Current Recommendations for Treating Dogs with Degenerative Valve Disease

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Degenerative valve disease (DVD) is the most common form of heart disease in the dog. It's common presence in small breed dogs, particularly the cavalier King Charles spaniel, toy and miniature poodle, Bichon frise, etc. suggests a genetic predisposition in some breeds, however a specific genetic mutation has not yet been identified. The ACVIM consensus statement offers a simple classification system for dogs with acquired valve disease that is helpful for prognostic and therapeutic planning.

Stage A- dog is not clinically affected with valve disease, but is of a breed which is at risk for later valve disease development (i.e cavalier King Charles spaniel)
Stage B- valve disease is present, but no evidence of congestive heart failure
Stage B1- no cardiac remodeling (the heart size is normal)
Stage B2- cardiac remodeling (heart size is increased)
Stage C- current or historic congestive heart failure
Stage D- refractory heart failure

Stage A dogs are clinically normal, but because of breed predisposition, may develop heart disease in the future. For owners of these dogs it is useful to discuss signs associated with heart disease and depending on their plans, discussion regarding breeding decisions may be warranted.

Stage B dogs by definition have a cardiac murmur. For staging purposes, thoracic radiographs, systemic blood pressure and a minimum database (creat, urine SG, PCV/TS) is recommended. If the heart size is normal on thoracic radiographs, the dog is considered to be in stage B1 (no cardiac remodeling). No cardiac medications have been shown to alter the progression of disease at this stage of disease. However, regular monitoring for cardiac enlargement with thoracic radiographs is recommended every 12 months. If heart enlargement is detected, the dog is considered to be in stage B2. The EPIC trial results demonstrated that pimobendan therapy resulted in delayed development of congestive heart failure when B2 dogs were started on pimobendan. Based on that trial, B2 criteria included an LA/AO of >1.6 and an LVIDD normalized to body weight > 1.7. Additional ancillary recommendations for B2 dogs include: supplementation with an N-3 fatty acid supplement and counseling the owner to keep a log of the dog's resting or sleeping respiratory rate.

Note that an echocardiogram is not necessarily needed in a dog with a signalment and findings highly likely to be degenerative valve disease (for example a small breed dog with a left apical systolic murmur). However, an echocardiogram is recommended in cases that "do not follow the book". For example, medium size dogs, which may have degenerative valve disease (DVD) or dilated cardiomyopathy (DCM); dogs in which the murmur is loudest on the right; dogs with an unusual pattern of cardiac enlargement.

Stage C dogs are dogs that have or have had congestive heart failure due to degenerative valve disease. In the acute stage, treatment of symptomatic congestive heart failure is similar whether the underlying cause is DVD or DCM. Life-threatening pulmonary edema is most effectively treated with intravenous furosemide. Depending on severity of clinical signs, 1-2 mg/kg is administered every 1-2 hours until there is a 25% reduction in respiratory rate, at which time frequency of dosing can be decreased. A constant rate infusion of furosemide (0.1-1.0 mg/kg/hr IV) appears to be superior to bolusing furosemide in severely affected patients. Dogs should be placed in an oxygen rich environment (oxygen cage). As soon as the dog can safely be given oral medications, pimobendan should be administered (unless the medications have already been administered). Pimobendan is orally

available within 1 hour of administration. Depending on the response to oxygen therapy, furosemide and pimobendan, additional therapy may be beneficial. Nitroprusside is an afterload reducer, which can be titrated to effect. Hydralazine is another afterload reducer, however it can result is reflex tachycardias. The addition of a positive inotropic agent such as dobutamine can also be helpful, particularly in dogs with profound myocardial failure. In some dogs, mild sedation with butorphanol is helpful.

Chronic maintenance therapy for dogs with congestive heart failure consists of sufficient furosemide to control congestion, an angiotensin converting enzyme inhibitor (ACEi) to reduce afterload and renin angiotensin aldosterone activity, and pimobendan. It is important to use the lowest dose of furosemide that controls congestion; in most dogs 1-2 mg/kg 2-3 times a day is adequate. If a higher dose is necessary, additional or alternative diuretics should be considered ("triple diuretic therapy" with the addition of hydrochlorothiazide and spironolactone or torsemide).

The most commonly used ACEI in veterinary medicine in the United States is enalapril (0.5 mg/kg twice daily), however benazepril also appears to be a good option in the dog. The benefit of ACEI therapy is conveyed over time and therefore the drug is not necessarily initiated during the initial CHF event, but once the dog is clinically stabilized. ACEI can impact the glomerular filtration rate because of dilatory effects on the efferent renal artery. Therefore it is important to evaluate the animal for azotemia within 1-2 weeks of starting this class of medications.

Pimobendan is a benzimidazole-pyridazinone inodilator (drug causing increased contractility and vasodilation). Venodilation and arteriodilation are via inhibition of PDEIII. Increased contractility is secondary to PDEIII inhibition effects and from a calcium sensitizing effect. Calcium sensitizers affect the interaction of calcium and the troponin C complex and therefore increase the extent of contraction for a given amount of intracellular calcium. This mechanism appears to have advantages because myocardial energy expenditure is lower than with positive inotropic agents operating via the cAMP pathway. In human studies, pimobendan may actually reduce myocardial oxygen consumption. Pimobendan also has favorable effects on left ventricular relaxation and end-diastolic pressure-volume relations. In small animal models, it has been shown to inhibit pro-inflammatory cytokines. At this time, the drug is approved only for use in dogs that have already developed congestive heart failure although one study showed early use in Dobermans with occult DCM delayed onset of heart failure. A study is currently underway to evaluate if pimobendan is beneficial in dogs with DVD prior to congestive heart failure (prior to stage C of disease).

For those patients with refractory heart failure (**Stage D**), additional medications may be beneficial in certain cases. For example, further reduction of afterload with amlodipine or heart rate control with digoxin and/or diltiazem may be warranted. Generally "triple diuretic therapy" (the combination of furosemide, hydrochlorothiazide and spironolactone) and/or torsemide is reserved for this stage of heart failure.

The drugs available to improve cardiac output work on the following formula:

$$\text{Cardiac output} = \frac{\text{Preload X Contractility}}{\text{Afterload}} \text{ X Heart rate}$$

Although reducing preload results in a reduction in cardiac output, because the Starling curve is flattened in patients with heart failure, a reduction in preload will optimally decrease filling pressure to alleviate pulmonary edema with minimal impact on cardiac output. The diuretics are the primary preload reducers with furosemide being the one most commonly used. Nitrates, such as nitroglycerine, are also preload reducers.

Drugs that decrease afterload, arterial dilators, result in improved cardiac output. Pimobendan is a vasodilator and one of its beneficial effects is a reduction in afterload. The ACEi agents are also vasodilators. Additional arterial dilators include amlodipine and hydralazine.

The only effective drug for chronic use that improves contractility is pimobendan. Although digoxin was historically considered a positive inotropic agent, the effect is trivial and it should not be chosen over pimobendan for inotropic support. In the acute heart failure setting, sympathomimetic agents, most commonly dobutamine, are often used for inotropic support. This synthetic catecholamine is rapidly metabolized and must be administered as a constant rate infusion.

When the heart rate is either very elevated or very slow, it will negatively impact cardiac output. In dogs with symptomatic valve disease, atrial fibrillation is the most common tachycardia that requires medical management. There are three main classes of drugs that can be considered for heart rate control in dogs with supraventricular tachycardias, such as atrial fibrillation: Beta adrenergic blockers, Calcium channel blockers and Digoxin. Beta blockers should be administered cautiously in dogs with poor myocardial (or uncertain) myocardial function as they reduce contractility. For this reason, beta adrenergic blockers should never be administered to patient in overt heart failure. Digoxin is a very effective negative chronotrope for chronic use, but the risk of toxicity with intravenous administration is so high that this administration route is not recommended. In the emergency setting, intravenous diltiazem can be used to control rapid supraventricular tachycardias.

References available upon request.