Diagnosis and management of a more advanced stage of preclinical myxomatous mitral valve disease in dogs without echocardiography

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Diagnose und Behandlung einer fortgeschrittenen, präklinischen myxomatösen Mitralklappenerkrankung bei Hunden ohne Echokardiographie

Die myxomatöse Mitralklappenerkrankung (MMVD) ist die häufigste Herzerkrankung bei Hunden. Eine angemessene Diagnose und Stadieneinteilung kann mit Hilfe einer echokardiographischen Untersuchung erfolgen. Frühe Krankheitsstadien können von einer Klappeninsuffizienz und, in fortgeschrittenen Stadien, von einer Herzdilatation begleitet sein. Eine korrekte Diagnose dieser präklinischen Phase und die Feststellung der Herzvergrösserung sollten durchgeführt werden, um eine angemessene medizinische Behandlung zu empfehlen. Wenn eine Echokardiographie nicht zur Verfügung steht oder von den Besitzern abgelehnt wird, können alternative Methoden zur Identifizierung der Krankheit und zur Vorhersage klinisch relevanter Kardiomegalie durchgeführt werden. Dazu gehören die Auskultation des Herzens und die Beurteilung der Intensität des Herzgeräuschs, die durch Thoraxradiographie ermittelten Herzmasse anhand der vertebralen Herzgrösse und kardiale Biomarker, insbesondere N-terminales Pro-B-Typ natriuretisches Peptid (NT-proBNP), die als Einzeltests oder in Kombination durchgeführt werden können, um Hunde mit erhöhtem Risiko für kongestives Herzversagen zu identifizieren, die frühzeitig mit Pimobendan behandelt werden müssen. Insbesondere eine Herzgeräuschintensität ≥3/6 (mässig oder lauter), eine aus einer latero-lateralen Thorax-Röntgenaufnahme ermittelte vertebrale Herzgrösse ≥11,5 Einheiten und Plasmakonzentrationen des N-terminalen Pro-B-Typ natriuretischen Peptids von > 1100 pmol/l sind Befunde, die mit guter Spezifität auf das Vorhandensein einer klinisch relevanten Kardiomegalie hinweisen können. Es wurde ein praktischer Algorithmus entwickelt, der den Arzt bei der Behandlung von Hunden mit Verdacht auf eine Herzklappenerkrankung anleitet, ausgehend von der klinischen Untersuchung und unter Verwendung der oben genannten zusätzlichen Tests, um geeignete Kontrollen und Therapien zu empfehlen.

Schlüsselwörter: Auskultation, Biomarker, Hund, Endokardiose, Pimobendan, Röntgenbild

Summary

Myxomatous mitral valve disease (MMVD) is the most common cardiac disease in dogs. Appropriate diagnosis and staging can be performed by means of an echocardiographic examination. Early disease stages might be accompanied by valvular insufficiency and, in more advanced phases, by cardiac dilatation. A correct diagnosis of this preclinical phase and identification of cardiac enlargement should be carried out in order to advise appropriate medical treatment. When echocardiography is not available or declined by the dog's owners, alternative methods to identify the disease and predict clinically relevant cardiomegaly, can be performed. Among these, cardiac auscultation and assessment of heart murmur intensity, cardiac dimensions obtained by thoracic radiography, by means of vertebral heart size, and cardiac biomarkers, in particular N-terminal pro-B-type natriuretic peptide (NT-proBNP), can be carried out as single tests or in combination, in order to identify dogs with increased risk of congestive heart failure, and needing an early treatment with pimobendan. In particular, a heart murmur intensity ≥3/6 (moderate or louder), a vertebral heart size ≥11,5 units obtained from a latero-lateral thoracic radiographic view, and plasma concentrations of N-terminal pro-B-type natriuretic peptide value > 1100 pmol/l, are findings that might suggest presence of clinically relevant cardiomegaly with a good specificity. A practical algorithm to guide clinicians in managing dogs with suspicion of valvular disease has been created, starting from clinical examination, and using the aforementioned additional tests in order to advise the appropriate controls and therapy.

Keywords: Auscultation, biomarker, canine, endocardiosis, pimobendan, radiography

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Introduction

The correct diagnosis and staging of cardiac diseases in dogs is crucial as it can impact survival and quality of life of these pets.[28] Echocardiography is the gold standard to diagnose valvular diseases in humans and animals, and in veterinary medicine it still represents the best way to assess cardiac dimensions.[14] The identification of cardiomegaly allows to appropriately detect advanced forms of cardiac diseases and therefore to correctly recommend treatments aimed to delay progression and improve survival.[10] Although echocardiography should always be advised in dogs suspected to have a cardiac disease, sometimes this tool might not be available or declined by the owners. Alternative methods to diagnose and stage valvular diseases in animals are therefore required. In this review, the author will give an overview of the most common canine valvular disease, the myxomatous mitral valve disease (MMVD), and review the available literature on diagnostic tests, alternative to echocardiography, that can be carried out in certain conditions. The final aim would be to offer a clinical tool to improve accurate diagnosis and staging of this common cardiac disease in dogs.

Canine myxomatous mitral valve disease

General aspects

Myxomatous mitral valve disease is the most common cardiac disease in dogs, approaching a prevalence of 100 % in small breeds in advanced age.[5] The mechanisms at the basis of MMVD formation and progression are only partially understood, with genetic, hemodynamic, and hormonal components all likely playing a role in the process.[39] These factors induce a progressive degeneration of the valvular leaflets with formation of myxomatous plaques on the free edges of the valve, that tend to coalesce and eventually produce a complete disruption of the valvular geometry.[5] Microscopic changes include, therefore, accumulation of proteoglycans and glycosaminoglycans in the spongiosa layer (the central layer of the leaflet), and fragmentation and loss of the fibrosa layer (the "skeleton" and structural support of the leaflet).[1] These abnormalities lead to an abnormal coaptation of the valvular leaflets and their prolapse, chordae tendineae elongation and rupture, and eventually to valvular insufficiency and cardiac enlargement. The cardiomegaly is a consequence of an increased preload and compensatory left ventricular eccentric hypertrophy. Myocardial fiber elongation and disruption accompany states of moderate to severe left atrial dilatation. In severe cases, the increase in left atrial dimension reflects a chronic increase in intraluminal pressure, predisposing for clinical signs related to congestive heart failure and arrhythmias.[17,18]

Since valvular changes are progressive, MMVD in dogs tends to worsen over time. However, mortality rate is low in dogs that are asymptomatic at the time of diagnosis, and only 13 % of these patients progress to more severe and clinically relevant stages, with a rate of cardiac mortality of 11 %.[6] While the disease appears therefore relatively benign, if dogs develop severe cardiomegaly and congestive heart failure, most of them die within 6–9 months.[5] Several factors might play a role in prognosticating death in dogs with MMVD. These can be mainly divided in clinical factors, such as increased age and heart rate, presence of syncope, dyspnea and arrhythmia, more severe class of heart failure, reduced exercise tolerance, laboratory parameters, such as increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I concentrations, and echocardiographic variables.[4,9,22,25] Among all these factors, echocardiographic variables represent the strongest and most studied predictors of death in cardiac patients. The veterinary literature has mainly focused on echocardiographic variables reflecting cardiac dimensions, namely left ventricular and left atrial diameters, usually normalized for body weight.[3,4,6,8,9,22,50] In MMVD the severity of the disease is affected by the regurgitant fraction of the mitral valve, that directly predisposes for cardiac enlargement. As the disease is usually a chronic and progressive process, the more severe are the valvular changes, the stronger is the cardiac remodeling, and therefore the degree of left atrial dilatation.[7,16] Along with the dimension of the left atrium, another variable usually retaining significance in prognosticating cardiac death in dogs with MMVD is the maximal velocity of the transmitral early diastolic wave.[3,6,9,43,50]

Classification

Over time several classification schemes have been proposed and adopted in order to stage MMVD in dogs. Although the progression of the disease is a "continuum" and dividing patients in discrete classes does not reflect the natural course of the disease, adopting a standardized classification scheme, has several advantages. These include improved communication between clinicians, when addressing a patient's status, providing recommendations of appropriate testing and controls over time, and offering indications for adequate treatment strategies. In general patients with MMVD are staged based on four main aspects, namely presence or absence of disease, systemic effects of the disease itself when present, and presence or absence of clinical signs, and response to therapy when clinical signs are present. With systemic effects of MMVD, it is mainly referred to the activation of compensatory mechanisms, that eventually induce activation of the renin-angiotensin-aldosterone system.[28] Therefore an important factor that affects the classification of MMVD in dogs is presence or absence of a significant cardiomegaly. Since MMVD induces valvular regurgitation, the type of remodeling that is naturally observed is an eccentric cardiomegaly, and therefore left atrial and left ventricular dilatation, rather than wall hypertrophy.[17]

The most recent classification scheme for MMVD, has been derived from human guidelines, and it has been adapted for

dogs by the American college of veterinary internal medicine (ACVIM) consensus statement, updated in 2019.[28] The consensus recognizes four different stages, indicated by an alphabetic letter. The classification scheme is reported, simplified, in Table 1. Excluding healthy dogs, predisposed to MMVD (stage A), the differentiation between stage B (asymptomatic) and stages C and D (symptomatic), is based on clinical findings and detection of congestive heart failure.[28] Clinical symptoms suggestive of heart failure are tachypnea, dyspnea, cough, representing signs of lung edema, that should be ideally objectified by detection of a interstitial and/or alveolar lung patter on thoracic radiographs.[7] What, instead, might be more difficult to do is recognizing the presence of cardiomegaly, and therefore discriminating between substages of MMVD (namely stages B1 and B2). Based on the consensus statement, stage B2 can be diagnosed based on presence of a typical left apical systolic heart murmur of moderate intensity (≥3/6), and imaging findings, including thoracic radiography and echocardiography.[28] When the cardiac dimensions are above a certain cut-off limit, in presence of typical signs consistent with MMVD, dogs are classified as stage B2 (see following paragraphs for more details about diagnostic criteria). The importance about correctly staging dogs with MMVD is crucial in the management of these patients.

Treatment of stage B2

Treatment of MMVD varies according to disease severity, stage of disease, presented clinical signs, and subjective variability of each individual patient. The ACVIM consensus statement provides general indications on how to treat dogs based on published literature, results of prospective clinical trials, and expert opinion. The reader is addressed to the ACVIM consensus statement[28] for a detailed description of these recommendations. In this review article, the author will only briefly focus on the treatment indications for dogs in stage B, as this stresses the importance of a correct recognition and classification of this disease stage.

Since stage B is subclassified in two substages, different treatment recommendations should be followed for each of them. In stage B1, the severity of MMVD is mild, and the heart shows almost no signs of remodeling (dilatation). There are no clinical studies in the literature where any type of treatment has been applied to this disease stage, and it is accepted that these dogs should not receive any pharmacologic, nor dietary treatment. Of course, since the disease might progress slowly over time, annual controls should be planned.[28] In stage B2, instead, the disease has reached a critical phase, where compensatory mechanisms have been activated leading to cardiac enlargement. At present a few studies have investigated the use of drugs trying to delay the progression of the disease and reduce mortality.[8,10,29] Among the different medications tested, pimobendan is the only one showing convincing results, and it is highly recommended at a dosage of 0,25–0,3 mg/kg q12h for this disease stage in the consensus statement.[11,28] The use of other medications, such as angiotensin converting enzyme inhibitors, or spironolactone, is not supported by published evidence, and they are not recommended by the author of this review. Dogs in stage B2 might benefit of a specific diet, with reduced sodium intake, high palatability and adequate protein and calories content.[28] Other medications, such as afterload reducers, like amlodipine, or beta-blockers might rarely be considered in specific cases, but their use is not supported by any scientific evidence, and therefore they are usually not prescribed, considering also risk of adverse effects, such as hypotension or kidney injury.

Identification of cardiomegaly

Cardiac auscultation

Cardiac auscultation is an essential part of the cardiovascular assessment of a dog. For a correct examination, cardiac auscultation should be performed in a quiet environment, with the dog in a standing position, possibly having a slow respiration, avoiding panting, in order to facilitate identification of heart sounds and cardiac murmurs. Heart murmurs typical for MMVD, are systolic left sided, with the point of maximal intensity localized on the cardiac apex. Although some dogs affected by mild MMVD, might not

Table 1: Classification scheme for dogs with MMVD modified from the American college of veterinary internal medicine consensus statement.

Disease stage	Description	Presence of cardiomegaly	Presence of congestive heart failure
Stage A	No identifiable structural heart disease, but at risk of possible future development (e.g. predisposed breeds)	No	No
Stage B1	Dogs with MMVD without severe enough cardiomegaly to justify a treatment	No or only mild	No
Stage B2	Dogs with MMVD with severe enough cardiomegaly to justify a treatment	Yes	No
Stage C	Dogs with MMVD, cardiomegaly and current or past clinical signs of congestive heart failure	Yes	Yes
Stage D	Dogs with MMVD, cardiomegaly and current or past clinical signs of congestive heart failure, refractory to standard therapy	Yes	Yes

MMVD: myxomatous mitral valve disease.

show any auscultation abnormality,[20] the presence of a clinically relevant mitral valve regurgitation almost always produces a turbulence of the blood flow that can be appreciated by a careful auscultation. A mitral valve regurgitation is not the only disease that might produce a murmur with these characteristics, therefore some differential diagnoses should be considered when a left sided systolic murmur is encountered during clinical examination.[16] Among the most frequent diseases leading to this type of murmur, we should consider innocent (typical of puppies of young age) and functional (anemic) murmurs, congenital heart diseases (like mitral valve dysplasia, subaortic stenosis, pulmonic valve stenosis), or cardiomyopathies (like dilated cardiomyopathy).[16] However, in most cases, a murmur with the aforementioned characteristics, in an adult or senile dog, with typical signalment (small breed, or typically predisposed breeds), is associated with MMVD. Therefore, identifying a systolic murmur in a dog, should always raise the suspicion of an acquired valvular disease, and it might need further clarification. Heart murmurs with different characteristics, such a continuous, diastolic or right sided, should always be investigated by means of an echocardiographic examination, since they are likely associated with a severe cardiac disease, needing specific management. Similarly, systolic heart murmurs in dogs not typically predisposed for MMVD, but rather for dilated cardiomyopathy (like Doberman Pinscher, great Danes, Irish wolfhounds), require further tests performed by a veterinary cardiologist.[16]

The intensity of a heart murmur in dogs with MMVD can be roughly used to predict the severity of the valvular insufficiency and the presence of cardiomegaly. Conventionally, heart murmur intensity is graded in six different degrees of severity (Table 2).[16] Some authors have tried to simplify this classification, showing that the use of only four categories of murmur intensity might be adequate to clinically discriminate between dogs with mild, moderate or severe MMVD.[35] Therefore, a systolic heart murmur of intensity graded as 1 or 2/6 using the traditional scheme, can be group in one single category, and defined as soft. Heart murmurs grade 3/6 can be considered as moderate, those of grade 4/6 as loud, and heart murmurs grade 5 and 6/6 can be named thrilling or palpable murmurs, as they are associated with a precordial thrill (Table 2).[35] The author of this review uses these two classification schemes interchangeably, as they might be both clinically useful.

Heart murmur intensity might help not only in raising the suspicion of MMVD, but also in grading its severity and predicting the stage. In general, the more intense is the murmur, the more severe is the MMVD, and therefore higher is the likelihood that the dog has cardiomegaly and requires a specific treatment. Low intensity murmurs (grade 1 and 2/6, or soft) are rarely associated with cardiomegaly, and therefore they predict the presence of a stage B1 MMVD. Palpable murmurs (grade 5 or 6/6) are usually associated with moderate to severe MMVD, therefore stage B2 or higher.[35] Heart murmurs of intermediate intensity (moderate or loud, therefore grades 3 and 4/6, respectively) can be associated with mild or moderate degrees of mitral regurgitation, and they are not very helpful in discriminating between stage B1 and stage B2.[35] In one study, 50 % of dogs in stage B1 had mild murmurs, but more than 40 % of them had already a moderate murmur, and the rest a loud murmur. On the other side, less than 10 % of dogs in stage B2 had a mild murmur, 30 % had a moderate murmur, and the remaining dogs showed loud or palpable murmurs.[35] This clarifies how using cardiac auscultation alone for identifying clinically relevant cardiomegaly and initiating pimobendan treatment in dogs with MMVD might be suboptimal, and it is therefore recommended to couple clinical examination to another diagnostic test, in order to improve diagnostic accuracy.

Echocardiography

In veterinary medicine echocardiography represents the gold standard to reach a definitive diagnosis and appropriate staging of dogs with MMVD. This method allows to assess valvular morphology, degree and distribution of the lesions, presence of leaflets prolapse and chorda tendineae rupture.

Table 2: Grading systems to classify intensity and severity of heart murmurs in dogs.

Grade	Characteristics	Intensity
1/6	Nearly imperceptible, may be heard with very careful auscultation in a quiet environment; always focal	Soft
2/6	Heard readily but very soft; always focal	Soft
3/6	Heard readily, moderate intensity; usually regional (can be heard in several auscultatory regions of the heart)	Moderate
4/6	Heard readily, loud, and usually radiates widely (can be heard in most or all auscultatory regions of the heart), but without a palpable thrill	Loud
5/6	Heard readily, loud, and associated with a precordial thrill, but the murmur is not heard with the stethoscope lifted off the surface of the thorax	Palpable
6/6	Heard readily, loud, associated with a precordial thrill, and the murmur remains audible with the stethoscope lifted 1 cm off the surface of the thorax	Palpable

(Modified from Côté et al., 2015).

Moreover, it represents the best way to measure the dimension and function of the cardiac chambers. With the use of Doppler, moreover, the presence and degree of valvular insufficiency and transvalvular flows can be accomplished.[14] The assessment of chamber dimension is crucial, not only for staging the disease but also to predict adverse events (such as congestive heart failure and atrial fibrillation), and to stratify for the risk of cardiac mortality.[2,3,9,44]

There are several systems applied in dogs to measure left ventricular and atrial dimensions. These include M-mode derived diameters, two-dimensional-derived linear measurements and volumes, and three-dimensional derived volumes.[14,26,51] At present, the most diffuse and studied methods are the M-mode or the two-dimensional derived linear assessment of internal chamber diameters. Internal chamber diameters of the left atrium and ventricle can be acquired both from short and long axis views of the heart. Long axis diameters own a good reproducibility, and they can be used to detect presence of cardiomegaly in dogs with MMVD.[49,53] However, most publications, have historically used cardiac diameters obtained from short axis views. These very measurements are those adopted in clinical trials to stage dogs with MMVD, and they have been proposed in the ACVIM consensus statement to discriminate between dogs in stage B1 and B2.[11,28] Considering the large variation in body size between canine breeds, cardiac dimensions should be normalized for body weight or aortic diameter, in order to obtain unique indexes that might be compared to simplified reference ranges. It is therefore accepted that clinically relevant cardiomegaly in dogs with MMVD, and therefore being diagnosed as stage B2 according to the consensus statement, is defined as:

left atrial internal diameter in short axis at the level of the cardiac base, during end-systole, divided by the aortic diameter obtained in the same frame ≥1,6 (Figure 3);[24]

and left ventricular internal diameter in short axis at end-diastole from an M-mode image at the level of the papillary muscles and normalized for body weight using an allometric scaling formula ≥ 1,7 (Figure 3).[15]

It is important to notice that, in the ACVIM consensus statement, the definition of stage B2 also includes presence of cardiomegaly detected on thoracic radiography, implying that the vertebral heart size (VHS) (see later) should be above the breed-adjusted limit of normality, or for every breed >10,5.[28] This mainly derives by the fact that these cut-offs have been used as inclusion criteria in the EPIC study, where the benefit of pimobendan in the preclinical phase of MMVD has been proven.[11] However, it is also accepted, as mentioned in the consensus statement, that echocardiography can be used alone as a method to assess cardiac dimensions, and therefore stage dogs with MMVD, as it represents the most accurate technique to identify cardiomegaly.[28]

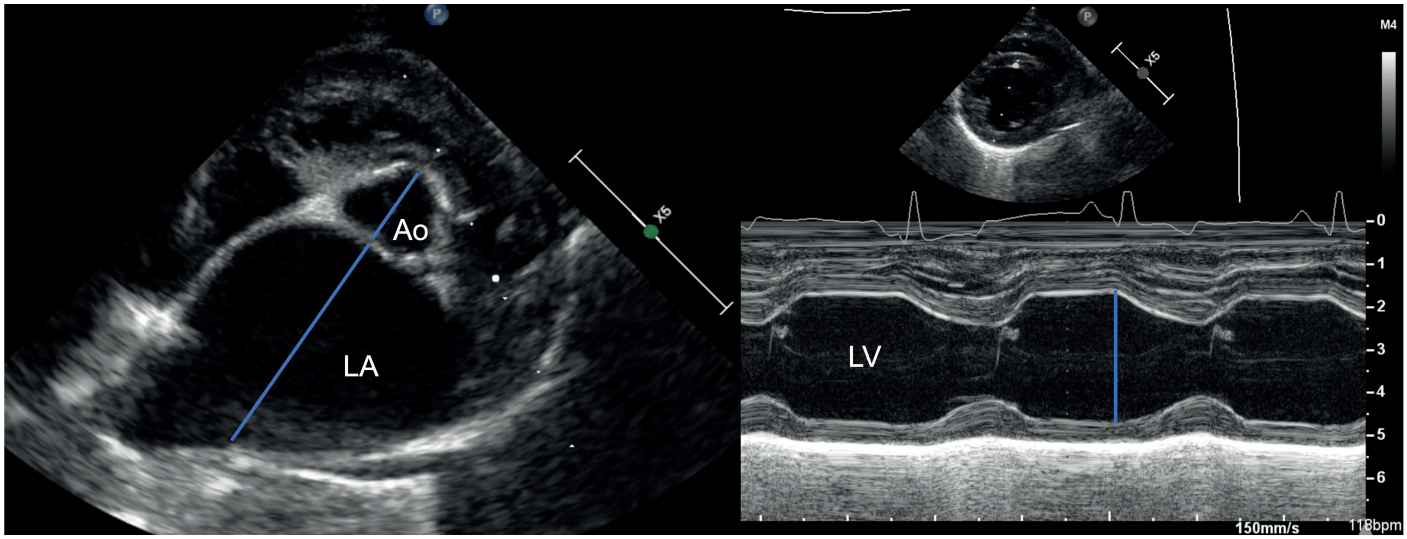

Figure 1: Echocardiographic images of a dog with myxomatous mitral valve disease. On the left panel, left atrial to aortic root diameters obtained from a short axis view at basilar level. The caliper crosses the aorta following the line between the non-coronary and left coronary cusp, using an inner edge-to-inner edge technique. Similarly the left atrial diameter is obtained by continuing the same line, until the free edge of the chamber. The image is obtained at end-systole, or on the first frame after closure of the aortic cusps. On the right panel, M-mode image of the left ventricle obtained from a two-dimensional-guided view at the level of the papillary muscles. The left ventricular internal diameter at end-diastole (LVIDD) is measured using a leading-edge technique, at the beginning of the QRS complex on the coupled electrocardiogram. The formula to normalize the left ventricular dimension is: LVIDD (cm)/body weight (kg)$^{0.294}$.[30]

As described in the following paragraphs, alternative methods to identify cardiomegaly and dogs with stage B2 MMVD, such as thoracic radiography and cardiac biomarkers, have been validated against echocardiography as the gold standard, and by using the cutoff values of left ventricular and atrial diameters reported above.

Thoracic radiography

Thoracic radiography is the diagnostic gold standard to detect signs of congestive heart failure due to cardiac disease. It allows to identify presence of cardiomegaly, pulmonary venous congestion and interstitial or alveolar lung pattern, with typical localization (Figure 2). Detection of cardiac enlargement might be a difficult task, especially for mild to moderate degrees of cardiomegaly. This might be dictated by the variability in chest morphology among breeds, technical factors, positioning, and the expertise of the reader.[36] In general, left sided cardiomegaly can be detected by evaluating the ratio between the chest cavity and the cardiac silhouette, the number of intercostal spaces occupied by the heart, and the displacement of adjacent structures, such as the trachea and the caudal vena cava.[36] This method of assessing cardiac dimensions is however purely subjective, and it does not deliver a quantitative assessment of the degree of cardiac enlargement.

Vertebral heart size might be a more objective way to assess the dimension of the cardiac silhouette in thoracic radiography, as it produces a numerical number, independent of body size. The measurement is performed on lateral projections, by measuring the two major and minor cardiac axes, and by counting the number of vertebral bodies included in these two (Figure 4A).[12,32,42] In most dogs the upper limit for normality of VHS is 10,5 units, however some differences might exist between canine breeds with different chest morphologies and cardio-thoracic ratios.[13,27,31] Therefore, when available, breed-specific reference ranges for VHS should be used in order to increase the accuracy in detecting cardiomegaly. Multiple studies have evaluated the usefulness of VHS, alone or in combination with other tests, to discriminate between dogs with MMVD in stage B1 and B2. Although some differences in cutoff values and sensitivity and specificity results exist between publications, in general values of VHS<10,5 tend to exclude stage B2, while values of VHS≥11,5 confirm it with high specificity.[21,42,54,55] Values of VHS between 10,5 and 11,4 units, remain in the grey zone and they are not helpful in predicting the disease stage. These dogs would benefit from an echocardiography to better assess their cardiovascular status. Since a rapid increase in cardiac dimensions over time in a single dog predicts future development of heart failure, VHS might be used to monitor the progression and stratify patients for

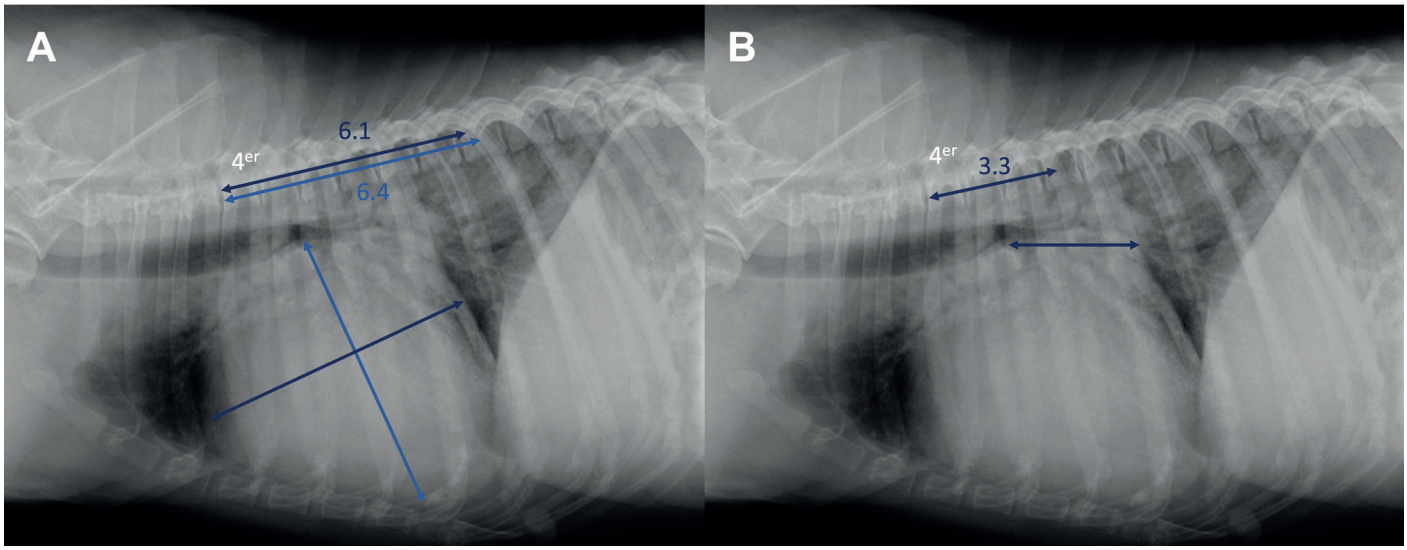

Figure 2: Thoracic radiography of a dog with advanced myxomatous mitral valve disease. Latero-lateral projection in right lateral recumbency. The vertebral heart size is obtained by measuring the long axis (from the ventral aspect of the main bronchus until the cardiac apex) and the short axis (perpendicular to the long axis, from the cranial aspect of the cardiac silhouette until the ventral aspect of the caudal vena cava) of the heart. The two dimensions are then compared to the vertebral bodies, starting counting from the cranial aspect of the fourth vertebral body, considering also the decimals. Then sum of these two values gives the vertebral heart size, that in this dog is 12,5 units (severely increased) (Figure 4A). The vertebral left atrial size is obtained by measuring the left atrial diameter starting from the ventral aspect of the main bronchus until the dorsal aspect of the caudal vena cava. As for the vertebral heart size, this line is then compared with the vertebral bodies, by counting how many of these are included in the line, starting from the cranial aspect of the fourth vertebra. In this dog the vertebral left atrial size is 3,3 units (Figure 4B).

their risk in experiencing a cardiovascular event.[11] For this reason, it is reasonable to start to treat a dog with MMVD using pimobendan, if an increase of >0,5 units in the VHS is recorded in subsequent visits.[21,28]

A more recent radiographic parameter used to quantify cardiac dimensions is the vertebral left atrial size (VLAS).[37] This parameter focuses on the measurement of the left atrial dimension derived from a lateral radiographic projection of the chest (Figure 4B). In the majority of healthy dogs, the upper value of VLAS does not exceed 2,2 units,[52] although breed specific differences might exist for VLAS as well. Several studies have now shown that VLAS is an accurate tool to discriminate between dogs in stage B1 and B2 MMVD. The optimal cutoff values able to detect relevant cardiomegaly vary between 2,8 and 3,1, depending on the study.[32,37,42,48,55] Therefore, a VLAS >3 predicts presence of clinically relevant cardiac dilatation, likely needing a treatment, with high specificity.[28,48] When adding VLAS to the traditional VHS in models using multiple tests, however, VLAS does not significantly improve the diagnostic value of VHS alone.[42] Moreover, VLAS has a higher intra- and inter-operator variability, making this test less reproducible in the clinical setting than VHS.[33] For this reason, VLAS is not added to the diagnostic algorithm later presented in this review.

Although VHS and VLAS represent valuable tools to stage dogs with MMVD, especially when echocardiography is not available, they still own high variability for unexperienced operators,[33,42] and a training curve is expected for veterinarians approaching this technique for the first time. The increasing in availability of teleradiology consulting, and the development of artificial intelligence-based software that can analyze the radiographs, might improve these limitations in the near future.[46]

Cardiac biomarkers

Among the cardiac biomarkers that can routinely be assessed in veterinary medicine, cardiac troponin I and NT-proBNP, are those mainly studied in clinical scenarios. Cardiac troponin I is an important enzyme in the sarcomere, and it is mainly released after myocardial damage.[40] Although plasma concentrations of cardiac troponin I in dogs with MMVD correlate with cardiac dimensions and offer some prognostic information, this biomarker is not accurate in discriminating between different stages of preclinical disease.[34,47,56]

Natriuretic peptides are small particles stored into the atrial and ventricular cells, and they are released in response to myocardial stretch. They own several functions, like natriuresis, and therefore diuresis, and vasoactive antifibrotic effects. For this reason, they have been studied as markers of cardiac disease, in order to identify underlying structural heart abnormalities, stratify for risk of cardiovascular events and death, and also to stage MMVD.[25,23,38] The brain or B-type natriuretic peptide is released as a precursor, and it is then rapidly cleaved by serum proteases into two fragments. The NT-proBNP represents the N-terminal component of this pro-enzyme. Although inactive, this fragment is more stable in the bloodstream and it reflects the concentrations of the active component released in response to a stimulus.[40] Therefore most of the research about natriuretic peptides in veterinary medicine used this specific assay, that is commercially available.[30]

In dogs, NT-proBNP correlates with heart rate, respiratory rate, VHS, left atrial and ventricular dimensions, and with kidney values (creatinine and urea), and it can be used to differentiate between dogs with dyspnea of cardiac and non-cardiac origin.[18,40] Therefore, considering the importance of differentiating dogs with preclinical MMVD in order to appropriately start a treatment as needed, in the recent years more research has been conducted on this biomarker, and a few studies have identified optimal cutoff values that are able to discriminate dogs in stage B1 and B2 of MMVD. In particular, in a study conducted on 1887 dogs of different breeds with preclinical MMVD, NT-proBNP was the most important variable to differentiate between stages, and it had the highest accuracy among all other parameters (that included clinical examination, radiography, and other laboratory variables) if used as single test. By using a cutoff value of 1100 pmol/l, the test had a sensitivity of 57 % and a specificity of 85 % (positive predictive values 57 %, negative predictive value 84 %) in discriminating between stage B1 and B2.[56] Similar results were observed in another study, conducted only on cavalier King Charles spaniels with different stages of MMVD. Also in this case, NT-proBNP appeared to be the test with the highest accuracy (area under the curve 0,855) to discriminate between disease stages, showing a sensitivity of 68,9 % and a specificity of 90,1 %, for a cutoff value of 1138 pmol/l.[48] This means that if the value of NT-proBNP is above the cutoff, it is likely that the dog is in stage B2.

Since NT-proBNP is affected by comorbidities, and it displays variations between and within individuals,[40,45,57] it might be reasonable to use it in combination with other tests in order to reduce the confounding effect of biological variability.

Combination of tests

Since no test is perfect, the use of several ancillary tests together might improve the accuracy in diagnosing stage B2 MMVD. Assuming that echocardiography always represents the gold standard to diagnose and stage dogs with MMVD, and it should be chosen as the preferred test, clinical examination, thoracic radiography, and cardiac biomarkers can be combined and used as substitutes to echocardiography for staging. A few studies have reported the implementing value of combining more tests together to

reach a diagnosis of stage B2.[42,54,55,56] For example, cardiac auscultation can be used to identify dogs that might deserve further tests. If the heart murmur intensity is moderate or severe (≥3/6), it is possible, but not sure, that the dog has a clinically relevant MMVD requiring a treatment.[35] In this case, cardiac auscultation can be combined to thoracic radiography and/or cardiac biomarkers to improve the identification of stage B2. In particular, in cavalier King Charles spaniels, combining physical examination with another test (such as radiography, NT-proBNP, or electrocardiography) improves substantially the accuracy in diagnosing stage B2 MMVD.[54] Neverthless, adding additional tests, by creating models containing more than two parameters (up to four), might only slightly increase the diagnostic accuracy. For example, adding NT-proBNP to cardiac auscultation and VHS, improves the specificity and sensitivity of detecting stage B2 from 91,7 % to 94,5 %, and from 57,8 % to 62,2 %, respectively.[54] In another study on dogs with MMVD of different breeds, the use of single tests to discriminate between stage B1 and B2 showed good accuracy, in particular for murmur intensity, and NT-proBNP. However, when adding additional clinical and laboratory variables together (age, appetite, body condition score, murmur intensity, and alanine aminotransferase, creatinine, and NT-proBNP concentrations), creating a multivariable model, the discriminatory ability increases substantially.[56] The use of such a model, might assist clinicians in staging dogs with MMVD, but it requires a relatively large set of information and it might be less practical in the clinical setting. Moreover, it seems quite unlikely that decrease appetite, for example, would be caused by early stages of MMVD. Also, using multivariate models does not always fit the real clinical scenarios encountered in the everyday practice, and it does not necessarily assist in correctly discriminating single clinical

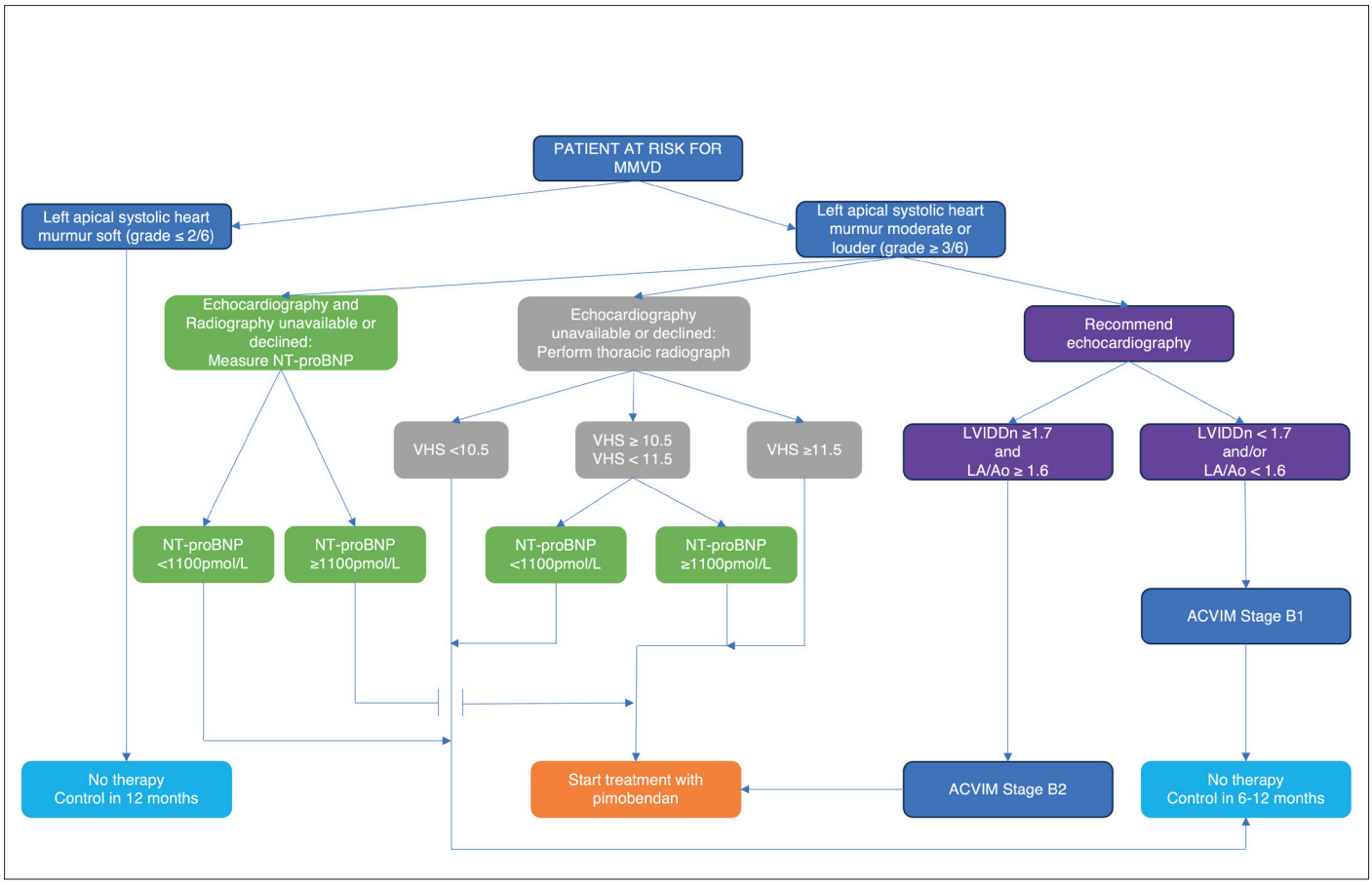

Figure 3: Proposed algorithm for management of dogs with MMVD, recommend clinical controls, diagnostic tests, and appropriate therapy. Based on the ACVIM consensus guidelines, recent publications, and expert opinion. ACVIM: American college of veterinary internal medicine; LA/Ao: ratio between the left atrial and left aortic root diameters; LVIDDn: left ventricular internal diameter at end-diastole normalized for the body weight; MMVD: myxomatous mitral valve disease; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VHS: vertebral heart size.

cases. While the study would apply to a large population of dogs, its value in making the decision in treating or not a single patient is questionable. ~~While,~~ As an alternative, following a few steps algorithm, by running two or three tests, could be easier to apply in the everyday routine, and still having a good discriminatory ability between stages B1 and B2 MMVD.

Diagnostic algorithm to identify stage B2 myxomatous mitral valve disease

This algorithm (Figure 5) has been generated in order to provide some practical guide to stage and treat dogs with asymptomatic MMVD. As previously stated, the ACVIM consensus statement recommends administering pimobendan (class 1 of recommendation) to dogs with stage B2 MMVD.[28] This is based on the results of a prospective, randomized, placebo-controlled, blinded, multicenter clinical trial (EPIC Study) (strong level of evidence).[11] Every dog with a heart murmur should be evaluated by a veterinary cardiologist or a person experienced on echocardiography, to identify the nature of the murmur, grade the severity of MMVD, presence of concomitant cardiac diseases other than MMVD, complicating factors such as chordae tendinea rupture or pulmonary hypertension. When echocardiography is not available, or declined by the dog's owner, alternative ways to identify cardiomegaly might be offered. The accuracy of every alternative test will be suboptimal when compared to echocardiography, but it might be considered clinically acceptable in certain conditions.

The algorithm refers to dogs at risk of MMVD, therefore every dog of typical age (adult to advanced/senile), typical breed (cavalier King Charles spaniel, Chihuahua, Dachshund, Maltese, and in general small breed dogs), showing a systolic heart murmur localized on the left hemithorax, toward the cardiac apex. Other types of murmurs (diastolic, continues, right sided) or other signalment (puppies and young dogs or large breed dogs predisposed to dilated cardiomyopathy) should follow another diagnostic and therapeutic protocol. If patients have the aforementioned characteristics, they can be divided based on heart murmur intensity. Soft murmurs (grade ≤2/6 or less) do not require further tests, nor therapy, as they likely indicate an early stage of MMVD (stage B1). Therefore, a routine clinical control with cardiac auscultation can be repeated after 12 months. Dogs with a moderate or louder murmur (≥3/6) deserve further clarification, as they might have a more advanced disease. Ideally echocardiography should be performed, and the dog treated with pimobendan if it meets the echocardiographic criteria indicative of stage B2. In case echocardiography is not available or declined by the owner, a thoracic radiograph could be performed to measure the VHS. For VHS<10,5 units, a control radiograph can be planned 6–12 months after, and no treatment should be advised. For VHS≥11,5 units, a cardiomegaly is likely present and there is a high chance that the dog is in stage B2, and therefore needing a treatment with pimobendan. For VHS values in the grey zone (between 10,5 and 11,4 units), NT-proBNP can be measured to help in stratifying the patient. Those dogs with a value<1100 pmol/l have likely no cardiomegaly and can be rechecked after 6–12 months. Dogs with higher NT-proBNP values (≥1100 pmol/l) are likely in stage B2, and they should be treated with pimobendan. Lastly, in case neither echocardiography nor radiography is performed, dogs can be solely tested by means of NT-proBNP, using the previously reported cutoff value. Based on the result, dogs can be then only rechecked or treated with pimobendan. Also dogs with a rapid increase of their VHS value (>0,5 units) in two consecutive visits, might deserve a treatment, as they likely will sooner or later develop symptoms related to their MMVD.

It must be stressed that this algorithm represents an aid to clinicians approaching a specific canine population, at a certain risk of cardiac disease, and that echocardiography always represents the best method to diagnose and stage MMVD. Therefore, possible staging errors and improper treatment might occur, and, for this reason, an echocardiography should be advised before any treatment is recommended.

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Abbreviation Table

ACVIM	America college of veterinary internal medicine
MMVD	Myxomatous mitral valve disease
NT-proBNP	N-terminal pro-B-type natriuretic peptide
VHS	Vertebral heart size
VLAS	Vertebral left atrial size

Diagnosis and management of a more advanced stage of preclinical myxomatous mitral valve disease in dogs without echocardiography

M. Baron Toaldo

Diagnostic et prise en charge d'un stade plus avancé de maladie myxomateuse préclinique de la valvule mitrale chez le chien sans échocardiographie

La maladie myxomateuse de la valve mitrale (MMVD) est la maladie cardiaque la plus fréquente chez le chien. Un examen échocardiographique permet de poser un diagnostic approprié et de déterminer le stade de la maladie. Les premiers stades de la maladie peuvent s'accompagner d'une insuffisance valvulaire et, dans les phases plus avancées, d'une dilatation cardiaque. Un diagnostic correct de cette phase préclinique et l'identification de l'hypertrophie cardiaque doivent être effectués afin de conseiller un traitement médical approprié. Lorsque l'échocardiographie n'est pas disponible ou qu'elle est refusée par les propriétaires, d'autres méthodes peuvent être utilisées pour identifier la maladie et prédire une cardiomégalie cliniquement pertinente. Parmi ces méthodes, l'auscultation cardiaque et l'évaluation de l'intensité du souffle cardiaque, les dimensions cardiaques obtenues par radiographie thoracique, au moyen de la taille vertébral du cœur, et les biomarqueurs cardiaques, en particulier le fragment amino-terminal du pro peptide natriurétique de type B (NT-proBNP), peuvent être effectués seuls ou en combinaison, afin d'identifier les chiens présentant un risque accru d'insuffisance cardiaque congestive et nécessitant un traitement précoce au pimobendan. En particulier, un souffle cardiaque d'intensité ≥3/6 (modéré ou plus fort), une taille vertébral du cœur ≥11,5 unités obtenue à partir d'une vue radiographique thoracique latéro-latérale, et des concentrations plasmatiques de fragment amino-terminal du pro peptide natriurétique de type B > 1100 pmol/l, sont des résultats qui peuvent suggérer la présence d'une cardiomégalie cliniquement pertinente avec une bonne spécificité. Un algorithme pratique a été créé pour guider les cliniciens dans la prise en charge des chiens présentant une suspicion de maladie valvulaire. Il part de l'examen clinique et utilise les tests supplémentaires mentionnés ci-dessus pour conseiller les contrôles et la thérapie appropriés.

Mots clés: Auscultation, biomarqueur, canine, endocardiose, pimobendan, radiographie

Diagnosi e gestione di uno stadio più avanzato della malattia preclinica mixomatosa della valvola mitrale nei cani senza ecocardiografia

La malattia mixomatosa della valvola mitrale (MMVD) è la malattia cardiaca più comune nei cani. La diagnosi e la stadiazione appropriate possono essere effettuate mediante un esame ecocardiografico. Le fasi iniziali della malattia possono essere accompagnate da insufficienza valvolare e, negli stadi più avanzati, ad una dilatazione cardiaca. Una diagnosi corretta di questa fase preclinica e l'identificazione dell'ingrandimento cardiaco devono essere effettuate al fine di consigliare un trattamento medico appropriato. Quando l'ecocardiografia non è disponibile o viene rifiutata dai proprietari, si possono eseguire metodi alternativi per identificare la malattia e prevedere una cardiomegalia clinicamente rilevante. Tra questi, l'auscultazione cardiaca e la valutazione dell'intensità del soffio cardiaco, le dimensioni cardiache ottenute mediante radiografia toracica, attraverso la dimensione vertebrale del cuore, e i biomarcatori cardiaci, in particolare il frammento ammino-terminale del pro-peptide natriuretico di tipo B (NT-proBNP), possono essere eseguiti come test singoli o in combinazione, al fine di identificare i cani con un aumentato rischio di insufficienza cardiaca congestizia e che necessitano di un trattamento precoce con pimobendan. In particolare, un soffio cardiaco di intensità ≥3/6 (moderato o più forte), una dimensione vertebrale del cuore ≥11,5 unità ottenuta da una proiezione radiografica toracica latero-laterale e concentrazioni plasmatiche di frammento ammino-terminale del pro-peptide natriuretico di tipo B > 1100 pmol/l, sono risultati che possono suggerire con una buona specificità la presenza di cardiomegalia clinicamente rilevante. È stato creato un algoritmo pratico per guidare i medici veterinari nella gestione dei cani con sospetto di malattia valvolare, partendo dall'esame clinico e utilizzando i suddetti test aggiuntivi per consigliare i controlli e la terapia appropriati.

Parole chiave: Auscultazione, biomarker, canino, endocardiosi, pimobendan, radiografia

Literaturnachweis

[1] Aupperle H and Disatian S: Pathology, protein expression and signaling in myxomatous mitral valve degeneration: comparison of dogs and humans. J. Vet. Cardiol. 2012; 14: 59–71.

[2] Baron Toaldo M, Mazzoldi C, Romito G, Poser H, Contiero B, Cipone M, Guglielmini C: Echocardiographic predictors of first onset of atrial fibrillation in dogs with myxomatous mitral valve disease. J. Vet. Intern. Med. 2020; 34: 1787–1793.

[3] Baron Toaldo M, Romito G, Guglielmini C, Diana A, Pelle NG, Contiero B, Cipone M: Prognostic value of echocardiographic indices of left atrial morphology and function in dogs with myxomatous mitral valve disease. J. Vet. Intern. Med. 2018; 32: 914–921.

[4] Borgarelli M, Abbott J, Braz-Ruivo L, Chiavegato D, Crosara S, Lamb K, Ljungvall I, Poggi M, Santilli RA, Häggström J: Prevalence and prognostic importance of pulmonary hypertension in dogs with myxomatous mitral valve disease. J. Vet. Intern. Med. 2015; 29: 569–574.

[5] Borgarelli M, Buchanan JW. Historical review, epidemiology and natural history of degenerative mitral valve disease. J. Vet. Cardiol. 2012; 14: 93–101.

[6] Borgarelli M, Crosara S, Lamb K, Savarino P, La Rosa G, Tarducci A, Haggstrom J. Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration. J. Vet. Intern. Med. 2012; 26: 69–75.

[7] Borgarelli M, Ferasin L, Lamb K, Bussadori C, Chiavegato D, D'Agnolo G, Migliorini F, Poggi M, Santilli RA, Guillot E, Garelli-Paar C, Toschi Corneliani R, Farina F, Zani A, Dirven M, Smets P, Guglielmini C, Oliveira P, Di Marcello M, Porciello F, Crosara S, Ciaramella P, Piantedosi D, Smith S, Vannini S, Dall'Aglio E, Savarino P, Quintavalla C, Patteson M, Silva J, Locatelli C, Baron Toaldo M: DELay of Appearance of sYmptoms of Canine Degenerative Mitral Valve Disease Treated with Spironolactone and Benazepril: the DELAY Study. J. Vet. Cardiol. 2020; 27: 34–53.

[8] Borgarelli M, Ferasin L, Lamb K, Chiavegato D, Bussadori C, D'Agnolo G, Migliorini F, Poggi M, Santilli RA, Guillot E, Garelli-Paar C, Toschi Corneliani R, Farina F, Zani A, Dirven M, Smets P, Guglielmini C, Oliveira P, Di Marcello M, Porciello F, Baron Toaldo M: The predictive value of clinical, radiographic, echocardiographic variables and cardiac biomarkers for assessing risk of onset of heart failure or cardiac death in dogs with preclinical myxomatous mitral valve disease enrolled in the DELAY study. J. Vet. Cardiol. 2021; 36: 77–88.

[9] Borgarelli M, Savarino P, Crosara S, Santilli RA, Chiavegato D, Poggi M, Bellino C, La Rosa G, Zabatta R, Häggström J, Tarducci A: Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. J. Vet. Intern. Med. 2008; 22: 120–128.

[10] Boswood A, Gordon SG, Häggström J, Vanselow M, Wess G, Stepien RL, Oyama MA, et al.: Temporal changes in clinical and radiographic variables in dogs with preclinical myxomatous mitral valve disease: The EPIC study. J. Vet. Intern. Med. 2020; 34: 1108–1118.

[11] Boswood A, Häggström J, Gordon SG, Wess G, Stepien RL, Oyama MA, Keene BW, et al.: Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly: The EPIC Study-A Randomized Clinical Trial. J. Vet. Intern. Med. 2016; 30: 1765–1779.

[12] Buchanan JW, Bücheler J: Vertebral scale system to measure canine heart size in radiographs. J. Am. Vet. Med. Assoc. 1995; 206: 194.

[13] Buchanan JW: Vertebral scale system to measure heart size in radiographs. Vet. Clin. North Am. Small Anim. Pract. 2000; 30: 379–393.

[14] Chetboul V, Tissier R: Echocardiographic assessment of canine degenerative mitral valve disease. J. Vet. Cardiol. 2012; 14: 127–148

[15] Cornell CC, Kittleson MD, Della Torre P, Häggström J, Lombard CW, Pedersen HD, Vollmar A, Wey A: Allometric scaling of M-mode cardiac measurements in normal adult dogs. J. Vet. Intern. Med. 2004; 18: 311–321.

[16] Côté E, Edwards NJ, Ettinger SJ, Fuentes VL, MacDonald KA, Scansen BA, Sisson DD, Abbott JA: Management of incidentally detected heart murmurs in dogs and cats. J. Vet. Cardiol. 2015; 17: 245–261.

[17] Dillon AR, Dell'Italia LJ, Tillson M, Killingsworth C, Denney T, Hathcock J, Botzman L: Left ventricular remodeling in preclinical experimental mitral regurgitation of dogs. J. Vet. Cardiol. 2012; 14: 73–92.

[18] Fox PR, Oyama MA, Hezzell MJ, Rush JE, Nguyenba TP, DeFrancesco TC, Lehmkuhl LB, Kellihan HB, Bulmer B, Gordon SG, Cunningham SM, MacGregor J, Stepien RL, Lefbom B, Adin D, Lamb K: Relationship of plasma N-terminal pro-brain natriuretic peptide concentrations to heart failure classification and cause of respiratory distress in dogs using a 2nd generation ELISA assay. J. Vet. Intern. Med. 2015; 29: 171–179.

[19] Fox PR: Pathology of myxomatous mitral valve disease in the dog. J. Vet. Cardiol. 2012;14 : 103–126.

[20] Franchini A, Borgarelli M, Abbott JA, Menciotti G, Crosara S, Häggström J, Lahmers S, Rosenthal S, Tyrrell W: The Longitudinal Outcome Of Canine (K9) myxomatous mitral valve disease (LOOK-Mitral registry): Baseline characteristics. J. Vet. Cardiol. 2021; 36: 32–47.

[21] Gordon SG, Saunders AB, Wesselowski SR: Asymptomatic Canine Degenerative Valve Disease: Diagnosis and Current and Future Therapies. Vet. Clin. North Am. Small Anim. Pract. 2022; 52: 819–840.

[22] Häggström J, Boswood A, O'Grady M, Jöns O, Smith S, Swift S, Borgarelli M, et al: Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. J. Vet. Intern. Med. 2008; 22: 1124–1135.

[23] Häggström J, Hansson K, Kvart C, Pedersen HD, Voulteenaho O, Olsson K: Relationship between different natriuretic peptides and severity of naturally acquired mitral regurgitation in dogs with chronic myxomatous valve disease. J. Vet. Cardiol. 2000; 2: 7–16.

[24] Hansson K, Häggström J, Kvart C, Lord P: Left atrial to aortic root indices using two-dimensional and M-mode echocardiography in cavalier King Charles spaniels with and without left atrial enlargement. Vet. Radiol. Ultrasound. 2002; 43: 568–575.

[25] Hezzell MJ, Boswood A, Chang YM, Moonarmart W, Souttar K, Elliott J: The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral valve disease. J. Vet. Intern. Med. 2012; 26: 302–311.

[26] Höllmer M, Willesen JL, Tolver A, Koch J: Left atrial volume and function in dogs with naturally occurring myxomatous mitral valve disease. J. Vet. Cardiol. 2017: 19: 24–34.

[27] Jepsen-Grant K, Pollard RE, Johnson LR: Vertebral heart scores in eight dog breeds. Vet. Radiol. Ultrasound. 2013: 54(1): 3–8.

[28] Keene BW, Atkins CE, Bonagura JD, Fox PR, Häggström J, Fuentes VL, Oyama MA, Rush JE, Stepien R, Uechi M: ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. J. Vet. Intern. Med. 2019; 33: 1127–1140.

[29] Kvart C, Häggström J, Pedersen HD, Hansson K, Eriksson A, Järvinen AK, Tidholm A, Bsenko K, Ahlgren E, Ilves M, Ablad B, Falk T, Bjerkfås E, Gundler S, Lord P, Wegeland G, Adolfsson E, Corfitzen J: Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. J. Vet. Intern. Med. 2002; 16: 80–88.

[30] Labor IDEXX Diavet, Tests and Services, cardiopet proBNP-Test-Zur Herzdiagnostik dei Hund und Katze. https://www.idexx.ch/de-ch/veterinary/reference-laboratories/cardiac-health-tests/ (accessed 05.01.2024).

[31] Lamb CR, Wikeley H, Boswood A, Pfeiffer DU: Use of breed-specific ranges for the vertebral heart scale as an aid to the radiographic diagnosis of cardiac disease in dogs. Vet. Rec. 2001; 148: 707–711.

[32] Levicar C, Granados-Soler JL, Freise F, Raue JF, Nolte I, Bach JP: Comparison of different radiographic scores with associated echocardiographic measurements and prediction of heart enlargement in dogs with and without myxomatous mitral valve disease. J. Vet. Cardiol. 2022; 44: 1–12.

[33] Levicar C, Nolte I, Granados-Soler JL, Freise F, Raue JF, Bach JP: Methods of radiographic measurements of heart and left atrial size in dogs with and without myxomatous mitral valve disease: intra- and interobserver agreement and practicability of different methods. Animals (Basel). 2022; 12: 2531.

[34] Ljungvall I, Höglund K, Tidholm A, Olsen LH, Borgarelli M, Venge P, Häggström J: Cardiac troponin I is associated with severity of myxomatous mitral valve disease, age, and C-reactive protein in dogs. J. Vet. Intern. Med. 2010; 24: 153–159.

[35] Ljungvall I, Rishniw M, Porciello F, Ferasin L, Ohad DG: Murmur intensity in small-breed dogs with myxomatous mitral valve disease reflects disease severity. J. Small. Anim. Pract. 2014; 55: 545–550.

[36] Lord PF, Suter PF: Radiology. In: Fox PR, Sisson D, Moïse NS (eds.), Textbook of canine and feline cardiology. W.B. Saunders company, Philadelphia, USA, 1999; 107–129.

[37] Malcolm EL, Visser LC, Phillips KL, Johnson LR: Diagnostic value of vertebral left atrial size as determined from thoracic radiographs for assessment of left atrial size in dogs with myxomatous mitral valve disease. J. Am. Vet. Med. Assoc. 2018; 253: 1038–1045.

[38] Moonarmart W, Boswood A, Luis Fuentes V, Brodbelt D, Souttar K, Elliott J: N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. J. Small Anim. Pract. 2010; 51: 84–96.

[39] Orton EC, Lacerda CM, MacLea HB: Signaling pathways in mitral valve degeneration. J. Vet. Cardiol. 2012; 14: 7–17.

[40] Oyama MA, Fox PR, Rush JE, Rozanski EA, Lesser M: Clinical utility of serum N-terminal pro-B-type natriuretic peptide concentration for identifying cardiac disease in dogs and assessing disease severity. J. Am. Vet. Med. Assoc. 2008; 232: 1496–1503.

[41] Oyama MA, Sisson DD: Cardiac troponin-I concentration in dogs with cardiac disease. J. Vet. Intern. Med. 2004; 18: 831–839.

[42] Poad MH, Manzi TJ, Oyama MA, Gelzer AR: Utility of radiographic measurements to predict echocardiographic left heart enlargement in dogs with preclinical myxomatous mitral valve disease. J. Vet. Intern. Med. 2020; 34: 1728–1733.

[43] Sargent J, Muzzi R, Mukherjee R, Somarathne S, Schranz K, Stephenson H, Connolly D, Brodbelt D, Fuentes VL: Echocardiographic predictors of survival in dogs with myxomatous mitral valve disease. J. Vet. Cardiol. 2015; 17: 1–12.

[44] Schober KE, Hart TM, Stern JA, Li X, Samii VF, Zekas LJ, Scansen BA, Bonagura JD: Detection of congestive heart failure in dogs by Doppler echocardiography. J. Vet. Intern. Med. 2010; 24: 1358–1368.

[45] Sjöstrand K, Wess G, Ljungvall I, Häggström J, Merveille AC, Wiberg M, Gouni V, Lundgren Willesen J, Hanås S, Lequarré AS, Mejer Sørensen L, Wolf J, Tiret L, Kierczak M, Forsberg S, McEntee K, Battaille G, Seppälä E, Lindblad-Toh K, Georges M, Lohi H, Chetboul V, Fredholm M, Höglund K: Breed differences in natriuretic peptides in healthy dogs. J. Vet. Intern. Med. 2014; 28: 451–457.

[46] Solomon J, Bender S, Durgempudi P, Robar C, Cocchiaro M, Turner S, Watson C, Healy J, Spake A, Szlosek D: Diagnostic validation of vertebral heart score machine learning algorithm for canine lateral chest radiographs. J. Small. Anim. Pract. 2023; 64: 769–775.

[47] Spratt DP, Mellanby RJ, Drury N, Archer J: Cardiac troponin I: evaluation I of a biomarker for the diagnosis of heart disease in the dog. J. Small Anim. Pract. 2005; 46: 139–145.

[48] Stepien RL, Rak MB, Blume LM: Use of radiographic measurements to diagnose stage B2 preclinical myxomatous mitral valve disease in dogs. J. Am. Vet. Med. Assoc. 2020; 256: 1129–1136.

[49] Strohm LE, Visser LC, Chapel EH, Drost WT, Boagura JD: Two-dimensional, long-axis echocardiographic ratios for assessment of left atrial and ventricular size in dogs. J. Vet. Cardiol. 2018; 20: 330–342.

[50] Tidholm A, Häggström L: Prognostic value of selected one-, two- and three-dimensional and Doppler echocardiographic methods to assess severity in dogs with myxomatous mitral valve disease. J. Vet. Cardiol. 2022; 39: 89–101.

[51] Tidholm A, Menciotti G, Borgarelli M: Current use of real-time three-dimensional transthoracic echocardiography in animals. J. Vet. Cardiol. 2023; 51: 97–104.

[52] Vezzosi T, Puccinelli C, Tognetti R, Pelligra T, Citi S: Radiographic vertebral left atrial size: a reference interval study in healthy adult dogs. Vet. Radiol. Ultrasound. 2020; 61(5): 507–511.

[53] Visser LC, Ciccozzi MM, Sintov DJ, Sharpe AN: Echocardiographic quantitation of left heart size and function in 122 healthy dogs: a prospective study proposing reference intervals and assessing repeatability. J. Vet. Intern. Med. 2019; 33: 1909–1920.

[54] Wesselowski S, Gordon SG, Fries R, Saunders AB, Sykes KT, Vitt J, Boutet B, Häggström J, Kadotani S, Stack J, Barnett BG: Use of physical examination, electrocardiography, radiography, and biomarkers to predict echocardiographic stage B2 myxomatous mitral valve disease in preclinical Cavalier King Charles Spaniels. J. Vet. Cardiol. 2023; 50: 1–16.

[55] Wesselowski S, Gordon SG, Meddaugh N, Saunders AB, Häggström J, Cusack K, Janacek BW, Matthews DJ: Prediction of clinically important acquired cardiac disease without an echocardiogram in large breed dogs using a combination of clinical, radiographic and electrocardiographic variables. J. Vet. Cardiol. 2022; 40: 126–141.

[56] Wilshaw J, Rosenthal SL, Wess G, Dickson D, Bevilacqua L, Dutton E, Deinert M, Abrantes R, Schneider I, Oyama MA, Gordon SG, Elliott J, Xia D, Boswood A: Accuracy of history, physical examination, cardiac biomarkers, and biochemical variables in identifying dogs with stage B2 degenerative mitral valve disease. J. Vet. Intern. Med. 2021; 35: 755–770.

[57] Winter RL, Saunders AB, Gordon SG, Buch JS, Miller MW: Biologic variability of N-terminal pro-brain natriuretic peptide in healthy dogs and dogs with myxomatous mitral valve disease. J. Vet. Cardiol. 2017; 19: 124–131.

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