

# Canine Degenerative Myxomatous Mitral Valve Disease: Natural History, Clinical Presentation and Therapy

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## KEYWORDS

• Canine • Mitral valve • Myxomatous degeneration • Therapy

Chronic degenerative mitral valve disease as a result of myxomatous degeneration (MMVD) is the most common acquired cardiovascular disease in the dog representing 75% of all cardiovascular disease in this species.<sup>1–3</sup> Although the disease is more commonly diagnosed in small-breed dogs, it can also occur in large-breed dogs.<sup>4,5</sup> The prevalence of the disease has been correlated with the age and the breed. In some breeds, such as the cavalier King Charles spaniel, the prevalence of the disease in animals older than 10 years is greater than 90%.<sup>6–9</sup> Males are also reported to develop the disease at a younger age than females, which means that the prevalence at a given age is higher in males than in females.<sup>2,3</sup>

## NATURAL HISTORY

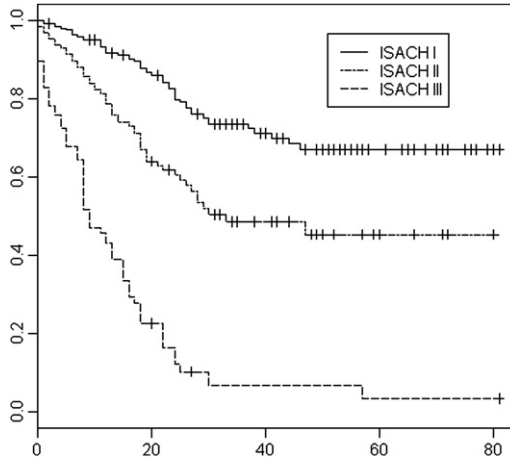
Although MMVD is a common cause of left-sided congestive heart failure (CHF) in dogs, there are few studies documenting its natural history, and most of the known data on survival for the affected dogs come from clinical trials or retrospective studies.<sup>10–16</sup> The disease is characterized by a long preclinical period and many dogs affected die for other reasons and do not progress to CHF.<sup>10,16</sup> In 1 study including 558 dogs affected by MMVD at different stages of CHF, more than 70% of asymptomatic dogs were alive at the end of the follow-up period of 6.6 years (**Fig. 1**).<sup>10</sup> In another recent study, 82% of asymptomatic dogs were still asymptomatic

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**Fig. 1.** Survival in 558 dogs with MMVD by heart failure classification according to the ISACHC. More than 60% of class I dogs were still alive at the end of the 70 months of observation period. Class ISACHC 2 dogs have 28 months median survival time. Class ISACHC 3 had a median survival time of 9 months. (From Borgarelli M, Savarino P, Crosara S, et al. Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *J Vet Intern Med* 2008;22:123; with permission.)

at 12 months from inclusion in the study.<sup>16</sup> A study aimed at evaluating the efficacy of treatment with enalapril, an angiotensin-converting enzyme inhibitor (ACE-I), in delaying the onset of heart failure in asymptomatic dogs showed a median time free of CHF of 851 days for the treated group and 778 days for the placebo group.<sup>17</sup> Another study with the same aim but including only cavalier King Charles spaniels reached similar results.<sup>11</sup> These data provide some evidence that asymptomatic MMVD is a relatively benign condition similar to what has been reported in people.

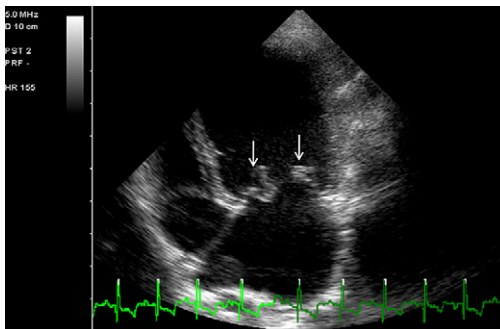
For dogs that progress to CHF, survival time can be related to several factors including owner compliance in providing adequate care, treatment, cardiovascular complications such as pulmonary hypertension or rupture of chordae tendinae, and the presence of other concomitant diseases. In our study of survival in MMVD, dogs with moderate or severe CHF (classes 2 and 3 according to the International Small Animal Cardiac Health Council [ISACHC] classification) had median survival times of 33 and 9 months, respectively.<sup>10</sup> Estimates of survival time in CHF caused by MMVD can also be inferred from the existing clinical trial data. The Long-Term Investigation of Veterinary Enalapril (LIVE) and BENazepril in Canine Heart Disease (BENCH) trials compared enalapril and benazepril, respectively, with placebo in canine patients with heart failure caused by either MMVD or dilated cardiomyopathy. More recently, QUEST was designed to compare the efficacy of pimobendan to benazepril in dogs receiving background therapy for furosemide with or without digoxin; heart failure caused by MMVD was the primary inclusion criterion. In the QUEST trial, the median survival time for all dogs to reach the primary end point represented by sudden cardiac death, euthanasia as a consequence of the cardiac disease, or treatment failure, was about 6 months.<sup>18</sup> Survival time was similar for the group of dogs in LIVE that were treated with enalapril.<sup>12</sup> In the BENCH study the mean survival time for dogs receiving benazepril was about 14 months.<sup>13</sup> Differences in these studies can be related to

differences in inclusion criteria and end points. The results of these studies suggest that dogs with moderate to severe CHF caused by MMVD can have relatively long survival with medical management.

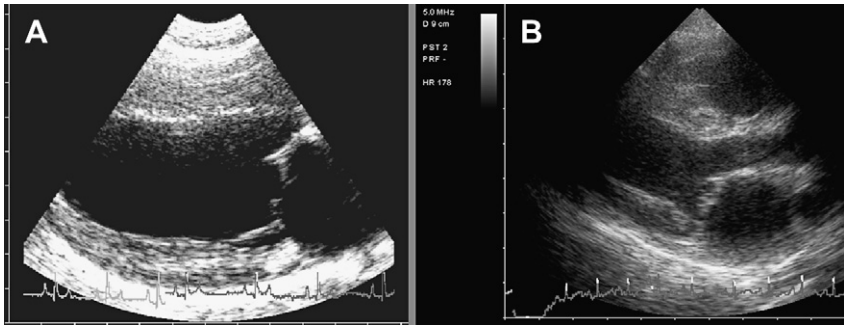
## DIAGNOSIS

Mitral valve regurgitation results in a systolic murmur that generally is heard best over the left cardiac apex. The diagnosis of MMVD can be suspected when this auscultatory finding is encountered in a patient of typical signalment. The intensity of the murmur has been correlated with the severity of MMVD in some studies.<sup>19,20</sup> In more severe cases, the murmur radiates toward the left heart base and to the right hemithorax as a consequence of left atrial and ventricular enlargement and in some patients, the concomitant presence of tricuspid regurgitation. In large-breed dogs the murmur may not correlate with the severity of the disease.<sup>5</sup> This difference might be because large-breed dogs affected by MMVD more commonly present with atrial fibrillation and myocardial failure; both these conditions can influence the intensity of the murmur. In the very early stage of the disease the only auscultatory finding may be the presence of a midsystolic click.<sup>21</sup> This sound is often intermittent and may be best heard using the diaphragm of the stethoscope. It is considered a reliable indicator of mitral valve prolapse (MVP) in people. The origin of the midsystolic click has been postulated to be caused by the tensing of redundant chordae tendinae and rapid deceleration of blood against the leaflets at maximum prolapse into the left atrium.<sup>22</sup>

Although the presence of a systolic left apical murmur in a typical breed is strongly suggestive of the presence of MMVD, echocardiographic confirmation of the diagnosis is required to exclude the presence of other cardiovascular diseases leading to mitral regurgitation, such as mitral valve dysplasia. The recently published American College of Veterinary Internal Medicine (ACVIM) consensus statement recommends that echocardiography should be performed to answer specific questions regarding the cause of the murmur of mitral regurgitation and presence of cardiac chamber enlargement in dogs with suspected MMVD.<sup>23</sup> The echocardiographic characteristics of MMVD include prolapse or thickening of 1 or both mitral valve leaflets (**Fig. 2**). MVP is characterized by an abnormal systolic displacement or bowing of the mitral valve leaflets from the left ventricle toward the left atrium. In dogs, some studies suggest that the right parasternal 4-chamber, long axis view is the gold standard view to identify the presence of MVP (**Fig. 3A**).<sup>24</sup> In people, the gold standard view to recognize MVP is a right parasternal long axis view that includes the left ventricular outflow tract (**Fig. 3B**). In people, the mitral valve has a saddle shape and reliance on other image



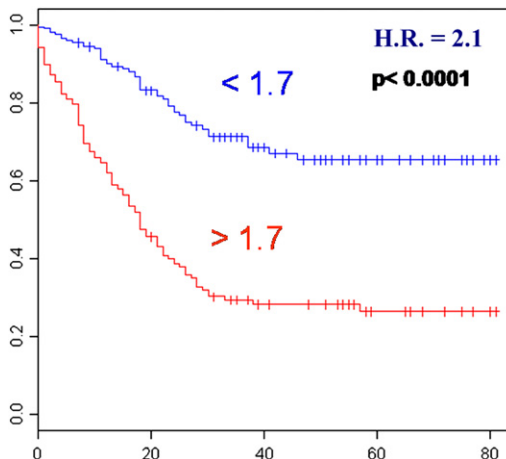
**Fig. 2.** Left apical 4-chamber view of a dog with MMVD. The arrows indicate the thick and irregular mitral valve leaflets.



**Fig. 3.** MVP in 2 dogs. (A) Right parasternal 4-chamber view. The anterior mitral valve leaflet appears displaced toward the left atrium. (B) Right parasternal long axis view. There is a mild prolapse of the mid portion of the anterior mitral valve leaflet with the parachute appearance of the valve.

planes, such as the apical view, can overestimate the prevalence of MVP.<sup>25</sup> In dogs, the mitral valve can have 1 of 2 different annular geometries, either circular or elliptical, and this could influence the echocardiographic estimation of the MVP (Borgarelli, personal communication, ACVIM Forum, Montreal, 2009). According to these data, we suggest that the presence of MVP in dogs should be confirmed in at least 2 echocardiographic views.

Echocardiography can also provide important information concerning the severity of the disease, such as the degree of left atrial and left ventricular enlargement, the presence of systolic or diastolic dysfunction and the diagnosis of pulmonary hypertension.<sup>26–29</sup> Some echocardiographic variables may be useful to identify individuals at increased risk of progression of the disease. Among these variables, left atrial enlargement seems to represent the most reliable independent indicator. In our study, the risk of death from cardiac disease for dogs with a left atrium/aortic root ratio exceeding 1.7 was 2.1 times that of dogs with smaller atria (**Fig. 4**).<sup>10</sup> Also, in the QUEST study, left



**Fig. 4.** Survival in 558 dogs with MMVD with a left atrium to aortic root ratio (La/Ao) less than 1.7 and in dogs with a LA/Ao greater than 1.7. Dogs without left atrial enlargement have a significantly longer survival time. OR, odds ratio.

atrial size was 1 of the independent predictors of outcome in dogs with symptomatic MMVD.<sup>18</sup>

The ACVIM consensus statement recommends thoracic radiography for all dogs with MMVD to assess the hemodynamic significance of the murmur and to obtain a baseline when the patient is asymptomatic.<sup>23</sup> Careful evaluation of thoracic radiographs may help in diagnosing concomitant primary respiratory diseases, such as tracheobronchial disease or lung tumors that may be the cause for the clinical signs, such as cough. Thoracic radiographs, together with physical examination, are also essential for monitoring dogs with MMVD. A recent study shows that radiographic assessment of left atrial size has higher interobserver agreement compared with assessment of left ventricular size in dogs with MMVD, and that left atrial size is most useful to assess the heart size and indirectly, the severity, of mitral regurgitation on radiographs.<sup>30</sup>

## CLINICAL PRESENTATION AND TREATMENT

MMVD is a chronic disease in which the clinical presentation is variable; some patients remain completely asymptomatic, whereas others develop life-threatening pulmonary edema. The authors of the ACVIM consensus statement proposed a modification of a staging system that has been used to classify human patients with heart failure. In this schema, dogs are placed in 1 of 4 categories according to clinical status and risk factors for the development of MMVD (**Table 1**).<sup>23</sup> This classification introduces the concept of patients at risk for developing heart disease but that currently do not have a heart disease. Included in this category are dogs of breeds predisposed to MMVD including the cavalier King Charles spaniel and the dachshund. The recognition of this stage should encourage the veterinary community to develop appropriate screening programs and adopt measures intended to reduce the risk for an animal of developing the disease. For the purpose of this review, 3 categories of patients are considered: the asymptomatic, the coughing, and the dog with documented presence of CHF.

### *The Asymptomatic Dog (Stage B ACVIM Consensus)*

This category includes dogs with MMVD that have not developed CHF. In our experience, this group represents most dogs presenting with MMVD. The minimum

| <b>Table 1</b>   |   |
|--|---|
| <b>Classification system for dogs affected by MMVD</b> |   |
|  | <b>Definition</b>   |
| Stage A  | Dogs at risk for developing MMVD that have no identifiable cardiac structural disorder (ie, Cavalier King Charles spaniel, dachshunds)  |
| Stage B1   | Dogs with MMVD that have never developed clinical signs and have no radiographic or echocardiographic evidence of cardiac remodeling  |
| Stage B2   | Dogs with MMVD that have never developed clinical signs but have radiographic or echocardiographic evidence of cardiac remodeling (ie, left-sided heart enlargement)  |
| Stage C  | Dogs with MMVD and past or current clinical signs of heart failure associated with structural heart remodeling (dogs presenting heart failure for the first time may present severe clinical signs and may require hospitalization) |
| Stage D  | Dogs with end-stage MMVD and heart failure that is refractory to standard therapy (ie, furosemide, ACE-I, pimobendan ± spironolactone)  |

*Adapted from* Atkins C, Bonagura J, Ettinger S, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med* 2009;26:1142–50; with permission.

suggested database for these dogs includes a physical examination and thoracic radiographs. Echocardiography is recommended to confirm the diagnosis. The ACVIM consensus statement includes the suggestion that asymptomatic dogs can be further subdivided: dogs without radiographic or echocardiographic evidence of cardiac enlargement are in stage B1 and dogs with left atrial and ventricular enlargement are in stage B2. This subclassification emphasizes that asymptomatic dogs are a nonhomogeneous group that includes patients with very mild disease and others that have not developed CHF but have more advanced disease and are at risk for progression to CHF. The heterogeneity of this group of dogs may be an explanation for the conflicting data concerning neurohormonal activation presented in the veterinary literature for dogs with asymptomatic MMVD.<sup>31–36</sup> The recognition that asymptomatic dogs are a heterogeneous group underlines the importance of identifying risk factors for the development of CHF. Proposed risk factors for death or progression of MMVD include age, gender, intensity of heart murmur, degree of valve prolapse, severity of valve lesions, degree of mitral valve regurgitation, and left atrial enlargement.<sup>6,37–39</sup> A recent study suggests that a change in radiographic or echocardiographic cardiac dimensions observed between 2 different time points may be a more powerful predictor of outcome than the absolute value of the measurement.<sup>40</sup>

In people, brain natriuretic peptide (BNP) has been shown not only to be an excellent biomarker for identifying the presence of CHF but also for identifying patients that are at high risk of CHF or death.<sup>41–43</sup> A recent study conducted on 72 asymptomatic dogs with MMDV showed, in agreement with previous studies,<sup>31</sup> that the N-terminal fragment of proBNP (NT-proBNP) is correlated with the severity of mitral regurgitation. In this study a cutoff of 466 pmol/L had 80% sensitivity and 76% specificity for predicting 12-month progression (cardiac death or CHF).<sup>16</sup> Although these data seem very promising, further studies are needed to confirm the value of BNP in distinguishing, among asymptomatic dogs, those that will progress to CHF. In our opinion the evaluation of risk progression for these dogs should be based on evaluation of multiple parameters.

Treatment of dogs with asymptomatic MMVD has been the subject of controversy. The ACVIM consensus group did not recommend treating dogs with MMVD in stage B1 of the disease. The same group however did not reach a consensus for dogs with cardiac enlargement.<sup>23</sup> Two multicenter double-blinded studies evaluating the efficacy of enalapril on delaying the onset of CHF in dogs with MMVD without clinical signs have shown no significant effect of ACE-I therapy on the primary outcome variable, which was time from inclusion in the study to the onset of signs of CHF.<sup>11,17</sup> Another recently published study reported a possible benefit of early treatment with benazepril.<sup>15</sup> However, this was a retrospective case series, and studies of this type are invariably associated with systematic errors. Consequently, the results should be interpreted with caution. A prospective, randomized, multicenter double-blinded study involving a larger number of dogs would be necessary to confirm the results of this study.<sup>44</sup> In our opinion, the currently available data from clinical trials and the observation that only a relatively small percentage of dogs with asymptomatic disease progress to CHF or die as a consequence of the disease, do not support the early treatment with an ACE-I. However, it is possible, although not proved, that dogs with MMVD and severe cardiac enlargement, but not CHF, may benefit from medical treatment. The authors believe that asymptomatic cases should be individually evaluated and therapeutic decisions taken on a case-by-case basis. The available data concern only treatment with an ACE-I. Hitherto, no studies have been conducted with other classes of drugs, such as  $\beta$ -blockers, pimobendan, spironolactone, or amlodipine.

### **The Coughing Dog**

The presence of cough and mitral valve murmur represents a challenging problem for the clinician. Cough as a consequence of pulmonary edema is a possible sign of CHF in dogs. However, cough is a general clinical sign of respiratory disease and its presence in a dog with a murmur should not be the reason for starting CHF treatment. Old small-breed dogs are commonly affected by tracheobronchial disease and by MMVD. In these patients, the cough is often the result of their primary respiratory disease and not heart disease. Thoracic radiographs should always be obtained in a coughing dog with a murmur typical for MMVD to determine if primary respiratory disease is the cause of the cough. This is also true for patients with a documented history of CHF that start to cough. In these patients the cough may be related to reasons other than worsening of CHF (**Fig. 5**). Cough in dogs with MMVD can also be related to compression of left mainstem bronchus by an enlarged left atrium. However, it has been suggested that this is more likely to occur in the presence of primary bronchomalacia.<sup>45</sup> Indeed, some unpublished data from our group seems to confirm this hypothesis. In a group of 68 dogs with MMVD at different stages, cough was not associated with the dimension of the left atrium or the presence of CHF. It was, however, associated with concomitant presence of tracheobronchial disease (Borgarelli, unpublished data, 2007). It is possible that coughing dogs with moderate to severe left atrial enlargement without evidence of CHF but with a primary tracheobronchial disease could benefit from treatments aimed at decreasing the left atrial volume, as the decrease in pressure on the main stem bronchus could decrease the stimulus for coughing. However, the types of drugs that have the potential to achieve this are all associated with potential adverse reactions. Furthermore, moderate to high doses of furosemide in dogs with tracheobronchial disease without CHF may not only dehydrate the dog but also worsen the cough as a consequence of drying the airways.

### **The Symptomatic Dog (Stage C ACVIM Consensus)**

According to the ACVIM consensus statement, patients with stage C mitral valve disease are those with a documented cardiac structural abnormality and current or



**Fig. 5.** Dorsoventral thoracic radiograph from a dog with severe MMVD. On the left, the radiograph shows a normally outlined right caudal bronchus (*arrow*). On the right, the same dog 1 month later. Radiographs were obtained because the owner was reporting the presence of cough. The arrow shows the presence of a collapsed right caudal main stem bronchus but no worsening of pulmonary venous congestion or presence of pulmonary edema.



previous clinical signs of CHF.<sup>23</sup> Management of these patients is based on administration of a combination of several drugs including diuretics, pimobendan, ACE-I, and others. Although no study has specifically addressed the question of efficacy of furosemide in dogs with MMVD, there is a general consensus that diuretics are essential for patients with CHF. Most dogs enrolled in the multicenter studies evaluating the efficacy of the ACE-I and pimobendan in symptomatic dogs with MMVD received concomitant treatment with furosemide.<sup>12-14,18,46</sup> In our opinion, the diagnosis of CHF should be reevaluated if it is possible to discontinue the furosemide administration in a patient without a reoccurrence of clinical signs. The dosage of furosemide should be adjusted to keep the patients free from clinical signs; the optimal dose likely being the lowest effective dose. Although the suggested mean dosage for these patients is 2 mg/kg by mouth every 12 hours, in our experience it could range from 0.5 mg/kg by mouth every 12 hours to 4 to 6 mg/kg by mouth every 8 hours. Dogs with refractory heart failure could also benefit from administration of 1 of the doses of the drug by subcutaneous injection. It has been shown in people that teaching the patients to adjust their furosemide dosage on the base of monitoring their weight and their clinical signs significantly reduces the number of hospitalizations and may be associated with prolonged survival.<sup>47</sup> The authors try to use this approach with the owners whenever possible. The use of an ACE-I together with furosemide in dogs with CHF caused by MMVD is based on evidence provided by several multicenter double-blind studies.<sup>12-14,48</sup> These studies, although recently the subject of criticism,<sup>49</sup> provide evidence that an ACE-I added to standard therapy improves quality of life and survival time in dogs with CHF caused by MMVD. ACE-I should be used at the dosage that has been shown to be effective in the clinical trials. There is no proven evidence that using ACE-I at dosages higher than the recommended dose presents any clinical advantage.

Two recent studies have shown that pimobendan improves survival and quality of life in dogs with MMVD and overt heart failure compared with standard treatment consisting of an ACE-I and furosemide. The first study was conducted as a blinded, randomized, positive-controlled, multicenter study and included 76 dogs. The study had a mandatory 56-day treatment period that was followed by optional long-term treatment. In this study pimobendan significantly improved the primary study variable represented by heart insufficiency score and also significantly improved survival.<sup>46</sup> One criticism of this study concerned concomitant treatment as only 56 dogs (31 in the pimobendan group and 25 in the standard treatment group) were on concurrent furosemide treatment, suggesting that the diagnosis of heart failure could be questioned in the remaining dogs. However, the results of a subanalysis of data provided only by dogs receiving concurrent furosemide were consistent with those of the entire dataset. Moreover, the long-term part of the study was conducted unblinded. The results of this study led to a larger study conducted on 260 dogs with MMVD and overt CHF. This was a prospective multicenter, randomized, single-blinded study and the primary end point was a composite of cardiac death, euthanasia for heart failure, or treatment failure. In this study treatment with pimobendan was associated with a significant improvement in survival time and this benefit persisted after adjusting for all baseline variables.<sup>18</sup> All dogs enrolled in this study were on concomitant furosemide treatment. It should be stressed that none of these studies addressed the possibility of an interaction between ACE-I and pimobendan; it is not known whether or not triple therapy consisting of furosemide, ACE-I, and pimobendan is superior to therapy consisting of pimobendan plus furosemide. The ACVIM consensus recommends that chronic management of stage C dogs includes all these drugs.<sup>23</sup>



Spironolactone has recently been approved in Europe for treatment of dogs with MMVD. A recent study shows that in dogs with moderate to severe MMVD spironolactone added to an ACE-I, furosemide  $\pm$  digoxin treatment reduces the risk of cardiac death and the risk of severe worsening of CHF.<sup>50</sup> The dosage used in this clinical trial was 2 mg/kg every 24 hours and this dosage seems to have little diuretic effect in normal dogs.<sup>51</sup> One possible mechanism of action for spironolactone could be related to the antifibrotic effects of this drug that have been shown in experimental studies.<sup>52,53</sup> A recent study has shown that geriatric dogs affected by MMVD have intramyocardial arterial changes associated with area of fibrosis, so-called replacement fibrosis.<sup>54</sup> The exact role of these findings in the pathogenesis of MMVD is still to be clarified as is the possible antifibrotic effect of spironolactone in natural occurring disease in dogs. Positive effects of blocking aldosterone in dogs with heart failure with a specific antagonist such as spironolactone could also be related to the phenomenon of aldosterone escape<sup>55,56</sup> that can occur in dogs with severe CHF. It has been shown the aldosterone concentration can be increased in dogs with MMVD receiving furosemide and an ACE-I.<sup>56</sup> This phenomenon is dependent on the dose of furosemide and has been attributed to the fact that ACE inhibition does not completely block ACE activity. In dogs in particular, it has been speculated that other enzymes such as chymase can play a major role in producing angiotensin II.<sup>1</sup> The exact mechanism of action through which spironolactone exerts its possible benefits in improving outcome in dogs with MMVD needs further studies.

Other drugs frequently used for treatment of dogs with overt CHF caused by MMVD are digoxin and amlodipine. Digoxin is commonly used to treat dogs with concomitant atrial fibrillation to control the heart rate. There are no controlled studies in veterinary medicine evaluating digoxin, but it is general expert opinion that its administration could improve clinical signs of heart failure in dogs. In humans, relative to placebo, the effect of digoxin on mortality of ambulatory human patients with heart failure is neutral. However, this drug decreases rates of hospitalization and there may be subpopulations of patients with heart failure in which digoxin has a favorable effect on longevity.<sup>57</sup> Amlodipine at the dosage of 0.05 to 0.1 mg/kg every 12 hours is listed in the ACVIM consensus statement as a possible agent for those dogs with a more advanced stage of heart failure (stage D) to obtain a more effective reduction in afterload<sup>23</sup> and improve cardiac output. Arteriolar vasodilation associated with the use of this drug can lead to severe hypotension in these patients. Therefore, slow up-titration of amlodipine dosage with monitoring of blood pressure is recommended to avoid serious hypotension. In our experience, the use of this drug or other intravenous vasodilators, such as sodium nitroprusside, can be of some help for dogs with uncontrolled CHF that experience an acute episode of pulmonary edema.

In our experience, most dogs with heart failure caused by MMVD can be managed using a combination of furosemide, an ACE-I, pimobendan, and spironolactone. Treatment should be individualized for each patients and the goal is to keep the dogs free of clinical signs of CHF as long as possible.

## SUMMARY

MMVD is a common condition in geriatric dogs. Most dogs affected are clinically asymptomatic for a long time. However, about 30% of these animals present a progression to heart failure and eventually die as a consequence of the disease. Left atrial enlargement, and particularly a change in left atrial size, seems to be the most reliable predictor of progression in some studies, however further studies are needed to clarify how to recognize asymptomatic patients at higher risk of developing

heart failure. According to the published data on the natural history of the disease and the results of published studies evaluating the effect of early therapy on delaying the progression of the disease, it seems that no currently available treatment delays the onset of clinical signs of CHF. Although the ideal treatment of more severely affected dogs is probably surgical mitral valve repair or mitral valve replacement, this is not a currently available option. The results of several clinical trials together with clinical experience suggest that dogs with overt CHF can be managed with acceptable quality of life for a relatively long time period with medical treatment including furosemide, an ACE-I, pimobendan, and spironolactone.

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