

Canine Myxomatous Valve Disease

Diagnosis, Outcomes, Staging & Management

John D. Bonagura, DVM, DACVIM (Cardiology, SAIM)

Professor Emeritus, the Ohio State University College of Veterinary Medicine

Adjunct Professor of Cardiology, NC State University College of Veterinary Medicine

The potential causes of atrioventricular valve dysfunction in dogs include various congenital malformations, functional disruptions due to ventricular and atrial dilation, infective endocarditis, and degenerative transformation of the valves. Of these etiologies, myxomatous or valvular disease (MVD) affecting the mitral and tricuspid valves is most important. These degenerative lesions (also termed endocardiosis or degenerative valvular disease) lead to mitral regurgitation (MR) and to a lesser degree tricuspid regurgitation (TR). Overall, myxomatous mitral valve disease (MMVD) is responsible for about 70% of all cases of canine heart disease, with incidence increasing with age.

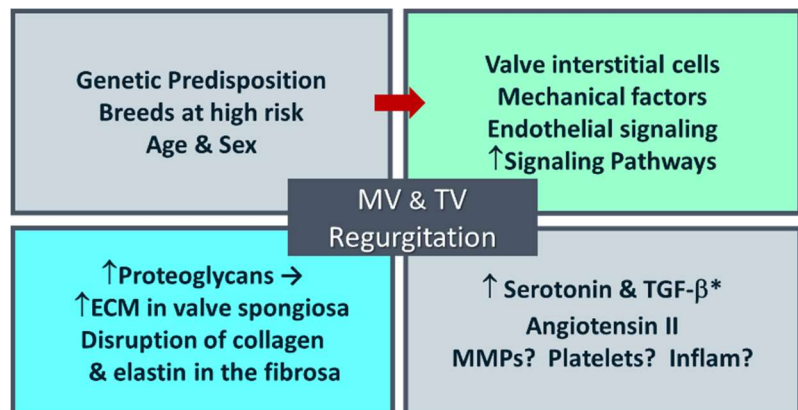
Lesions, Pathogenesis & Pathophysiology

Myxomatous valve degeneration results in nodular thickenings and expansion of the atrioventricular valves. The valvular endocardial surface retains its smooth and glistening appearance, however, the leaflets become expansive and often prolapse into the atrium. Histologically the central mitral valve layers are disrupted and expanded by acellular proteoglycans. The histologic lesions can extend into valve chords. Disease severity varies from mild thickening or subtle valve prolapse to extensive club-like expansions of the leaflets.¹ Flail leaflets with loss of valve support stem from ruptured valve chords.

As demonstrated by classic veterinary pathology literature ¹ and recent pet insurance claims reported by Nationwide®, MVD is most prevalent in “senior” dogs. A number of small and toy breeds exhibit a high prevalence of disease, compatible with genetic predisposition. At this time genetic screening for MVD is clinically unavailable to guide breeding. The proposed pathogenesis of MVD has been reviewed by Markby and colleagues and by Oyama and colleagues.^{2,3}

Pathogenesis

Valve transformation is promoted by serotonergic, TGF-beta, metalloproteinase activity, and potentially angiotensin II signaling. Valve interstitial cells are altered functionally and myxomatous change occurs over a prolonged period (years). These are potential



therapeutic targets for treatments to delay MVD, but no effective treatments are available currently.

Progressive Chamber Remodeling Progressive MR causes enlargement of both the left atrium (LA) and the left ventricle (LV), readily explainable by the progressive volume overload affecting both chambers. Whether activation of neurohormonal compensations are operative or even similar to canine dilated cardiomyopathy (DCM) is largely unstudied, but there are probably differences. MMVD in small breed dogs seems different from “typical” heart failure due to reduced ejection fraction observed in DCM (or in most humans with CHF). As such treatments might differ and some of the therapies used in people (beta-blockers, SGLT inhibitors, RAAS inhibition) might not be as effective.

Myxomatous valve disease is largely centered on the left side of the heart. The right-sided chambers dilate to varying degrees, becoming most prominent with combinations of severe TR, pulmonary hypertension (PHT), atrial fibrillation (AF), and right-sided CHF as these all increase systemic venous pressures.

Ventricular Function Primary MR differs from canine DCM in terms of preservation of global systolic LV function, the severity of valvular regurgitation, and the influence of the left atrial V-wave of valvular regurgitation (this raises LA pressure at end-systole). Both systolic and diastolic ventricular function are challenging to assess in the setting of primary mitral valve disease due to altered (pre- and after-) loading conditions.

Natural History MMVD demonstrates a prolonged period of disease with most dogs never experiencing clinical heart failure. With some exceptions, a *four- to six-year interval* is common between the initial detection of a soft systolic murmur and the development of congestive heart failure (CHF). This allows many dogs to remain *asymptomatic* throughout life. However, a loud murmur of MR, accompanied by moderate cardiac remodeling, does predict a higher risk for cardiac-related death.^{4,5}

Congestive Heart Failure The volume of regurgitant blood along with the compliance of the LA and LV are major factors determining the size of the regurgitant pressure wave (V-wave), mean LA pressure, and the LV end-diastolic

Abbreviations Used
2DE – two-dimensional echocardiography
ACE – angiotensin converting enzyme
AF – atrial fibrillation
NT-proBNP – Nitrogen terminal of the prohormone of B-type natriuretic peptide
CHF – Congestive heart failure
EF – ejection fraction (stroke volume/end-diastolic volume)
LA – left atrium, left atrial
LA/Ao – ratio of LA to aortic dimension
LV – left ventricle, left ventricular
LVEDDN – left ventricular diastolic dimension normalized to body weight
MR – mitral regurgitation
MVD – myxomatous valve disease
MMVD – myxomatous mitral valve disease
PHT – pulmonary hypertension
RAAS – renin-angiotensin-aldosterone system
RV – right ventricle, right ventricular
TR – tricuspid regurgitation
VHS - vertebral heart scale (sum, size)
VLAS – vertebral left atrial size (score)

pressure (higher values for any of these increase the risk of decompensated HF with pulmonary edema). Marked reduction of forward (aortic) blood flow has been demonstrated once severe MR develops, although cardiogenic shock is uncommon due to compensatory mechanisms (vasoconstriction, tachycardia). Cardiac size is variable: dramatic left-heart cardiomegaly can develop without overt CHF in slowly progressive MMVD; however, rupture of mitral valve chords can precipitate pulmonary edema with only modest cardiomegaly evident.

Heart failure is a clinical syndrome – not a disease – caused by a cardiac lesion and what are considered maladaptive compensations for maintaining arterial filling. Presumably the development of *congestive heart failure* (CHF) involves the aforementioned hemodynamic abnormalities as well as renal and neurohormonal responses associated with increased left atrial pressures and limited forward flow. Activation of the renin-angiotensin-aldosterone system occurs,⁶ although inhibition of this system has met with disappointing or incompletely defined benefits in terms of delaying or managing CHF (see later).

Outcomes in Brief Because this disease is ubiquitous in older dogs, MVD represents an important cause of cardiac *murmurs, cardiomegaly, cardiac morbidity* and *mortality*. The major clinical outcome is *left-sided CHF*. Biventricular or *right-sided failure* can also develop and often leads to profound exercise intolerance and ascites. Other recognized direct complications of MMVD with severe MR include post- and precapillary *pulmonary hypertension* (PHT); *left atrial tearing* causing cardiac tamponade or an acquired atrial septal defect; *atrial arrhythmias* (especially premature atrial complexes and atrial fibrillation); and (while controversial) *bronchial compression* from an expanding atrium. Comorbidities including *intrinsic renal disease, systemic hypertension*, and a host of *bronchopulmonary, airway*, and pleural diseases than can complicate the differential diagnosis and make challenging the medical management.

Recognition & Diagnosis of Myxomatous Valve Disease

This common disorder is readily identified with a stethoscope. In the setting of a mature dog with no prior history of a left-sided murmur (which practically excludes congenital heart disease), the differential diagnoses are quite limited. These include MR from MMVD, DCM (uncommon in smaller breeds eating normal diets), or infective endocarditis (these patients are usually systemically ill). Functional systolic ejection murmurs do occur in dogs but are usually localized more cranially and dorsally, though they can be confused with mild MR. Murmurs loudest over the right side in mature dogs usually indicate tricuspid regurgitation stemming from MVD, pulmonary hypertension (including heartworm disease), or secondary to DCM.

Clinical Examination in Preclinical & Symptomatic Dogs

The typical signalment is the smaller mixed- and purebred dog of late-middle and older age. These canine patients are at highest epidemiologic risk for developing MVD. Some breeds with high prevalence include the Cavalier King Charles spaniel, Cavachon, Japanese chin, Chihuahuas,

dachshund, shih tzu, Maltese, and toy poodle, among many others. Some dogs of these breeds will show subtle auscultatory or Doppler echocardiographic abnormalities at relatively young ages (2-3 years of age). Larger breed dogs (>20 kg) are not devoid of MVD, but their natural history is often somewhat different as valve thickening is less dramatic and overt LV systolic dysfunction seems more common, and often confused with dilated cardiomyopathy. Reports on breed prevalence for MVD likely relate in part to geographic breed popularity.

Clinical Signs These range from none beyond a systolic murmur (typical preclinical disease); to exercise intolerance (often overlooked as aging or arthritis); to respiratory or abdominal signs of CHF; to (uncommonly in smaller breeds) sudden cardiac death. Typical clinical problems that might be associated with MVD and prompt veterinary examinations include *exertional collapse* or syncope, *cough* (from cardiac or from primary bronchopulmonary disease), *restlessness* (reduced appetite and weight loss are also common with CHF), and *tachypnea or respiratory distress*. A dog's quality and duration of life are limited once cardiac failure supervenes and lifespan is markedly shortened unless CHF is promptly recognized and treated.⁹⁻¹¹

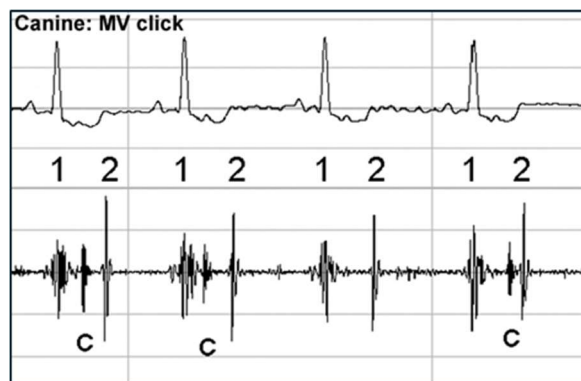
The clinical sign of *cough* is common in dogs with MMVD, especially in dogs with moderate to severe LA dilation with compression of principal bronchi^{7,8}. However, it is even more often due to concurrent airway disease, especially chronic bronchitis. Tachypnea and respiratory distress in a dog with MMVD often signal *pulmonary edema*, although concurrent pulmonary fibrosis, neoplasia, pneumonia, heartworm disease, thromboembolism, and idiopathic PH must also be considered. Cardiogenic pleural effusion is uncommon in MMVD but noncardiac causes of pleural effusion can cause dyspnea in a dog with otherwise compensated MR. These dogs often have lung cancer.

As noted previously, a smaller fraction of dogs develops signs of overt *right-sided CHF*, usually from combinations of PHT, TR, and AF. Right-heart failure in MVD often manifests as a loud right-sided murmur, exertional weakness or collapse, along with anticipated findings of jugular vein distension, hepatomegaly, and ascites.

Some dogs with MVD and syncope are found to have reflex-mediated ("vasovagal type") on ambulatory ECG recordings, with marked bradycardia or periods of asystole. Therefore routine anti-arrhythmic drug therapy such as sotalol is discouraged in dogs with MMVD who are fainting. Additionally some of these dogs are likely to have severe pulmonary hypertension, which is treated differently.

Cardiac Auscultation The hallmark auscultatory findings of MVD are those of systolic clicks due to mitral or tricuspid valve prolapse and the holosystolic murmur of MR over the (palpable) left apex and mitral valve area. Palpation of the left apex not only orients the examiner to the mitral valve listening area, but in cases of moderate to severe cardiomegaly, the clinician will find the apical impulse displaced caudally from the usual fifth intercostal space and somewhat more ventrally as well.

Brief, focal, and soft left apical murmurs (grades 1/6 and 2/6) in an asymptomatic dog usually indicate mild MR unlikely to benefit from any therapy.¹³ Loud systolic, holosystolic murmurs of MR, even those with precordial thrills (grades 5/6 and 6/6), occur in both asymptomatic dogs and those with CHF. The intensity of the first sound usually increases in primary MR due to MVD (in contrast, it can be soft when MR is due to dilated cardiomyopathy).



Once a murmur of MR radiates (grades 3/6 or louder), further diagnostic evaluation is recommended as cardiac remodeling is more likely. The murmur of MR usually radiates directly across the thorax to the right with a similar quality but lower intensity.

Concurrent *tricuspid regurgitation* (TR) is suggested by a prominent murmur over the right thorax (near and above the palpable right ventricular impulse). Concurrent TR is particularly likely if a precordial thrill or a murmur of different character is identified.

Blood pressure affects ventricular systolic pressures and murmur intensity. Rupture of the LA with cardiac tamponade can induce hypotension and a marked dampening of murmur intensity. In contrast, systemic hypertension increases the intensity of MR, while PHT the loudness of TR. When the murmur of TR is louder than that of MR, either PHT or a laterally directed regurgitant jet will be identified on Doppler echocardiographic imaging.

Diagnostic Studies

Additional diagnostic testing can be used to verify the presence of MVD, stage the severity of valvular regurgitation, and identify the clinical outcomes of chronic valvular disease. In terms of a diagnostic testing, systemic blood pressure screening, electrocardiography, clinical laboratory testing (including biomarkers), thoracic radiography, thoracic ultrasonography, and echocardiography are considered on a case-by-case basis. Routine *heartworm* antigen and microfilaria tests should be obtained from dogs living in or arriving from geographic regions endemic for dirofilariasis. Patients with heart failure should have baseline and followup serum *clinical chemistries*, in particular renal function and serum electrolytes along with a PCV/plasma protein or CBC (if relevant to screen for anemia, volume contraction, or systemic inflammation).

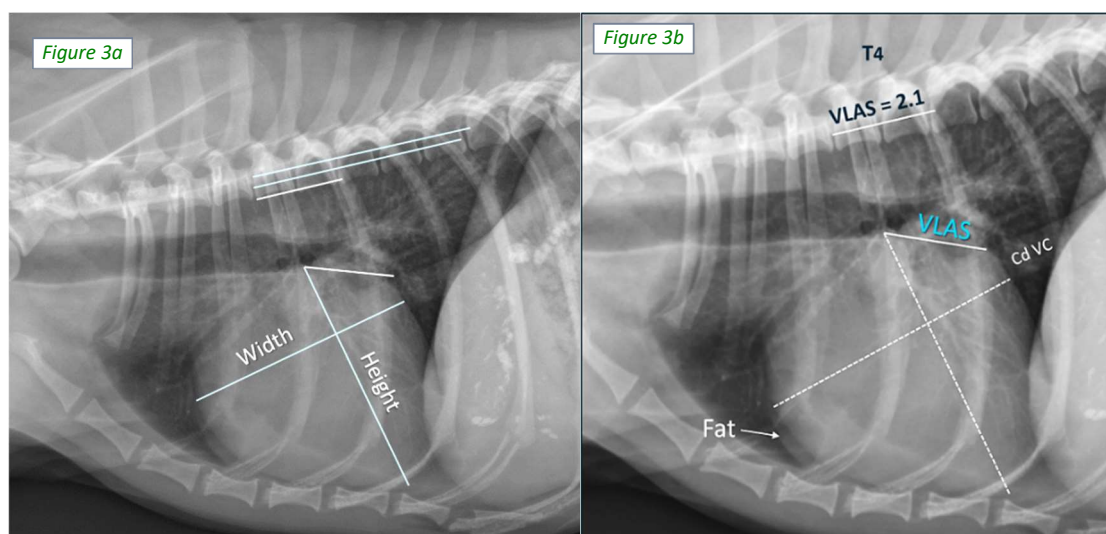
Noninvasive blood pressure – BP measurements are used to screen for systemic hypertension (HTN) or hypotension in dogs with active CHF. Hypertension also should be considered when 2DE identifies LV wall thickening. Increased afterload worsens MR and causes difficult-to-treat pulmonary edema. Risk factors for HTN include chronic kidney disease and Cushing’s disease.

Electrocardiogram – The value of the standard or Holter ECG as a routine diagnostic test in MMVD depends in part on presence of any arrhythmias identified by auscultation. *Atrial premature complexes* are common, and these premature beats can precipitate atrial fibrillation (AF),

especially in larger breeds or in dogs with severe atrial dilation. Dogs with sustained atrial tachycardias or AF will require additional antiarrhythmic therapy such as diltiazem (see below). Verification of heart rhythm disturbances requires an ECG. However, a 1- or 6-lead ECG recording in dogs with sinus rhythm is of uncertain value for staging or decision-making. It might provide preanesthetic documentation of rhythm if that is considered important. Holter monitoring is not routine in MVD but can be useful in dogs with syncope or with documented ventricular ectopy.

Natriuretic Peptides – Progressive increases in natriuretic peptides including A-type (atrial) and B-type (brain) natriuretic peptide (BNP – mainly derived from the left ventricle) occur with cardiac dilation. Measurement of the inactive nitrogen terminal of the prohormone of *B-type natriuretic peptide* (NT-proBNP) can be used to track progressive LV dilation and correlates to the stage of disease, especially if combined with murmur intensity and radiographic heart size.¹³ Conversely, lower NT-proBNP concentrations (especially <1500 pmol/L) argue against severe remodeling or impending CHF. Because some dogs with compensated disease and marked cardiomegaly have quite high NT-proBNP concentrations, *therapy should never be based only on a biomarker test.*

Radiography – Thoracic radiographs can support the diagnosis of MMVD, verify the presence of CHF, exclude some noncardiac causes of respiratory signs, and help stage the severity of disease (also see below). Radiography can identify (within knowledge of *breed variability*) findings suggestive of cardiomegaly and of left-sided CHF. The *vertebral heart size* (sum, scale; VHS) is commonly used to identify cardiomegaly objectively. Although a single VHS cutoff is unreliable across all breeds for disease staging, serial radiography to measure VHS and *rate of change* or VHS “velocity” are useful, especially when echocardiography cannot be done.^{14,15} A VHS exceeding 11.5 (to 11.7) vertebral bodies is suggestive of clinically relevant cardiomegaly in most breeds typical of



stage B2 MMVD (staging is discussed below). The VHS can be augmented by determination of a *vertebral left atrial size* or VLAS. Values >2.3 VB are abnormal for most breeds and a VLAS of 3.0 or higher usually indicates at least moderate LA dilation, typical of stage B2 or stage C of MMVD.

In general, thoracic radiographs should be obtained when a dog presents with a moderately loud (radiating) murmur of MR. Depending on the availability of echocardiography, X-rays can be followed every 9-12 months and repeated if there are concerns about impending CHF, including: an increment in a dog's sleeping/resting respiratory rate; when the sleeping respiratory rate consistently exceeds 30 to 35 breaths per minute;¹⁴ if the dog cannot sleep or rest comfortably; or if any coughing becomes progressive. Radiographic features of CHF are summarized below.

Echocardiography – Cardiac ultrasound offers definitive noninvasive diagnosis of valvular disease along with objective measures of cardiac size needed for optimal staging. The usual 2DE findings are of thickened, nodular, and prolapsing mitral valve leaflets. Progressive LV and LA dilation are observed on serial examinations. Dimensions should be normalized (allometrically) to body size or indexed to the aorta (*Table 2*). For most breeds, a normalized diastolic dimension of ~1.65 to 1.7 (using a scaling exponent of 0.315 to 0.33) suggests LV dilation, but *sighthounds* and a number of *spaniel breeds* do not adhere to these guidelines (a point most relevant to those performing echocardiography). Ruptured chordae tendineae might be visualized and cause flail leaflets.

{The following paragraph is more advanced and mainly for echocardiographers}

Cardiologists and those with advanced imaging experience will evaluate the heart with Doppler echocardiography. The characteristic color Doppler jet of primary MR is eccentric, though central and multiple jets also are common. Grading severity of MR by color Doppler is especially important in selecting candidates for valve repair or transcatheter edge-to-edge mitral repair. These incorporate approaches beyond the “receiving chamber” analysis of regurgitant jet to left atrial area – a ratio that is overemphasized and often poorly correlates to MR severity. More quantitative are assessment of the regurgitant orifice size estimated by the vena contracta (where a 4 to 5 mm diameter VC generally indicates severe MR in a small dog); identification of a proximal isovelocity area (PISA) at some distance from the regurgitant orifice (where a 4 to 5 mm PISA in a small dog at aliasing velocity of ~35 cm/s indicates moderate to severe MR); and volumetric calculations (Simpson's method for LV total stroke volume and aortic stroke distance for forward flow) that quantify actual regurgitant fractions.

When pulsed-wave Doppler measures of transmitral filling waves are < 1 m/s active CHF is unlikely; whereas an early filling (E-)wave ≥ 1.3 to 1.5 m/s indicates a higher risk for CHF. In terms of ventricular function, there are many challenges and nearly every small-breed dog develops a hyperdynamic LV chamber with progressive primary MR. Estimating volumes and systolic function from M-mode studies are inaccurate despite their recurrent popularity (and publication). Similarly, diastolic function is hard to assess as LV preload and systolic function are increased, LV wall tension decreases as MR begins prior to ejection, and early filling velocity is accentuated by the LA V-wave (demanding exorbitant pulsed-wave Doppler E/e' ratios before left-sided CHF can be reliably identified using that method).

Tricuspid valve disease is very common in MMVD and identified by leaflet prolapse or thickening, TR, and variable amounts of right-sided chamber enlargement. Often the RV and RA sizes are underwhelming. Dilation of the pulmonary trunk, branch pulmonary arteries, and a high velocity TR jet indicate PHT. In left-sided CHF, the pulmonary veins are dilated relative to arteries, and the right pulmonary vein-to-pulmonary artery ratio is increased. In PHT the branch PAs increase in size.

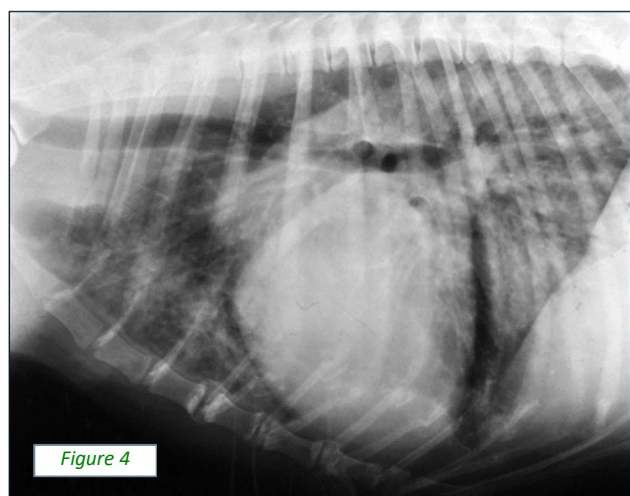
Outcomes of Myxomatous Valve Disease

Cardiac Remodeling – Cardiomegaly and in particular LA and LV dilation are the usual consequences of chronic MR. Right-sided enlargement is variable. These abnormalities have been summarized previously and are discussed more under *Staging*. What is less known about this remodeling are changes that occur at the tissue level, such as intramural arterial sclerosis and myocardial fibrosis. Similarly, the contractile properties of the myocardial cell have mainly been studied in acute canine models using large-breed dogs, not in spontaneous cases. Thus the potential benefits of drug therapies at the tissue level is uncertain in spontaneous MVD. Presumably, drugs inhibiting RAAS should delay tissue remodeling, but this has not been proven or has only shown trends in clinical trials (BESST). Currently *only pimobendan has been shown to delay progression to CHF* or to definitively *reduce cardiac size* in advanced, preclinical MMVD.

Congestive Heart Failure – Heart failure is manifested clinically through signs of reduced cardiac output, such as exercise intolerance, and complications of organ congestion and edema. *Tachypnea* is the typical but nonspecific feature of left-sided CHF and therefore helpful in identifying dogs with impending pulmonary edema. This more rapid (but shallow) ventilatory pattern probably represents a mechanical compensation (faster, more shallow breaths) for the pulmonary congestion and interstitial edema that stiffen the lungs. Physical examination at this stage might only reveal a prominent murmur and loud bronchial breathing (“bronchovesicular” sounds) unless there is concurrent pulmonary fibrosis or chronic bronchitis causing crackles or wheezes. Progressive alveolar pulmonary edema induces hypoxemia, hyperpnea (both rapid and deeper breaths), anxiety, orthopnea, and respiratory distress. Cough is common at this stage if not already present for other reasons. The typical dog with alveolar pulmonary edema will not lie down and often assumes a sitting position with abducted elbows and extended neck. Cyanosis or coughing up of foamy froth might be witnessed. At this stage auscultable pulmonary crackles are likely and a point of care ultrasound (POCUS) exam will demonstrate multiple B-lines. These nonattenuating reverberations are generated by the interface of intrapulmonary air and liquid.

Key radiographic findings of left sided CHF include dilation of the LA and LV, pulmonary venous congestion or distension, and pulmonary infiltrates compatible with cardiogenic edema. Cardiomegaly can be severe in chronic MVD or more subtle in the setting of major (strut) chordae tendineae rupture.

Pulmonary densities of left-sided CHF are usually bilateral, interstitial and alveolar infiltrates, located around the bronchial hilum. Fulminant lung edema is often widespread, and a right-sided preponderance is not surprising.



Any pleural effusions related to CHF in MVD tend to be small. Moderate to large effusions usually relate to end-stage CHF with AF, cardiac tamponade from an unrelated disease, or to a concurrent thoracic infection or malignancy.

Clinical implications: These clinical findings accompanying the typical murmur of MR are sufficient to initiate diuretic, oxygen and sedation therapy for CHF in dogs with resting tachypnea or overt dyspnea. Diagnosis should be confirmed by radiography once the patient is stable. Diuretics doses should reduce clinical, radiographic and ultrasound signs of pulmonary edema within 24 to 48 hours, and this is often accompanied by a reduction in overall heart and pulmonary vascular size.

Metabolic Disturbances – A number of biochemical disturbances can be observed in dogs with MVD suffering from CHF. These might relate to organ *congestion* (arterial hypoxemia from pulmonary edema; azotemia from renal congestion¹², protein losing enteropathy from gut congestion); *reduced cardiac output and oxygen delivery* (prerenal azotemia and lactic acidosis), and diuretic therapy that contracts the plasma volume (causing azotemia) and depletes electrolytes (especially chloride, potassium and magnesium leading to metabolic alkalosis, diuretic resistance, and ectopy). Drugs that alter vascular responses and blood pressure (vasodilators, ACE-inhibitors, diuretics) can lower blood pressure and alter intra-renal hemodynamics, occasionally causing acute kidney failure. Uncommonly comorbidities *precipitate* CHF in a stable MMVD dog; namely moderate to severe anemia, iatrogenic thyrotoxicosis, or systemic infection with fever.

Pulmonary hypertension – PHT is an elevated pressure in the pulmonary artery (PA systolic pressure exceeding 35 to 40 mm Hg; normally it is <25 mm Hg). The PHT found in dogs with MMVD can involve different etiologies or “groups”. Typically the cause of PH in MMVD is elevated LA pressure (Group II, PHT). Mean LA pressures in dogs often exceed 40 mm Hg (>4x normal) and the end-systolic, regurgitant V-wave commonly approaches 50 to 60 mm Hg in severe MR (normal <10 mm Hg). Unfortunately, noninvasive diagnosis of PH in MMVD requires Doppler echocardiography.

Therapeutic implications: The *post-capillary PH* due to left heart failure is not treated with sildenafil or related drugs; lowering LA pressure (post-capillary PHT) and reducing (precapillary) reactive pulmonary vasoconstriction from high LA pressure and lung edema are the goals. In contrast some dogs demonstrate persistent evidence for Group I (arterial), III (lung disease) or potentially IV (pulmonary embolic) PHT. These are challenging to diagnosis with certainly without advanced imaging diagnostics. Dogs symptomatic (collapse, ascites) with these forms of “precapillary” PHT often have relatively smaller left heart chambers and some benefit from the PDE-V inhibitors like sildenafil (1-3 mg/kg, PO t.i.d.) and tadalafil (same daily dose, divided b.i.d.).

Cardiac Arrhythmias – As summarized earlier, atrial arrhythmias are the main ECG abnormality identified in clinical patients with MMVD. Although isolated APCs are not treated, sustained atrial tachycardia or atrial fibrillation will require heart rate control. The *therapeutic implication* then is for limited use of digoxin and diltiazem to delay atrioventricular conduction and control the resting hospital ventricular rate to <140/minute (and average home rate to <110-120/min) should these

supraventricular tachyarrhythmias occur. Spontaneously conversion to sinus rhythm sometimes occurs, mainly in smaller breeds (with or without therapy). Holter ECGs are helpful in AF to objectively determine the heart rate; inexpensive “rate monitoring” Holter ECGs often suffice.

Comorbidities – Other diseases can influence the clinical *presentation, differential diagnosis, and management* of dogs with MMVD, including *common respiratory disorders* like laryngeal dysfunction, tracheal collapse, idiopathic chronic bronchitis, and idiopathic pulmonary fibrosis. These can cause variably coughing, tachypnea, dyspnea, and inspiratory lung crackles. The latter sign is easily confused with the crackles of acute or recurrent pulmonary edema. Many dogs are also affected by chronic kidney diseases that can worsen with onset or after treatment of CHF.

Systemic hypertension due to renal disease or Cushing’s disease can impair left heart function and increases the magnitude of MR by increasing LV systolic pressure. Although the so-called cardiorenal syndrome requires better definition in dogs, systemic venous congestion and CHF are known to impair canine renal function.¹² The *therapeutic implications* include more preemptive use of ACE-inhibitors and considering vasodilators such as amlodipine or hydralazine or intravenous treatments with nitroprusside or IV nitroglycerine (in emergency/critical care centers).

Staging of Myxomatous Mitral Valve Disease

The four major clinical stages of myxomatous valve disease have been classified by a consensus panel of the ACVIM and are summarized in **Table 1**.⁹ There are a number of controversies regarding staging of MMVD, and as therapy is guided by this organization, understanding the stage definitions and the echocardiographic indices underpinning these are relevant. Stage **B1** is consistently misidentified – even in the current literature – as representing a “normal” heart size. Although cardiac size might fall within normal prediction limits, Stage B1 was revised to also include those dogs with mild cardiomegaly, a common finding in MVD. ⁹ For example, mild LV dilation and mild LA dilation (based on 2D, long-axis, LA to aortic ratios exceeding 2.65) are often identified by 2D echocardiography. However, treatment should not begin prematurely based on finding “cardiomegaly” but instead focus on specific criteria summarized in **Table 2**.

Table 1. ACVIM Stages of Myxomatous Mitral Valve Disease
Stage A – Dogs at risk for developing myxomatous valvular disease
Stage B – A dog with objective evidence of MMVD (murmur of MR) without signs of heart failure
B1 – Heart size is either normal or cardiomegaly is present but insufficient to begin therapy
B2 – Sufficient remodeling has occurred to begin treatment based on clinical trial evidence
Stage C – A dog is currently in congestive failure or previously experienced CHF (on therapy)
Stage D – A dog with CHF refractory to “standard” drug therapy and standard dosages

Stage **B2** is identified by results of clinical examination and cardiac imaging (*Table 2*). This stage is defined as a dog with MMVD exhibiting *sufficient cardiac remodeling to warrant treatment proven*

to delay CHF based on a clinical trial. Currently this stage is defined by the pivotal EPIC clinical trial.⁹ Similar entry criteria have been used for recent studies for medical treatments to delay CHF.¹¹

The key echocardiographic features used for staging asymptomatic dogs with MMVD (i.e. Stages B1 and B2) are the normalized LV end-diastolic dimension allometrically normalized to body size (LVEDDN) and the size of the left atrium. Of these the LVEDDN is most consistent and predictive, and this is readily measured and calculated by clinicians holding basic 2DE imaging skills.

For this determination the LV internal diastolic dimension in cm should be divided by the bodyweight (in kg) raised to the 0.294 power. Assuming the left atrium is also dilated the dog is staged as B2 based on current ACVIM guidelines. The LA was measured in the EPIC trial from the short-axis ratio of LA/Ao but considerable variability occurs with those measurements. Realistically, a long-axis, end-systolic image can also be used. When the LA(cm)/BW (kg)^{0.31} equals or exceeds 1.8 to 1.9 there is LA dilation. One can also determine LA enlargement from VLAS.

Table 2. EPIC Study Criteria for Stage B2 of Myxomatous Mitral Valve Disease
Small breed (<20 kg), older dog (6 years of age or greater)
Grade 3/6 murmur or louder murmur of mitral regurgitation (<i>i.e.</i> , a radiating murmur)*
Normalized LV end-diastolic dimension (LVEDDN) ≥1.7. Calculated from M-mode (or 2D) echocardiogram as: LVEDDN = LVEDD (cm)/bodyweight(kg) ^{0.294}
LA/Ao (<u>short-axis method</u>) ≥1.6 indicating left atrial dilation
Vertebral heart sum/scale/score (VHS) >10.5 [#]
*Ideally mitral regurgitation is confirmed using Doppler echocardiography ^The exponent 0.294 should be used for staging MMVD based on the EPIC trial; however, exponents of 0.31 to 0.33 are more applicable for identifying LV dilation in non-sighthound dogs #Normal VHS for many dogs; this cutoff should not be used to initiate therapy (see text)

Progressive increases in cardiac size detected by radiography and natriuretic peptides (NT-proBNP) also can contribute to recognizing Stage B2, *especially when echocardiography is unavailable*.^{5,11,13-15} A rate of change in VHS of ≥0.1 VB/month over six months or more^{14,15}, in combination with a VLAS ≥3.0, justifies classifying a dog in Stage B2 in the author’s experience and is supported by at least three studies. An absolute VHS of 11.5 to 11.7 also supports a staging of B2, but various *breed exceptions* demand the clinician review *on-line charts and references* before using those cut-offs. As most dogs are never examined by echocardiography, these are practical alternatives, provided serial examinations are performed consistently and with attention to detail.

To summarize, Stage B1 can include dogs with mild cardiomegaly. Until new data are presented, the EPIC clinical trial provides the distinction between Stages B1 and B2 (*Table 2*).⁹ Although some clinicians assume that simply finding LA dilation is sufficient to initiate treatment, that approach is unsupported by clinical trial data, including EPIC. The criterion of LVEDDN ≥1.7 (using an exponent of 0.294) seems equally—if not more—important,⁵ and LV chamber dimension at end-diastole is

more consistent to measure than the 2D, short-axis, LA/Ao in “early” diastole. Additionally, the radiographic VHS criterion of >10.5 vertebral bodies used in EPIC should not be used in isolation to classify or initiate therapy in stage B2; it is normal in many healthy dogs, including the Cavalier King Charles spaniel. Again values exceeding 11.5 – 11.7 VB are likely to related to stage B2.

A second staging issue that affects treatment is deciding if respiratory signs in dogs with MVD are due to CHF (Stage C or D) or from primary airway or pulmonary disease. Both cardiac and primary respiratory disease often occur together, and in the absence of definitive respiratory diagnostics, empiric treatments – Including short courses of antimicrobials (doxycycline) or prednisone (for airway inflammation) – might be needed to address this confusion.

Two additional challenges in staging are establishing a definitive diagnosis of PHT and defining Stages D. The first problem relates to the need for Doppler echocardiography to confirm this pathophysiology, quantify the severity of PHT, and determine if sildenafil or another phosphodiesterase-V inhibitor should be started for precapillary PHT. The distinction between stages C and D is somewhat arbitrary, in part because cardiologists are not in full agreement about “standard” therapy and dosages. Clinically this is of minor practical importance as clinicians will escalate therapy as needed to control “symptoms” of advanced CHF (see later in these notes).

Medical Therapy of Myxomatous Valve Disease – In-Brief

From the author’s perspective, these six things matter most when considering therapy of dogs with degenerative valvular disease: 1) Does a clinical trial of representative dogs show that the onset of *CHF is delayed* by a treatment?; 2) Does the treatment allow patients to *live longer*?; 3) Is the *quality of life* maintained or improved with treatment?; 4) Are *unplanned hospitalizations* (and related euthanasia) reduced?; 5) Are frequency and severity of *adverse drug effects* acceptable; and 6) Is cardiac therapy *cost-effect* to the client?

In addition to studies that yield a “statistically significant” difference, understanding the *magnitude* of any diagnostic or treatment *effect size* is more important. Giving a medicine for three years to obtain a two-month delay in CHF would not be very meaningful to most clients or veterinarians and such only adds actual inconvenience to our clients’ and patients’ lives. The ability of a client to *administer the medications* is also relevant when prescribing long-term drug therapy. Poor *medication compliance* or difficult-to-treat dogs can thwart even the best treatment plans.

Perspective on Clinical Trials of MMVD

Most clinical trials provide useful information, but none are without limitations and nearly all directed by pharmaceutical companies whose studies often failure to address all the questions of relevance to clinicians caring for dogs with heart disease. When there is a *trend* for efficacy or a *theoretical* (mechanistic) benefit of a treatment, some clinicians will empirically recommend that therapy. Others will demand stronger evidence. Clients should understand the basics related to available evidence, magnitude of any treatment benefit, cost, and potential for adverse effects. As an example, despite the theoretical benefits, most studies of chronic degenerative valvular heart disease in dogs have failed to show a clear or quantitatively

important benefit of renin-angiotensin-aldosterone system (RAAS) inhibition in stage B2 of the disease. While there was a trend for benefit in the VETPROOF trial of the angiotensin converting enzyme (ACE) inhibitor enalapril, the overall treatment benefit for delaying CHF was relatively short. Other studies such as SVEP and DeLAY have not shown any benefit of ACE-inhibition or combined RAAS inhibition (benazepril + spironolactone) on prolonging the onset of Stage B2 to CHF or sudden cardiac death. Aspects of most of these studies have been debated among cardiologists in terms of the *patient sampling, study design, and especially drug dosing*. Regardless, the evidence of benefit for RAAS inhibition in Stage B2 degenerative valvular disease can be summarized (in the author's opinion) as lacking or modest. In support of this view, the current ACVIM Consensus Panel on treatment of MMVD (Keene, et al., 2019) recommends RAAS inhibition for Stages B2 and C but the panel members were largely split on that opinion, especially for Stage B2. While there might be other indications for considering an ACE-inhibitor prior to CHF, including dogs with other medical disorders (systemic hypertension, chronic kidney disease), compelling evidence of benefit for RAAS inhibition is currently lacking. Nevertheless many cardiologists in North America do prescribe RAAS inhibition citing insufficient trial designs and too-low dosing, and the fact that most of these drugs are generic in the USA (this is not true for Europe and many other countries). Some cardiologists defer RAAS activation to "late Stage B2" dogs – citing B2 is not a homogenous class and that dogs with severe cardiomegaly and what is presumed as incipient CHF would likely benefit.

Similarly, the evidence for RAAS inhibition in Stage C of myxomatous mitral valve disease (MMVD) – CHF – has been debated, mainly related to its incremental value in dogs already receiving a loop diuretic and pimobendan. Enalapril, benazepril and combined RAAS inhibition have been beneficial in a number of studies when compared to a loop diuretic and placebo; however, a definitive study that involves optimal RAAS inhibition in conjunction with pimobendan has not yet been performed (in the author's opinion). Similar concerns have been expressed about pimobendan trials that have used relatively modest dosages of ACE-inhibitors as opposed to what many consider optimal RAAS blockade.

Treatment Across the Four Stages of MMVD – Summary

Stages **A** and **B1** are not treated. Therapy in **Stage B2** has been evaluated in four clinical trials: SVEP, VETPROOF, EPIC, and DeLAY.^{10,11,16,17} The major findings are that pimobendan is effective in delaying the onset of CHF in dogs with Stage B2 MMVD by approximately 15 months (on average). In contrast, renin-angiotensin-aldosterone system (RAAS) inhibition has either been ineffective or demonstrated only modest trends toward delaying CHF. Thus, dogs in Stage B2 should receive pimobendan (0.2 to 0.3 mg/kg PO twice a day was the trial dosage), but the use of RAAS inhibition is considered optional, and there is no clear consensus about this therapy. It might be more justified if serial radiographs show marked progression to cardiomegaly and doses of 0.5 mg/kg of enalapril or benazepril b.i.d. are recommended at this stage of "delay" of CHF.

Additionally, *no specific diet* can be recommended at this stage based on objective evidence. The recent CARMINE diet study (unpublished) has been reported as negative for delaying stage B1 to B2. However, maintaining an optimal weight and restricting high-sodium treats seem reasonable, and high-legume diets might be worth avoiding due to uncertain effects on cardiac function.

Inasmuch as surgical and transcatheter repairs of the valve are impractical for all but a handful of dogs, medical treatments are needed for stages B2 through D. Some drugs used to treat CHF exert

strong hemodynamic effects (loop diuretics, pimobendan, vasodilators), while others (angiotensin-converting enzyme inhibitors and spironolactone) are used to blunt the RAAS.

Patients in **acute CHF from MVD** (usually **Stage C**) should receive intravenous furosemide, oral or intravenous pimobendan, and sedation (butorphanol) and oxygen as needed. Abdominocentesis is indicated to relieve pressure on the diaphragm and abdominal organs when a large volume of ascites is present. Thoracocentesis is rarely needed but important for moderate to large pleural effusions. In selected cases, LV load reduction with sodium nitroprusside, nitroglycerin (IV or ointment), amlodipine, or hydralazine (oral or IV) can be helpful for treating fulminating pulmonary edema or concurrent systemic hypertension.

The author’s approach to **home therapy** in **Stages C and D** is summarized in **Table 3**. This medical therapy typically involves “quad therapy” using furosemide, pimobendan, enalapril or benazepril and spironolactone, accepting the level of evidence for this combined medical treatment is incomplete. Medical therapy should be augmented with appropriate dietary measures that progressively reduce sodium intake (while maintaining sufficient caloric intake), ensure consumption of sufficient calories and high-quality protein, and potentially include additional micronutrients or dietary supplements. Some of the cardiac diets (e.g. Purina CardioCare® dry and canned and Royal Canin Early Cardiac Support Diet® dry) can be suggested to clients who want specific recommendations. Importantly the patient must eat the food! Restricted exercise along with regular patient home- and clinic monitoring are important.

Table 3. Medical Therapy of Myxomatous Mitral Valve Disease	
Furosemide (Torsemide)	Loop diuretics (torsemide for Stage D)
Pimobendan	Inodilator (positive inotrope + vasodilator)
Enalapril Benazepril Quinapril	Angiotensin converting enzyme inhibitors
Spironolactone	Mineralocorticoid receptor blocker
Other vasodilators (see text)	For acute pulmonary edema; resistant systemic or pulmonary hypertension; Stage D CHF (see text)
Antiarrhythmic drugs	If needed for atrial fibrillation or ventricular ectopy

Although different clinical trials both support and refute prescribing all four of these drugs for chronic CHF, in the author’s opinion, no published study has *optimally* combined loop diuretics, pimobendan, and RAAS inhibition. Published clinical trials have mainly compared one drug class (or drug combination) to either placebo or another drug class,¹⁸⁻²⁰ without incorporating an optimally-dosed “quad-therapy” treatment group. The main controversy resides in the value (and cost-benefit) of adding RAAS inhibition to background therapies of a loop diuretic and pimobendan for CHF due to MMVD. The recent BESST study²⁰ demonstrated a benefit of more aggressive benazepril + spironolactone RAAS inhibition (with furosemide), compared to the loop diuretic and

benazepril alone. However, this trial failed to include pimobendan – an approved standard of care – in either treatment group. Clearly additional studies are needed.

Progressive CHF (Stage D) might require switching to another loop diuretic (torsemide) with better absorption properties and duration of action; prescribing pimobendan (extralabel) at higher and more frequent (3 times a day) doses (e.g. 0.5 to 0.6 mg/kg PO t.i.d.); and adjusting ACE-inhibitors and vasodilator therapies to manage acute or progressive azotemia or unload the LV. Here a cardiologist can be helpful in managing challenging canine patients or reassuring the treatment plan is optimal. Digoxin (beware: renal elimination; measure trough serum concentration aiming for 0.8 to 1.2 ng/ml) and diltiazem (initially 4-6 mg/kg daily in divided doses) are prescribed for AF if present. Sildenafil is used for severe, symptomatic precapillary PHT after left-sided CHF has been medically managed. Clients are instructed to monitor sleeping respiratory rate (<30 breaths per minute is good), ensure medication compliance, and observe for quality-of-life indicators (appetite, exercise capacity, level of interest, and clinical signs).

Medical Therapy of Myxomatous Valve Disease – DETAILS

The following provides the author’s approach to managing different canine patients with MVD at different stages or with other comorbidities.

Managing Initial Clinical Signs In Mitral Valve Disease

Perhaps the major classification and management challenge for dogs in subclass B2 are those with a murmur and cardiomegaly, but where *coughing or tachypnea* is unrelated to CHF or left overt mainstem bronchial compression. As many dogs – especially those of smaller breeds – suffer from both myxomatous mitral valve disease (MMVD) and primary bronchopulmonary comorbidities the clinical signs can be confusing. Thus, laryngeal disease, tracheal collapse, *chronic bronchitis*, *bronchomalacia*, and *pulmonary fibrosis* need to be considered as causes of respiratory signs, and these comorbidities might require noncardiac medicines (at this and any stage of MMVD). Distinguishing a dog with Stage B2 of MMVD and concurrent pulmonary disease from a dog with “early” Stage C heart failure is challenging, even with a full cardiac and respiratory workup. Definitive respiratory evaluation often requires airway endoscopy and sampling, or even computerized tomography; these tests are rarely done or client-accepted. When coughing or tachypnea is due to MMVD (explained by bronchial compression or development of CHF), the dog should reasonably fulfill EPIC criteria and be started on cardiac drugs. Dogs not fulfilling these criteria and with “normal for age” pulmonary fields likely have primary airway disease.

The author’s approach to management of these dogs is to recommend a respiratory workup if the patient’s anesthetic risk is reasonable, and most Stage B2 dogs can be safely anesthetized for these procedures or others like short to moderate length dentistry. As nearly all of these evaluations are refused, we determine if the dog fulfills criteria for Stage B2, and if so prescribe pimobendan (0.2 to 0.3 mg/kg PO q12h) and if symptomatic enalapril (0.25 mg/kg q12h PO for two weeks then 0.5 mg/kg q12h PO thereafter); benazepril also can be used at targeted dose between 0.25 to 0.5

mg/kg q12h PO. Additionally, a low dose of furosemide (between 1-2 mg/kg PO once or twice daily) is prescribed for 7 to 10 days, and the patient reassessed by phone or in the clinic in about a week. In most cases, if the cough improves by >75% the therapy with pimobendan and the ACE-inhibitor is continued (some lesser response is common to observe). The furosemide can be stopped if sleeping respiratory rate is normal and reinstated if clinical signs or coughing or tachypnea recur. If the benefit of this cardiac therapy is marginal, the cough is likely due to airway disease (or tachypnea due to another cause such a pulmonary fibrosis) and the patient will require either respiratory diagnostics or empirical therapy (see below). The dog's oral cavity also should be assessed, and dental procedures considered – these are better completed now than after the dog has manifested CHF. Dental procedures can permit assessment of laryngeal function during intubation and at least a blind bronchoalveolar lavage procedure for airway cytology and culture at the time of the dentistry; these can be done in <5 minutes at the onset of the procedure.

If a dog with MMVD does not fulfill B2 criteria, or if a “B2 dog” fails to respond to the above treatment, in particular the low dose of a diuretic and pimobendan, the cause of the coughing or tachypnea is reconsidered. In addition to airways diseases, pneumonia, thoracic neoplasia, and heartworm disease should be entertained. When diagnostic testing is limited to thoracic radiography and blood testing, a second opinion regarding the radiographs should be obtained and empirical treatment considered. The author starts with a trial course of doxycycline for 10 days, and if beneficial, it is continued for three weeks. If this treatment fails to substantially improve coughing, a short course of prednisone at an anti-inflammatory dose (e.g., 0.5 mg/kg/day) is likely to reduce signs when these are caused by noninfective bronchitis. Cough suppressants such as hydrocodone can be prescribed as a last resort for symptom relief (starting at 0.1 to 0.2 mg/kg PO b.i.d. to t.i.d.; then PRN, expect incremental doses will be needed). Surprisingly (to me), the occasional dog seems to respond to long-acting theophylline (up to 10 mg/kg q12h PO).

Stages C & D: Acute Pulmonary Edema from Left-Sided CHF

The combination of sedation, oxygen, furosemide, pimobendan, and potentially topical nitroglycerine (or sodium nitroprusside) is recommended for dogs with respiratory distress or hyperpnea caused by pulmonary edema. This can be remembered by the mnemonic “**SO FINE**”, for **S**edation, **O**xygen, **F**urosemide, **I**notropic support (pimobendan), **N**itroglycerine, and **E**xtra treatments (such as abdominocentesis or antiarrhythmic drug therapy if indicated). Sedation is accomplished with butorphanol (0.15 to 0.2 mg/kg IV or 0.20 to 0.3 mg/kg IM, repeated in 30 to 60 minutes if needed). If patients become heavily sedated, the torso is positioned in sternal recumbency, elbows abducted, chin supported with a towel or soft pad and the neck extended. Nasal oxygen prongs can be inserted for better oxygenation of saturations remain low. After an initial IV or IM bolus of 2 to 3 mg/kg furosemide, the dosage, route, and frequency of furosemide can be adjusted to the clinical response (respiratory rate, anxiety, auscultation, point-of-care ultrasound of the lung). Doses are repeated if the respiratory rate and effort fail to decrease, or if the bladder does not fill (or void) within 60-90 minutes. In life-threatening pulmonary edema, a

constant rate infusion of furosemide (0.66 mg/kg/hour; occasionally using higher doses) can be considered. Once prominent diuresis occurs the infusion or bolus doses are reduced. With acute pulmonary edema there is often a lag between diuresis and the return to more normal pulmonary function, especially if the pulmonary capillary membranes have been damaged by high pressure edema. Whether continual high-dose infusions or boluses of furosemide are beneficial or simply coincidental with improved lung function over time has not been well studied in spontaneous CHF. The author is guided in part by the volume of urine produced and is probably more patient than many in terms of dose escalation. Although IV preparations of pimobendan are available outside the US, oral administration of Vetmedin® is typical (dosed at 0.25 to 0.3 mg/kg and given q8h for acute CHF; frequency is reduced to the labeled q12h once the dog is stable). Many cardiologists do not use nitrates in this setting of acute pulmonary edema due to a lack of definitive evidence; however, the author includes topical 2% nitroglycerine ointment (¼ to ½ inch for a 5 to 15 kg dog) for life-threatening pulmonary edema. Critical care and emergency centers have the option to switch to nitroprusside (starting at 1 mcg/kg/minute with constant blood pressure monitoring and titrating systolic BP to 90 mm Hg) or intravenous nitroglycerine if initial therapy is ineffective. In general practice, edema severe enough to cause expectoration of froth should prompt consideration of adding nitroglycerine ointment and an arterial dilator such as amlodipine (0.1 mg/kg PO) or hydralazine (1 – 2 mg/kg PO), so long as the systolic BP exceeds 100 mm Hg.

With this treatment plan, anxiety is reduced; diuresis is initiated; oxygen saturation is increased; ventricular loading and the tendency towards pulmonary edema are decreased; and myocardial contractility is supported. Aggressive afterload reduction with sodium nitroprusside or direct arterial vasodilators are usually reserved to cases of “white-out lungs” or when the dog is expectorating froth and fatiguing. In these dogs, the only remaining option is artificial ventilation.

Arrhythmias in Acute CHF

Compared to dilated cardiomyopathy, dogs with MMVD are less often affected by serious heart rhythm disturbances. However, atrial fibrillation can precipitate CHF in previously stable canine patients. This problem is usually managed with heart rate control as opposed to cardioversion (to normal rhythm). Rate control involves initiation of oral digoxin (0.005 to 0.01 mg/kg PO q12h) with introduction of increasing doses of oral diltiazem within hours of admission. Diltiazem is titrated to a resting hospital heart rate of 120 to 160/min and is optimally evaluated at follow up with a 24-hour (Holter) ECG (optimal 24h rate unknown but likely in the 90 to 120/minute range). Effective treatment of CHF is also useful as it allows for some withdrawal of sympathetic tone with reduction of ventricular rate response. Electrical cardioversion from AF to sinus rhythm has been used by some in managing this arrhythmia, but our experience is that dogs in CHF usually revert to AF in relatively soon, so we mainly recommend rate control. Isolated premature ventricular complexes (PVCs) are not treated in CHF cases. However, sustained runs of rapid ventricular tachycardia require treatment to maintain BP; these are managed with boluses of lidocaine followed by a constant rate infusion of lidocaine. Mexiletine, sotalol and amiodarone are all

potentially useful for suppression of life-threatening ventricular tachycardia, but each drug carries serious adverse effects.

Chronic Home Management Of CHF (Stages C & D)

The *transition from hospital to home therapy* of CHF usually begins within 48 hours of admission. During that interval, the initial diagnostic workup should have been completed. The typical transition to “Home Therapy” includes the following steps: 1) sedatives are discontinued; 2) oxygen is reduced and stopped; 3) parenteral furosemide is replaced with oral furosemide; 4) pimobendan is continued twice daily (digoxin is used only for rate control in AF and the dose should be conservative pending recheck of serum concentrations); 5) nitrates (if used) are replaced by an ACE-inhibitor or a combination ACE-inhibitor with spironolactone (Cardalis®); and the client is counseled regarding a sodium-restricted diet and pros/cons of various nutraceuticals. Most dogs have some mild azotemia and hypokalemia/hypochloremia following aggressive diuresis. For that reason many cardiologists delay RAAS inhibition to the first recheck. However, if renal function is normal or <2x baseline values, most can be started on 0.5 mg/kg enalapril or 0.25 to 0.5 mg/kg of benazepril once daily; the dose can be increased at the time of first recheck assuming acceptable serum BUN and creatine.

The basic home treatment plan for chronic CHF in the dog with Stage C degenerative valve disease involves “**Dogs Are For Special People**” therapy: Dietary modifications (modest sodium restriction and superior quality protein; see prior diet suggestions); an ACE-inhibitor, Furosemide, Spironolactone, and Pimobendan. This therapy is different than standard heart failure treatment in humans (see “Future Directions” below); veterinarians are likely to be asked about this by other healthcare providers. Most dogs are treated twice daily with furosemide (2-4 mg/kg PO q12h) and pimobendan (0.25-0.3 mg/kg PO q12h). Various once or twice daily approaches are used for RAAS antagonists (ACE-inhibitors and spironolactone), although recent work suggests both enalapril and benazepril should be given twice daily with targeted total doses of 0.75-1.0 mg/kg/day for enalapril and 0.5 to 1.0 mg/kg/day for benazepril. Generic spironolactone (2 mg/kg day) can be prescribed in a single or divided dose at release or at recheck. A combined product of benazepril/spironolactone (Cardalis®) is now approved for use in the USA. This formulation can be more convenient to give for some owners but will increase medication costs and includes a fixed-dose approach. As noted, the author usually increases the frequency of administration of enalapril and of benazepril to twice daily at the first recheck if renal function is relatively stable.

Additional therapy may be useful for treating special problems, or should the dog progress from Stage C to stage D. In cases of severe PH with symptoms such as exertional collapse or ascites, sildenafil (1-3 mg/kg PO q8h of the generic Revatio® 20 mg tablet) is considered as a relatively selective pulmonary vascular vasodilator to unload the right ventricle (tadalafil or generic Cialis® at the same total daily dose, divided b.i.d.). When AF complicates CHF, both digoxin and diltiazem are used to gain better heart rate control. The trough serum digoxin concentration (8-12 hours post-pill) should be about 0.8 to 1.2 ng/ml (the author prefers this to the laboratory recommended

4h post-pill sample with higher concentrations). Monitoring of blood concentration is crucial to avoid adverse effects of anorexia, vomiting, diarrhea, and arrhythmias that might be misinterpreted as signs of progressive CHF. Long-acting diltiazem (e.g., Dilacor® or diltiazem-XR) is usually given twice daily for heart rate control of atrial fibrillation. Total daily doses of standard or long-acting diltiazem usually ranges from an initial daily dose of ~4-6 mg/kg/day to 6 to 10 mg/kg per day in divided doses, titrated to heart rate. Diltiazem can cause anorexia and GI disturbances in some dogs (often overlooked). Isolated premature ventricular complexes (PVCs, VPCs) and nonsustained runs of VT are not treated, unless the QRS morphology or timing appear “dangerous” (such as R on T; very rapid; multiform VT; or torsade de pointes): In reality, most clients are willing to assume a risk of sudden death for their dog (and most hope that will occur instead of intractable CHF or euthanasia). Sustained ventricular arrhythmias – especially when causing signs – are managed with mexiletine (4-8 mg/kg PO q8h), sotalol (1.5-2 mg/kg PO q12h – once CHF is controlled as it is a negative inotrope), or amiodarone (read about it! – initial dose of 4-6 mg/kg PO q12h).

Strategies for managing refractory pulmonary edema or ascites (**Stage D**) include first reviewing client compliance and optimizing the dosages of currently-prescribed drugs. Pimobendan (Vetmedin®) dosage is generally increased to 0.4 to 0.5 mg/kg PO q8h (extra-label dosing). Torsemide is substituted for furosemide at approximately 1/8 to 1/12 of the furosemide daily dose, divided b.i.d. For example, if the dog received 50 mg of furosemide daily, the torsemide dose would be ½ of a 5 mg tablet, PO, twice daily. In general, the author considers torsemide substitution for dogs needing more than 8 mg/kg/day of furosemide or in dogs with severe right-sided CHF with ascites. Abdominal paracentesis should be considered to reduce tense ascites when present and sildenafil (generic Revatio®) or tadalafil is offered when severe PH is documented by echocardiography and causing clinical signs of ascites or exertional collapse.

Follow-Up Evaluations

Rechecks for dogs with chronic CHF are scheduled initially at about one week after release, then one month later, then every 3 to 4 months or as needed. Drug dosing, compliance and adverse effects of treatments are discussed with the client at all stages of therapy. Many clients benefit from the veterinarian’s or veterinary technician’s experience regarding “how to medicate” dogs. Emphasis for effective treatment is on quality of life (*eating well, sleeping comfortably, capacity for walking/mobility, family interaction, sleeping respiratory rate, and clinical signs of disease or drug toxicity*). Additional examinations of importance include physical examination findings indicating controlled CHF; bodyweight/cachexia; arterial blood pressure; renal function and electrolytes; heart rhythm; and thoracic radiography if respiratory symptoms are still present. Many dogs can be evaluated with a good history, physical examination, and radiographs if indicated based on history, respiratory rate and exam. Repeated echocardiography adds little to patient management. One exception is when cardiac tamponade occurs from rupture of the left atrium (these dogs present with collapse, hypotension, and softer murmurs and can benefit from

judicious pericardiocentesis of 10 to 20 ml of blood). Another indication for Doppler echocardiography is when signs of precapillary pulmonary hypertension develop (ascites in a dog without atrial fibrillation; recurrent exertional collapsing or syncope; relatively “clear” lung fields).

PROGNOSIS

The prognosis is a key client question, and it is difficult to predict the outcome for a single canine patient, and most outcome studies are retrospective and allow euthanasia as an outcome. In such cases client expectations, perceptions and economic resources will likely exert as much influence on the outcome as the skill of medical therapy and the client’s ability to medicate their dog. These issues are rarely if ever included in the data analysis.

The general prognosis for canine heart disease and CHF depends on the cause, severity (Stage), and care received. Most dogs survive >6 months on b.i.d. “quad therapy” and many >1 year following the first signs of CHF (Stage C). This is provided they receive optimal veterinary and home care. It may take weeks to fully stabilize the seriously ill dog with CHF. Clients should understand that not every dog will be well overnight, and regrettably, some clients run out of patience or financial resources and request euthanasia before treatment can really kick-in. As patients become managed, other problems might become evident. Some dogs with chronic left-sided CHF appear to develop pulmonary fibrosis at an accelerated rate. This comorbidity should not be misdiagnosed as uncontrolled CHF; the usual findings are tachypnea + crackles + “clear lung fields” radiographically. Dogs with chronic airway disease (tracheal or primary bronchus collapse, chronic bronchitis) may become symptomatic due to these diseases requiring other treatments for control (doxycycline, prednisone, cough suppressants). One of the most common reasons for treatment failure is the development of chronic renal failure with moderate to severe azotemia, especially if diuretic dosages cannot be reduced due to progressive fluid accumulation. A number of small studies have evaluated biomarkers (especially NT-pBNP) in dogs with CHF in terms of prognostic considerations. There is a statistical trend for higher levels to portend a worse outcome and a failure of blood natriuretic peptides to decrease with therapy is also a poor prognostic sign. Specific guidelines for modifying therapy based on natriuretic peptides are still needed. Dogs in Stage D are more likely to succumb within 3 to 6 months, even with aggressive therapy.

Summary & Future Directions

Degenerative valvular heart disease – the most important cause of canine cardiac disease and heart failure – is characterized by myxomatous change of the mitral and tricuspid valves. These morphologic changes lead to valvular regurgitation, typical murmurs of mitral and tricuspid regurgitation, and secondary cardiac remodeling. The diagnosis can be confirmed by echocardiography and staged with cardiac and thoracic imaging and measurement of circulating biomarkers. The ACVIM stages of MVD can guide appropriate diagnostics, pharmacotherapy, dietary management, monitoring, and lifestyle modifications.

Valvular heart disease in humans – and increasingly in dogs – is treated surgically or with transcatheter devices²¹ that reduce the amount of MR or TR. Surgical repair of the mitral valve can be effective but is very expensive and not widely available. Catheter delivered devices designed for dogs offer promise for improving clinical disease; currently these are available at limited centers. The technique of *left atrial decompression* (creating an acquired atrial septal defect to reduce left atrial pressure) has been beneficial to some dogs with Stage D CHF,²² and is currently under investigation. If proven more effective than escalating drug treatment, the procedure should be relatively available at referral centers.

In terms of newer or different medical therapies, as noted above, one cannot assume that dogs with MVD will respond to the same drug treatments used for human heart failure. For example, people with a “DCM phenotype” and many with heart failure and preserved LV EF (diastolic or combined diastolic/systolic heart failure) are treated with beta-blockers, SGLT inhibitors, antihypertensives, and neutral endopeptidase inhibitors (Entresto®); yet, none of these drugs are established therapies for dogs with CHF, although some are under study. In contrast, people are usually prescribed relatively small doses of diuretics on a per kg basis, and inotropic drugs are uncommonly used. (Pimobendan is specifically not approved for human use in North America due to the risk of proarrhythmia and sudden death). Appreciating these differences in treatments can be helpful when discussing therapy with clients who are also medical professionals.

Clearly questions persist about the *introduction and optimal dosing* of drugs used to delay and treat congestive heart failure in canine MVD. Treatments that delay or reverse the primary valvular lesion are currently unavailable but would be ideal. Device treatment of MMVD holds promise but also carry logistical and practical limitations for widespread delivery.

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