overall clinical improvement. As of now, studies have shown that PB is indicated in class 3A or 3B CHF due to AV valvular disease. Comparison between traditionally treated CHF groups and PB groups shows that the PB group dropped the RHR from 140-112, RR from 54-38, and showed a 10% reduction in arrhythmias. In addition, the PB group demonstrated a 75% lower mortality rate. MST of the traditional group was 3.5 months from Dx of CHF. While the PB+traditional TX group lived often beyond 15 months frequently living long enough to expire from other causes. PB treated CHF patients tend to eat better and require less hospital time given that fast absorption on an empty stomach is key in anorexic hospitalized patients.

In addition, a synergistic effect was found between PB and spironolactone, similar that of enalapril and other current cardiac medications. The dose is **0.25-0.3 mg/kg BID**. Cost is approximately 70$/month through Internet sources.

A recent study (Roland et al ACVIM 2006) suggests that Pimobendan is safe and effective in improving overall cardiomegaly and LV internal overload in valvular insufficiency CHF patients that are currently being administered diuretics and ace inhibitors. Positive effects are seen within 24-48 hours

Our team advocates the use of PB in Stage C dogs with evidence of congestive heart failure (lasix dependent heart disease, also treated with ACEi). Triple therapy (Lasix, enalapril and Pimobendan) is now considered to be the standard of care when treating heart failure in the dog due to CVD (and DCM). Treatment is preferably based on echocardiogram results to ensure that left sided CHF is truly present as opposed to other cardiomegalic states where PB would be vehemently contraindicated, such as subaortic stenosis or pulmonic stenosis for example.

Sprionolactone: Bobinnec (2011) et al suggest spiro use in non symptomatic patients based on these arguments: 1) results from human cardiology, 2) In asymptomatic stages, there is no increased level of aldosterone EXCEPT in case of feeding with a low sodium diet or in case of left ventricular dilation, 3) ACE Inhibitors failed in this indication, and also seem to be inefficient to control in increasing aldosterone levels.

Carvedilol (CVD)(Coreg, Smithkline Beecham) which has calcium channel blocking activity and is a class I antiarrhythmic, a positive inotrope, a free radical scavenger and has ace inhibiting effects is also another therapeutic option. CVD is a third generation B1 and A1 blocker with mild B2 blocking effects. CVD is also an antioxidant raises the fibrillation threshold preventing arrhythmic activity. This drug inhibits myocardial remodeling antagonizing renin/angiotensin stimulation and increases renal blood flow and urine output. Up regulation of beta receptors, increased myocardial O2 supply, blockage of damaging neurohormone activity (BNP and ANP), and inhibition of toxic effects of doxorubicin are more of its attributes. Carvedilol is a *B*1, Alpha 1 blocker with mild *B*2 blocking effects. **Potent vasodilatation**, however, allows for its main side effect of hypotension and, therefore must be introduced gradually with careful blood pressure monitoring during its administration. Oyama's trial on 8 DCM cases suggest a **titrating dose** of 0.05mg/kg bid increasing to 0.1, 0.2, and 0.3 mg/kg weekly over a 4 week period without evident side effects. Gordon et al. suggests a general dose is 0.2-1.6 mg/kg BID. This dose is achieved after up titration from 0.25-0.6 mg/kg to target 1 mg/kg eventually. Adjustments are made every 2 weeks to reach ideal dose. **Target blood levels are 40-100 ng/ml** 2 hours post pill with a clinical response of 50% reduction in HR. Carvedilol can be utilized with enacard and spironolactone. Gordon recommends its usage with moderate volume overload in **AV valvular cases** when echo parameters demonstrate and LA/AO ratio of 1.3-1.6.

Cost of compounded formulation is approximately **22-50$/month**. Weekly blood pressure and heart rates need to be evaluated to avoid excessive bradycardia (<*80bpm*) and hypotension (<*110mmHG* systolic). Extensive human trials demonstrate a decreased mortality of 65-73%. Carvedilol should not be administered in patients with compromised liver function, bradycardia,

and hypotension. Gordon and Miller's study at ACVIM 2004 demonstrated a significant increase in lifespan for MVD cases with these criteria demonstrating the usefulness of Beta blockade in remodeling heart disease. Carvedilol (or other similar beta-blockers) may prove to become the ideal drug to halt the progression of class2/3 MVD and DCM. As stated above, there is no consensus on the usage of beta-blockers and they are not introduced once congestive heart failure is present

The preceding is a summary of material obtained from, but not exclusive to, ACVIM 2001, 2002, 2006, 2008, 2009, 2011

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