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FUTURE DIRECTIONS FOR DIAGNOSIS
TREATMENT AND MANAGEMENT STRATEGIES

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Mitral regurgitation (MR) secondary to degenerative myxomatous changes of the left atrioventricular valve (CVD) is reportedly responsible for approximately 75% of all cardiovascular disease, representing the most important cause of cardiovascular morbidity and mortality in the dog.

CVD is easily diagnosed in its early stages by the presence of a characteristic left apical systolic murmur. Clinical progression of CVD is typically slow but can be punctuated by acute exacerbations. Although not all dogs with CVD develop clinical signs of heart failure, all dogs with CVD experience disease progression. The number of dogs with CVD that eventually develop clinical signs of congestive heart failure (CHF) is currently unknown.

The preferred treatment for primary MR in people is open-heart surgery to repair or replace the faulty valve. Definitive therapy of this nature, although now available in veterinary medicine, is cost prohibitive for many clients and relatively contraindicated in dogs with some co-morbidities (renal insufficiency). Additionally, there is no proof that any medication used during the prolonged asymptomatic phase of CVD can delay its progression. In fact, recent evidence suggests that the most common medication recommended for treatment of these dogs, an angiotensin converting enzyme inhibitor (ACEI) with modest afterload reduction properties (enalapril), offers no benefit over placebo in delaying the onset of CHF in dogs with CVD. Therefore, current recommended therapy for dogs with CVD focuses on relieving clinical signs when they develop. Despite conventional therapy including diuretics, an ACEI, +/- digoxin, these dogs have a poor long-term prognosis following the onset of CHF. More recently, adjunctive therapy with pimobendan (Vetmedin®) in symptomatic dogs with CVD has appeared to offer additional morbidity and mortality benefits when used in combination with appropriate diuresis, both in the presence and absence of an ACEI. Thus clinical recommendations developed from review of available clinical efficacy data support the use of no therapy in the asymptomatic stage of CVD and an ACEI in combination with pimobendan and appropriate diuresis. However, additional therapies may be warranted based on scientific rationale or failure to respond clinically to evidence based therapies. The best method to identify potential pharmacologic candidates is to review the pathophysiology of CVD. Using this framework, a few clinically relevant agents will be discussed.

The left ventricular (LV) work associated with MR represents a model of pure volume overload because the excess volume is ejected into the relatively low pressure of the left atrium. In contrast, LV work associated with other forms of volume overload such as aortic insufficiency represents a combination of pressure and volume overload because the LV ejects the excess volume against relatively high aortic diastolic pressures. Although patients with chronic MR develop compensatory LV remodeling in the form of eccentric hypertrophy, the hypertrophic response is reportedly inadequate contributing to increased LV wall stress with commensurate increases in myocardial oxygen consumption. Researchers have suggested that inadequate hypertrophy is the result of the relatively low LV afterload (systolic wall stress) in this condition, which is a key mechanical signal for hypertrophy. This premise argues against the utility of afterload reduction in patients with MR, and perhaps offers insight to the failure of afterload reduction to delay its progression. Nonetheless, the historic therapeutic rationale for human patients with chronic MR has focused on a reduction in systemic afterload, which should result in a decrease in the diastolic pressure differential between the left atrium and aorta. This should result in an increase in forward LV stroke volume and a decrease in regurgitant volume. Acute evaluations of afterload reducing agents have demonstrated predicted increases in forward LV stroke volume and reductions in regurgitant volume. However, premise that patients with chronic MR may benefit from afterload reduction is rational based on acute hemodynamic studies but remains unproven, perhaps in part due to the already low systolic wall stress characteristic of primary MR.

Additionally, reduced LV systolic function has been demonstrated in an experimental canine model of chronic MR and in chronic spontaneous human MR. The proposed mechanism for the systolic dysfunction characteristic of primary MR is related to elevations in sympathetic nervous system (SNS) tone, resulting in both a reduction in the number of contractile units and cardiomyocytes. Elevated levels of circulating catecholamines (norepinephrine [NE]) are characteristic of chronic heart failure in humans, and have been documented in canine patients with symptomatic spontaneous CVD and in a chronic canine model of experimental MR. However, circulating NE doses do not appear to accurately identify the magnitude of organ specific SNS tone and thus does not identify the onset of SNS up regulation. It is however, the onset of enhanced organ specific SNS tone that may be both the result of inadequate hypertrophy and perpetuate the inadequate hypertrophy by leading to sarcomere and cardiomyocyte loss. This positive feedback cycle may therefore represent a rational clinical target for pharmacotherapy in primary MR. Selective and non-selective β-blockers including carvedilol (Coreg®) have been shown to significantly increase systolic function and survival in human patients with heart failure secondary to dilated cardiomyopathy (DCM). Additionally, high dose atenolol (2-5 mg/kg PO q 24hr), a 2nd generation selective β-blocker, improved LV function in an experimental canine model of chronic MR. The improvement was associated with enhanced innate contractile function of isolated cardiomyocytes due to an increase in the absolute number of contractile elements. The reported beneficial effects of gradual β-blockade represent a biologic effect that is not immediate upon initiation of therapy. In fact, the pharmacologic negative inotropic and chronotropic properties of these agents make decompensation a relative risk, in the short-term and mandate gradual initiation of therapy in the form of an up-titration protocol. However, improved systolic function and LV remodeling have been demonstrated in every human study greater than 3 months in duration.

Early evaluations of β-blockade for the treatment of heart failure focused on second-generation β₁-selective agents (metoprolol, atenolol) to avoid increases in afterload characteristic of nonselective β-blockade. However, β₁ and β₂ receptors are present in the myocardium and both are important in mediating adrenergic effects in cardiomyocytes. Additionally, in human heart failure, cardiac β₁ receptors are down regulated while β₂ receptor numbers remain...
unchanged. Therefore, due to the relative increase in β₂ receptors, more comprehensive cardiac adrenergic blockade can be achieved with the use of non-selective β-blockers. Carvedilol is a 3rd generation nonselective β-blocker/α₁-blocker with ancillary antioxidant effects and thus combines the potential benefit of a nonselective β-blocker with the afterload reduction properties of an α₁-blocker. Additionally, the antioxidant properties may decrease the oxidant stress associated with progressive heart failure. Carvedilol is currently the only β-blocker approved by the American FDA for the treatment of human heart failure and has recently been shown to be superior to metoprolol with respect to survival in human DCM.

It is not uncommon to evaluate ‘relatively’ asymptomatic dogs with CVD that on further evaluation are found to have compensatory cardiac remodeling including, left atrial enlargement +/- left ventricular eccentric hypertrophy (dilation). A subset of these patients also demonstrate systolic dysfunction based crudely on an increased LV end-systolic diameter (LVIDs). The combination of nonselective β-blockade and afterload reduction in concert with the antioxidant properties offered by carvedilol is rationale and may delay the development of overt clinical signs of heart failure in this population of dogs. Additionally, given the relative risk of decompensation associated with β-blockade in patients with CHF, gradual β-blockade is likely to have less risk in asymptomatic dogs with CVD and no obvious systolic dysfunction (normal LVIDs). In dogs with mild clinical signs and stable CHF the relative risks of initiating β-blockade may be best addressed in the future by offering gradual β-blockade on a background of pimobendan. In this patient population pimobendan may be used either long-term or perhaps as a bridge while awaiting the biologic effects of β-blockade to develop. The combination of pimobendan and β-blockade has potential benefits in terms of limiting the potential negative side effects of both agents simultaneously. This premise has been recently explored and found to be beneficial in human patients with CHF secondary to DCM.

There is currently limited data on the pharmacokinetics and pharmacodynamics of carvedilol in dogs. Abbott et.al. 2003 and Arsenault et.al. 2003 reported the pharmacodynamics of chronic oral carvedilol administration in normal conscious dogs. Their combined data evaluated dose ranges between 0.05-1.5 mg/kg and demonstrated the ability of carvedilol to offer significant β-blockade based on an isoproterenol challenge with little effect on systemic blood pressure and heart rate even at the highest dose reported. Additionally, Arsenault et.al. 2003 reported a statistically significant correlation between plasma carvedilol levels and the percent attenuation of an isoproterenol induced tachycardic response and suggested that plasma carvedilol levels of 60-100 ng/ml may be necessary for near maximum β-blockade in healthy, conscious hound dogs. The pharmacokinetic profile of oral and intravenous carvedilol in healthy, conscious hound dogs was also reported, suggesting a 6 hour dosing interval and a low and variable oral bioavailability (approximately 1/10⁰ of that reported in humans). Conversely, the available pharmacodynamic data suggest a 12 to 24 hour dosing interval will be adequate to ensure β-blockade. Sasaki et.al. 2002 reported the cardiovascular and renal effects of oral carvedilol (0.2-0.8 mg/kg q 24 hours) in dogs with experimental MR and control dogs. They demonstrated β-blockade with oral carvedilol, suggested that a dose of 0.4 mg/kg PO q 24 hours may be a reasonable target dose based on their pharmacokinetic data, and cautioning against over zealous β-blockade in dogs with heart disease. However, the majority of investigators who have worked with an experimental model of canine MR and demonstrated beneficial effects associated with β-blockade, alone or on a background of ACEI, have used atenolol at an initial dose of 12.5 mg/day (0.5-0.8 mg/kg PO q 24 hours) gradually increasing to a target dose of 50-100 mg/day (2-5 mg/kg PO q 24 hours) over a few weeks. The target dose was designed and proven to offer essentially complete, likely non-selective, β-blockade. Thus, if we wish to repeat the results of these studies in spontaneous CVD we may need to seek the highest tolerated dose which would be easiest in asymptomatic dogs with relatively normal systolic function (normal LVIDs).

These data combined with the reported rise in norepinephrine in dogs with spontaneous CVD and the systolic dysfunction that is now recognized to occur in spontaneous primary human MR beg the question of whether or not β-blockade alone or on a background of neurohormonal modulation such as that offered by an ACEI, spironolactone, digoxin can delay the progression of CVD in dogs. Although carvedilol is currently used by some clinicians for the treatment of CVD and other cardiac diseases, dosing until recently was empirical. The availability of pharmacokinetic and pharmacodynamic data in normal dogs and those with experimental MR greatly aids in the determination of an evidence based dose and dosing interval for carvedilol. However, further insight offered by the evaluation of dogs with spontaneous heart disease receiving carvedilol has suggested a target oral dose of 1.0 mg/kg q 12 hours. Reportedly, this dose is well tolerated in dogs with asymptomatic CVD can be safely achieved with 3 staged up titration protocol that may be facilitated by determination of an occasional plasma carvedilol level (2 hours post oral dose during chronic dosing). Determination of plasma levels could be particularly important given the reported high individual variation in oral bioavailability in normal dogs and those with spontaneous heart disease as well as the reported increases in carvedilol plasma levels with standard oral doses in human patients with spontaneous cardiovascular disease versus normal control subjects. In addition, evaluation of the biologic effects of chronic carvedilol therapy in dogs with asymptomatic CVD may provide insight into their potential utility in delaying the progression of CVD. The preliminary results of a 4-5 month prospective study designed to evaluate the biologic effects of chronic oral carvedilol in dogs with asymptomatic CVD will be presented during this talk. However, the true utility of carvedilol in dogs with CVD awaits prospective placebo controlled studies.

Additional pharmacologic agents may also warrant investigation in dogs with CVD. The neurohormonal modulation properties of aldosterone antagonists such as spironolactone or eplerenone warrant evaluation in both symptomatic and asymptomatic dogs with CVD. The link between aldosterone and deleterious cardiac fibrosis leading to arrhythmias and diastolic dysfunction argue that aldosterone antagonism is a rational pharmacologic target in many forms of asymptomatic heart disease in addition to its utility as adjunctive therapy in CHF.

Currently, appropriate diuresis in dogs with CHF is achieved primarily with the loop diuretic furosemide. Frequently, furosemide is used in combination with the
aldosterone antagonist, spironolactone in an attempt to both exploit its antifibrotic properties and limit hypokalemia, one of the common side effects of loop diuretics. Clinically, a percentage of canine patient with CHF fail to be maintained free of clinical signs of congestion with this combination at which time a third diuretic is usually added. However, both during high dose furosemide therapy and especially following the addition of a second loop diuretic such as hydrochlorothiazide most dogs experience significant albeit expected electrolyte and acid base abnormalities which may be limited by substituting (or adding) an aquaretic (vasopressin receptor antagonist = vaptans), such as tolvaptan (OPC-41061). Tolvaptan is selective V2 receptor antagonist, which is showing promise in the acute and chronic treatment of human CHF. In contrast to loop diuretics like furosemide, V2 receptor antagonism has demonstrated free water excretion with little to no sodium loss. In addition, the water loss associated with V2 antagonism has not been associated with activation of the RAAS in contrast to the loop diuretics. Thus, this novel class of agents may prove to be a good addition to our pharmacologic arsenal against CHF.

Pulmonary artery hypertension (PAH) represents an end stage complication in a proportion of dogs with CVD. PAH is a devastating sequellae of CVD, primarily because dogs with PAH experience severe clinical signs such as recurrent, diuretic refractory, ascites, exercise intolerance and frequent collapsing spells, particularly with excitement. With the exception of oxygen supplementation there is no medical therapy recognized to provide selective pulmonary arterial dilation. Although, newer agents such as prostacycline and selective endothelin receptor blockers (bosenten) appear to beneficial in the treatment of some forms of human PAH, these therapeutic options are unlikely to be evaluated in the dog due to route of administration problems (prostacycline) and cost (bosenten). However, the phosphodiesterase (PDI) 5 inhibitor, sildenafl (Viagra), may have clinical utility and is available as an oral product that may not be cost prohibitive. In addition, pimobendan through its PDI 5 effects may potentiate the PDI 5 effects of sildenafl. The future of evidence based CVD pharmacotherapy awaits further placebo-controlled trials. However, appropriate utilization of available scientific literature to determine novel pharmacologic agents worthy of investigation is necessary. In addition, given the expense associated with adequately powered placebo controlled studies and the time required to carry them out it is likely that we as veterinarians will continue to treat empirically.