

Diagnosing canine myxomatous mitral valve disease

Henrik D. Pedersen, DVM

Associate Professor, Department of Anatomy and Physiology, Royal Veterinary and Agricultural University, Copenhagen, Denmark

KEY POINTS

- Mitral regurgitation caused by myxomatous valvular disease is the most common cause of congestive heart failure in dogs.
- The murmur intensity correlates well with the degree of mitral regurgitation.
- The likelihood of diagnosing mild regurgitation by auscultation depends on observer experience, circulatory status and how difficult the dog is to examine.
- By measuring the degree of mitral valve prolapse (abnormal leaflet protrusion), predisposed dogs can be identified at an early age.
- Other echocardiographic measurements of disease severity are jet size (colour Doppler), leaflet thickness and in later stages, left ventricular and atrial dimensions.
- The disease is highly hereditary, making control schemes feasible in predisposed breeds.

Introduction

Myxomatous valvular disease, also known as mitral valve disease, chronic valvular disease or endocardiosis, is a common disease in the dog that particularly affects the mitral valve (1). The prevalence and severity of the disease increases with age. At post mortem, more than half the population of old dogs have markedly distorted mitral valves. As a consequence of the progressive valvular degeneration, the valve becomes increasingly

insufficient and, in some cases, the degree of mitral regurgitation (MR) becomes so severe that the dog develops congestive heart failure.

Recent studies have shown that the disease can be diagnosed echocardiographically at an early stage – for example, by measuring the degree of mitral valve prolapse (MVP), i.e. the degree of abnormal leaflet protrusion towards the left atrium in systole. This early detection, and the hereditary nature of the disease, means that it is feasible to design control schemes aimed at reducing the prevalence of the disease in predisposed breeds. It should be noted that it is not possible to diagnose early stages of mitral valve disease, where there is no MR, by using cardiac auscultation alone. Even in cases with mild MR, there is often no perceivable murmur. As the degree of MR worsens, however, so, too, does the murmur intensity and thus the likelihood of diagnosing the disease by auscultation increases.



Henrik D. Pedersen, DVM

Henrik graduated as DVM from the Royal Veterinary and Agricultural University in Copenhagen in 1992. He worked for 3 years at the university's Small Animal Hospital before moving to the Department of Anatomy and Physiology where he is now Associate Professor in veterinary physiology. His research has focused on the early stages, causality and control of myxomatous mitral valve disease in the dog. Much of his research concerns echocardiographic findings and the renin-angiotensin system. He has demonstrated that canine valvular disease is very similar to primary mitral valve prolapse in humans and that it can be diagnosed echocardiographically at an early stage.

Aetiology and Pathogenesis

The aetiology of canine myxomatous valvular disease has not been ascertained, but the fact that certain breeds are far more afflicted than others suggests that genetic factors play a major role. Two recent studies, each of which included dogs from only one breed, have provided stronger evidence that the disease is hereditary. In one of these studies (2), the presence and severity of regurgitant murmurs in five-year-old Cavalier King Charles (CKC) spaniels was shown to correlate strongly with the parental cardiac status (**Figure 1**). In the other study (3), which included 18 Dachshund families consisting of both parents and at least four offspring, the mean parental MVP status (leaflet protrusion in millimetres) was shown to correlate well with the mean MVP status in the litters (**Figure 2**). Analysis of both studies, suggested a polygenic mode of inheritance – i.e. that several genes are involved.

It is widely believed that progressive myxomatous degeneration is a response to repeated impact with the leaflets. This theory is supported by



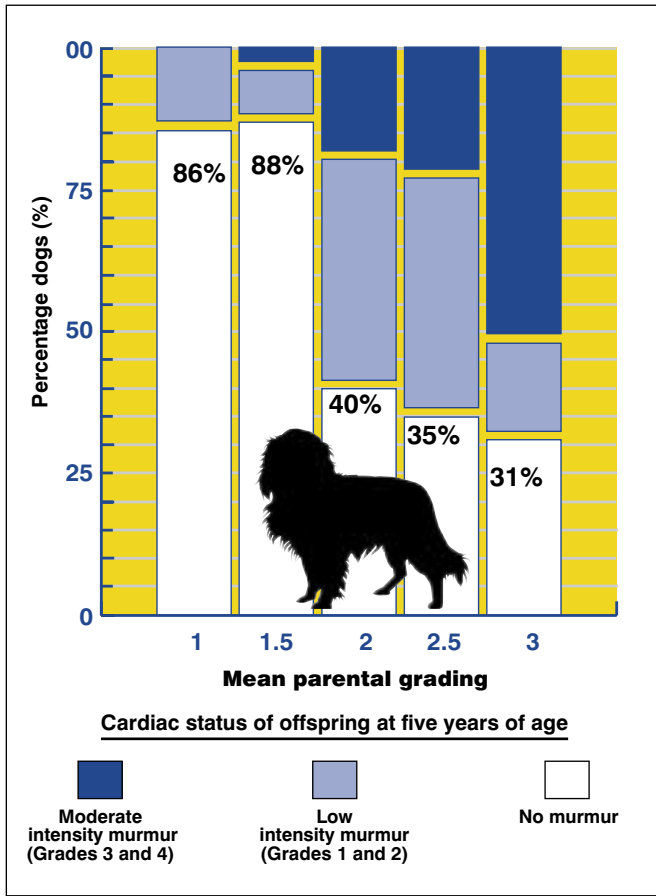


Figure 1 Relationship between mean parental cardiac status and presence and intensity of murmurs in offspring (all Cavalier King Charles spaniels) at five years of age. As can be seen, in general, the worse the cardiac status (higher score) of the parents, the worse the MR status of the offspring. Reprinted from (2) with permission from the editor.

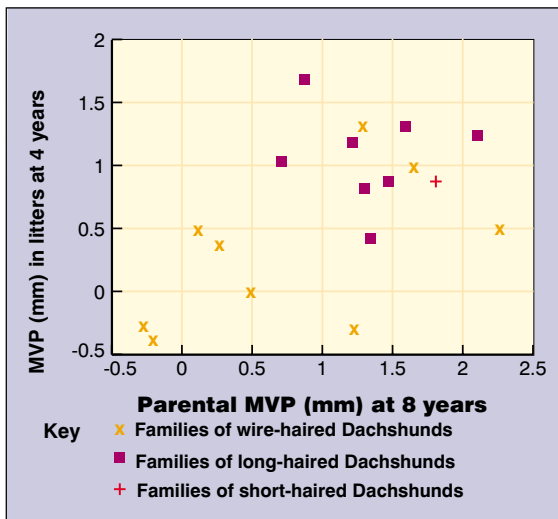


Figure 2 Relationship between the mean parental MVP severity and the average MVP severity in 18 different Dachshund litters, each consisting of four or more siblings. The MVP severity of the offspring and the parents were adjusted to four and eight years of age, respectively. Reprinted from (3) with permission from the editor.

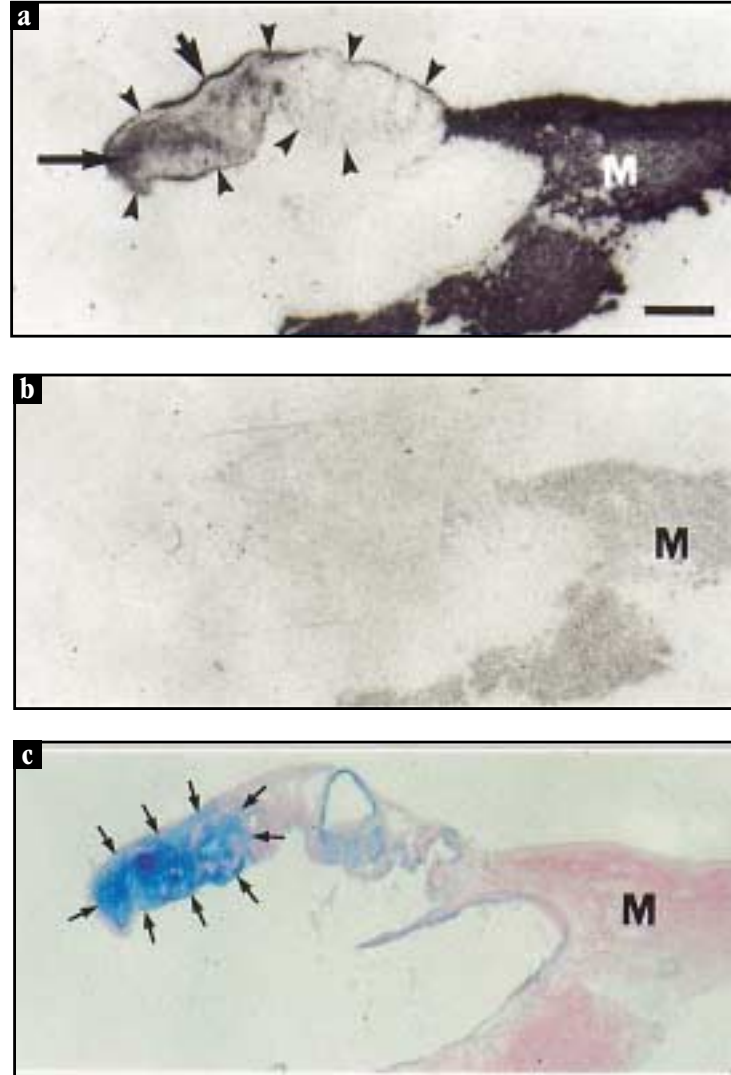


Figure 3 Sections of the posterior mitral valve leaflet (arrowheads) from a 13-year-old cross-breed dog with myxomatous mitral valve disease. (a) Autoradiographic localisation of endothelin (ET) receptors (binding of radio-labelled ET-1). As can be seen, areas with high ET-receptor density were found both within the leaflet (long arrow) and at the leaflet surface (short arrow). (b) Illustration of the typical low level of non-specific binding obtained by co-incubation in the presence of unlabelled ET-1. (c) Section stained with periodic acid-Schiff (PAS)/Alcian blue/haematoxylin in which both collagen degeneration (small arrows) and deposition of mucopolysaccharides (blue) are seen. Key: M = myocardium; scale bar = 1 mm. Reprinted from (4) with permission from the editor.

the fact that the valvular changes usually begin where the leaflets are brought into apposition with each other and progress in severity with advancing age. Once the disease is initiated – by some genetic defect(s) – the progression is likely to become a vicious circle: abnormal valvular closure/MVP together with MR cause shear stress to the endothelium, which, in turn, releases a number of vasoactive factors mediating more valvular degeneration and thus more MVP and MR.

It appears that endothelin is one of the vasoactive factors involved in the pathogenesis. A recent autoradiographic study (4) documented that canine mitral valve leaflets with myxomatous changes display a high density of endothelin receptors (Figure 3) whereas normal leaflets and normal-

looking areas of otherwise diseased leaflets display a low density of endothelin receptors. This could turn out to be a very important finding, inasmuch as endothelin receptor blockers will be available in a few years. Such blockers have been shown to have marked protective effects on human coronary restenosis, another condition in which endothelial damage causes (comparable) subendothelial changes.

Pathology

The typical gross findings are elongated chordae tendineae and enlarged, thickened mitral valve leaflets that display interchordal hooding (5). In late stages, the findings include dilation of the left ventricle, mitral annulus and left atrium and, in many cases, jet lesions, ruptured chordae tendineae and secondary fibrosis of the leaflets. Similar, albeit usually minor, lesions are also often found in the tricuspid valve. Histologically, the disease is characterised by a deposition of glycosaminoglycans in the spongiosa and fibrosa layers of the leaflets and by a concomitant fragmentation and disruption of the collagen bundles in the fibrosa (5).

The disease is often far worse in some parts of the mitral valve than in others. It is important to recognise that the valve is usually not insufficient because the leaflets are shrunken and cannot span the annulus, but rather because the enlarged leaflets at some point along the line of closure do not coapt properly. When performing a post mortem examination, one should try to imagine how the valve may have looked in systole with blood exerting a high pressure on it. It is not necessarily the most thickened part that caused the most insufficiency.

Epidemiology and Natural History

Myxomatous valvular disease is a common disease in dogs. The prevalence and severity of the disease increases with age, with more than half the population of old dogs suffering from markedly distorted valves. In general, small dogs are afflicted more than large dogs, but there are great differences in prevalence (6). A breed consistently reported as being highly predisposed is the CKC spaniel. At three years of age, approximately 90% of CKC spaniels have echocardiographic evidence of MVP (7, 8). The prevalence of regurgitant murmurs in this breed increases from less than 10% in one-year-old dogs to 50% in six-year-old dogs and to more than 90% in dogs older than ten years (8, 9).

Myxomatous valvular disease is usually a relatively benign disease. Most affected dogs will have a normal life expectancy, despite the fact that the disease usually emerges in the young animal. Even in the highly predisposed CKC spaniel breed, 'only' 15–20% will die or be subject to euthanasia before ten years of age because of their heart disease (9). The gender of the dog is a major risk factor for the development of severe MR and congestive heart failure. Male dogs are approximately twice as likely as female dogs to develop severe disease in old age (1, 2). Interestingly, in young dogs, there is no appreciable gender difference in the prevalence and severity of the disease, irrespective of whether the influence of gender is assessed from echocardiographic or auscultatory screenings (3, 8, 9).

The fact that small dogs are generally more affected than large dogs suggests a negative correlation with body weight. In support of this, a negative correlation was recently found between body weight and degree of MVP in a series of dogs coming from one breed, namely the CKC spaniel breed (8). This finding was reproduced in a recent echocardiographic study of a large series of clinically healthy Dachshunds, but only when the statistical calculations were performed without including different measurements of the thoracic size (3). It appeared that the disease grew worse with decreasing circumference and/or width of the thoracic cage and that the thorax measurements had a stronger influence on the disease severity than the body weight. Thus, a small or narrow thorax seemingly

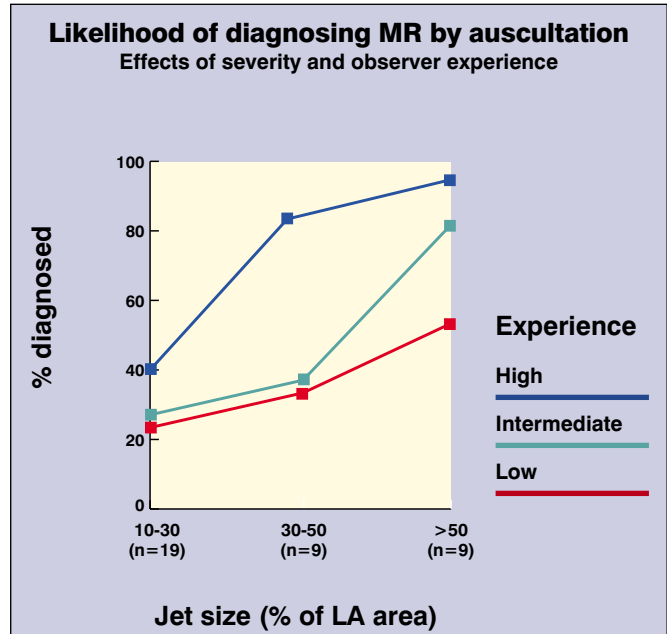


Figure 4 The likelihood of diagnosing mitral regurgitation by cardiac auscultation shown as a function of the jet size – i.e. the degree of regurgitation assessed by colour flow Doppler. The three curves represent six observers (two with high, two with intermediate and two with low levels of experience in cardiac auscultation) who auscultated the same series of clinically healthy Cavalier King Charles spaniels.

This Figure is based on results published elsewhere (11).

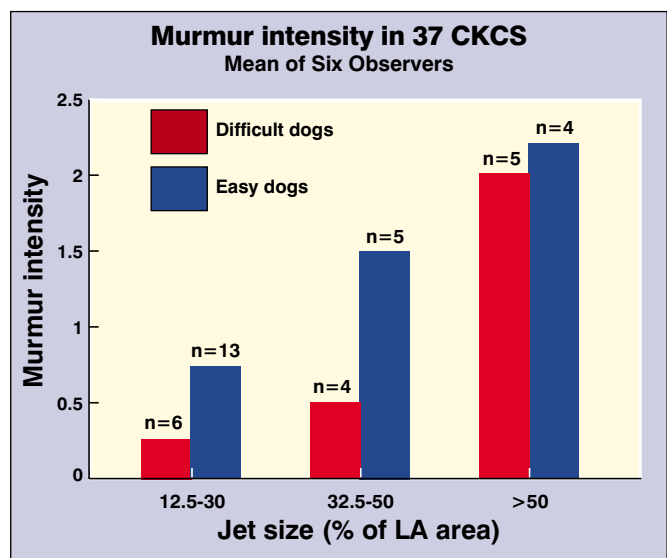


Figure 5 An illustration of how the murmur intensity (mean of six observers) increases with increasing jet size in clinically healthy Cavalier King Charles spaniels. As can be seen, whether a mildly affected dog is easy or difficult (even slightly so) to examine due to panting or shivering, for example, plays a major role. In dogs with severe regurgitation, such factors play only a minor role for the auscultatory findings.

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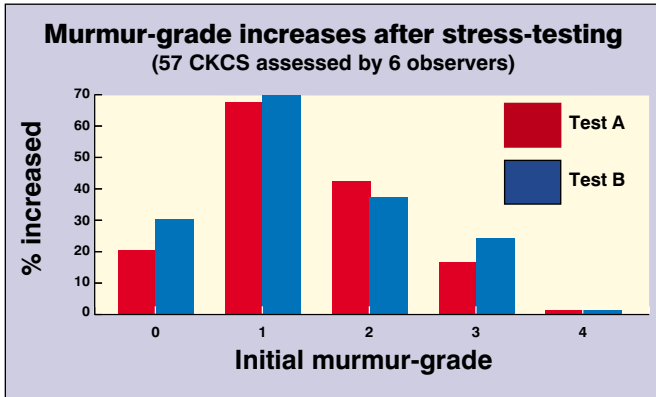


Figure 6 The percentage of murmurs in which the initial grades (grade 0 = no murmur) increased by a grade or more after stress testing. In stress test A, cardiac auscultation was performed immediately after the dogs had been lifted down to the floor and back up again in one quick movement and in stress test B, they had run 10–20 metres immediately before the auscultation. The results are based on six observers auscultating 57 clinically healthy Cavalier King Charles spaniels. Of the 342 evaluations made, the initial murmur grading was 0 in 173, 1 in 60, 2 in 72, 3 in 33 and 4 in 4. Modified from (11).

predisposes a dog to myxomatous valvular disease, an observation supported by the fact that the disease in humans (so-called primary MVP) is often related to a low antero-posterior chest diameter.

Cardiac Auscultation

Several recent studies have documented that the degree of MR correlates with the intensity of the associated regurgitant murmur (3, 8, 10, 11). In accordance with this, it has been shown that the likelihood of diagnosing the disease by cardiac auscultation increases with the increasing degree of MR. In other words, a murmur will not be observed in many dogs with mild to moderate MR (11). It should be noted that mild MR is usually associated with relatively short-lived (typically early systolic) murmurs whereas severe MR is associated with holosystolic murmurs (11). In addition to the degree of MR, the likelihood of noting a murmur in a dog with mild disease has been shown to correlate with the degree of observer experience in cardiac auscultation (Figure 4). The state of mind of the animal is also important – i.e. whether the dog is even slightly difficult to examine due to panting or shivering, for example (Figure 5) (11).

The likelihood of diagnosing a dog with mild MR by cardiac auscultation can be increased by performing some kind of dynamic auscultation/stress testing. Thus, two simple physical manoeuvres (lifting the dogs down to the floor and back up again in one quick movement or running 10–20 metres with them) performed immediately prior to auscultation were recently shown to have a marked influence on the auscultatory findings in a series of clinically healthy CKC spaniels. Approximately 25% of the dogs that initially did not have a murmur developed one after stress testing. In approximately 70% of the dogs with murmurs of very low intensity (grade I of VI), the murmur intensity increased a grade or more (Figure 6) (11).

It should be noted that ‘innocent’ or ‘physiological’ murmurs associated with a high-flow state are also likely to be provoked by stress testing. Such murmurs appear to be an important differential diagnosis – only highly experienced observers can discern them from soft regurgitant murmurs (11) and they are not uncommon in predisposed dogs. Thus, 5–10% of clinically healthy CKC spaniels apparently have such murmurs, even when stress-testing is not performed (8, 11).

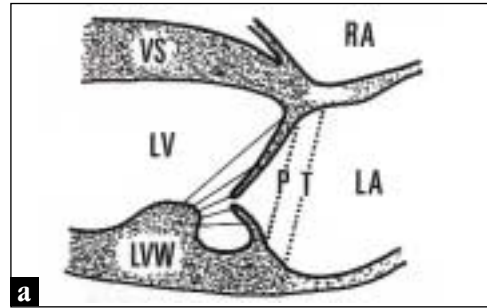


Figure 7 Criteria that can be used to diagnose MVP echocardiographically using the right parasternal long-axis four-chamber view. (a) Drawing illustrating the mitral annulus plane (line P, drawn between the hinge points of the two leaflets) and the borderline between mild and severe prolapse (line T, drawn from the middle of the elliptical echogenic area at the lower part of the atrial septum to the atrioventricular junction). (b) Echocardiogram of a normal mitral valve. (c) Valve with mild prolapse. (d) Valve with severe prolapse. Key: RA = right atrium; VS = ventricular septum; LV = left ventricle; LA = left atrium; LVW = left ventricular wall. The arrowheads point at the mitral valve leaflets. Reprinted from (12) with permission from the editor.

Finally, it should be mentioned that an anxious dog will often appear to be more diseased (i.e. have a louder murmur) based on an auscultatory examination than a calm dog with the same (mild) degree of disease because of the marked influence of the circulatory status on the auscultatory findings. Furthermore, a veterinarian accustomed to auscultating dogs immediately after they have been lifted up onto the examination table will probably diagnose more murmurs than a veterinarian who usually waits some time before performing the cardiac auscultation.

Other auscultatory features associated with early stages of the disease are mid-systolic clicks and an increased ratio between the intensity of the first and second heart sound (10, 11). In humans with mild disease, a clear mid-systolic click is often found by cardiac auscultation. Based on a recent phonocardiographic study, it appears that such clicks are also common in dogs with early stages of the disease. However, most of the clicks are not found by auscultation, even by experienced observers, apparently because they have low audibility in the dog (11).

Echocardiography

Echocardiographically, the degree of myxomatous mitral valve disease can be assessed in several ways, even in early stages. A recent study showed that the degree of leaflet protrusion/MVP, the leaflet thickness and the degree of MR (jet size) all correlated well with each other over a broad spectrum ranging from normal valves to clearly abnormal, insufficient ones (3). Details of how to assess the degree of leaflet protrusion, leaflet thickening and MR is listed below:

Degree of leaflet protrusion/MVP

The basis of measuring the degree of leaflet protrusion is a well-defined mitral annulus plane. In all the recent studies that have been published on canine MVP, the hinge points of the two leaflets (imaged in the right parasternal long-axis view) have been used to define this plane (Figure 7a). For several reasons, this appears to be a good way of defining the annulus plane. First, it gives a low day-to-day variation as well as intra- and inter-observer repeatabilities comparable to those obtained in humans (12). Second, it seemingly makes it possible to clearly separate dogs with mildly affected valves from dogs without valvular changes. Thus, young CKC spaniels currently without murmurs were clearly separated in a blind manner from age- and sex-matched control dogs in one study (7) and, in another study, dogs with mild MR were clearly separated from mixed-breed dogs without MR (13). Finally, it is an obvious advantage that the right parasternal long-axis view allows images of acceptable quality to be obtained in the vast majority of dogs.

There are three methods described for assessing the degree of leaflet protrusion relative to the mitral annulus plane. The first and most simple method is to assess whether the valve has no, mild or severe prolapse by using the criteria illustrated in Figure 7 (7, 12). The second method is to measure the exact protrusion above the annulus plane (in millimetres) of the coaption point of the two leaflets or, if the leaflets do not coapt properly, the tip of the more protruding leaflet (13). The third method is to measure the maximal protrusion (in millimetres) of the anterior leaflet, the posterior leaflet and the coaption point (or the more protruding tip) and then strike an average of those three measurements (14). At present, it is difficult to say which method is best.

The degree of leaflet protrusion has been shown to correlate well with the degree of MR irrespective of which method is used (3, 13, 15). With regard to using the degree of MVP to predict the subsequent development of MR in young predisposed dogs, only future longitudinal studies can determine which method is best. However, irrespective of which method is used, it is important to carefully scan through the entire valve since the lesions are

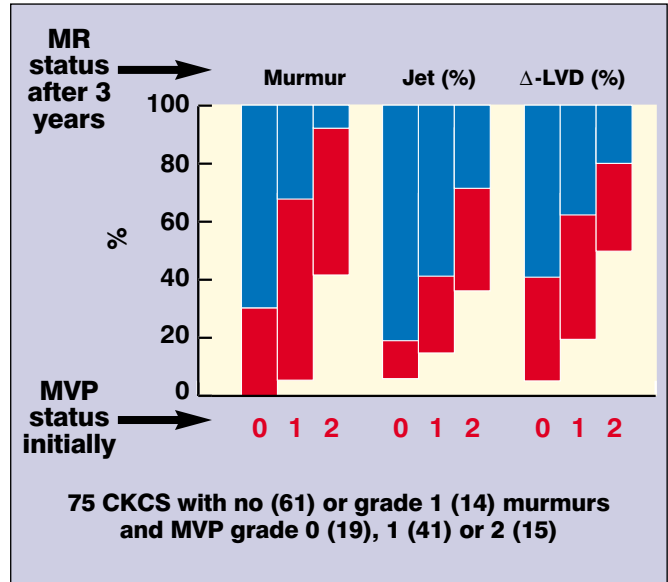


Figure 8 Results from a recent three-year follow-up study of 75 Cavalier King Charles spaniels with no murmur ($n = 61$) or a grade I murmur ($n = 14$). Note that the three columns represent three individual figures based on the same 75 dogs. The MVP status at the initial examination is shown at the bottom: 19 of the dogs had no or very mild MVP (grade 0), 41 had mild MVP (grade 1) and 15 had moderate or severe MVP (grade 2). The three columns show how the initial MVP status correlated strongly with the murmur intensity at the follow-up examination as well as with the jet size (in percentage of the left atrial area) at follow-up and the percentage increase in the left ventricular end diastolic volume (Δ -LVD) over the three-year follow-up period. The presence of a grade I murmur was not a useful prognostic indicator.

Based on data published in (8).

often very unevenly distributed.

In predisposed dogs without murmurs, or with murmurs of very low intensity, the degree of leaflet protrusion appears to be of prognostic importance. Thus, in a series of 75 CKC spaniels without murmurs or with grade I murmurs studied recently (8), the degree of MVP correlated well with the degree of MR three years later, irrespective of whether the degree of MR was assessed from the murmur intensity or from the size of the regurgitant jets found by colour flow mapping (Figure 8). As shown in this figure, the initial MVP severity also correlated with the percentage increase in the left ventricular end diastolic diameter over the three-year follow-up period.

Leaflet thickness

In humans with myxomatous mitral valve disease, the thickness of the mitral valve leaflets is an important prognostic marker. In the dog, there has been little investigation of how leaflet thickness should be measured echocardiographically or of the prognostic importance of such a measurement. However, since leaflet thickness reflects the deposition of glycosaminoglycans (a fundamental feature of the disease) and holds prognostic information in humans, an assessment should be made of the maximal leaflet thickness. It is important to remember that a leaflet assessed in diastole (when it is unstressed) will look thicker than it really is because of factors such as leaflet redundancy and overlap. It is also important to realise that the apparent leaflet thickness is gain-dependent and that it therefore may be useful to compare the mitral valve leaflets to other structures at similar depth such as the aortic valve cusps or the posterior aortic wall (16).



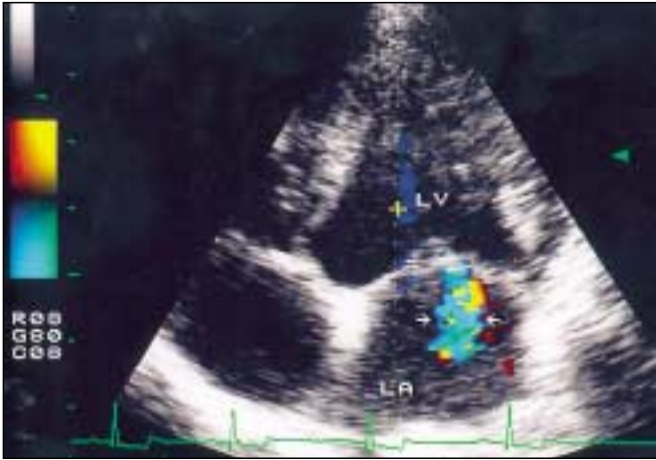


Figure 9 Colour Doppler echocardiogram (left caudal four-chamber view) from a five-year-old Cavalier King Charles spaniel with mild mitral regurgitation. Note the small regurgitant jet (arrows) that occupy only approximately 10–15% of the left atrial area. Key: LV = left ventricle; LA = left atrium.

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Degree of MR

In dogs with myxomatous valvular disease, an indication of the degree of MR is given by the left ventricular end diastolic diameter and the size of the left atrium. It should be noted, however, that there is quite a wide normal range for these measurements, even in dogs of approximately the same size. Furthermore, it is important to realise that a dog that has developed a given degree of MR over a period of several years will display more chamber enlargement than a dog that has developed the same degree of MR more acutely. A more direct assessment of the degree of MR can be made if one has access to an echocardiograph that allows colour flow mapping to be performed. This also makes it possible to evaluate the degree of MR in dogs with mild/moderate MR in which there is often no noticeable cardiac enlargement.

One of many colour Doppler methods that may be used to make an assessment of the degree of MR is to measure the size of the regurgitant jets – an example of this is given in **Figure 9**. The jet size is often reported as the percentage of the left atrial area occupied by the jet and, in most instances, it will be sufficient to assess this percentage by eye (11). The jet area method requires a good beam penetration and in dogs with myxomatous valvular disease (which are usually small and narrow-chested), the beam penetration is often good. Several other factors, however, also influence the jet size and it is important to understand that the jet area approach only gives a semi-quantitative assessment of the degree of MR and is not a gold standard.

The Doppler technique underestimates flow that is poorly aligned with the ultrasound beam. Thus, colour flow mapping should be performed using the left apical four-chamber view in dogs with MR. If the right parasternal long-axis four-chamber view is used, the degree of MR will be underestimated in many cases (11). In agreement with this observation,

the author has found that most jets are well aligned with the ultrasound beam in the left apical four-chamber view. However, if a jet is eccentric, another consequence of the requirement for good beam-flow alignment is that the degree of MR in such a dog may be better graded by using another colour Doppler method. One of these, the proximal flow convergence method, is to measure the radius of the so-called ‘proximal isovelocity surface area’ (PISA), the semi-circular area of aliasing flow (flow above a given velocity) that reflects the acceleration of flow proximal to the regurgitant orifice. This method also allows for an assessment of the degree of MR in dogs with severe disease that, with commonly used pulse repetition frequencies, all have jets that occupy the whole atrium and thus cannot be classified based on jet size.

Electrocardiography

Dogs with severe MR often have a wide P-wave and an increased width and amplitude of the QRS complex. These findings, however, are not specific for MR and, furthermore, they are not found until late in the course of the disease. In dogs with mild disease, electrocardiography is of little help in establishing a diagnosis. Nevertheless, if a clinically healthy dog has severe respiratory sinus arrhythmia – i.e. if R-R intervals are less than half that of a neighbouring interval (**Figure 10**) – this may suggest that it has myxomatous mitral valve disease. From studies in both CKC spaniels and Dachshunds, it seems that there is an association between the presence and severity of MVP and such severe sinus arrhythmia (7, 15).

Future Directions

Further studies should be performed in order to evaluate how mild disease is best diagnosed echocardiographically, since early diagnosis has several advantages. One advantage is that the disease severity can be assessed in young animals, thus control schemes aimed at reducing the disease prevalence in predisposed breeds can be designed. Other advantages of being able to monitor early stages of the disease are that more can be learned about the disease and its course and the effects of various drugs on disease progression can be evaluated. It may become possible to perform clinical trials aimed at evaluating whether prolonged treatment with a given drug – for example, an endothelin receptor blocker – can inhibit the ongoing myxomatous degeneration.

As discussed elsewhere, canine myxomatous mitral valve disease is very

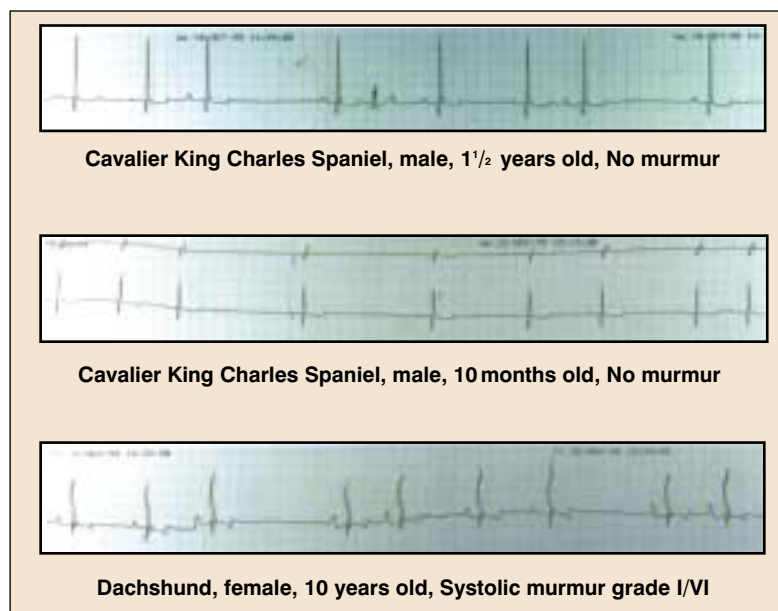


Figure 10 Electrocardiogram (lead II) from three clinically healthy dogs with severe respiratory sinus arrhythmia (defined as presence of R-R intervals being less than half that of a preceding or subsequent interval). Such severe sinus arrhythmia is often seen in dogs that, like these three dogs, have mitral valve prolapse.

similar to primary MVP in man in several important respects, including pathology (5), epidemiology (3, 8), auscultatory findings (11), presence of hypomagnesaemia (17) and changes in the circulating renin-angiotensin system (14, 17). Since primary MVP in humans is associated with platelet abnormalities, it is thought-provoking that clinically healthy CKC spaniels often have thrombocytopaenia and macrothrombocytosis (18, 19). Further studies should be designed to elaborate on these comparative aspects. In all likelihood, more will be learned about the canine disease if parallels are drawn with the many findings continuously being made in the human field. Conversely, the dog could turn out to be a valuable model of MVP in humans.

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