Get More with Four: Treating MMVD and What is BESST for Our Patients

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Introduction

Myxomatous mitral valve disease (MMVD) is a very common canine cardiac disease. Given the prevalence of MMVD in the general canine population is near 15%[1], it is imperative general practitioners have a comfort with diagnosing and treating this disease. This talk will briefly review the stages of MMVD and the renin angiotensin aldosterone system (RAAS). There will be an emphasis on the treatment for MMVD at the various stages based on current literature evidence.

Stages of MMVD

The ACVIM has published an updated consensus[1] on the diagnosis and treatment of MMVD. There are four main stages of MMVD.

- Stage A is a dog at risk for the disease.
- Stage B dogs have thickening of the mitral valve and usually an audible heart murmur.
    - Stage B1 dogs do not require therapy as there has been no consistent evidence for medication when there is minimal to mild cardiac remodeling.
    - Stage B2 dogs have at least moderate cardiomegaly. The recommendation is to initiate pimobendan +/- ACE inhibition at this stage
- Stage C dogs have had an episode of congestive heart failure (CHF)
    - Therapy with diuretics is well established
    - Therapy with pimobendan and renin angiotensin aldosterone system (RAAS) suppression is recommended and beneficial
- Stage D dogs have CHF that requires higher doses of Stage C therapy or additional therapy to control clinical signs.

Heart Failure and Congestive Heart Failure

Heat failure (HF) is usually a chronic state in which the heart cannot keep up with the metabolic needs of the body. These patients have decreased cardiac output and may have minimal or no significant clinical signs. Dogs with MMVD Stage B2 may not have congestive heart failure, but they may have clinical signs of syncope or exercise intolerance with exertion or cough from mainstem bronchial compression.

Congestive heart failure (CHF) is when there is fluid accumulation (usually in the form of pulmonary edema or cavitary effusion). These patients usually have more significant clinical signs and require diuretic therapy to treat the fluid accumulation. In veterinary medicine, the terms HF and CHF are often

used interchangeably but it is important for the practitioner to understand the differences between these terms as they guide therapeutic recommendations and prognosis.

The Renin Angiotensin Aldosterone System (RAAS)

Chronic RAAS activation has several negative cardiovascular consequences. Both angiotensin II (AngII) and aldosterone both cause vasoconstriction and vascular remodeling, sodium and water retention, and cardiac fibrosis/remodeling[2]. The RAAS is activated due to decreased cardiac output in HF and especially so in the setting of CHF. Furthermore, the diuretic therapy indicated in CHF further activates RAAS. Fortunately, there are therapies such as angiotensin conversion enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists MRA) that reduce the end products and/or negative chronic sequelae of RAAS activation. The most investigated drugs in the setting of MMVD and congestive heart failure are the ACEi and MRA classes.

Treatment of MMVD B2

Pimobendan is an inodilator. This drug increases contractility via calcium sensitization of the cardiac troponin C molecule. Furthermore, pimobendan reduces afterload on the left ventricle due to its vasodilatory effect via phosphodiesterase-3 inhibition. The EPIC trial in 2016 showed dogs with at least moderate cardiac remodeling secondary to MMVD treated with pimobendan (Vetmedin) had a significant delay in onset of Stage C (congestive heart failure) by 15 months compared to dogs that received placebo[3]. As with any study, there are limitations and bias but most cardiologists consider pimobendan an essential drug in the management of MMVD. Therefore, pimobendan (0.25-0.3 mg/kg po bid) is recommended in dogs with physical exam findings, radiographic and/or echocardiographic evidence of MMVD and at least moderate cardiomegaly. These parameters include a grade III/VI or louder left apical systolic murmur, a vertebral heart score > 11, a vertebral left atrial score > 2.5, and/or an LA:Ao > 1.6 and LVIDdN > 1.7 on echocardiogram.

ACE inhibitors (ACEi) inhibit the classical activation of Angiotensin I to Angiotensin II. There have been some studies evaluating if ACEi have an effect of delaying the onset of congestive heart failure in dogs with asymptomatic MMVD. Studies such as VETPROOF[4] and SVEP[5] have shown different results; VETPROOF showed a more significant difference between ACEi dogs and placebo in terms of CHF onset whereas the SVEP trial did not show a significant benefit to ACEi therapy. Some of this discrepancy may be due to the stage of heart disease in the enrolled dogs (i.e. B1 dogs and B2 dogs) as well as the breed of dogs (Cavalier King Charles Spaniels have been shown to have polymorphisms of the ACE gene that may affect the efficacy of ACE inhibitors). Cardiologists have varying opinions on the use of ACE inhibitors in MMVD B2 disease. Overall, ACEi seem to be well-tolerated with minimal side effects and are rarely cost-prohibitive in the United States. This cardiologist recommends ACE inhibitor therapy if there is moderate to severe cardiomegaly and/or there is evidence of early systemic hypertension (systolic BP > 150 mmHg). A typical dosing strategy is 0.5 mg/kg po sid for benazepril or bid for enalapril.

Spironolactone is an MRA that directly inhibits the action of aldosterone. Despite effective ACEi, approximately 30% of dogs are suspected to have a phenomenon called aldosterone breakthrough[6]. Therefore, aldosterone can still be produced in excessive levels without AngII. The DELAY[7] study sought to determine if, would delay the onset of congestive heart failure in asymptomatic MMVD dogs. This study did not show a significant delay in CHF but did show an improvement in the NT-proBNP which may

suggest some cardio protection. The clinical relevance of spironolactone in this stage of disease is still unclear. Therefore, spironolactone is not routinely recommended in stage B2 MMVD.

Treatment of MMVD C and Beyond

Diuretics are essential in the management of congestive heart failure (CHF). Loop diuretics such as furosemide and torsemide are the most commonly used diuretics in veterinary medicine. Both of these drugs act at the thick ascending loop of Henle and inhibit the potassium/sodium/2 chloride pump. This results in increased urine production, decreased intravascular volume, decreased hydrostatic pressure, and resolution and/or prevention of pulmonary edema and CHF effusions. Possible hematologic side effects include prerenal azotemia, hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. The dose can be adjusted as needed to mitigate these side effects; small changes in these parameters are usually tolerated if the dose of diuretic is required to control the clinical signs of CHF.

Pimobendan has proven to yield significantly improved median survival time in this stage of MMVD[8-10]. Therefore, if a patient has not yet been initiated on pimobendan during Stage B2, pimobendan should be used as part of stabilization along with the diuretic therapy and continued long term. Pimobendan therapy was superior to benazepril therapy when combined with diuretic therapy for CHF according to the QUEST study[9].

ACE inhibitors have proven their place in dogs with CHF secondary to MMVD. Dogs receiving ACE inhibitor therapy have improved survival[11,12]. As mentioned previously, RAAS activation is persistent in CHF and has many negative sequalae. Therefore, ACEi therapy is routinely recommended for dogs with MMVD Stage C and D.

Spironolactone is also recommended for patients in this stage of MMVD. Due to the phenomenon of aldosterone breakthrough despite ACEi therapy, MRAs are considered beneficial for patients in CHF. A typical dose is 2 mg/kg po sid based on studies showing tolerance and improved survival with this dose[13,14]. The BESST trial studied a combination of ACE-inhibition and spironolactone (Cardalis) in Stage C MMVD patients. The results of the study showed the combination of spironolactone and benazepril was superior to benazepril therapy alone in terms of patient survival. These patients were not on pimobendan but were all on diuretic therapy. Further studies are needed to determine if the results of this study would change in the presence of pimobendan therapy.

In summary, quadruple therapy including a diuretic, pimobendan, ACE-inhibitor, and spironolactone are recommended for MMVD Stage C patients. Patients with Stage D will require higher doses of these medications and/or adjunctive therapies. Examples include hydrochlorothiazide, sildenafil for secondary pulmonary hypertension, amlodipine for afterload reduction, or cough suppressants to control their clinical signs[1].

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