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ALL YOU NEED TO KNOW ABOUT TREATING ASYMPTOMATIC MVD IN DOGS

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CONTENTS

SETTING A PRECEDENT IN THE TREATMENT OF MVD

Welcome to your guide for diagnosing and treating asymptomatic mitral valve disease (MVD) in dogs.

This booklet has been created as a source of knowledge for you, summarising the EPIC study results, presenting the current opinions of veterinary specialists and highlighting the groundbreaking advance in the treatment of asymptomatic MVD.

Over the past 20 years Vetmedin has revolutionised the way vets treat dogs with heart failure; significantly extending survival times and improving their quality of life.

Vetmedin is licensed for dogs with asymptomatic MVD* as it has been shown to delay the onset of heart failure by around 15 months and prolong overall survival.

Taking the 'watch and wait' approach to murmurs is no longer enough. In this booklet you will find everything you need to know about how you can improve the outcome for your patients with asymptomatic MVD.

With Vetmedin, murmurs now mean so much more.

* and cardiomegaly

GET TO THE HEART OF THE PROBLEM

MVD is the most common acquired heart disease in dogs. But when it goes by different names, including 'Myxomatous Mitral Valve Disease' and 'Endocardiosis', it can seem more confusing than it really is! Our articles, written by leading veterinary cardiologists, have been created to help you understand the progression of asymptomatic MVD and how to interpret a clinically significant murmur.

UNDERSTAND THE HEART

INTRODUCTION

Mitral valve disease (MVD) is the most common acquired heart disease in dogs, making up approximately 75–80% of cases.[1,2] Despite its familiarity, and perhaps because of it, MVD is known by a number of different names including 'myxomatous mitral valve disease' and 'endocardiosis'. Both terms refer to the nodular lesions that form on the mitral valve leaflets. 'Degenerative mitral valve disease' and 'chronic atrioventricular valve disease' are also terms that are sometimes used and reflect the chronicity of this progressive disease. MVD typically affects small and medium breed dogs (<15kg) and males tend to be overrepresented.[2]

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In MVD, the body of the mitral valve, leaflet margins and even chordae tendinae (which anchor the valve to the papillary muscles) become thickened, nodular and distorted. This leads to poor leaflet positioning, resulting in a lack of normal mitral valve closure. The resultant back-flow of blood down a pressure gradient from left ventricle to left atrium in systole causes blood turbulence and vibration of cardiac structures, leading to an audible heart murmur. It is important to understand the progression of MVD, from the early pre-clinical or 'asymptomatic' phase, through to the 'symptomatic' phase when a patient develops clinical signs of congestive heart failure (CHF). The vast majority of dogs at any one time with MVD are asymptomatic, with a typical left apical murmur being the only detectable finding on physical examination. This asymptomatic phase can last for years – many dogs with MVD never display clinical signs of CHF and may die of another disease entirely – and overt signs of CHF only become apparent in a minority of affected dogs. The symptomatic CHF phase is shorter than the asymptomatic phase, with dogs typically only surviving for about 9 to 12 months once signs of CHF are detected (Figure 1).[3]

The traditional evidence base, incorporated into textbooks and veterinary school doctrine until very recently, has been that medical treatment of heart disease patients is not indicated until the onset of heart failure symptoms (typically tachypnoea or dyspnoea, sometimes associated with cough). As a result, many first opinion vets have considered the diagnosis and characterisation of heart disease prior to clinical signs as an academic exercise without great clinical benefit to the patient. Importantly, we now understand that dogs with MVD and cardiomegaly are more likely to develop heart failure in the next 1 to 2 years[4] than those without cardiomegaly and that staging the heart disease can significantly impact our care plan for the individual patient. Therefore, there is now a very good reason to investigate all clinically significant murmurs in any small breed dog to ascertain if cardiomegaly is present. Detecting cardiomegaly in asymptomatic MVD will enable you to decide upon an appropriate management and monitoring plan for that individual animal and assess likely prognosis.

Understanding the disease process and the clinical features of MVD is fundamental to achieving a diagnosis of asymptomatic MVD, as well as enabling effective owner communication and clinical decision making.

Dogs at risk of MVD
(Stage A)

'At risk' dogs are those that fulfil the typical signalment for MVD patients but have not yet developed detectable heart disease. These are most often determined by the absence of a heart murmur. Although any small breed dog and some larger breeds (eg. the Border Collie or German Shepherd) can develop MVD, the breed that first comes to mind for UK vets when we think about MVD is the Cavalier King Charles Spaniel (CKCS). Outside the UK, although the Cavalier is predisposed, vets often see other breeds such as the Norfolk, Maltese, Yorkshire and Jack Russell terriers, the Miniature Dachshund, Miniature Schnauzer, Pekingese, Chihuahua and the Japanese Chin, which also seem to be predisposed. Males of all breeds have a higher chance of developing MVD than females and may develop the disease at a younger age.[2] Although the CKCS appears to have a more prevalent and progressive disease, the prevalence increases with age in all breeds. In the CKCS, the proportion of dogs diagnosed with MVD over 12 years old is estimated at 80%.[5]

Essentially, any small breed dog (<15kg) should be considered at risk of developing MVD and should therefore be monitored regularly at routine health checks for the development of a murmur typical of the disease.

Early asymptomatic
(Stage B1)

Dogs in the early asymptomatic phase are defined as those with MVD and therefore have an audible murmur – but no cardiomegaly and no outward symptoms of cardiovascular or respiratory compromise. The heart murmur is usually detected incidentally at a routine physical examination as part of annual vaccination or health screening.

In the early phase of the disease, small nodules form on the body and free edge of the mitral valve. Histopathologically, these nodules demonstrate an abnormal collagen matrix, myxomatous degeneration and an altered population of valve interstitial cells. Grossly, they prevent normal valve closure and promote bending of the valve back into the left atrium during systole (valve 'prolapse'). The backwards leak of blood leads to a characteristic murmur. In the early asymptomatic phase of the disease, the murmur typically has a lower intensity (grade 1/6 or 2/6) reflecting haemodynamically insignificant regurgitation through the mitral valve.

The likelihood of a dog with early asymptomatic MVD developing signs of heart failure in the next 1 to 2 years is small; however, patients should be monitored regularly for an increase in heart murmur intensity. This could indicate a transition from early asymptomatic to late asymptomatic disease. Therefore, in small breed dogs with suspected MVD, most cardiologists would recommend imaging of the heart when a murmur intensity of grade 3/6 or above is detected.

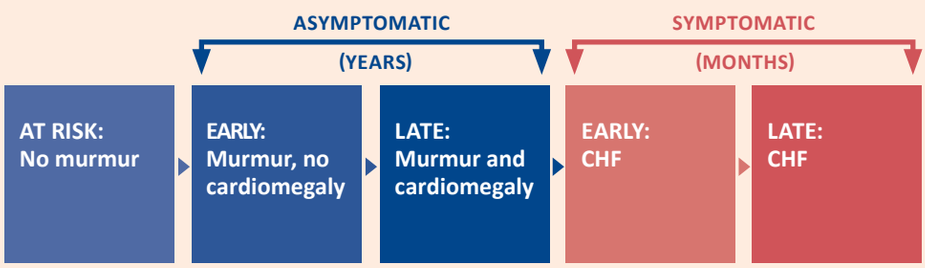

Figure 1: Staging mitral valve disease – characterising cardiomegaly is vital to differentiate between dogs in early and late asymptomatic disease. Based on the ACVIM Consensus Statement published in 2009.[2]

OF THE PROBLEM

Late asymptomatic
(Stage B2)

MVD is a progressive disease, but the factors that determine rate of progression are not yet fully understood. As the disease progresses, the pathological lesions on the mitral valve margins gradually coalesce. They form large plaques that distort the valve tissue further and spread to affect the chordae tendineae. These developments further worsen mitral regurgitation, leading to a more advanced clinical disease stage. In addition, involvement of the chordae poses a risk of chordal rupture, which is a relatively common cause of acute deterioration in patient condition and is a risk for sudden cardiac death.

Dogs in late asymptomatic MVD are those with an audible murmur and cardiomegaly (detectable by X-ray and/or ultrasound) but with no outward symptoms. We now know from the EPIC study[4] that these dogs are likely to develop CHF in the next 1 to 2 years and could therefore benefit from specific alterations to their care plan. Identifying these dogs is critical if we are to manage them appropriately and diagnose CHF at the earliest possible timepoint. Dogs with late asymptomatic MVD should be re-examined frequently (every 6 months) for early signs of CHF and owners can be taught to monitor the resting respiratory rate (RRR) of dogs at home (best done when asleep) to more sensitively detect changes in patient status.

As the degenerative changes to the mitral valve worsen over time, the backwards regurgitation of blood into the left atrium increases. The resultant reduction in cardiac output activates compensatory mechanisms, which aim to normalise blood pressure. These systems (activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system) evolved to survive an episode of acute haemorrhage or severe hypovolaemia. They are over-activated in diseases with progressive reduction in cardiac output. Blood volume and vascular resistance are both increased, but this increases myocardial workload and contributes to cardiac enlargement and progressive changes which lead to worsening of disease. As such, the activation of compensatory mechanisms is 'maladaptive' when MVD is present.

Initially, compensatory changes allow the dog to remain asymptomatic. However, with time they lead to cardiomegaly, reduced cardiac efficiency and a greater risk of heart failure. In the clinic environment, we can see how the identification of cardiomegaly is a key risk factor for progression of disease to clinical signs of heart failure, and how dogs in the late asymptomatic stage of MVD warrant an increased intensity of monitoring at home and at the vets.

Dogs with MVD causing cardiomegaly typically have a louder heart murmur (≥ grade 3/6), reflecting the increased volume of regurgitation and greater vibration of damaged valve structures. Approximately half of dogs with a grade 3/6 murmur caused by MVD have cardiomegaly on imaging, and the proportion of dogs with cardiomegaly increases as the murmur grade increases.[6] A murmur intensity of grade 3/6 or greater is therefore clinically significant and warrants imaging (either radiography or echocardiography) to assess the dog's heart size. It is important to remember that disease stage – and therefore risk – is based on imaging the heart rather than murmur intensity. For example, if a dog with a loud heart murmur is found to have a normal heart size, they can be considered as having early asymptomatic MVD (stage B1) with annual monitoring recommended. A dog with the same intensity murmur that displays cardiomegaly on imaging would be classified as late asymptomatic (stage B2).

Early CHF
(Stage C)

Dogs in early CHF are those that have developed symptoms of tachypnoea, dyspnoea and possibly cough. At this stage, intensification of treatment (crucially featuring diuretic medicine) is indicated. In this stage, we see the end result of chronic vasoconstriction and increased blood volume; pressure in the left atrium and pulmonary venous bed have increased so much that fluid leaks from the pulmonary capillaries into the interstitium and alveoli of the lung – this is pulmonary oedema. Decompensation is often gradual, where left atrial stretch and increased pulmonary lymphatic uptake appear to 'keep up' with changes and blunt the effect for some weeks or months, leading to a slower onset of respiratory compromise. In some individuals, the tipping point appears as an acutely life-threatening dyspnoea – often caused by a ruptured chordae tendon, which leads to a sudden increase in left atrial pressure – with severe signs often requiring hospitalisation. The earliest sign of pulmonary oedema may be detected by an astute owner who is already monitoring RRR at home, as RRR rises with the onset of failure. This requires the MVD to have been previously diagnosed and staged as above, with recommendations for home monitoring by a vet. A reduced ability to exercise or a prolonged recovery period may also be an early warning sign of heart failure, but these are rarely reported by owners unless they have been discussed in advance as a possible sequel to MVD. Again, this requires a previous staging of the disease in response to detection of a murmur.

Late CHF
(Stage D)

Dogs with late CHF are in end-stage CHF and are considered refractory to standard treatment. Examples of refractory patients may be those with resistance to diuretics, significant cardiac arrhythmias or pulmonary hypertension. These patients often require specialised management and may benefit from referral to optimise their treatment regime to maintain a good quality of life. The prognosis for these dogs is poor, with many surviving less than 6 months once considered as stage D patients.

Summary

Although the clinical suspicion of MVD is very high in an older, small breed dog with an asymptomatic left apical murmur, we should no longer recommend monitoring solely for clinical signs of disease before taking action. We now understand that, although asymptomatic, dogs with cardiomegaly benefit from being identified. Staging their heart disease using radiography or echocardiography is recommended for dogs with a grade 3/6 or louder heart murmur, even in the absence of clinical signs.

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WHEN IS A MITRAL VALVE

INTRODUCTION

Cardiac auscultation is the most valuable physical examination procedure for any animal with suspected heart disease.

Mitral valve disease (MVD) is by far the most common heart disease that we encounter in dogs. Normally, the first sign of MVD that is detected on clinical examination is a characteristic murmur. This murmur will typically be found during a routine examination, such as at vaccination, and the owner will report that the dog is well at that time. The information that we can gather by listening to the murmur will enable us to determine the most appropriate and relevant further investigations to not only confirm the diagnosis, but also to establish how far the disease has progressed. Only with this information can we provide the owner with an accurate prognosis and develop an appropriate monitoring and management plan to optimise our patient's quality of life.

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We now know that dogs with asymptomatic MVD who have a moderate-to-loud mitral valve murmur (grade 3/6 or above) have what is known as a 'clinically significant murmur'. These murmurs are clinically significant because dogs with a murmur ≥ 3/6 are much more likely to have cardiomegaly than dogs with a grade 1 or 2 murmur.[1] This is important since dogs with asymptomatic MVD and cardiomegaly are very likely to develop congestive heart failure (CHF) in the next 1 to 2 years.[2]

Knowing that the dog is at risk of developing CHF in the near future enables closer monitoring and therefore the identification of CHF symptoms at the earliest possible stage. Ultimately, this means that you as the clinician are in the best possible position to intervene with treatment at the earliest opportunity, improving that dog's outcome.

The best way to become proficient at auscultation is to listen to as many hearts as possible. This article will describe how to carry out a good auscultation exam and how to identify a clinically significant murmur in dogs with asymptomatic MVD.

Auscultation technique

When performing cardiac auscultation, it is recommended to develop a routine so that no important information is missed. Ideally, find a quiet room where there is minimal background noise. Keep the patient calm and cool to avoid panting and overexcitement, and keep the patient in a standing position as recumbency changes the heart's position within the chest.

It is important not to rush cardiac auscultation and to listen for long enough to be able to assess the heart rhythm for any irregularities. Palpate the femoral pulses simultaneously to ensure there is a palpable pulse for each heartbeat and record the heart rate in the patient's records. Recording the heart rate is important, as one of the compensatory mechanisms when the heart is struggling to maintain cardiac output is to increase heart rate. By recording the resting heart rates in the clinical notes, you will be able to monitor the progression of the dog's heart disease over time. This small but important detail is often overlooked by vets in first opinion practice, but it can help to build a clear clinical picture and allow you to make decisions about how well the heart is functioning and when interventions are necessary.

Before you start listening to the heart, place the palm of your hand over the left apex to identify the presence or absence of a precordial thrill. Place the stethoscope over this region (**Figure 1**). This is the location of the mitral valve and is where a murmur of mitral regurgitation is loudest.

Slowly move the stethoscope one rib space cranially and slightly dorsally from the left apex to the left base; this is where a murmur of aortic stenosis will be loudest (**Figure 2**). To auscultate the pulmonic valve area, move the stethoscope two rib spaces cranially and horizontally from the left apex. A murmur of pulmonic stenosis is loudest in this region (**Figure 3**).

Next, the right apex beat should be palpated and the stethoscope moved into this region. This is the tricuspid region, where a murmur of tricuspid regurgitation is most easily detected (**Figure 4**). Slowly move the stethoscope cranially to listen over the right heart base. By following this technique, you will have listened to the whole of the heart over each individual valve area.

Normal heart sounds

The first heart sound (S1) occurs at the onset of systole and is associated with the closure of the mitral and tricuspid valves. The second heart sound (S2) is associated with the closure of the aortic and pulmonic valves at the end of systole.

The third and fourth hearts sounds (S3 and S4), also known as gallop sounds, should not be audible in normal, healthy dogs. If you ever hear a gallop sound in a small animal, you should investigate it further.

Variations in heart sound intensity

Heart sound intensity may be decreased in obese animals and in those with pleural or pericardial effusions. Conversely, the intensity may be increased in animals that are young, thin, tachycardic or anaemic.

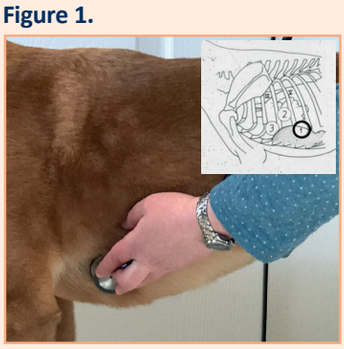
Murmur description

Murmurs are characterised by their intensity, location and timing.

Intensity

The intensity of a heart murmur normally directly correlates with disease severity. In MVD, the murmur intensity tends to increase as the disease worsens. Murmurs are most commonly graded on a 1 to 6 scale, with a grade 1 murmur being the softest and a grade 6 murmur being the loudest (**Figure 5**).

Figure 1.



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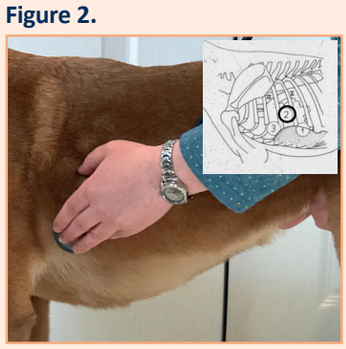

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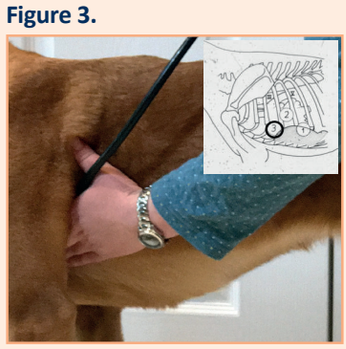

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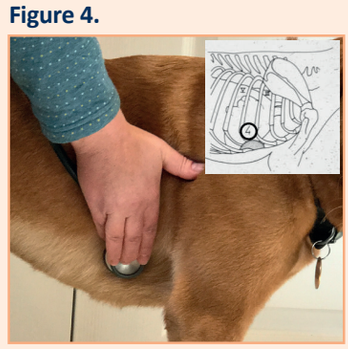


E MURMUR SIGNIFICANT?

Figure 5.

GRADE					
1	2	3	4	5	6
This murmur is **very soft** and is heard only in a **quiet room** and after **close concentration.**	This murmur is **faint** but can be **easily heard** when the stethoscope is placed **on the point of maximum intensity.**	This murmur is **moderately loud** and may be described as being **as loud as the heart sounds.**	This murmur is **loud** and can be **heard over several areas** across the chest.	This murmur is **very loud** and is accompanied by a palpable **precordial thrill.**	This murmur is **very loud** with a **precordial thrill** and can be heard with the **stethoscope just removed from contact with the chest.**

In MVD, about 50% of dogs with a grade 3/6 murmur have cardiomegaly; the proportion of dogs with cardiomegaly increases as the intensity of the murmur increases.[1] Dogs with a grade 3/6 murmur or more are at a greater risk of going into CHF within 1 to 2 years.[2] A moderate-to-loud murmur in these patients therefore warrants further investigation to assess for the presence of cardiomegaly. This will enable you to develop an appropriate management plan, as well as offer the owner a more accurate prognosis. It is important to record the intensity of the murmur in the patient records to allow for an assessment of disease progression over time.

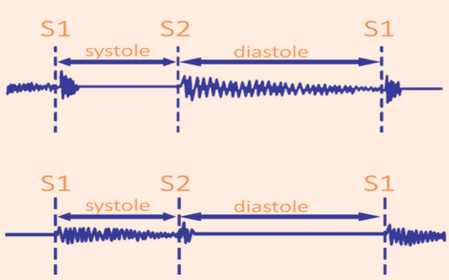
Location

Note the position where the murmur is the loudest (the point of maximum intensity or PMI). The PMI of a mitral valve murmur is the left apex (**Figure 1**).

Timing

It is important to describe the timing of the murmur relative to the cardiac cycle. Systolic murmurs occur when the heart is contracting between the first and second heart sounds – S1 and S2 (**Figure 6**). Mitral regurgitation which we detect as a MVD murmur is always systolic. Diastolic murmurs start immediately after the second heart sound and are audible through diastole. Continuous murmurs are audible through systole and diastole.

Figure 6.



Murmurs in asymptomatic MVD

Many dogs with MVD seem normal to their owners and have no outward symptoms of heart disease. As described above, auscultation of a moderate or loud mitral valve murmur (≥ grade 3/6) warrants further investigation for cardiomegaly. The presence of cardiomegaly means that the dog is likely to go into CHF over the next 1 to 2 years[2] and so, by gaining this information, you and the dog's owner will be in the best position to identify early symptoms of heart failure and begin medication at the most appropriate time.

Screening

Early diagnosis of MVD often requires a conscious effort by vets to look for the disease. This is because the asymptomatic phase of the disease when the dogs have a leaky mitral valve but no outward symptoms can last for many years. This fact emphasises the importance of cardiac screening. Screening for MVD is simple and should ideally be performed annually in "at risk" dogs (all middle age or older dogs weighing <15kg). Cardiac auscultation using a stethoscope is an effective screening tool for MVD in these "at risk" dogs.

MVD is characterised by the presence of a typical left apical systolic heart murmur due to mitral regurgitation. Remember that the loudness of the murmur gives an approximate indication of the size of the leak across the mitral valve and thus the severity of the disease. Dogs with a large enough volume of mitral regurgitation to cause cardiomegaly will typically have a murmur of grade 3/6 or louder;[1] these dogs are at an increased risk of going into CHF within the proceeding 1 to 2 years,[2] and therefore require closer monitoring.

Further Diagnostics

It is important to remember that the presence of a heart murmur simply tells you that heart disease is present. Further diagnostic imaging (cardiac ultrasound [echocardiography] and/or thoracic X-rays) is required to identify the presence or absence of cardiomegaly.

Monitoring

Remember – failing to detect cardiomegaly on X-ray and/or ultrasound in a dog with MVD is a positive sign! Cardiomegaly is one of the first signs of impending CHF and so, although it cannot be guaranteed, a normal sized (albeit a diseased) heart is a reassuring finding. In a dog with asymptomatic MVD but no current evidence of cardiomegaly, it is typically recommended to monitor for an increase in loudness of the murmur using cardiac auscultation every six months.

In dogs with asymptomatic MVD, the heart will enlarge slowly over time. Thoracic radiographs and/or cardiac ultrasound should therefore be repeated annually to monitor for changes in heart size.

Once there is evidence of heart enlargement in an asymptomatic dog with MVD, very close monitoring is prudent as CHF is likely to be imminent. The owner should be educated to count the resting/sleeping respiratory rate at home, as this is a very sensitive indicator of the development of pulmonary congestion and early CHF.[3,4] Recording the resting/sleeping respiratory rate and the resting heart rate on your clinical notes will allow you to detect when these rates start to rise. This is one of the first symptoms of heart failure and indicates that the dog needs treatment.

In summary, careful auscultation of these smaller middle-aged dogs is a reliable, inexpensive, non-invasive and straightforward screening tool to detect MVD before a dog develops symptoms associated with CHF. If you can easily hear a characteristic mitral valve murmur, it is likely to be significant (≥ grade 3/6). Dogs with a significant mitral valve murmur are more likely to have cardiomegaly[1] and, if they do, they are likely to develop CHF in the next 1 to 2 years.[2] Hearing a significant murmur should therefore be a trigger for further investigation to establish the size of the heart. With this information, you can give the owner an accurate prognosis as well as develop an appropriate monitoring plan. This will enable you to start treatment at the most appropriate time to optimise the patient's quality and length of life.

MEANINGFUL MURMURS WEBINAR

Available to view at https://www.boehringer-academy.co.uk/

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THE EPIC STUDY THAT CHANGED EVERYTHING

The EPIC study is the largest veterinary cardiology study carried out to date, pushing evidence-based veterinary medicine to a new level. The EPIC study took seven years to complete and involved 360 dogs and 36 investigators from eleven countries, across four continents.

The EPIC study results are of significant clinical relevance and challenge the existing view of managing asymptomatic MVD.

Dogs with asymptomatic MVD and cardiomegaly are more likely to go into heart failure within 1 - 2 years. This can be delayed by treating with Vetmedin.

Where previously a 'watch and wait' approach was appropriate, the EPIC study has demonstrated that many of these dogs will live longer symptom-free if they are treated with Vetmedin before the onset of heart failure.

THE EPIC STUDY: WHAT WAS IT ABOUT, AND WHAT DOES IT MEAN FOR PRACTITIONERS?

*The acronym EPIC stands for "**E**valuating **P**imobendan **I**n dogs with **C**ardiomegaly". The EPIC study, the main results of which were published last year, was a large, blinded, placebo-controlled clinical trial that set out to demonstrate whether or not the administration of pimobendan to dogs with cardiac enlargement secondary to degenerative mitral valve disease (DMVD) would result in an improved outcome for those dogs.*[1]

Prior to the EPIC study, two prospective clinical trials had been conducted to evaluate the effectiveness of angiotensin converting enzyme inhibitors (ACEi) in dogs with DMVD before the onset of congestive heart failure (CHF).[2,3] *Neither trial conclusively demonstrated any benefit of ACEi therapy, and therefore there was no consensus amongst cardiologists about the most effective treatment at this stage of the disease.*[4]

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Background

Mitral valve disease is a very common but slowly progressive disease that typically affects older small breed dogs. It is the most prevalent cardiac disease in dogs, as well as the most common cause of an acquired murmur. The disease begins with degeneration of the mitral valve, which results in incompetence of the valve. This results in a leak in the valve, which then gives rise to a characteristic systolic murmur. This necessitates an increase in the amount of blood pumped by the left side of the heart to compensate for the amount of blood that leaks back into the left atrium each time that the heart contracts.

The disease may pass through a number of stages (**Figure 1**). In the first stage of the disease, the only detectable abnormality is the presence of a heart murmur. If diagnostic tests such as radiography or echocardiography (cardiac ultrasound) are performed, these dogs will have normal-sized hearts. The leak in their valve is small, and therefore the volume of blood that leaks back on each cardiac contraction is also small and can be compensated for without the need for the heart to enlarge. In the classification system proposed by the American College of Veterinary Internal Medicine (ACVIM), these dogs would be described as being at 'stage B1' of the disease.[4] Many dogs affected by the disease never progress beyond stage B1 and never develop any clinical signs attributable to the disease.

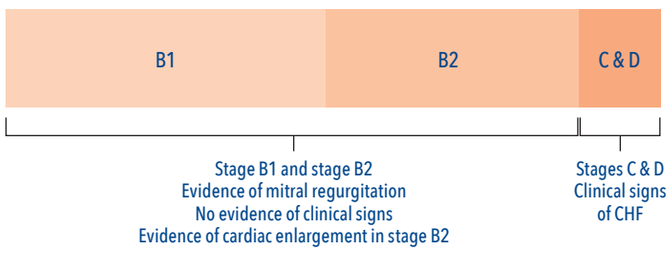


Figure 1

Some dogs have progressive degeneration of their valve, such that over time the volume of blood leaking back into the left atrium increases. In order to compensate for this leak, the heart must increase in size. These dogs with enlarged hearts, but not yet in heart failure, are described as being at 'stage B2'. Importantly, the enlargement of the heart typically precedes the onset of clinical signs.

Outwardly, it may not be possible to distinguish a dog with more advanced disease (a stage B2 dog) from a dog at the earlier stage of the disease (stage B1). Dogs with a murmur ≥ grade 3/6 are more likely to have an enlarged heart, but a murmur alone cannot be used to distinguish a B1 dog from a B2 dog.[5] Many stage B2 dogs remain apparently normal to their owners, but during stage B2 dogs may start to develop subtle signs evident to the owners such as coughing or exercise intolerance. It has been shown that cough is more likely to be present in dogs with an enlarged heart although cough is not a reliable sign of the presence of pulmonary oedema.[6] Stage B2 dogs do not have overt signs of CHF such as breathlessness due to pulmonary oedema. Typically, once a dog has developed cardiomegaly, they are at a greater risk of developing CHF within the next 2 years.[1]

If the disease progresses beyond stage B2, dogs go on to develop signs of CHF. Typically, when dogs develop CHF secondary to DMVD they develop signs of left sided CHF, most commonly breathlessness due to the development of pulmonary oedema. Elevated resting respiratory rate has been shown to be a useful indicator of the development of left sided heart failure. Confirmation of the presence of pulmonary oedema usually requires a thoracic radiograph. Dogs that develop signs of CHF are said to be at 'stage C' of the disease.

Although prior to the EPIC study there was a lack of consensus regarding the effectiveness of treatment before the onset of CHF (prior to stage C), there was agreement regarding the appropriateness of, and necessity for, treatment of stage C dogs. Since there was no clear benefit of treating dogs before the onset of CHF, it made sense to wait until clinical signs developed before investigating dogs with DMVD and initiating treatment.

Rationale and study design

From the foregoing description of DMVD, it can be seen that dogs with this condition that have evidence of cardiac enlargement (stage B2 dogs) exhibit evidence of progressive disease. These dogs are at highest risk of eventually developing signs of CHF. If we intend to see if a treatment can delay the onset of signs of CHF, it makes sense to evaluate that treatment in a population of dogs with stage B2 disease and observe if it delays their progression to stage C.

This is the approach we took in the EPIC study. We set out to recruit a population of dogs that had not yet developed signs of CHF but were at risk of doing so because their hearts were enlarged. We selected dogs on the basis of a number of criteria, which included three measurements of heart size. We could therefore be confident that the dogs were affected by DMVD and, as a consequence of that disease, their hearts were showing some signs of enlargement.

The three heart size criteria that we used were:

- A vertebral heart sum (VHS) of > 10.5 from a thoracic radiograph
- A left atrial to aortic ratio of ≥ 1.6 from a cardiac ultrasound examination, and
- A 'normalised' left ventricular diameter in diastole of ≥ 1.7, again obtained from a cardiac ultrasound examination

We felt sure that because all dogs entering the study met these three criteria they would definitely be at stage B2 of the disease and at risk of developing CHF. Importantly, despite having cardiomegaly none of the dogs recruited to the study had current or previous evidence of CHF and the vast majority were not perceived by their owners to have any signs of cardiac disease such as coughing or exercise intolerance.

We estimated that we would need to recruit 360 dogs to the study to have a reasonable chance of showing an effect of the treatment. Half of these dogs were randomised to receive pimobendan, while the others were randomised to receive the placebo. The 'primary endpoint' of the study was the onset of signs of CHF or the death of the patient for reasons attributable to their cardiac disease. We were interested to know whether the administration of pimobendan would prolong the time it took dogs to reach the primary endpoint. We therefore set out to compare the time that it took dogs in the two groups to progress to stage C and quantify the 'relative risk' of the two groups of dogs. The relative risk expresses how much more likely it is that a dog in one group will reach the primary endpoint by comparison to a dog in the other group.

Results

Due to the slow rate of progression of DMVD, we expected that the study would take a long time to complete – and we were right. The study took over 4.5 years to run from beginning to end, not including the time taken to plan the study and analyse the results. In total, it took over six years to conduct the entire study.

As planned, we recruited 360 dogs to the trial at 36 different centres in eleven countries, which makes this study the largest clinical trial of its kind conducted in veterinary cardiology. It also means that the results are readily generalised to a worldwide population of dogs with DMVD. The study clearly showed that there was a benefit in the administration of pimobendan to these dogs and that benefit can be expressed in several ways. Firstly, the median time to the onset of heart failure or death in the group receiving pimobendan was 462 days longer than in the placebo group (1228 days versus 766 days) (Figure 2). The median time is an estimate of the time it took for 50% of the dogs in each group to reach the primary endpoint. This result therefore equates to a prolongation of the period before the onset of heart failure or death of about fifteen months for the average dog in the pimobendan group compared to placebo, with a strong significant difference between groups. There was a marked reduction in the risk of developing heart failure or death in the pimobendan group with a reduction in risk of over one third by comparison to the placebo group. This means that a dog in the pimobendan group was only 2/3 as likely to develop the primary endpoint at any given time compared with a dog that received the placebo. Alternatively, a dog on placebo had 1.5 times the chance of developing the primary endpoint compared with a dog on pimobendan.

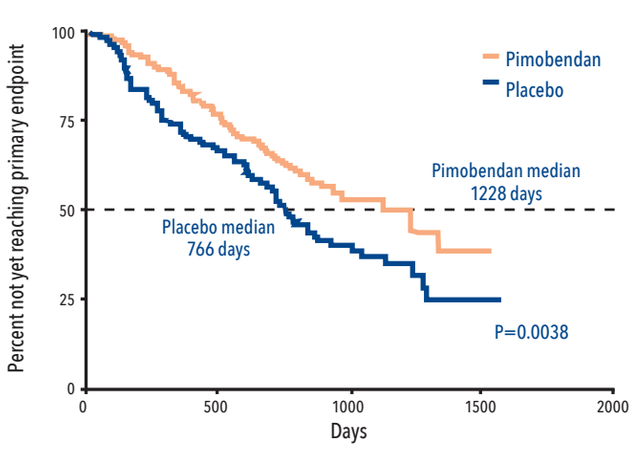


Figure 2. Kaplan-Meier survival curves showing the time to the onset of heart failure or death in the two treatment groups. Median time in the placebo group was 766 days (95% CI: 667–875) compared to 1228 days in the pimobendan group (95% CI: 856–NA), representing a prolongation of the period before the onset of CHF or death of about 15 months for dogs receiving pimobendan.

(CI: confidence interval; NA: not able to calculate)

Finally, although the primary aim of the study was to show a delay in the onset of heart failure, the study also showed that on average the dogs in the group receiving pimobendan lived longer than those receiving placebo. Therefore, there was a clear survival benefit alongside the prolongation of the period before the onset of heart failure.

Conclusions and ramifications

As a result of the findings of the EPIC study, we can conclude that there is indeed a benefit of administration of pimobendan before the onset of signs of CHF in dogs with DMVD. However, we cannot conclude that all dogs with DMVD will benefit. No dogs without cardiac enlargement (stage B1 dogs) were recruited to the study, and therefore we can only conclude that there is a benefit associated with the administration of pimobendan to dogs with DMVD that have enlarged hearts (stage B2 dogs).

The majority of dogs recruited to the study were completely free of any outward signs of disease. The majority of dogs' owners did not consider their dog to be coughing, nor did they feel that their dog's exercise tolerance was in any way compromised. This has the important implication that dogs appear to benefit from therapy before they are showing any signs. This in turn means that taking the approach of waiting until signs develop may now result in some dogs being denied potentially life-prolonging and life-improving therapy.

It is this point that highlights the key change in the management of patients with mitral valve disease that the EPIC study has brought about. Previously, taking a 'watch and wait' approach was entirely justified on the basis of the available evidence. A patient would be expected to demonstrate some signs – such as coughing, exercise intolerance or increased respiratory rate – either prior to or at the time when the introduction of therapy was justified on the basis of the best evidence available. If one waits until clinical signs are present before investigating a patient's disease, it is possible that a stage of disease during which that patient would have benefited from therapy would already have elapsed by the time treatment is started and the opportunity to help that patient would have been missed.

So, how can one find dogs that will benefit from early therapy? Dogs like those recruited to the EPIC study will benefit from therapy; therefore, to determine whether or not a dog may benefit from therapy will require that dog undergoing diagnostic imaging to determine whether or not its heart is enlarged. Dogs entering the EPIC study underwent both echocardiography and radiography. Of those two techniques, echocardiography is probably the better for demonstrating evidence of subtle cardiac enlargement. Ideally, dogs suspected of having DMVD should undergo echocardiography to determine if their heart is enlarged or not. This is not to imply that radiography is of no value in determination of heart size. It is very likely that a dog with a clearly enlarged cardiac silhouette on a thoracic radiograph will have echocardiographic evidence of enlargement. However, breed differences in heart size (and VHS) mean that, where fine distinctions need to be made between normal and enlarged hearts, echocardiography is superior.

It is impractical to suggest that all dogs with a left-sided heart murmur should undergo echocardiography. As was mentioned above, dogs with moderate-to-loud murmurs are more likely to have enlarged hearts. This means that efforts to characterise a dog's heart size should be greater if there is evidence from clinical examination of more advanced disease, such as a murmur of an intensity greater than or equal to a grade 3/6.

In conclusion – watching and waiting, although a previously sensible approach, may no longer be enough to enable you to offer the best evidence-based care to your patients with DMVD. If you are suspicious that a patient may have progressive DMVD, even in the absence of any outward clinical signs, it is worth recommending that the dog undergoes diagnostic imaging. If such a dog is shown to have cardiomegaly, initiating treatment with pimobendan at that stage will probably result in the dog having a longer period before the development of signs of heart failure and prolong the dog's life.

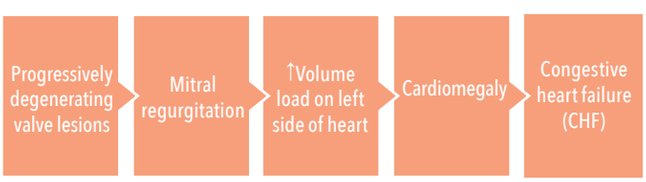
References: 1. Boswood A *et al.* (2016) *J Vet Intern Med* 30: 1765–1779. **2.** Atkins CE *et al.* (2007) *J Am Vet Med Assoc* 231: 1061–1069. **3.** Kvart C *et al.* (2002) *J Vet Intern Med* 16: 80–88. **4.** Atkins C *et al.* (2009) *J Vet Intern Med* 23: 1142–1150. **5.** Ljungvall I *et al.* (2014) *J Small Anim Pract* 55: 545–550. **6.** Ferasin L *et al.* (2013) *J Vet Intern Med* 27: 286–292.

A SUMMARY OF THE EPIC STUDY[1]

Background

Mitral valve disease (MVD) is the most common cardiovascular disease in the dog.

The pathophysiology of MVD, which can lead to heart failure, is summarised here:



Dogs with MVD can progress through various stages of the disease:

- Stage A – those at risk of developing the disease
- Stage B – those with mitral regurgitation but no signs of CHF
- Stage C – those with signs of CHF
- Stage D – those with signs of CHF that are refractory to treatment

Stage B can be further subdivided:

- Stage B1 – those with disease but no evidence of cardiomegaly
- Stage B2 – those with disease and cardiomegaly

A number of therapies are considered effective in dogs with Stage C disease, including Vetmedin, which has been shown to significantly improve survival and maintain quality of life.

Until recently, there was no consensus about the effectiveness of medical treatment in Stage B. There are 2 published, prospective, randomised clinical trials evaluating ACE inhibitor (ACEi) treatment at this stage; however, no clearly beneficial effect of ACEi was found in either trial.

Due to the long duration of the asymptomatic period, any treatment that is effective in prolonging it could have a major impact on the longevity and quality of life of affected dogs.

Hypothesis/Objectives

To determine whether the administration of Vetmedin (0.4 - 0.6 mg/kg/day) to dogs with asymptomatic MVD and cardiomegaly would delay the onset of signs of CHF and cardiac-related death or euthanasia.

Materials and Methods

The EPIC trial was the largest prospective, randomised, placebo-controlled, blinded, multicentre clinical trial in veterinary cardiology ever to be conducted. The investigators were guaranteed the right to publish the results of the study irrespective of the outcome.

The study involved:

- 360 dogs
- 36 investigators
- 11 countries
- 4 continents

Inclusion criteria:

- ≥ 6 years of age
- Body weight 4.1 – 15 kg
- Stage B2 MVD:
  - Evidence of asymptomatic MVD on auscultation (≥ grade 3/6 murmur) and echocardiography
  - Evidence of cardiomegaly on radiography and echocardiography

Dogs were randomised into two groups:

- 180 dogs into the Vetmedin group
- 180 dogs into the placebo group

Study endpoints

Primary endpoint – this was defined as the point at which the dog either developed CHF or experienced cardiac-related death or euthanasia.

Secondary endpoints – there were two secondary endpoints in the EPIC study. The first was "all-cause mortality", which was death due to any cause. The second was "time to first event" which was the point at which the dog experienced any event; this could include reaching the primary endpoint, having an unscheduled veterinary visit, receiving a precluded medication, or the owner becoming non-compliant.

Results

The study was terminated early after the interim analysis demonstrated a significant benefit in favour of administering Vetmedin to dogs with asymptomatic MVD and cardiomegaly.

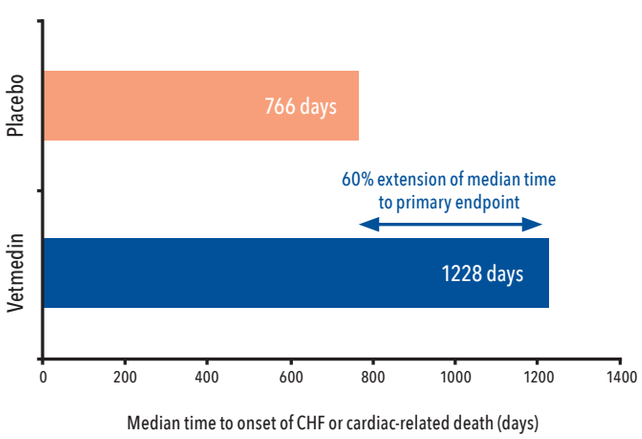
A SUMMARY OF THE EPIC STUDY[1] CONTINUED

Primary endpoint analysis

The median time to the primary endpoint for each group was:

- Vetmedin – 1228 days
- Placebo – 766 days

Dogs receiving Vetmedin took on average an additional 462 days (approximately 15 months) to either develop CHF or die from cardiac disease (p=0.0038). This represents around a 60% extension of the asymptomatic period.



Secondary endpoint analysis

Dogs receiving Vetmedin had an extended time to first event (p=<0.0001) and lived longer (p=0.012) compared with dogs receiving placebo.

Safety

There were no significant differences in adverse event occurrence between the Vetmedin and placebo groups.

Conclusions and clinical importance

MVD is the leading cause of heart disease, and the development of CHF results in substantial morbidity and mortality. The EPIC study has shown, for the first time, convincing evidence of the benefit of treatment before the onset of CHF in dogs with asymptomatic MVD (Stage B2). Dogs receiving Vetmedin:

- Experienced a 60% extension in the asymptomatic period
- Took approximately 15 months longer to develop clinical signs associated with CHF
- Had an overall longer survival time
- Took longer to experience an event
- Did not experience any increase in adverse events compared to the placebo group

This substantial degree of prolongation of the asymptomatic period is of clinical relevance and is of importance to vets and owners of dogs affected by this common disease.

Reference: 1. Boswood A, Häggström J, Gordon S, *et al.* Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly: The EPIC Study—A Randomized Clinical Trial. (2016) J Vet Intern Med. 30: 1765–1779.

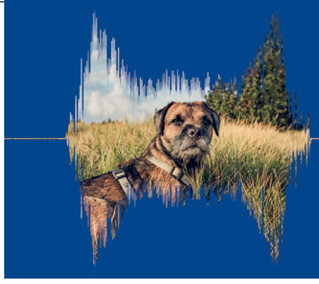
IDENTIFYING DOGS WHO WILL BENEFIT FROM TREATMENT

Based on the findings of the EPIC study, dogs with clinically significant MVD murmurs (≥ grade 3/6) should be investigated for cardiomegaly.

There are two ways of detecting cardiomegaly in dogs: chest X-ray or cardiac ultrasound.

Identifying cardiomegaly in dogs with asymptomatic MVD allows you to treat with Vetmedin to:

- Delay the onset of heart failure by approximately 15 months
- Extend the dog's overall survival time
- Improve the dog's quality of life



EVALUATING ASYMPTOMATIC

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INTRODUCTION

Mitral valve disease (MVD) is the most common cardiac condition in dogs. MVD is most common in small to medium breed, middle-aged to older dogs.

In MVD, thickening and degeneration of the mitral valve leads to mitral regurgitation, which is heard as a murmur. Many dogs cope with mild mitral regurgitation and remain stable, but a considerable proportion progress. In these dogs, progressive valvular degeneration and increasing mitral regurgitation cause volume overload on the left side of the heart leading to cardiomegaly and, eventually, congestive heart failure (CHF). MVD has a long disease course with a prolonged asymptomatic phase of approximately 2–3 years' duration. Once CHF develops (symptomatic phase) survival times are short, typically 6–9 months.

Asymptomatic MVD is often first suspected based on the presence of a heart murmur which is commonly detected as an incidental finding during a routine appointment or at the time of vaccination. In MVD, the murmur grading is directly proportional to the quantity of mitral regurgitation[1] with higher grades indicating more mitral regurgitation and more severe disease.

Small to medium breed dogs with a clinically significant murmur (≥ grade 3/6) are more likely to have cardiomegaly.[1] Dogs with cardiomegaly are likely to develop CHF within the next 1–2 years.[2] The EPIC study demonstrated that dogs with asymptomatic MVD and cardiomegaly treated with Vetmedin® experienced on average a 15 month extension of the asymptomatic phase and lived significantly longer compared with dogs receiving placebo[2]. Therefore, investigating asymptomatic small to medium breed dogs with murmurs ≥ grade 3/6 is vitally important; a traditional watch and wait approach is no longer appropriate.

DIAGNOSTIC IMAGING

Determining the degree of cardiomegaly requires cardiac imaging. Imaging provides information on cardiomegaly at that time point, but progression of disease should be anticipated even in dogs not currently showing evidence of cardiomegaly. Regular monitoring is therefore of paramount importance and these dogs will require repeat imaging in order to decide when to commence treatment.

Further investigations of cardiomegaly are best performed using either chest x-rays or cardiac ultrasound. There are clear advantages and disadvantages of each, and the choice often comes down to the individual vet's preference or equipment availability.

CARDIAC ULTRASOUND

Cardiac ultrasound has many potential advantages over chest x-rays. It allows assessment of individual chamber sizes and is more accurate for absolute assessment of left atrial and ventricular chamber dimensions. The two most important measurements are the LA:Ao ratio (Figure 1) which assesses left atrial size and the left ventricular internal dimension in diastole (LVIDD) which assesses left ventricular dilation (Figure 2). There are breed specific reference intervals for these measurements; however, LVIDD should be normalised to body weight, known as LVIDDN,[3] using the Cornell Formula. A LVIDDN calculator is available on the Boehringer Academy (**www.boehringer-academy.co.uk**). Both LA:Ao ≥ 1.6 and LVIDDN ≥ 1.7 are diagnostic of cardiomegaly.

Ultrasound also allows subjective assessment of heart muscle function and allows assessment of the mitral valve. This can be done by evaluating the valve leaflets, the apparatus (papillary muscles and chordae tendinae) and the degree of thickening and prolapse. Ultrasound also allows the practitioner to exclude other cardiac conditions as well as identifying the type and extent of underlying heart disease. For assessment of cardiomegaly, ultrasound is more specific (low false positive rate) than chest x-rays. Additionally, sedation is not typically required to perform a cardiac ultrasound.

While there are clearly a number of advantages to ultrasound, not all practices have access to machines capable of imaging the heart accurately. It is also potentially more expensive as it may take longer to perform than chest x-rays. Finally, operator experience may vary which can have a profound impact on the accuracy of measurements. Nevertheless, cardiac ultrasound is accessible to many vets in first opinion practice, and with adequate training and practice, the measurements required to identify cardiomegaly can be relatively easily carried out.

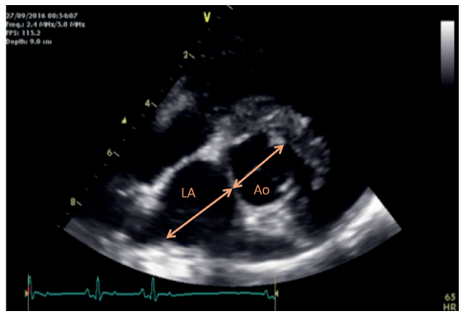

Figure 1. The LA:Ao ratio assesses left atrial size.

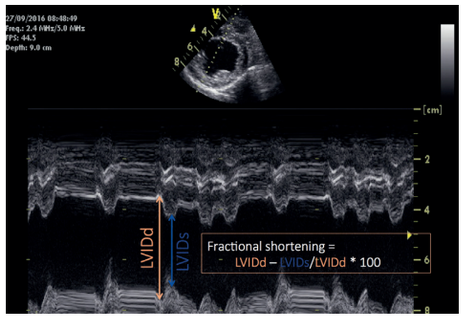

Figure 2. The left ventricular internal dimension in diastole (LVIDD) assesses left ventricular dilation.

MVD: X-RAY OR ULTRASOUND?

CHEST X-RAYS

Chest x-rays are another important tool for assessing cardiomegaly. X-ray is more commonly available in general practice than cardiac ultrasound. Veterinary surgeons are also typically more familiar with interpreting chest x-rays than cardiac ultrasound. It is convenient and allows evaluation of the pulmonary parenchyma, airways and pulmonary vessels as well as assessment of the cardiac silhouette. Assessment of the cardiac silhouette should include assessment of the vertebral heart score (VHS)[4] to provide an objective measurement of cardiomegaly (Figure 3). A normal VHS is typically <10.5; however, there can be breed variation therefore breed specific ranges should be used. A table of these is available on the Boehringer Academy (**www.boehringer-academy.co.uk**). Due to the progressive nature of MVD, heart size increases over time in line with disease severity, and VHS is a useful tool to track this.

Chest x-rays do pose some disadvantages compared to ultrasound, namely the inability to assess heart function or the heart valves. It is a less sensitive method to detect cardiomegaly, i.e. significant enlargement is required before seeing cardiomegaly on x-ray. VHS is considered a crude method of assessing heart size, as x-rays might not accurately depict the true degree of cardiac enlargement. In addition, individual chambers cannot be assessed in as much detail and diagnostic x-rays require a compliant patient (Figure 4). Sedation and/or general anaesthesia may be required for diagnostic quality x-rays and breed variation (e.g. increased sternal contact in wide, barrel chested dogs) can result in misinterpretation and potentially misdiagnosis.

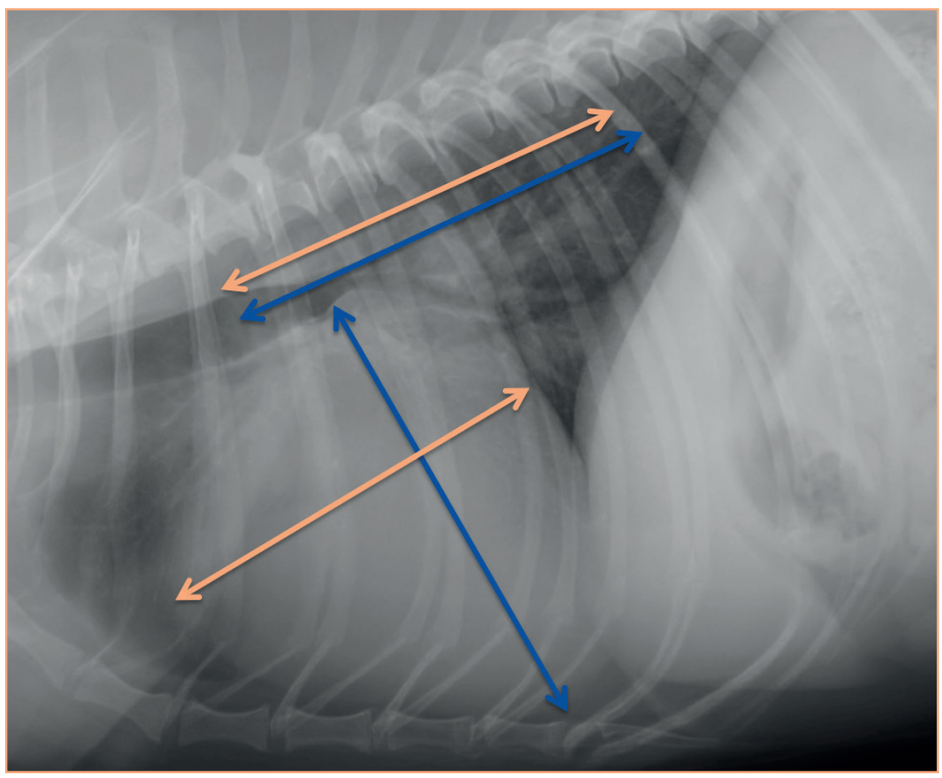

Figure 3. The vertebral heart score (VHS) provides an objective measurement of cardiomegaly.

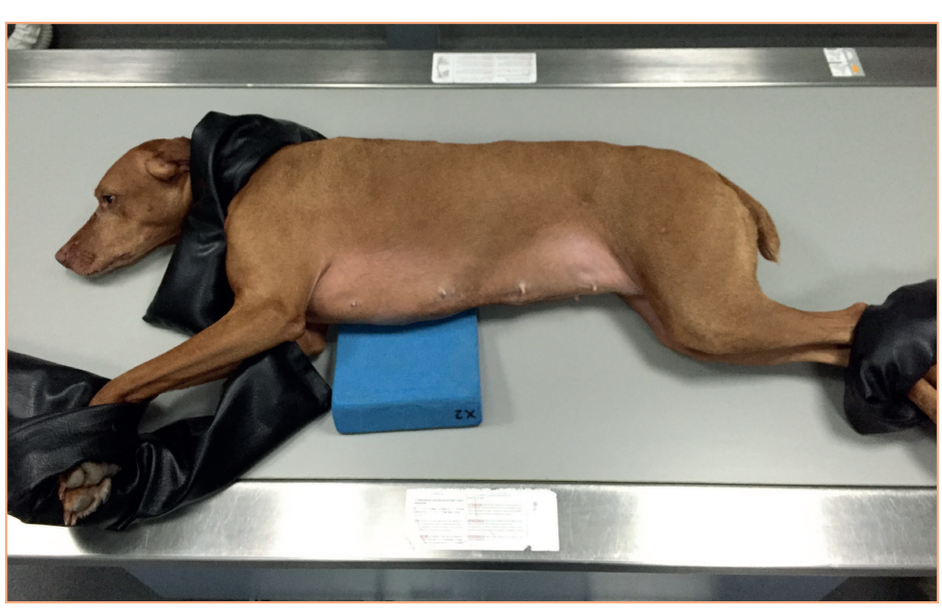

Figure 4. Diagnostic x-rays require a compliant patient.

SUMMARY

MVD in small to medium breed dogs typically has a long asymptomatic phase. Progression of disease should be suspected if a murmur increases in grading. Small and medium breed dogs with a ≥ grade 3/6 murmur need to be investigated to establish the presence or absence of cardiomegaly. Investigations can be with either x-ray or ultrasound or preferably both. There are clear advantages and disadvantages for each technique and the practitioner should use the test(s) they are most comfortable with. Improving skills to be able to accurately measure LA:Ao ratio and LVIDD with ultrasound, and the VHS on thoracic x-rays, is recommended. Dogs with cardiomegaly should be monitored closely as they are more likely to develop CHF within the next 1–2 years[2]. The recently published EPIC study demonstrated that dogs with asymptomatic MVD treated with Vetmedin experienced on average a 15-month extension in the asymptomatic phase of MVD. Therefore, dogs with asymptomatic MVD and cardiomegaly should be treated with Vetmedin.

BOEHRINGER ACADEMY

For more information on cardiac ultrasound including practical "how to" videos, visit www.boehringer-academy.co.uk.

References:
1. Ljungvall, I. *et al.* (2014) J Small Anim Pract. 55: 545–550
2. Boswood, A. *et al.* (2016) J Vet Intern Med. 30: 1765–1779
3. Cornell, C. *et al.* (2004) J Vet Intern Med. 18: 311–321
4. Buchanan, J.W. & Bücheler, J. (1995) JAVMA 206(2): 194–199

HOW TO USE RADIOGRAPHY TO BETTER

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Mitral valve disease (MVD) is the most common acquired canine heart disease. Around 11% of dogs have heart disease[1], and 75% of these are thought to have MVD[2]. MVD typically affects small to medium sized dogs. The incidence of disease increases with age; approximately 20–25% of all dogs between the ages of 9 and 12 years[3] have MVD.

MVD is a degenerative pathological process that causes the valve leaflets to become shortened and thickened. As the valvular lesions worsen, the affected valve becomes increasingly incompetent, resulting in progressive mitral regurgitation. The left ventricle dilates in order to cope with the extra regurgitant blood volume. In time, left ventricular filling pressures increase, which dilate the left atrium leading to left-sided congestive heart failure (CHF).

It can take more than 3 years for mild mitral regurgitation to develop into left-sided CHF. However, once clinical signs of CHF develop, survival time ranges from 6 to 9 months with appropriate medical management. The triggers for disease progression are poorly understood but it is clear that genetic factors play a large role in at-risk breeds like Cavalier King Charles Spaniels and Dachshunds[4].

IDENTIFYING DOGS AT RISK OF DISEASE PROGRESSION

Asymptomatic MVD is often first suspected based on the presence of a heart murmur, which is commonly detected as an incidental finding during a routine appointment or at the time of vaccination. Murmur grade correlates with disease severity[5], with higher-grade murmurs indicating higher levels of mitral regurgitation. Asymptomatic dogs with a soft systolic murmur (grade 1–2/6) are very unlikely to have cardiomegaly, whereas more than half of asymptomatic dogs with moderate or loud murmurs (≥ grade 3/6) have cardiomegaly, with the percentage of affected dogs increasing as the murmur grade increases[5]. A murmur of grade 3/6 or louder is therefore clinically significant and warrants further investigation. MVD is a progressive disease in some patients but disease progression is by no means a foregone conclusion. While all dogs with a heart murmur characteristic of MVD should be monitored closely, the majority of dogs with low-grade murmurs will never develop left-sided CHF.

Dogs with cardiomegaly are at greater risk of developing CHF within 1–2 years than dogs without cardiomegaly[6]. In addition, the EPIC study demonstrated on average a 15-month extension in the asymptomatic phase and longer overall survival in dogs with asymptomatic MVD and cardiomegaly treated with Vetmedin®, compared to placebo[6].

Making a presumptive diagnosis of MVD is relatively straightforward. Definitive diagnosis requires competent echocardiography. However, arguably the greatest diagnostic challenge is identifying the dogs whose disease is likely to progress, given that the majority of geriatric small breed dogs are likely to have a mitral murmur of no long-term consequence. Therefore, identifying cardiomegaly in dogs with suspected MVD is key.

DIAGNOSTIC TESTS

So, what are our options for identifying cardiomegaly in dogs with a clinically significant murmur?

Cardiac ultrasound is the diagnostic test of choice because it combines quantitative identification of cardiomegaly with definitive diagnosis, and rarely requires sedation. However, competent cardiac ultrasound requires significant expertise as well as appropriate equipment. Access can therefore be an issue in some veterinary practices.

Thoracic radiography is available in the vast majority of small animal practices and is therefore very convenient. It is effective in the identification of cardiomegaly, particularly in dogs with more advanced disease. However, it cannot provide a definitive diagnosis of MVD. In addition, sedation or general anaesthesia is usually required to obtain diagnostic quality images. Despite this, it is likely to be the most commonly used diagnostic test in general practice.

CHEST RADIOGRAPHY

It is best to take at least two views. Right lateral and dorsoventral views of the thorax are the most useful in dogs with suspected cardiomegaly (Figure 1 and Figure 2).

Interpreting chest radiographs is not an easy task, even for an experienced radiologist, so ensure optimal image quality for easier interpretation. Critically assess the quality of the images taken by asking the following questions:

- Is the patient well positioned?
- Could overlying forelimbs be hiding any cranial thoracic pathology?
- Are the exposure factors optimal?
- Are the lungs adequately inflated?
- Do the radiographs include the entire area of interest?

A detailed review of cardiac radiographic assessment is beyond the scope of this article. We will instead focus on assessing cardiomegaly using the vertebral heart score (VHS).

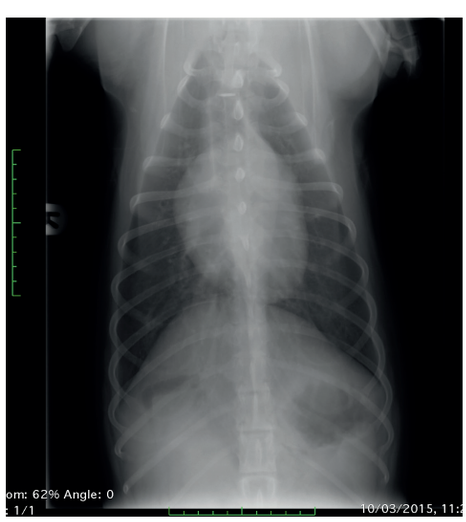


Figure 1. Dorsoventral view of the thorax.

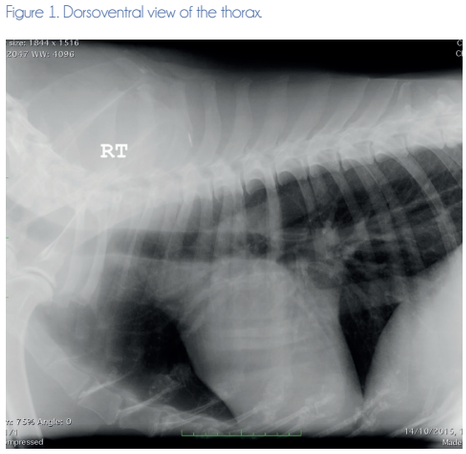
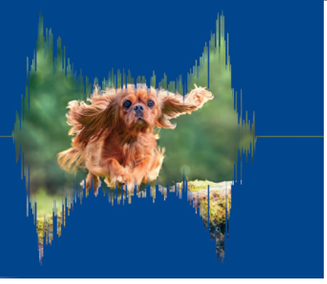


Figure 2. Right lateral view of the thorax.

MANAGE ASYMPTOMATIC MVD CASES



VERTEBRAL HEART SCORE (VHS)

The VHS assesses cardiac size, and the technique is particularly useful for those new to evaluating cardiac size on radiographs. It is also useful for the sequential assessment of cardiac size on repeat radiographs of the same patient.

To measure the VHS, take a well-positioned right lateral chest radiograph. Using a ruler, callipers or digital callipers, measure the long axis of the heart from the ventral border of the carina (ventral border of the tracheal bifurcation) to the most distant ventral contour of the cardiac apex. This dimension reflects the combined size of the left atrium and left ventricle. Starting at the cranial edge of the fourth thoracic vertebral body, count the number of vertebral bodies along the spine equal to this measurement. Next, measure the maximal short axis of the heart in the central third region, perpendicular to the long axis. Convert this measurement to the number of vertebral bodies as described above, and add the two figures together to get the VHS (Figure 3).

The VHS is undoubtedly a good guide to cardiac size in dogs with significant cardiomegaly. However, there are some important factors to bear in mind when interpreting the values obtained.

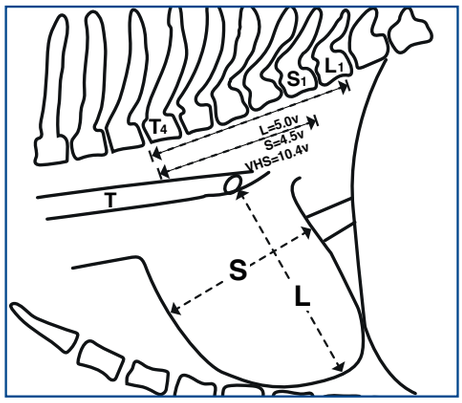


Figure 3. Measurements required to calculate the VHS. (L=Long Axis, S=Short Axis, T=Trachea)

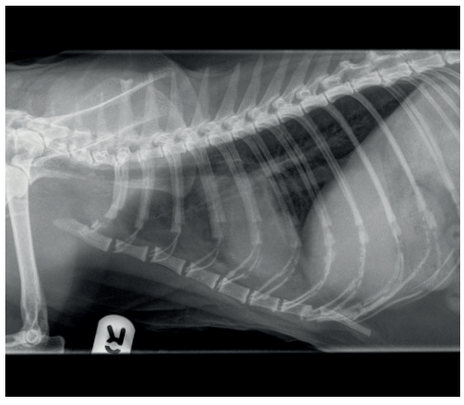


Figure 4. Right lateral view of the thorax demonstrating pericardial fat.

1 The canine heart varies between different dog breeds, and breed-associated conformational variation is the biggest cause of variation in the normal canine cardiac silhouette. Consequently, using a single normal cut-off value of <10.5 can result in breed-dependent false positives and false negatives. Instead, breed-specific normal values are recommended where published (Table 1).

BREED	Normal VHS Range from a Right Lateral Radiograph
Normal VHS range (non-breed-specific)	9.2–10.5[7]
Boston Terrier	10.3–13.1[8]
Boxer	10.8–12.4[9]
Bulldog (English/French)	11.0–14.4[8]
Cavalier King Charles Spaniel	10.1–11.1[9]
Labrador Retriever	10.2–11.4[9]
Pomeranian	9.6–11.4[8]
Pug	9.8–11.6[8]
Whippet	10.5–11.8[10]

Table 1: Breed-specific VHS ranges. This table is also available to download from the Boehringer Academy (www.boehringer-academy.co.uk).

2 An incorrect diagnosis of cardiomegaly is often made in animals with a large amount of pericardial fat. Pericardial fat contributes to the overall size of the cardiac silhouette but it is often possible to identify the presence of fat on careful inspection. Pericardial fat has a lower opacity compared with the heart and the cardiac margin is often not as sharp (Figure 4).

3 Variations in respiratory cycle can affect the VHS by up to one vertebral body (vertebral unit). Therefore, it is important to ensure that thoracic radiographs are consistently taken towards the end of inspiration.

4 The VHS is dependent on identification of specific radiographic landmarks that can be subject to interpretation. This introduces inter-observer variability that can affect the VHS by up to one vertebral unit.

The VHS assesses cardiac size. It is also important to look for corroborating radiographic evidence of cardiomegaly including specific chamber enlargement, tracheal elevation and pulmonary venous congestion. Dogs with MVD often have concurrent chronic respiratory disease, so it is important to review the respiratory system on radiographs as well.

SUMMARY

Dogs with cardiomegaly are at greater risk of developing CHF within 1–2 years than dogs without cardiomegaly[5]. In small and medium middle-aged dogs with a clinically significant murmur (≥ grade 3/6), diagnostic tests to identify cardiomegaly are required. Cardiac ultrasound is the diagnostic test of choice because it combines quantitative identification of cardiomegaly with a definitive diagnosis. Chest radiography is available in the vast majority of small animal practices and is therefore very convenient. It is effective in the identification of cardiomegaly, particularly in dogs with more advanced disease. If cardiac ultrasound is not an option then chest radiography is the most useful diagnostic test to identify cardiomegaly.

The EPIC study demonstrated a 15-month extension in the asymptomatic phase and longer overall survival in dogs with asymptomatic MVD and cardiomegaly when treated with Vetmedin, compared to placebo[6]. Dogs with asymptomatic MVD and cardiomegaly should therefore be treated with Vetmedin.

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USING ULTRASOUND TO IMPROVE THE M

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Referral Service, Solihull

INTRODUCTION

Mitral valve disease (MVD) is the most common cardiac condition in dogs. MVD is most common in small to medium, middle-aged to older dogs.

In MVD, thickening and degeneration of the mitral valve leads to mitral regurgitation, which is heard as a murmur. Many dogs cope with mitral regurgitation and remain stable but a smaller proportion progress. In these dogs, progressive valvular degeneration and increasing mitral regurgitation cause volume overload on the left side of the heart leading to cardiomegaly and, eventually, congestive heart failure (CHF). MVD has a long disease course with a prolonged asymptomatic phase of approximately 2–3 years' duration. The symptomatic (CHF) phase is much shorter, typically 6–9 months.

Asymptomatic MVD is often first suspected based on the presence of a heart murmur which is commonly detected as an incidental finding during a routine appointment or at the time of vaccination.

In MVD, the murmur grading is directly proportional to the quantity of mitral regurgitation[1] with louder murmurs indicating more severe disease.

Small and medium breed dogs with a clinically significant murmur (≥ grade 3/6) are more likely to have cardiomegaly[1]. Dogs with cardiomegaly are more likely to develop CHF within the next 1–2 years[2]. The EPIC study demonstrated that dogs with asymptomatic MVD and cardiomegaly treated with Vetmedin® experienced a 15 month extension in the asymptomatic phase and lived longer overall compared with dogs receiving placebo. Therefore, investigating asymptomatic small and medium breed dogs with murmurs ≥ grade 3/6 is vitally important; a traditional watch and wait approach is no longer appropriate.

DIAGNOSTIC IMAGING

Determining the degree of cardiomegaly requires cardiac imaging. Imaging provides information about heart size at that time point; however, progression of disease should be anticipated in dogs not currently showing evidence of cardiomegaly. Ongoing monitoring is therefore of paramount importance, and these dogs will require repeat imaging in order to decide when to commence treatment.

Further investigations of cardiomegaly are best performed using either chest x-rays or cardiac ultrasound. Cardiac ultrasound is superior for the evaluation of chamber dilation and there are a number of ultrasound measurements which more strongly predict outcome than thoracic x-rays. However, practitioners should use the imaging modality with which they are most comfortable.

PREPARING THE PATIENT FOR CARDIAC ULTRASOUND

Preparation for cardiac ultrasound helps the practitioner to obtain diagnostic images. For optimal image quality, position the patient in right lateral recumbency. For basic ultrasound of the asymptomatic MVD patient, only right-sided views are required. To avoid lung interference, scan the patient from underneath. Restraint with one or two people holding is often sufficient without sedation. A padded table or foam tabletop improves patient comfort and compliance (Figure 1). Clip the fur in the area over the apex beat and two rib spaces cranially and caudally, from sternum to mid-thorax. Apply a generous amount of ultrasound gel to reduce artefacts from poor contact. Finally, choose a dark, quiet room that is ideally not a thoroughfare; this is particularly important for lively or fractious patients.

To achieve an optimal image, probe selection is important. For cardiac ultrasound, it is preferable to use a sector transducer probe. It has a small scanning surface, enabling viewing between the rib spaces. If a sector probe is not available, use a small microconvex probe as it also has a small surface which allows it to be manoeuvred between the ribs. Use low or medium frequency probes (5.0–7.5MHz) for assessing small to medium sized dogs for cardiomegaly.

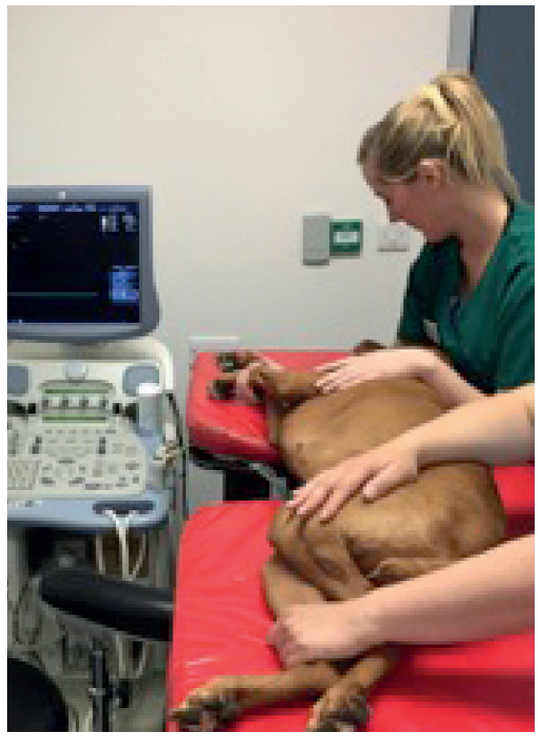
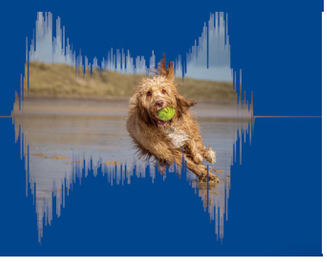


Figure 1. For basic ultrasound of the asymptomatic MVD patient only right-sided views are required. A padded table or foam tabletop improves patient comfort and compliance.

E MANAGEMENT OF ASYMPTOMATIC MVD



ULTRASOUND MEASUREMENTS TO ASSESS HEART SIZE IN THE ASYMPTOMATIC MVD PATIENT

There are two key measurements for assessing heart size in the asymptomatic MVD patient. The left atrium to aortic ratio (LA:Ao) assesses left atrial size, whereas left ventricular internal diameter in diastole (LVIDD) assesses left ventricular size. These are the two best ultrasound measurements for the detection of cardiomegaly in asymptomatic MVD cases[2].

Good repeatability is key for these measurements. Otherwise, patients may be misdiagnosed or incorrect treatment decisions made. Obviously, two measurements make for a very focused ultrasound examination; undertaking a complete ultrasound assessment with colour and spectral Doppler may be considered to more accurately examine an MVD patient. In addition, assessment of the mitral valve and its apparatus should form part of every examination.

LA:Ao

LA:Ao measures left atrial size and determines the degree of left atrial dilation. Use a short axis view at the level of the heart base (Figure 2) for this measurement. Take the measurement on the image one frame after aortic valve closure (i.e. early diastole) as the size of the left atrium will vary if different time points are used. Make sure the aorta is in complete cross-section with the aortic valve leaflets visible (this looks like the "Mercedes-Benz" sign – see Figure 3). Failure to achieve this will result in suboptimal images for measurement. Include the whole of the left atrium on the screen and take care to avoid measuring into the pulmonary veins (see Figure 2). A LA:Ao ≥ 1.6 represents left atrial dilation and cardiomegaly.

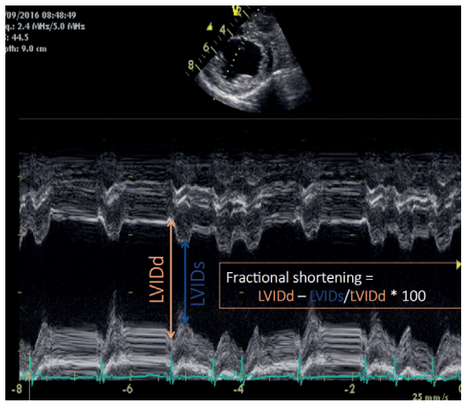


Figure 2. A short axis view at the level of the heart base is used to measure the size of the left atrium using the LA:Ao. Care should be taken to avoid measuring into the pulmonary vein.

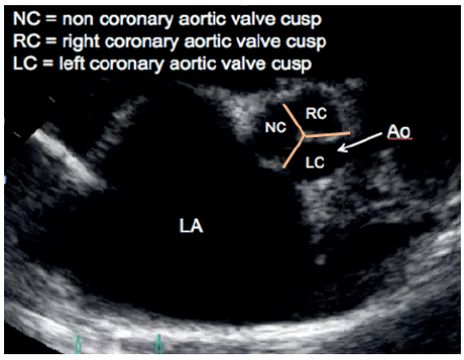


Figure 3. When the aorta is in complete cross section with the aortic valve leaflets visible it is similar in appearace to the "Mercedes-Benz" sign.

LVIDD

LVIDD measures left ventricular size and determines the degree of left ventricular dilation. The relationship between the diameter of the left ventricle and body weight is not linear; a 20 kg dog does not have a left ventricle double the size of a 10 kg dog. Therefore, the measurement of the LVIDD is indexed to body weight, known as LVIDDN. A good method is to use a "normalised" index using the Cornell formula[3], which is shown below.

LVIDDN = LVIDD (cm) ÷ (Body weight $^{0.294}$)
Left ventricular dilation if LVIDDN is ≥ 1.7

Cornell formula for LVIDDN[3]

An easy-to-use LVIDD calculator is available on the Boehringer Academy website (**www.boehringer-academy.co.uk**). It simply requires the dog's body weight to provide the LVIDDN cut-off for that dog. Compare the measured LVIDD to this cut-off to determine if the left ventricle is enlarged.

This measurement can be taken from the 2D right-sided long or short axis views, but reference values for LVIDDN are based on the M-mode measurement. M-mode is a time-motion display of a chosen line through the heart where the movement of the heart is plotted on an x-y axis time graph (Figure 4). This often provides several cardiac cycles to enable an average measurement value to be acquired. The measurement is timed to just before the start of the Q wave on an accompanying ECG. Where an ECG is not available, measurement is taken at maximal left ventricular (LV) dilation.

Prior to acquiring the M-mode image, make sure the left ventricle is circular on the 2D short-axis image, and take the image at the level of the papillary muscles ("the mushroom view").

Use the cursor to bisect directly through the centre of the left ventricle, and between the two papillary muscles. If the cursor is not bisecting the left ventricle, the measurements will underestimate LV dimensions. A LVIDDN ≥ 1.7 represents cardiomegaly.

The EPIC study demonstrated a clear extension of the asymptomatic period by a median of 15 months and an increase in overall survival in dogs with asymptomatic MVD and cardiomegaly receiving Vetmedin[2]. Dogs with these measurements should therefore be treated with Vetmedin. The recommended daily dose of Vetmedin is 0.5 mg/kg/day split into 2 equal doses 12 hours apart.

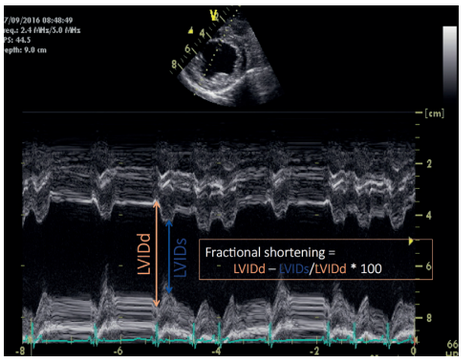


Figure 4. The left ventricular internal dimension in diastole (LVIDD) assesses left ventricular dilation.

SUMMARY

MVD in small and medium breed dogs typically has a long asymptomatic phase. Progression of disease should be suspected if a murmur increases in grading. Small to medium breed dogs with a ≥ grade 3/6 murmur need to be investigated to establish if cardiomegaly is present. Cardiomegaly can be diagnosed with either x-ray or ultrasound and there are benefits and disadvantages of each technique; the practitioner should use the method they are most comfortable with. Improving skills to accurately measure LA:Ao ratio and LVIDDN with ultrasound is recommended. An increased LA:Ao and LVIDDN confirm the presence of cardiomegaly. Dogs with cardiomegaly should be monitored closely as they are more likely to develop CHF within the next 1–2 years. The recently published EPIC study demonstrated that dogs with asymptomatic MVD treated with Vetmedin experienced a 15-month extension of the asymptomatic phase of MVD and lived longer overall[2]. Therefore, dogs with asymptomatic MVD and cardiomegaly should be treated with Vetmedin.

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1. Ljungvall, I. *et al.* (2014) J Small Anim Pract. 55: 545-550.
2. Boswood, A. *et al.* (2016) J Vet Intern Med. 30: 1765-1779.
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VETMEDIN: WHY MURMURS M

Vetmedin is licensed to treat dogs with asymptomatic mitral valve disease (MVD)*, delaying the onset of heart failure. Don't delay; improve the outcome for your patients with MVD.

Dr Charlotte Richards MRCVS
Brand Technical Adviser, Boehringer Ingelheim Animal Health

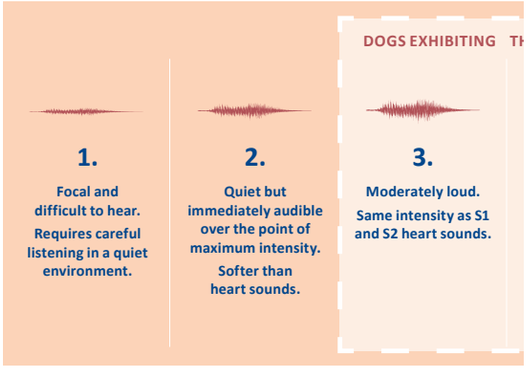


Figure 2. Murmurs are graded on a scale of 1 to 6. All dogs with a grade 3 or above m

MITRAL VALVE DISEASE

Mitral valve disease is the most common heart disease in dogs and is encountered weekly, if not daily, in general practice. MVD tends to occur in middle-aged, small to medium sized dogs and the first identifiable sign is a typical MVD murmur on the left-hand side of the chest which is loudest over the mitral valve area (Figure 1), in an otherwise apparently healthy dog. Although some breeds are predisposed to developing MVD, all dogs weighing less than 20 kg are at risk of developing the disease.

Dogs can live with MVD for many years without displaying any outward symptoms; this is the asymptomatic phase of the disease. In these dogs, the only marker of the disease identifiable on clinical examination is the typical MVD murmur which is audible on auscultation. In the asymptomatic phase, the disease can slowly progress for some time as the heart is able to accommodate the increased volume load by enlarging (cardiomegaly). As the disease progresses further and the valve degeneration becomes more severe, the enlarged heart is no longer able to compensate. This is when the symptomatic or congestive heart failure (CHF) stage commences. Only at this stage will the dog show outward symptoms of their disease.

THE EPIC STUDY

Until now, no medications were licensed to treat asymptomatic MVD; instead vets had little choice but to take a 'watch and wait' approach to MVD before starting treatment at the onset of heart failure. This has all changed since the publication of the EPIC study. The EPIC study set out to establish whether using Vetmedin to treat dogs with asymptomatic MVD could improve their outcome by delaying the onset of heart failure or cardiac-related death. It is the largest veterinary cardiology study conducted to date and involved 360 dogs with asymptomatic MVD. 36 investigators in 11 different countries were involved and all of the investigators were independent veterinary cardiologists. Importantly, the lead investigators were guaranteed the right to publish the results irrespective of outcome.

The 360 dogs were randomised into two groups; 180 dogs received Vetmedin (median dose 0.25 mg/kg BID) and 180 were given a visually identical placebo.

Following an interim analysis, the study was terminated early. Due to the significant benefit of administering Vetmedin to dogs with asymptomatic MVD, it was deemed unethical for dogs to continue receiving placebo.

The primary endpoint of the study was the onset of left-sided heart failure, or cardiac-related death/euthanasia. Vetmedin extended the time to the primary endpoint by around 60% on average, giving treated dogs around 15 months additional symptom-free time (Vetmedin median 1228 days; placebo median 766 days $p = 0.0038$). In addition, the dogs receiving Vetmedin lived longer overall and experienced no differences in adverse events compared to dogs receiving placebo.[1]

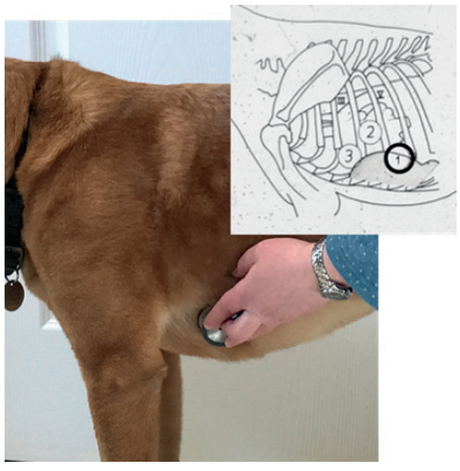


Figure 1. A typical MVD murmur is normally the first identifiable marker of disease in an asymptomatic dog.

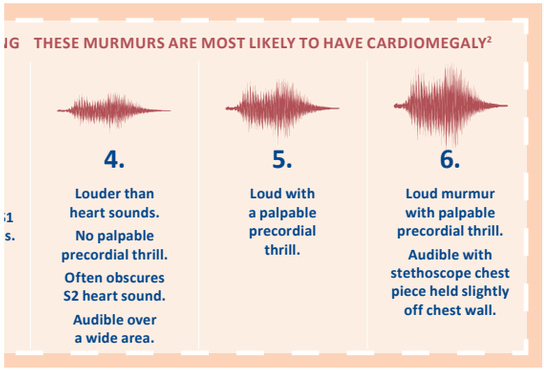
WITH VETMEDIN, MURMURS MEAN SO MUCH MORE

EPIC clearly demonstrates the importance of using Vetmedin to delay the onset of MVD symptoms and it is now the only medication licensed to treat asymptomatic MVD in dogs*. Following EPIC and the granting of Vetmedin's new indication, the 'watch and wait' approach to outwardly healthy dogs with a typical MVD murmur is no longer appropriate. To offer the best standard of care to these patients, vets should now investigate for the presence of cardiomegaly. If cardiomegaly is present, EPIC has shown that the dog will benefit from receiving Vetmedin. Vets should now follow a **"listen, investigate, treat"** approach to dogs with MVD.

LISTEN

A grading system from 1 to 6 should be used to assess murmur intensity (Figure 2). Put simply, the best screening tool to identify dogs with asymptomatic MVD is a stethoscope. An MVD murmur tends to get louder as the disease progresses, therefore cardiomegaly is more commonly found in dogs with a moderate or loud murmur (≥ grade 3/6). Cardiomegaly is present in about 50% of dogs with a grade 3/6 murmur and the proportion of dogs with cardiomegaly is even higher in dogs with louder murmurs[2]. The grade of the murmur is therefore important to determine which dogs require further investigation to establish whether cardiomegaly is present. Identifying cardiomegaly in a dog with asymptomatic MVD enables treatment with Vetmedin to be started so that they can benefit from not just a longer life but, very importantly, more symptom-free quality life before the onset of heart failure symptoms. Therefore, all dogs with MVD murmurs that are ≥ grade 3/6 should be investigated for cardiomegaly.

NOW MEAN SO MUCH MORE



e murmur require further investigation to establish whether cardiomegaly is present

INVESTIGATE

Cardiomegaly can be diagnosed using either X-ray or cardiac ultrasound.

CHEST X-RAYS

To determine whether a dog's heart is enlarged using chest X-rays, a right lateral view should be taken and the heart size assessed using the vertebral heart score (VHS) (Figure 3). A dog has cardiomegaly and would benefit from Vetmedin treatment if the VHS ≥11.5. If the VHS is <10.5, the heart is not currently enlarged and the dog should be examined and X-rayed again in 12 months' time. If the VHS is between 10.5 to <11.5, an ultrasound examination is recommended to determine whether the dog would benefit from treatment (see below). If it is not possible to perform a cardiac ultrasound, the VHS should be rechecked in 6 months' time. An increase in VHS of >/= 0.5 over 6 months indicates cardiomegaly and treatment would be warranted.

CARDIAC ULTRASOUND

When carrying out an ultrasound assessment of a dog with asymptomatic MVD, the most helpful measurement to use is the LA:Ao (Figure 4). If a dog has an enlarged left atrium (LA:Ao ≥1.6), it has cardiomegaly and would benefit from Vetmedin treatment. If the left atrium is not enlarged, then the size of the left ventricle should be measured. If the left ventricle is enlarged (LVIDDN ≥1.7) cardiomegaly is present and the dog would benefit from Vetmedin treatment. If neither the left ventricle nor the left atrium is enlarged then the dog should be examined again in 6–12 months and the ultrasound examination repeated.

TREAT

Vetmedin is licensed to delay the onset of heart failure in dogs with MVD. By prescribing it to dogs with asymptomatic MVD* at the preferable dose of 0.25 mg/kg BID it will not only extend their life overall, but it will also provide them with more quality time without symptoms. Diagnose dogs with asymptomatic MVD* and treat with Vetmedin today to help them live longer, happier lives.

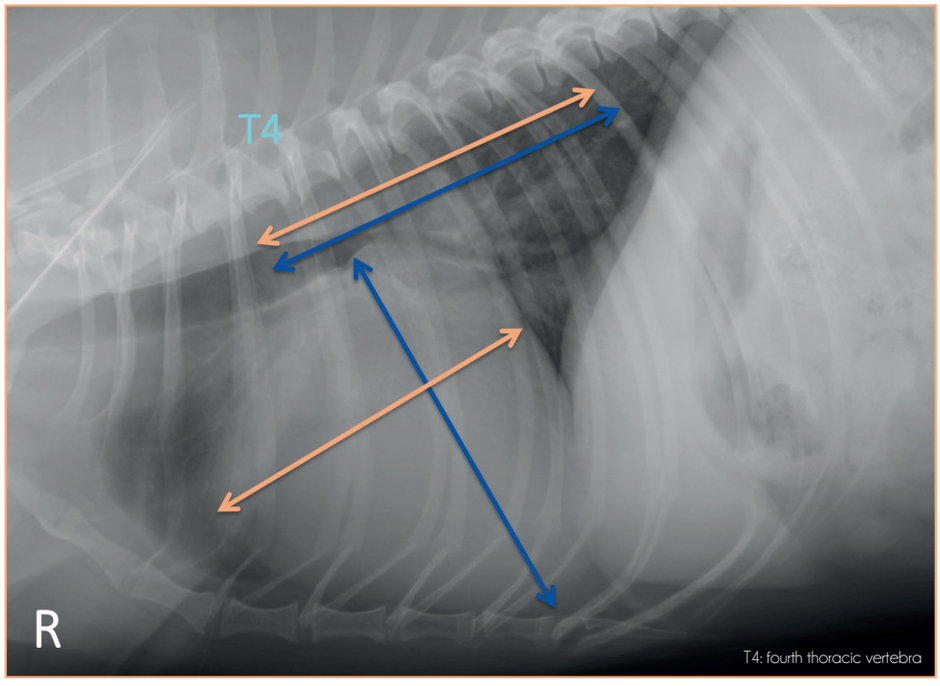


Figure 3. The vertebral heart score (VHS) can be used to determine whether cardiomegaly is present by objectively assessing the size of the cardiac silhouette.

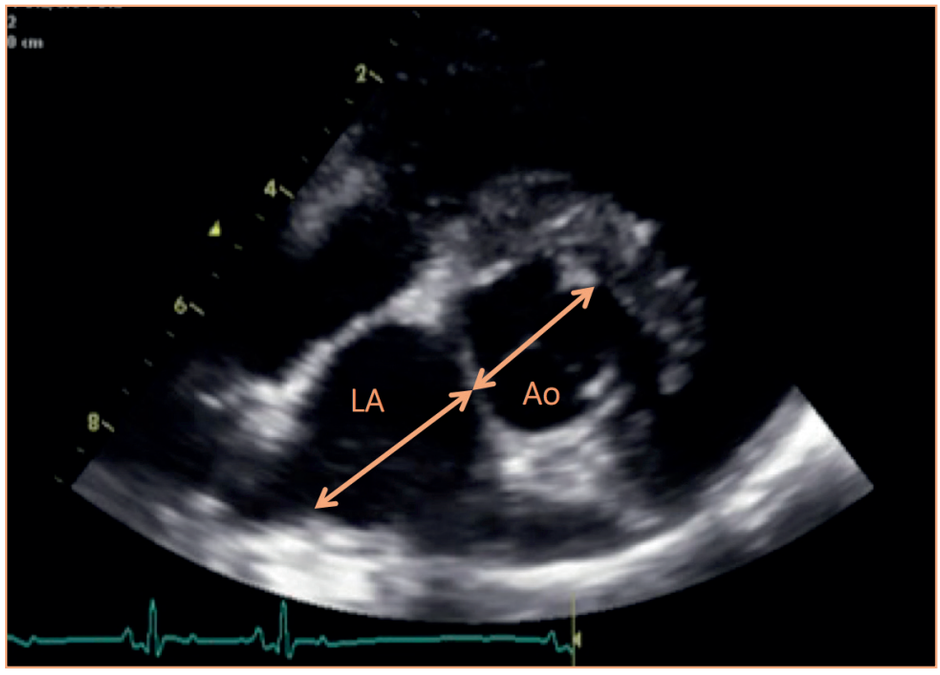


Figure 4. The left atrial-to-aortic ratio (LA:Ao) is the most helpful ultrasound measurement to determine whether an asymptomatic dog with MVD has cardiomegaly and requires treatment with Vetmedin.

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For more information about the EPIC study and diagnosing cardiomegaly using X-ray and ultrasound including practical "how to" videos, visit **www.boehringer-academy.co.uk.**

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*with cardiomegaly
LVIDDN: normalised left ventricular internal diameter in diastole
LA:Ao: left atrial-to-aortic ratio
BID: twice daily

References:
1. Boswood, A *et al* (2016) J Vet Intern Med. 30: 1765–1779.
2. Ljungvall, I *et al* (2014) J Small Anim Pract 55: 545–550.

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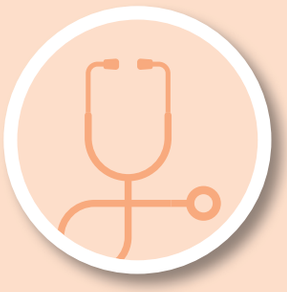
VETMEDIN CAN CHANGE EVERYTHING FOR DOGS WITH MVD

The EPIC study demonstrates the importance of using Vetmedin in asymptomatic MVD to delay the onset of heart failure. Vetmedin is licensed to treat asymptomatic MVD* in dogs.

Following the EPIC study and the granting of Vetmedin's indication, the 'watch and wait' approach to clinically healthy dogs with a typical MVD murmur is no longer appropriate.

To offer the best standard of care to these patients, vets should investigate for the presence of cardiomegaly. If cardiomegaly is present, the EPIC study has shown that the dog will benefit from receiving Vetmedin.

Vets should now follow a "**Listen, Investigate, Treat**" approach to dogs with asymptomatic MVD.



* and cardiomegaly

Explore the Boehringer Academy for interactive tools, an MVD murmur quiz and expert short videos including:

HOW TO

take and interpret chest X-rays

HOW TO

perform a focused cardiac ultrasound

THE EPIC STUDY

Objectives
Results
Implications

HOW TO

help owners understand why a significant murmur needs investigating

HOW TO

help owners understand the significance of a heart murmur

HOW TO

overcome potential barriers to investigating and treating asymptomatic MVD

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Vetmedin Chew 1.25 mg, 5 mg and 10 mg chewable tablets for dogs. Active substance: Pimobendan. Uses: For the treatment of canine congestive heart failure originating from dilated cardiomyopathy or valvular insufficiency (mitral and/or tricuspid valve regurgitation). (See also section 4.9 of the SPC). For the treatment of dilated cardiomyopathy in the preclinical stage (asymptomatic with an increase in left ventricular end-systolic and end-diastolic diameter) in Doberman Pinschers following echocardiographic diagnosis of cardiac disease (see sections 4.4 and 4.5 of the SPC). For the treatment of dogs with myxomatous mitral valve disease (MMVD) in the preclinical stage (asymptomatic with a systolic mitral murmur and evidence of increased heart size) to delay the onset of clinical symptoms of heart failure (see sections 4.4 and 4.5 of the SPC). Further information: Please refer to the product packaging and leaflets for information about side effects, precautions, warnings and contra-indications. Legal category: UK: POM-V, IE: POM.

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