

## Myxomatous Mitral Valve Disease in Dogs, 37 Cases (2010-2015)

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### Abstract

Myxomatous mitral valve disease is by far the most common cardiac disease in small to medium breeds of dogs. Diagnosis is based on physical examination and diagnostic imaging findings. In this study, 37 dogs with myxomatous mitral valve disease, older than 4 years were evaluated by the means of clinical findings (including history, physical examination, and auscultation), radiographic, echocardiographic, and electrocardiographic signs. Based on modified New York heart association 7 dogs were categorized to class I, 11 dogs to class II, 15 dogs to class III, and 4 dogs to class IV of congestive heart failure. Exercise intolerance, cough, dyspnea, and syncope were seen in 78.3%, 40.5%, 37.8%, and 24.3% of dogs, respectively. Eighty-one percent of dogs had radiographic signs related to disease while 88.7% and 27% of dogs had echocardiographic and electrocardiographic signs of disease, respectively. Left atrial enlargement (75.6%) and increased atrial to aorta ratio (78.3%) were among the most common radiographic and echocardiographic signs, respectively. P mitral (increase the duration of P wave) was the most common electrocardiographic sign. This study is a case series report and describes qualitative and quantitative diagnostic evaluations for mitral valve endocardiosis in dogs. We have evaluated and described co-occurrence of physical and diagnostic imaging findings in affected dogs. Furthermore, the significance of various clinical findings in disease diagnosis was described.

**Keywords:** Valvular Disease; Radiology; Echocardiography; Electrocardiography

### Abbreviations

MMVD: Myxomatous Mitral Valve Disease; CHF: Congestive Heart Failure; MR: Mitral Regurgitation; EF: Ejection Fraction; FS: Fractional Shortening; LA: Left Atrium; LV: Left Ventricle; MVE: Mitral Valve Endocardiosis; MD: Myxomatous Degeneration; VHS: Vertebral Heart Score

### Introduction

Myxomatous mitral valve disease (MMVD) is the most common heart disease in dogs. The prevalence of MMVD is related to the dog's age [1]. It is estimated that more than 75% of dogs over the age of 13 years have MMVD, but it can affect dogs at much earlier ages (dogs as young as 2 years of age have been reported) [2]. Although MMVD may affect any breeds of dogs, clinical forms of MMVD are seen most often in small-breed dogs. Breeds such as Cavalier King Charles Spaniels, Miniature Poodles, Pomeranians, Yorkshire Terriers, Chihua-

huas, and cocker spaniels are more commonly affected [3]. MMVD is caused by a progressive myxomatous degeneration (MD) of the atrio-ventricular (AV) valves [4]. MMVD is characterized by slow progression from mild to severe [5]. MMVD is often suspected by auscultation of a typical systolic heart murmur in the middle-aged to old, small to medium-sized dogs and the diagnosis is usually made by ancillary examinations such as radiography and echocardiography (Abbott, *et al.* 2008).

Initial signs of heart failure due to mitral regurgitation (MR) usually include exercise intolerance, cough, and dyspnea or tachypnea with exertion. Syncope may occur frequently or may be seen as occasional spills. The most notable feature of the physical examination is a systolic heart murmur. There are no differences between the murmur caused by MMVD and other disorders such as dilated cardiomyopathy [3].

Radiography and echocardiography are essential tools, both for diagnosis and evaluation of MMVD in dogs [6] and help to determine the onset of heart failure [7]. Determination of global cardiac size and the presence of pulmonary congestion and edema could be achieved by thoracic radiography (Boon 1998). Left atrial enlargement is one of the earliest and most consistent radiologic features of MMVD [8]. Vertebral heart score (VHS) is among the most important radiographic findings in dogs with congestive heart failure (CHF) [9]. Echocardiography is performed to evaluate the structure of the mitral valve apparatus, calculating chamber size, and determination of systolic or diastolic heart failure [5]. Doppler echocardiography determines the direction and size of the regurgitant jet area across the valve [5]. Although electrocardiographic changes are of less diagnostic value presence of P-mitral and a wide QRS complex may be seen in dogs with MMVD. Supraventricular tachyarrhythmia may also occur during later stages of the disease. The main goals of medical management are to prolong preclinical phase, controlling clinical signs, and improve the quality of life and survival of the patients.

In 2009, an American college of veterinary internal medicine (ACVIM) consensus panel published a statement and recommended to stage dogs with MMVD into four groups of dogs: from stage A to D (Table 4). Based on their recommendations, stage A represents healthy dogs at risk for developing heart disease (like cavalier king Charles spaniels) and stage B represents asymptomatic dogs that have heart murmur and mitral regurgitation (MR) without cardiomegaly (stage B1) and those that have hemodynamically significant MR and cardiomegaly (stage B2). Stage C represents dogs with past or current signs of congestive heart failure (CHF) and stage D demonstrates dogs with end stage CHF that are refractory to standard CHF therapy (Keene, *et al.* 2019). Canine CHF can also be classified based on modified New York Heart Association (NYHA) recommendation to class I to IV. Class I describes asymptomatic dogs with heart disease and class II describes patients with heart disease that causes clinical signs only during strenuous exercise. Class III consists of patients with heart disease that with daily routine activities or mild exercise causes clinical signs. Class IV describes patients with heart disease that causes severe clinical signs even at rest [1].

### Aim of the Study

The aims of the present study are 1) to describe the most common findings in dogs with MMVD 2) to determine any relationship between clinical signs of MMVD and radiological and echocardiographical findings and 3) to classify each case to specific stage of disease based on ACVIM consensus panel and modified NYHA. Furthermore, the most common echocardiographical, radiological, and clinical signs of disease in each stage will be addressed.

### Materials and Methods

In this study, dogs suspected of cardiac diseases, including those with exercise intolerance, coughing, dyspnea, and syncope was examined for mitral valve endocardiosis and included in our study. All dogs were referred to Small Animal Polyclinic of Science and Research Branch, Islamic Azad University, Tehran-Iran from October 2010 to September 2015. The criteria used for selection of the 37 dogs were (1) being older than 4 years (2) small to medium-size breeds and (3) having clinical signs related to mitral valve endocardiosis. The only

exclusion criterion was other organ diseases. The dogs comprised 15 male (40.5%) and 22 females (59.5%) with mean  $\pm$  SD body weight was  $6.2 \pm 2.2$  kg (Table 1).

Age (Yr.)	Mild MMVD	Moderate MMVD	Severe MMVD
Mean	6.8	7.5	9.3
Range	4 - 8	4-11	7-13
<b>Weight (kg)</b>			
Mean	7.3	6.8	5.8
Range	2 - 11	2 - 12	3 - 10
<b>Breeds</b>			
Mixed-Breeds	0	2	1
Poodle	1	1	1
Pekingese	2	3	1
Pomeranians	0	2	0
Shih Tzu	3	4	1
Dachshund	1	1	2
Cocker Spaniels	0	2	0
Yorkshire Terrier	1	1	1
Terriers (Mixed)	3	2	1
Total	11	18	8

**Table 1:** Distribution of 37 dogs with myxomatous mitral valve disease within category of severity, age, weight, and breeds.

All echocardiographic examinations were performed with a commercially available system (ESAOTE AU5, ESAOTE BIOMEDICA; Via Siffredi 58; 16 153 Genova, Italy) with 3.5 - 5 and 7.5 - 10 MHZ multi-frequency sector transducer. Echocardiography was performed with animals restrained in lateral recumbency without any sedation, and the transducer was applied to the right parasternal view of fifth intercostal space. Echocardiography was performed according to the American college of veterinary internal medicine (ACVIM) recommendations (Thomas, *et al.* 1993). Both M-mode and 2-D echocardiograms for the measurement of the aorta (AO) and left atrium (LA) were obtained from a short-axis plane at the level of the aortic valves. The 2-D image was used to guide the placement of the M-mode cursor line. To obtain the LA/AO ratio, AO diameter was measured at end-diastole and LA internal diameter was measured at end-systole. For the 2-D measurements (AO and LA) the first frame after the aortic excursion was used. In 2-D mode, transverse dimension of AO and LA was measured. For AO, the first caliper was placed at the midpoint of the convex curvature of the wall of the right aortic sinus. The second caliper was positioned at the point where the aortic wall and the non-coronary and the left coronary aortic cusps merge. The LA was measured by extending the line from the same point where the second caliper was positioned at the blood-tissue interface of the LA wall. Dimensions of the left ventricle in end-systole (LVESD) and end-diastole (LVEDD) were measured in the short axis plane just below the mitral valve. A lead II ECG was simultaneously recorded. Measures of shortening fraction and ejection fraction (EF) were calculated by the standard formula. Shortening fraction was calculated by linear measurements of the left ventricular internal diameter at end-diastole (LVIDD) and end-systole (LVIDs). Ejection fraction measured by 2D echocardiography using a single-plane (long axis and apical) image of the left ventricle (LV). The M shape of the Mitral valve leaflets was assessed in M mode when the image was obtained by directing the beam plan to the level of the mitral valve in right parasternal short axis view of the heart.

The diagnosis of MMVD has been established according to the American college of veterinary internal medicine (ACVIM) consensus statement for the diagnosis of mitral valve disease [1]. Basic information from the echocardiographic examination allowing for the diagnosis of MMVD included lesions of the mitral valve with regurgitation, lesions of the tricuspid valve with regurgitation, enlarged left atrium, increased left ventricular end-diastolic diameter, increased left ventricular end-systolic diameter, hyperdynamic left ventricular motion and hypodynamic left ventricular motion Color-flow echocardiography used to determine the presence of regurgitated jet flow and the presence of mitral valve leaflet prolapse to LA during systole.

All radiographic examinations were performed using a Siemens Polydoros 50S generator (Siemens-Elema AB) with a standard rotating anode 150 kilovolt X-ray tube. The focal-film distance was 100 centimeter and exposure setting was at 1.25 milliamper-second and 85 to 99 kilovolt depending on the size of the dog. Both dorsoventral (DV) and lateral (LAT) radiograph views were taken. Attempts were made to expose all films at peak inspiration. The VHS method for measuring the heart size was used as described elsewhere [5]. All measurements were done in the lateral view. Cardiomegaly and dorsal deviation of the left main bronchi were evaluated in each radiograph at least by two professionals. Inter-observer and intra-observer variability and agreement were assessed by comparing blinded measurements by four trained observers on a standardized set of images. Measurements were compared for agreement using the limits of agreement analysis.

Heart sounds were evaluated, especially for the presence of an audible systolic heart murmur. Littmann Cardiology III Stethoscope was used for cardiac auscultation.

Data were analyzed using SPSS database (SPSS-18). All values were reported as the mean ± SD unless otherwise specified.

**Results**

History, clinical examination, Radiologic, and echocardiographic findings are summarized in table 2. Exercise intolerance was seen in many cases. Fifty-two percent of these dogs had a mild exercise intolerance while 36% had moderate and 12% had a severe exercise intolerance. Forty-four percent of dogs with cough had a productive cough and 68% of them had the nocturnal cough. Twenty-one percent of dogs with syncope had multiple episodes of syncope while 79% of them had just one episode of syncope. Syncope in 78% of cases triggered by excitation. Soft systolic murmur (68%) was seen in large part in dogs with classes I to III of CHF (based on NYHA classification system), although harsh systolic murmur was seen mainly in dogs with severe MMVD (mostly dogs with classes III and IV of CHF). Left atrial enlargement (75.6%) and dorsal deviation of main stem bronchi (45.9%) were two major radiographic findings. Other radiographic signs, including total cardiomegaly (75.6%), enlargement of the left ventricle (48%), and lung patterns (47.5%) were observed.

	Frequency	Percent
Murmur	37	100
Exercise Intolerance	29	78.3
Cough	15	40.5
Dyspnea-Tachypnea	14	37.8
Syncope	9	24.3
Radiographic Signs	28	75.6
Echocardiographic Signs (other than mitral regurgitation in Doppler)	29	78.3
Electrocardiographic	10	27

**Table2:** Frequency of evaluated clinical signs in 37 dogs with myxomatous mitral valve disease.

In echocardiography of dogs with MMVD, linear measurement of the left atrium was used to calculate the left atrium to the aortic ratio (LA/AO). The ratio greater than 1.6 was seen in 78.3% of dogs with MMVD and was the most common echocardiographic sign after mitral valve regurgitation (100%). The occupied space of the LA region with the regurgitant jet area was calculated in all cases of mitral regurgitation. In dogs with mild MMVD, less than one-fifths of the LA region were occupied with the color jet flow while in severe cases more than half of the LA region was occupied with the color flow of the regurgitant jet.

Left ventricular systolic function was determined by the means of calculating SF and EF. SF and EF were decreased by 14% and 17% of dogs, respectively.

The most common electrocardiographic change was P-Mitral followed by supraventricular tachyarrhythmia. Electrocardiographic signs of left ventricular enlargement (wide QRS complex) and atrial fibrillation were also observed in two cases.

The severity of CHF in dogs with MMVD was also determined based on modified New York Heart Association (NYHA) (Table 3). Based on this classification, most of the dogs with MMVD had class III of CHF in which decompensated heart failure occurs.

	Cases	Clinical Examination			Echo		Radiology	
		Systolic Murmur	Coughing	Exercise Intolerance	Increased LA/AO <sup>a</sup>	Mitral Regurgitation	Dorsal Deviation	Cardiomegaly
Class I	7	7	0	3 <sup>b</sup>	1	7	0	1
Class II	11	11	3	7	10	11	3	9
Class III	15	15	9	15	14	15	11	14
Class IV	4	4	3	4	4	4	3	4

**Table 3:** Summary of some clinical, radiological, and echocardiographic findings in different classes of congestive heart failure (CHF) based on modified New York Heart Association (NYHA) in 37 dogs with myxomatous mitral valve disease.

<sup>a</sup>LA/AO- Left atrium/Aorta <sup>b</sup>-Very mild.

All the dogs were staged based on ACVIM recommendations (Table 4). All the dogs in the stage B1 had heart murmur and MR in echocardiography. Increased chamber size, as shown by LA/Ao ratio and left ventricular end diastolic dimension in echocardiography, was seen in dogs with stage B2, C, and D. There was no correlation between LA/Ao ratio and the stage of disease (p < 0.001), however all dogs with stage D had increased LA/Ao ratio greater than 1.6. Similarly, all dogs with stage B2, C, and D had radiographic signs of cardiomegaly, including LA and LV enlargement as well as increased VHS values (greater than 9.6).

Stages	Diagnostic Criteria	Percent
Stage A	Patients at high risk for developing heart disease but that currently have no identifiable structural disorder of the heart	0
Stage B	Patients with structural heart disease (e.g. the typical murmur of mitral valve regurgitation is present) but that have never developed clinical signs caused by heart failure	
Stage B1	Asymptomatic patients that have no radiographic or echocardiographic evidence of cardiac remodeling in response to canine valvular heart disease	24
Stage B2	Asymptomatic patients that have hemodynamically significant valve regurgitation, as evidenced by radiographic or echocardiographic findings of left-sided heart enlargement	31
Stage C	Patients with past or current clinical signs of heart failure associated with structural heart disease	39
Stage D	Patients with end-stage disease with clinical signs of heart failure caused by chronic valvular heart disease that are refractory to "standard therapy."	6

**Table 4:** Classification of 37 dogs with myxomatous mitral valve disease based on American college of veterinary internal medicine (ACVIM); the consensus panel adapted the 2001 American College of Cardiology/American Heart Association classification system for the treatment of heart disease and failure in human patients to the management of canine myxomatous mitral valve disease.

## Discussion

Diagnosis of MMVD in dogs is not usually a big concern in veterinary medicine. The most important issue here is to determine the stage of disease and classify the CHF to design therapeutic plan and determine the prognosis of the disease. The consensus panel of ACVIM has adapted the 2001 American College of Cardiology/American Heart Association classification system for the treatment of heart disease and failure in human patients for the management of canine myxomatous mitral valve disease (Table 4). Based on their classification most of our dogs were classified to stage C, the stage when a patient starts to show clinical signs of MMVD due to decompensated CHF. At this stage, exercise intolerance was remarkable and at least one-third of them had either cough or dyspnea/tachypnea or both. Asymptomatic patients with significant valve regurgitation in echocardiography were classified to stage B2 based on ACVIM classification. At this stage, all dogs had a systolic heart murmur and some of them had very mild exercise intolerance. Presence of exercise intolerance should be investigated in all dogs suspected to MMVD since the presence of a systolic heart murmur in conjunction with exercise intolerance in predisposed breeds, which are older than four years are of relative diagnostic value. Dogs with MMVD stage D had obvious clinical signs of decompensated CHF, although the severities of clinical signs in this group of dogs were considerably different. Cough, particularly productive cough, was one of the prominent clinical signs in dogs with stage D of MMVD; however, not all dogs in this stage suffer from cough. The first step in the diagnosis of MMVD is cardiac auscultation [10]. A soft systolic murmur may be heard at the point of mitral valve (left 5<sup>th</sup> intercostal space). The intensity of this murmur varies from III/VI to VI/VI. Change in heart sounds is the first clinical sign of MMVD and may be heard as early as 4 years old in affected dogs [11]. The systolic mitral valve murmur is used for early diagnosis and screening test of highly predisposed breeds like Cavalier king Charles Spaniel or Cocker Spaniels [1]. All dogs in our study had a systolic murmur which was our inclusion criteria. Systolic murmurs were soft in nearly two-thirds of cases, and harsh sounds were typically heard in dogs with signs of severe pulmonary edema and those with increased cardiac preload due to increased LA filling pressure. The intensity and quality of heart murmurs correlated well with the severity of CHF in patients. Harsh and loud systolic murmurs with increased respiratory sounds were seen in dogs that had a severe cough and exercise intolerance. In contrast, in dogs with very subtle clinical signs of MMVD, soft systolic murmur with low intensity was found. Among the various clinical signs of MMVD exercise intolerance and cough are the prominent signs [2]. Mild exercise intolerance was reported by owners of three dogs with class I CHF, although according to modified NYHA functional classification of heart failure, dogs with class I are asymptomatic even with strenuous exercise. Although the episodes of cough were observed throughout the day in some cases, nocturnal and early-morning coughs were reported more by the owners. Nocturnal coughs were seen mostly in the first months, but their occurrence time extended to 24 hours of the day gradually. Nearly half of the dogs with cough had a productive cough. As expected, productive coughs were seen in dogs with moderate to severe MMVD (class III and IV CHF) and dry coughs were seen mostly among dogs with class II CHF.

Syncope may occur frequently in dogs with MMVD [12], but in our study, there were just a little number of dogs, which had been experienced one or more episodes of syncope previously. Syncope in most of the dogs was associated with excitation. Dyspnea and or tachypnea mainly was seen in dogs with moderate to severe MMVD and was associated with dogs with decompensated CHF.

Radiology is one of the most useful diagnostic tools in dogs with MMVD [13]. Radiographic signs of MMVD were seen in 81% of dogs. Early radiologic findings were related to LA enlargement and were included dorsal deviation of main stem bronchi and left atrial enlargement in the lateral view of the thorax. Global cardiomegaly was assessed by vertebral heart score measurement. Cardiomegaly was seen in all four classes of CHF, mainly in class III and IV of heart failure. The majority of dogs with LA dilatation had concurrent signs of LA enlargement both in radiography and echocardiography. Signs of pulmonary edema were seen mainly in dogs with decompensated heart failure (stage C of ACVIM). Nearly all dogs with productive cough had radiographic signs of pulmonary edema, however, dogs with dry cough just had the radiologic sign of main stem bronchi compression (dorsal deviation of the main stem bronchi in lateral view of the thorax).

Echocardiography plays an exclusive role in MMVD diagnosis [6]. Measurement of heart chamber's dimension, evaluating valvular structures and function, and evaluation of myocardial contractility force can be obtained by the means of echocardiography (Muzzi RAL.,

*et al.* 2003). Right parasternal short and long axis view of the heart plus the left cranial and or apical views should be used for echocardiography. Increased LA/AO ratio was seen in many dogs with class III and IV CHF (based on NYHA classification). Mitral valve was evaluated in right parasternal short axis view. Presence of various degrees of MR in Doppler echocardiography was seen in all dogs with class II, III, and IV CHF, although the size of the regurgitant jet area was significantly different between various degrees of mitral regurgitation. In mild cases, the color jet occupied less than 20% of the LA area, while in severe MR cases, it occupied more than 50% of the LA area. Thickening of leaflets was seen in 12 cases. Chordae rupture and leaflet prolapse were seen in two dogs with class III and IV CHF, which could be a consequence of MMVD or seen as a simultaneous condition.

Electrocardiographic changes in dogs with MMVD are, at least in part, due to left atrial dilation.

Supraventricular premature beats could result from an enlarged atrium. Increase the duration of the P wave in electrocardiography, which is known as P mitral, is associated with left atrial dilatation. Increasing the height and duration of QRS complex due to left ventricular enlargement is another electrocardiographic sign, which may be seen in dogs with MMVD.

Since the publication of the EPIC study in 2016 (Boswood., *et al.* 2016), the importance of early diagnosis of MMVD in dogs has increased dramatically. The EPIC study showed that administration of pimobendan in earlier stages of MMVD in dogs, that have echocardiographic and radiographic evidence of heart enlargement, could effectively delay the onset of CHF. In many cases mild to moderate MMVD is not associated with any signs of disease other than mild exercise intolerance and systolic heart murmur. Most of the dogs with MMVD remain asymptomatic for most of the time they have a typical systolic heart murmur. Thereby every effort should be done to diagnose the disease at earlier stages through the complete history taking, physical examination, and diagnostic imaging [14-25].

### Conclusion

An early presumptive diagnosis of MMVD could be achieved by careful history taking and cardiac auscultation. Furthermore, early clinical signs in dogs with decompensated CHF are usually mild and may be ignored by many owners. Nocturnal cough, tachypnea, and dyspnea gradually appear and progress in dogs with decompensated heart failure. At this stage, the most striking radiologic and echocardiographic signs of MMVD are present and should be used by clinicians to plan their treatment and define the accurate prognosis of disease in each case precisely.

The results of the present study could be outlined as below:

- The most common clinical signs of MMVD in dogs are exercise intolerance, cough, dyspnea, tachypnea, and syncope.
- Dogs with stage B1 of MMVD have no clinical signs, though a mild exercise intolerance may be reported by some owners at this stage. At this stage, there is a mild mitral regurgitation in Doppler echocardiography (regurgitant jet area is less than 20 percent of left atrial area). A soft systolic murmur should be heard during auscultation, however low intensity murmurs may be undiagnosed at this stage.
- Dogs with stage B2 of MMVD commonly show signs of mild to moderate exercise intolerance. A systolic murmur presents at this stage and first radiographic signs of LA dilatation with or without dorsal deviation of left main stem bronchi should be noted. VHS may increase mildly during this stage. Echocardiographic sign of LA dilatation (increased LA/Ao ratio) is usually present. Regurgitant jet area is usually around 20 percent of left atrial area in Doppler echocardiography. Mild thickening of mitral valve and chordae tendineae may be seen in echocardiography of dogs with stage B2 MMVD.
- Dogs with stage C of MMVD are in decompensation phase of CHF and mild to moderate clinical signs of left sided CHF gradually developed at this stage. Exercise intolerance, cough, dyspnea, tachypnea, and syncope are common clinical signs of this stage however many dogs may show just one or two of these signs. Radiological signs of pulmonary edema, increased VHS, and left chamber enlargement are usually present at this stage. Marked changes in echocardiographic measures occur during this stage. The first clinical signs are usually mild however these signs may be aggravated within days to weeks. Increased LA and or Pulmonary venous pressure, reduced LV outflow, and finally increased right atrium filling pressure and increased venous pressures are main pathophysiologic events, respectively responsible for the clinical signs of MMVD at this stage.

- Stage D, or bad CHF, is usually accompanied by moderate to severe clinical signs of decompensated heart failure. All dogs at this stage suffer from marked exercise intolerance, severe mitral regurgitation (more than 50 percent of left atrial area in Doppler echocardiography), and high intensity murmurs. Cough, dyspnea, and tachypnea are more common during this stage and are present most of the time during the day.

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