

MYXOMATOUS VALVE DEGENERATION: A LOOK AT THE LATEST DEVELOPMENTS OF THE DISEASE

Juan Pablo Reyes-Mantilla, Est. MVZ₁, Fabián Alejandro Gómez-Torres*, MVZ, M.Sc. (c)₁;
Favio Sánchez-Pico, MVZ, Esp.₁, Javier Hernando Albarracín-Navas, MVZ₁,
Édgar Hernando Toledo-Cáceres, MV₁

₁ Faculty of Veterinary Medicine and Animal Husbandry, Universidad Cooperativa de Colombia, Bucaramanga campus

Recibido: January 18, 2013 Aprobado: April 24, 2013

* **Autor de correspondencia:** Fabián Alejandro Gómez Torres, Animal Science Research Group, Faculty of Veterinary Medicine and Animal Husbandry, Universidad Cooperativa de Colombia, (577) 6356624, calle 30A No. 33-51 of 603, Bucaramanga, Colombia, e-mail: fabian.gomez@campusucc.edu.co

Cómo citar este artículo: Reyes-Mantilla JP, Gómez-Torres FA, Sánchez-Pico F, Albarracín-Navas JH, Toledo Cáceres EH. Myxomatous valve degeneration: A look at the latest developments of the disease. *Spei Domus*. 2013; 9(18): 49-58.

Abstract. This review article is an analysis of the most recent published scientific articles about myxomatous valve degeneration (MVD) and was conducted over a five month period. The aim of this review is to consolidate information about the most recent medical developments in regards to myxomatous degeneration in the mitral valve. The authors of this article reached a consensus on both the development of the disease and the most effective type of diagnosis and treatment that is available today. Myxomatous valve degeneration is the most common heart disease in the canine population. It is identified by a loss of mechanical integrity in the heart due to structural changes in the valvular components. Degenerative changes occur due to an accumulation of mucopolysaccharides in the leaflets and chordae which affect the proper operation of the valve apparatus. This is caused by faulty coaptation of the leaflets, resulting in mitral or tricuspid regurgitation, dilated ventricles and annuli, which are lesions that eventually cause the rupture of the chordae tendineae, leading to complications or possibly death. Due to the gradual progression of the disease and the presence or absence of clinical signs, it is very important that veterinarians accurately diagnose and follow-up on these patients in order to achieve stabilization and provide a suitable prognosis and treatment plan. The current ideal treatment of the disease is a low-sodium diet, administration of the ACE inhibitor (angiotensin-converting-enzyme inhibitor) spironolactone and a diuretic in order to reduce the presence of pulmonary edema and avoid the progression of the disease to congestive heart failure.

Keywords: AV valves, canine, heart, Myxomatous degeneration, treatment.

Degeneração valvar mixomatosa. Um olhar nos últimos avanços em todos os aspectos da doença

Resumo. Este artigo de revisão se realizou durante um período de cinco meses. Incluíram-se, neste, os últimos avanços publicados em artigos científicos. Conseguiu-se realizar um consenso quanto ao desenvolvimento da doença, ao tipo de diagnóstico mais adequado e ao tratamento que melhores resultados está mostrando na atualidade. O objetivo desta revisão foi conhecer as últimas atualizações sobre a degeneração valvar mixomatosa. A degeneração valvar mixomatosa é a doença cardíaca mais comum na população canina, na qual há uma perda da integridade mecânica devido a mudanças estruturais nos componentes valvulares. As mudanças se devem a uma acumulação de mucopolissacarídeos nas cordas tendíneas e nas valvas as quais iniciam com falhas na coaptação das valvas gerando uma regurgitação mitral ou tricúspidiana, dilatação dos ventrículos e do anel valvar, levando a complicações ou morte do paciente. Devido ao progresso gradual das lesões na doença e à manifestação ou não de signos clínicos, o diagnóstico exato e seguimento apropriado desses pacientes é de grande importância para os médicos veterinários com o objetivo de prognosticar e instaurar o tratamento adequado. O melhor tratamento na atualidade para a doença consiste em uma dieta baixa em sódio, administração de um Inibidor da Enzima Convertidora de Angiotensina (IECA), espironolactona e um diurético a fim de diminuir a presença de signos associados a edema pulmonar e evitar o progresso desta a uma insuficiência cardíaca congestiva.

Palavras-chave: válvulas AV, canino, coração, degeneração mixomatosa, tratamento.

Degeneración valvular mixomatosa. Una mirada a los últimos avances en todos los aspectos de la enfermedad

Resumen. Este artículo de revisión se realizó durante un periodo de cinco meses, en el que se incluyeron los últimos avances publicados en artículos científicos. Se logró realizar un consenso en cuanto al desarrollo de la enfermedad, el tipo de diagnóstico más adecuado y el tratamiento que mejores resultados está mostrando en la actualidad. El objetivo de esta revisión fue conocer las últimas actualizaciones acerca de la degeneración valvular mixomatosa. La degeneración valvular mixomatosa es la enfermedad cardíaca más común en la población canina, en la cual hay una pérdida de la integridad mecánica debido a cambios estructurales en los componentes valvulares. Los cambios se deben a una acumulación de mucopolisacáridos en las cuerdas tendinosas y las valvas, lo cual inicia con fallas en la coaptación de las valvas, generando una regurgitación mitral o tricúspidiana, dilatación de los ventrículos y del anillo valvular, llevando a complicaciones o muerte del paciente. Debido al progreso gradual de las lesiones en la enfermedad y a la manifestación o no de signos clínicos, el diagnóstico exacto y seguimiento apropiado de estos pacientes es de gran importancia para los médicos veterinarios con el fin de pronosticar e instaurar el tratamiento adecuado. El mejor tratamiento en la actualidad para la enfermedad consiste en una dieta baja en sodio, administración de un IECA (Inhibidor de la Enzima Convertidora de Angiotensina), espironolactona y un diurético con el fin de disminuir la presencia de signos asociados al edema pulmonar y evitar el progreso de esta a una insuficiencia cardíaca congestiva.

Palabras clave: válvulas AV, canino, corazón, degeneración mixomatosa, tratamiento.

Introduction¹

Myxomatous thickening and poor coaptation of the AV valves are major causes of morbidity and mortality in dogs. [1] This condition is known as myxomatous valve degeneration (MVD), a heart disease commonly acquired by small dog breeds during adulthood. [2] The disease does not have a defined etiology, and for this reason several hypotheses have arisen about the ways in which genetics and hemodynamic and endogenous factors may affect the disease. [3-5] MVD is the most common cause of heart failure in dogs and is considered to comprise 70-80% of heart-related diseases affecting this species. [6-7] Chronic valvular heart disease most often affects the mitral valve, but approximately 30% of cases involve the tricuspid valve. There is a particularly high incidence of the disease in certain breeds such as the Cavalier King Charles Spaniel (CKCS), in which it can be present in 90% of cases. [8] It has been reported that around 50% of CKCS that have a secondary murmur, degenerative lesions and mitral regurgitation at the age of 5-6 years tend to progress faster in the disease than other breeds. [7] MVD is also considered an important clinical event since it has similarities with the pathophysiology of humans [9] and is therefore recognized as a natural model for the human disease. [10] According to the American Heart Association (AHA), in 2003 cardiac valvular disease directly caused around 19,989 deaths and contributed to 42,590 deaths. [11] This disease is characterized by the loss of mechanical integrity in the valves, failure of proper coaptation of the leaflets during ventricular systole and regurgitation of blood throughout the leaflets. [12] The loss of mechanical integrity is the result of the destruction of the fibrous layer, expansion of connective tissue in the spongiosa layer and an excessive accumulation of glycosaminoglycans [9], thus generating an audible murmur during auscultation.

MVD typically progresses slowly and becomes severe over the years. This progression can lead to congestive heart failure (CHF) and due to the variable disease pathology can also lead to sudden death. [13, 14] The aim of this review is to further understand the latest developments of myxomatous degeneration in order to prevent these complications.

Diagnosis

Although some dogs with MVD remain asymptomatic for several years or even for their entire lives, severe complications can occur that lead to the death of the patient. For this reason the exact diagnosis and monitoring of the progression in a timely manner is of critical clinical interest in order to be able to predict the risk of decompensation, determine a prognosis and adopt an appropriate medical prescription.

An important assessment in the clinical examination of patients is auscultation, through which we can detect and classify a heart murmur, depending on its intensity and the presence of precordial shock. There is evidence that the intensity of the murmur detected during auscultation depends on the degree of regurgitation and is prognostic for the progression of heart failure. Therefore, the degree of the murmur can be a useful indicator for the diagnosis of MVD. [13] However, it is possible for MVD to manifest itself without the specific presence of this sign. The severity of heart murmur is usually graded out of six by auscultation according to its intensity and the presence of a precordial thrill. There is evidence that the intensity of the murmur detected by auscultation is dependent on the degree of mitral regurgitation and is prognostic for the progression of heart failure. Thus, the grade of murmur would appear to be an adequate diagnostic indicator of the severity of mitral valve disease. This indicates that cardiac degeneration occurs undetected for a long period of time and therefore the presence of a murmur should always be assessed by echocardiography to determine the remodeling of the ventricles and atria. [15]

Transthoracic echocardiographic evaluation is now considered the method of choice for non-invasive diagnoses in detecting valvular lesions. With this method, we can assess the severity of regurgitation, the impact on cardiac remodeling, myocardial functioning, the filling pressure of the ventricles and the pulmonary artery pressure. Even though transthoracic echocardiographic evaluation is considered the main diagnostic tool, it has its limitations because of the way the patient is handled and the extent of knowledge necessary to use the equipment correctly. [16] M-mode echocardiography views are obtained from a right parasternal position and are used to obtain left ventricular and atrial dimensions, using a short axis to measure the rate of the aorta and left atrium. [17] Myxomatous mitral valve disease can be diagnosed by identification of characteristic valve leaflet abnormalities (thickening and/or prolapse) and evidence of flow of regurgitation across the mitral valve detected by color-flow Doppler. [18]

¹ This article is the result of a research project of the National Committee for Research Development (Conadi according to its initials in Spanish) at Universidad Cooperativa de Colombia.

The tissue Doppler imaging (TDI) technique has been shown to be more sensitive than conventional echocardiography in detecting systolic and diastolic myocardial alterations in humans as well as in experimental or spontaneous heart diseases in animals, as demonstrated by our research group in a dog model of dilated cardiomyopathy. [figure 1] One important TDI application is the assessment of diastolic function, which may be impaired in aged dogs with MVD. [19]

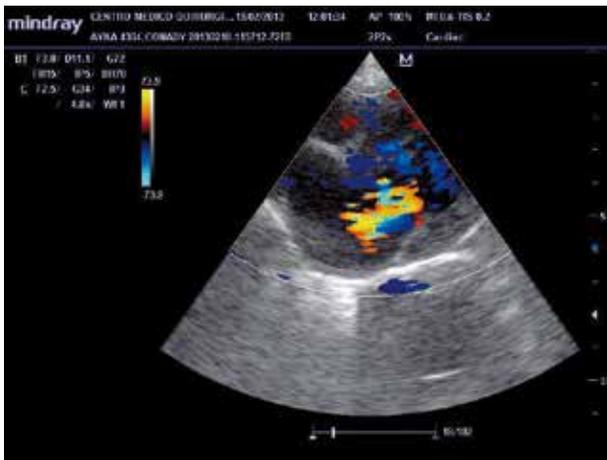


Figure 1. Doppler imaging showing mitral regurgitation
Source: elaborated by the authors

In radiographic cardiomegaly, evidence of the disease is usually detected by an enlarged left side of the heart. The left atrium (LA) is enlarged and compressed or the left main bronchus is elevated. Pulmonary venous congestion is commonly observed with pulmonary edema, especially in the perihilar area. [20]



Figure 2. Radiography of a dog with heart failure showing perihilar edema
Source: elaborated by the authors

One of the most important methods used with radiographic evidence is the measurement of the vertebral heart size. [21] Electrocardiographic findings are usually nonspecific, showing a P wave and wide QRS secondary to enlargement of the left atrium and the left ventricle (LV). [20]

Structure and function

AV valves are a unique tissue exposed to a complex mechanical environment that consists of two leaflets: the anterior (septal) and the posterior (parietal) with unique morphological characteristics. [22] The cellular component of the cardiac valves consists mainly of endothelial, interstitial and smooth muscle cells, of which the interstitial cells play a critical role in maintaining valvular competence and counteracting biomechanical problems. [23] This means they are an active and dynamic component of the valves, which allows them to remodel in response to stressors. [24] These structures are subjected to four mechanical forces in the valve: the opening (flexure), the allowing of the passage of blood (shear), the closure (flexure), and the prevention of blood reflux (tension and compression). [10]

The anterior leaflet area is larger, has less chordae and a large number of elastic components. The posterior leaflet is smaller and thinner with a large number of chordae tendineae that provide mechanical support and compensate for its delicate structure. Both leaflets show a soft tissue biomechanical response to stretching.

The annular region is more rigid than the free edge and is less flexible than the atrial or ventricular. These properties correspond to the microstructure of each area, which is influenced by the presence or absence of chordae tendineae.

Chordae tendineae are classified into three subtypes, based on location and function: strut, primary and secondary. The chordae tendineae modulate stress transmission to the leaflets, which is evidenced by the heterogeneity of mechanical properties and microstructure of the insertion of the strings in the leaflet. [22]

The functions of the mitral and tricuspid apparatus are to keep the valve open during diastole to allow proper filling of the ventricles and to close smoothly without allowing blood backflow during ventricular systole. [27] In order for this heart valve to work properly, many related structures must also function correctly, such as the AV ring, the AV leaflets, the chordae that hold them, the papillary muscles and the myocardium. [28]

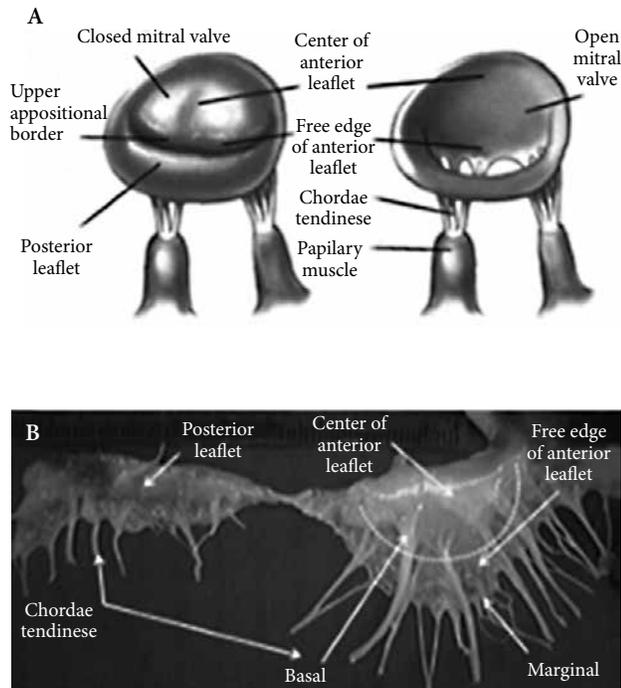
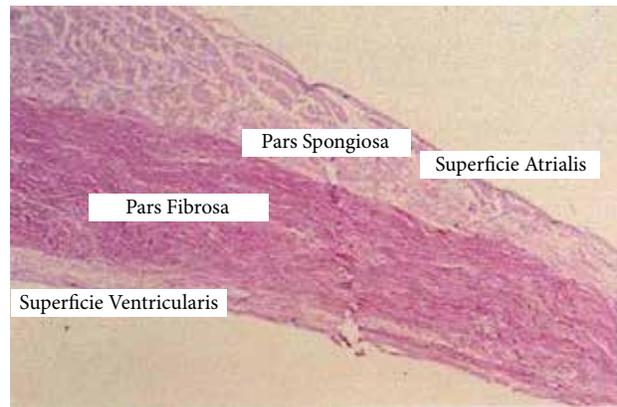


Figure 3. Cardiac valve anatomy
Source: Connell [25]



Atrialis: endocardium, continuation of atrial.
Spongiosa: a rare collection of fibers and bundles of collagen, with some elastic fibers with mucopolysaccharides.
Fibrous: a dense layer of collagen fibers.
Ventricularis: endocardium, continuous with the ventricular lining [26]

Figure 4. From the histological point of view, we can divide the normal mitral valve into 4 layers, from the atrium to the ventricle. Hematoxilin-eosin 10x
Source: Mucha [26]

Pathology

MVD most commonly affects atrioventricular valves, but the disease can affect all cardiac valves. Myxomatous changes have been reported in mitral valve disorders in 62% of dogs, with mitral and tricuspid comprising 32.5% and tricuspid 1.3%. [28]

The pathology of myxomatous valves in humans and in dogs includes increased cellularity, disorganization

of valve structure as well as transdifferentiation of valve endothelial cells and valve interstitial cells. [29] In MVD we see the development of degenerative connective tissue, which manifests itself in excessive stromal destruction and alteration of the valve with loss of collagen organization and accumulation of proteoglycans and glycosaminoglycans in the leaflets and chordae. [25]

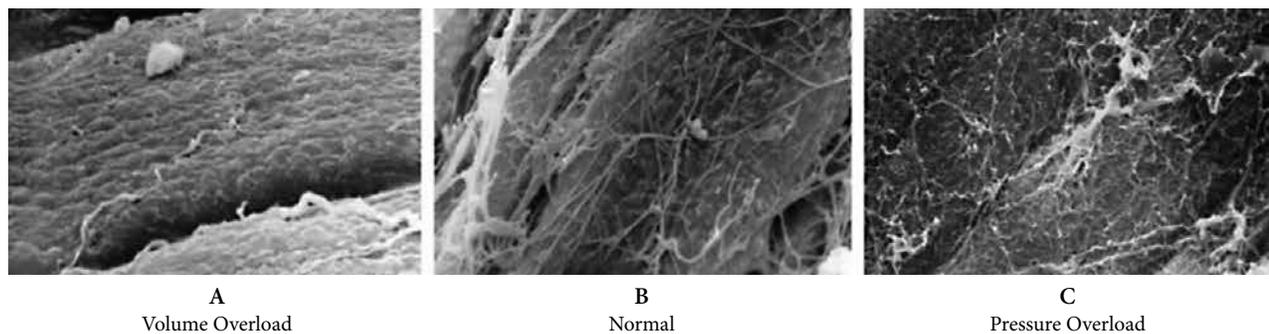


Figure 5. A collagen decrease in a canine with a volume overload caused by mitral regurgitation, B collagen in a canine with a normal heart and C increased collagen in a canine with pressure overload caused by experimental aortic stenosis
Source: Dillon [30]

A study by Hadian et al. showed a 10% reduction in total collagen and a 20% reduction in fibrillar collagen content in the myxomatous areas of canine valves with mild to moderate MVD. [31]

These alterations are known as mucopolysaccharidoses (MPSS), which are characterized by a functional deficiency caused by a genetic mutation of a lysosomal enzyme that acts on the sequential catabolism of glycosaminoglycans. It has been reported that all MPS syndromes affect the heart and that an absence of heparan sulfate and dermatan sulfate is a common feature in MPS I, II, and VI. [32]

Histopathologically MVD is characterized by the expansion of the pars spongiosa that invades and produces a focal disruption of the fibrous pars, generating changes such as hyalinization and dilation, fragmentation of the bundles and in severe cases isolated fragments that can be observed in the fibrous layer. [26]

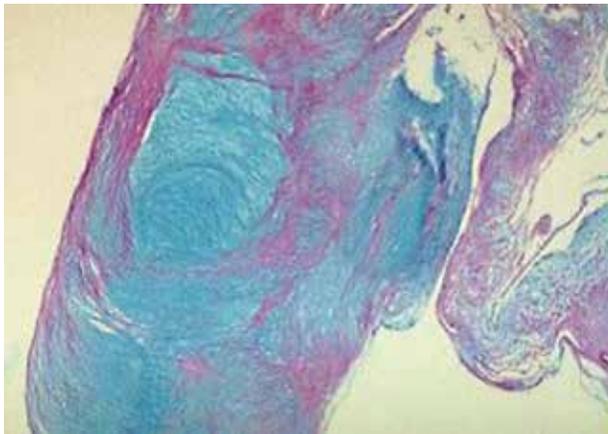


Figure 6. Valvar contact area, showing a severe infiltration of MPSS (blue) separately and invading the collagen structure (purple). Alcian Blue / PAS. 40x

Source: Mucha [26]

Matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs) appear to play an important role in maintaining a normal physiological extracellular matrix, which is affected by MVD. MMPs are a family of proteolytic enzymes that are involved in the protein degradation in the extracellular matrix and play an important role in remodeling. It has been shown that in a canine mitral valve with advanced MVD, the expression of MMPs decreases and TIMPs increases. [33] Early pathological lesions are nodules usually located in the zone of apposition on the atrial

surface of the leaflets. [25] A roughened area of the valve on the side where the nodules connect with the ventricular chordae is predisposed to suffer myxomatous degeneration. [25]

Risk factors associated with the progression of the disease or death in dogs with MVD include age, gender, intensity of the heart murmur, degree of valve prolapse, degree of mitral regurgitation (MR), degree of left atrial enlargement, severity of eccentric hypertrophy, rupture of chordae tendineae and increasing concentrations of natriuretic peptides. [34]

MVD lesions occur gradually and do not show clinical signs at the beginning of the first structural changes. [35] The progression of the disease which occurs leads to inadequate coaptation of the leaflets by increasing the blood flow in the atrium, known as mitral regurgitation (MR). This causes an increase in the LV volume overload and as a result leads to an increase in cardiac oxygen demand, [36] causing dilatation of the LV and the mitral ring accompanied by ejection injuries and rupture of the chordae. [35] Patients with acute MR generally show high pulmonary venous pressure, while those with chronic MR shown an enlarged ventricle with decreased pulmonary vein pressure. [35]

As a result of these injuries we find mitral systolic murmurs [25], which generate CHF by reaching the left and then the right side of the heart due to pulmonary hypertension. [16] This sign is taken as the pressure increase of the LA and a vasoconstrictive reaction of the pulmonary artery associated with acute or chronic hypoxia. [37] The insufficiency of the tricuspid valve can also occur in dogs, leading to heart failure. This valve malfunction is associated with focal or diffuse thickening of the valves and reduced performance of the chordae and papillary muscles, causing regurgitation in the atrium that finally leads to right atrium and ventricle dilatation. The clinical signs related to right heart failure are accumulation of fluid in the abdominal and chest cavity, swelling of the limbs, discomfort and difficulty finding a comfortable position to rest, lack of appetite, weight loss and lethargy.

CHF begins when the body is unable to provide the required oxygen to different tissues and cells trigger a response mechanism. The first response is the activation of receptors β in the aorta because of changes in pressure. As days go by these receptors are saturated and several hormones (endothelin, aldosterone, atrial natriuretic peptide and renin) are released in an attempt to correct the problem. These receptors retain

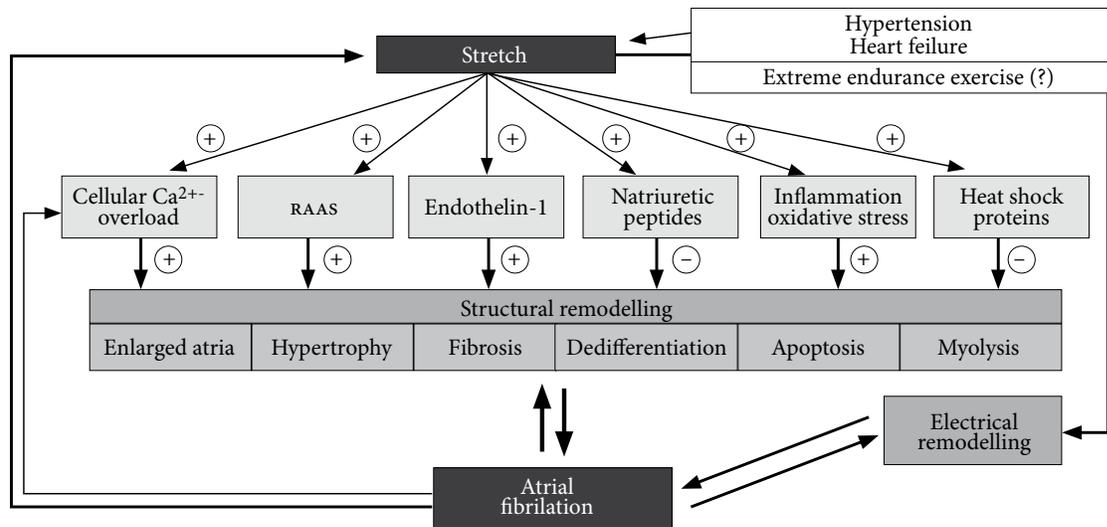


Figure 7. Flow chart showing the series of events caused by stretch. Hypothetical scheme of stretch induced by hypertension, heart failure and possibly extreme endurance exercise leading to calcium overload, activation of the renin-angiotensin-aldosterone system (RAAS) and release of different factors, resulting in structural remodelling and finally in AF

Source: De Jong et al. [38]

the fluid for the purpose of increasing blood volume and output of blood and oxygen to the heart. For several months these compensation mechanisms help the situation, but eventually increased fluid retention becomes detrimental to the capillaries in the lungs, abdomen and other tissues. [38]

The most important sign of failure in the left side of the heart is pulmonary edema and in the right is ascites and pleural and pericardial spills. [39] When CHF is secondary to MVD it can cause sudden death due to arrhythmias, hypoxemia, pulmonary embolism and multiple organ failure. [27]

Mechanical stress contributes to phenotypic changes in the mitral valve that undergoes degeneration, suggesting that these factors contribute to the development of MVD in canines. This is why scanning is required not only in vivo but in vitro, to allow for a specific analysis of the signaling mechanisms of the disease. [40]

Clinical signs

Clinical signs of dogs with MVD include manifestations of CHF on the left side of the heart, such as exercise intolerance, cough, dyspnea and syncope. The cough is usually associated with the elevation of the left main bronchus due to enlargement of the LA. It is described

as a dry cough, occurring after exercise, excitement or in the evening. Syncope may be related to an inadequate flow, pulmonary hypertension or cardiac arrhythmia. [20]

Clasification of CHF (ACVIM)

The challenge for veterinarians facing patients with this disease is to establish a proper diagnosis by recognizing the progressive stage of the disease in order to treat the patient appropriately. [41]

There are several ways to categorize heart disease in dogs, but the latest has been published by the American College of Veterinary Internal Medicine (ACVIM). The ACVIM uses a classification from A to D. Category A dogs do not have heart disease but are at risk, such as the Cavalier King Charles Spaniel and Poodle. Category B dogs have mild heart disease, both without cardiac remodeling (B1) and with cardiac remodeling (B2), but with no evidence of present or historical CHF. Category C dogs have signs of heart failure and are either hospitalized (C1) or treated at home (C2). Category D dogs are terminal with refractory symptoms of heart failure, either treated in a hospital (D1) or at home (D2). The classification of patients can change their category according to decompensation, disease progression and treatment. [42]

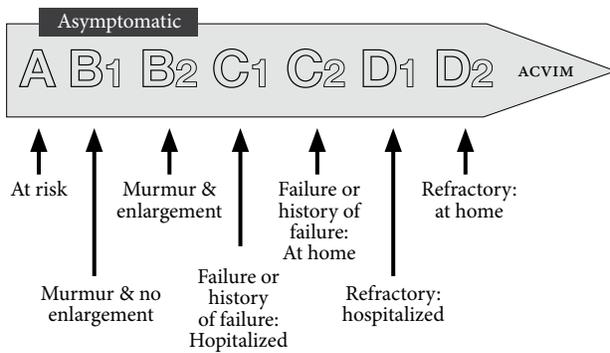


Figure 8. ACVIM Cardiac Disease Classification

Source: Atkins [42]

Treatment

One of the compensatory mechanisms in patients with MVD is the activation of the renin angiotensin aldosterone system (RAAS), which is favorable in cardiac patients, since the action of angiotensin II leads to an increase in vascular and arterial pressure. [43] This mechanism becomes detrimental after a prolonged period in these patients because it increases the volume of regurgitation and causes eccentric hypertrophy. Because of this, the suppression of this system is of great importance, which is why treatment should start with an angiotensin-converting enzyme inhibitor (ACE inhibitor), which blocks the production of angiotensin II, thereby increasing levels of bradykinin and improving the functioning of the left ventricle and skeletal muscle circulation. [44]

Conventional treatment for heart failure includes ACE inhibitors and furosemide. However, ACE inhibitors are poor suppressors of aldosterone secretion and furosemide increases the secretion of this hormone, which in turn increases extracellular fluid volume, putting more stress on the heart. This has a direct negative effect on the heart muscle and vasculature. For this reason spironolactone is added to the conventional treatment as a selective inhibitor of aldosterone [38], which acts on the distal tubule to increase sodium and water excretion and decrease potassium excretion. [45] Another of its virtues is to decrease cardiac fibrosis and norepinephrine release. [46]

Patients in stage A are asymptomatic and do not require drug therapy because the physiological compensation does not allow for the presence of clinical signs. Treatment should be set up in patients with stage B in which the sympathetic system has been altered

and the activation of RASS has occurred, increasing the pressure and volume with sodium retention secondary to the vasoconstriction caused by angiotensin II. Over time this system generates changes in the myocardium that should be prevented by an ACE inhibitor such as enalapril and benazepril, as currently accompanied by potassium savers such as spironolactone that in prolonged low doses prevent cardiac remodeling. The use of Pimobendan is also recommended to potentiate the inhibition of cardiac remodeling in patients with this pathology. Patients with stage C progression demonstrate critical clinical signs such as pulmonary edema due to mitral valve insufficiency, for which it is useful to use furosemide.

In a recent study the administration of 2 mg/kg of spironolactone for a period of 15 months successfully reduced morbidity and mortality by 55% in patients with heart disease compared to those receiving conventional therapy with ACE inhibitors such as furosemide and digoxin. [44] Since the progression of MVD can in fact cause CHF, the administration of spironolactone must be accompanied by an ACE inhibitor and a loop diuretic, which have been of great importance for the treatment of CHF in humans and veterinary patients because of their ability to reduce clinical signs associated with pulmonary congestion and pulmonary edema. In veterinary patients furosemide has been the loop diuretic of choice, but according to studies of dogs receiving high doses of furosemide (4-8 mg/kg), they continue suffering from congestion. Poor performance of furosemide is reflected not only in the progression of the disease but also in diuretic resistance. In humans with advanced heart disease, diuretic resistance is well described in the literature. [47] There are studies of a loop diuretic called torasemide being used in human patients with CHF that acts upon the nephron ascending loop of Henle, promoting the excretion of sodium, chlorine and water. This diuretic has a high bioavailability in humans, a long half-life and duration of action greater than that of furosemide, resulting in a stronger and more effective diuresis. It further demonstrated a significant reduction in morbidity and cardiac death. The superiority of torasemide over furosemide is due to its antifibrotic effects on the myocardium that appear to be mediated by the antagonism of aldosterone in a way similar to that of spironolactone. [48]

Since sodium retention is a major contributor to congestion, the restriction of electrolytes in the diet has been used in the management of heart failure. It has recently become clear than the extreme restriction

of sodium activates RAAS and may contribute to renal dysfunction, particularly when ACE inhibitors are used. For this reason the use of moderate-salt diets with 22% sodium for kidney patients are recommended in early stages of heart failure, as well as restriction diets with 10% sodium for patients with refractory therapy. [49]

Valve repair or replacement through open heart surgery with the use of cardiopulmonary bypass has also been reported in dogs with MVD. However, this treatment is expensive, not widely available, and has limitations depending on the size of the patient. Surgical intervention is focused on reducing the circumference of the mitral annulus in order to decrease the RM and reduce MVD progression. [30, 50]

Conclusions

MVD is a disease of great clinical interest because it is an acquired heart disease that affects a large percentage of the dog population and has great pathophysiological similarity to humans. Due to the nature of the progression of the disease, which often is nearly undetectable, constant revision by the veterinarian is important to be able to diagnose the stage of the disease and to stabilize and treat patients appropriately. A better understanding of the pathophysiology of myxomatous valvular degeneration would help prevent or treat existing lesions and prevent progression of the disease to CHF.

References

- [1] French AT, Ogden R, Eland C, Hemani G, Pong-Wong R, Corcoran B et al. Genome-wide analysis of mitral valve disease in Cavalier King Charles Spaniels. *The Veterinary Journal*. 2012; 193(1): 283-6.
- [2] Gordon SG, Saunders AB, Hariu CD, Boggess MM, Miller MW. Retrospective review of carvedilol administration in 38 dogs with preclinical chronic valvular heart disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 243-52.
- [3] Reynolds CA, Brown DC, Rush JE, Fox PR, Nguyenba TP, Lehmkühl LB et al. Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: The predict cohort study. *Journal of Veterinary Cardiology*. 2012; 14(1): 193-202.
- [4] Aupperle H, März I, Thielebein J, Kiefer B, Kappe A, Schoon HA. Immunohistochemical characterization of the extracellular matrix in normal mitral valves and in chronic valve disease (endocardiosis) in dogs. *Research in Veterinary Science*. 2009; 87: 277-83.
- [5] Heaney AM, Bulmer BJ, Ross CR, Schermerhorn T. A technique for in vitro culture of canine valvular interstitial cells. *Journal of Veterinary Cardiology*. 2012; 11(1): 1-7.
- [6] Nogueira RB, Silva AC, Reis GF, Muzzi RA, Mantovani MM. Muscular arterial impedance in dogs with chronic degenerative mitral valve disease. *Research in Veterinary Science*. 2012; 93(3): 1434-8.
- [7] Parker HG, Kilroy-Glynn P. Myxomatous mitral valve disease in dogs: Does size matter. *Journal of Veterinary Cardiology*. 2012; 14(1): 19-29.
- [8] Atkins C, Bonagura J, Ettinger S, et al. ACVIM Consensus Statement: Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med*. 2009; 23: 1142-50.
- [9] Hadiana M, Corcoran BM, Bradshaw JP. Molecular changes in fibrillar collagen in myxomatous mitral valve disease. *Cardiovascular Pathology*. 2010; 19(5): e141-8.
- [10] Lacerda CM, MacLea HB, Kisiday JD, Orton EC. Static and cyclic tensile strain induce myxomatous effector proteins and serotonin in canine mitral valves. *Journal of Veterinary Cardiology*. 2012; 14(1): 223-230.
- [11] Sacks MS, Merryman WD, Schmidt DE. On the biomechanics of heart valve function. *J Biomech*. 2009; 42(12): 1804-24.
- [12] Hadian M, Corcoran BM, Han RI, Grossmann JG, Bradshaw JP. Organization in Canine Myxomatous Mitral Valve Disease: An X-Ray Diffraction Study. *Biophysical Journal*. 2007; 93(7): 2472-6.
- [13] Lewis T, Swift S, Woolliams JA, Blott S. Heritability of premature mitral valve disease in Cavalier King Charles spaniels. *The Veterinary Journal*. 2011; 188(1): 73-6.
- [14] Borgarelli M, Savarino P, Crosara S, Santilli RA, Chiavegato D, Poggi M et al. Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *J Vet Intern Med*. 2008; 22: 120-8.
- [15] Gómez L. Degenerative valve disease in dogs: update on diagnosis, treatment and prognosis. *Rev Colomb Cienc Pecu*. 2011; 24: 201-8.
- [16] Chetboul V, Tissier R. Echocardiographic assessment of canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 127-48.
- [17] Griffiths LG, Fransioli JR, Chigerwe M. Echocardiographic assessment of interventricular and intraventricular mechanical synchrony in normal dogs. *Journal of Veterinary Cardiology*. 2011; 13(2): 115-26.

- [18] Hezzell MJ, Boswood A, Moonarmart W, Elliott J. Selected echocardiographic variables change more rapidly in dogs that die from Myxomatous mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 269-79.
- [19] Chetboul V, Tissier R. Echocardiographic assessment of canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 127-48.
- [20] Pedersen HD, Häggström J. Mitral valve prolapsed in the dog: a model of mitral valve prolapse in man. *Cardiovasc. Res*. 2000; 47: 234-43.
- [21] Buchaman JW, Bucheler J. Vertebral scale system to measure canine Heart size in radiographs. *Journal of Veterinary Internal Medicine*. 1995; 206: 194-9.
- [22] Richards JM, Farrar EJ, Kornreich BG, Moise NS, Butcher JT. The mechanobiology of mitral valve function, degeneration, and repair. *Journal of Veterinary Cardiology*. 2012; 14(1): 47-58.
- [23] Orton EC, Lacerda CM, MacLea HB. Signaling pathways in mitral valve degeneration. *Journal of Veterinary Cardiology*. 2012; 14(1): 7-17.
- [24] Stephens EH, Durst CA, Swanson JC, Grande-Allen KJ, Ingels JR NB, Miller C. Functional Coupling of Valvular Interstitial Cells and Collagen Via $\alpha 2$ $\beta 1$. *Cellular and Molecular Bioengineering*. 2010; 3(4): 428-37.
- [25] Connell PS, Han RI, Grande-Allen KJ. Differentiating the aging of the mitral valve from human and canine myxomatous degeneration. *Journal of Veterinary Cardiology*. 2012; 14(1): 31-45.
- [26] Mucha CJ. Degeneración Valvular Mixomatosa. *RED-VET*. 2007; 8(7): 1-7.
- [27] O'Leary, Wilkie I. Cardiac Valvular and Vascular Disease in Bull Terriers. *Vet Pathol*. 2009; 46: 1149.
- [28] Fox PR. Pathology of myxomatous mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 103-26.
- [29] Disatian S, Ehrhart III EJ, Zimmerman S, Orton EC. Interstitial cells from dogs with naturally-occurring myxomatous mitral valve disease undergo phenotype transformation. *J Heart Valve Dis*. 2008; 17(4): 402-12.
- [30] Dillon AR, Dell'Italia LJ, Tillson M, Killingsworth C, Denney T, Hathcock J. Left ventricular remodeling in preclinical experimental mitral regurgitation of dogs. *Journal of Veterinary Cardiology*. 2012; 14(1): 73-92.
- [31] Aupperle H, Disatian S. Pathology, protein expression and signaling in myxomatous mitral valve degeneration: Comparison of dogs and humans. *Journal of Veterinary Cardiology*. 2012; 14(1): 59-71.
- [32] Braunlin EA, Harmatz PR, Scarpa M, Furlanetto B, Kampmann C, Loehr JP et al. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. *J Inherit Metab Dis*. 2011; 34: 1183-97.
- [33] Aupperle H, März I, Thielebein J, Dinges G, Schoon A. Histomorphological findings and expression of matrix metalloproteinases and their tissue specific inhibitors (TIMPs) in normal tricuspid valves and in chronic tricuspid valvular disease in dogs. *The Veterinary Journal*. 2010; 183: 176-83.
- [34] Borgarelli M, Buchanan JW. Historical review, epidemiology and natural history of degenerative mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 93-101.
- [35] Gaasch WH, Meyer TE. Left Ventricular Response to Mitral Regurgitation: Implications for Management. *Circulation*. 2008; 118: 2298-303.
- [36] Fukunaga K, Fujii Y, Chiba N, Ueshima A, Wakao Y, Mishima K. Pharmacokinetics of nicorandil in dogs with mild mitral regurgitation. *Research in Veterinary Science*. 2011; 90(1): 95-8.
- [37] Kellihan HB, Stepien RL. Pulmonary hypertension in canine degenerative mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 149-64.
- [38] De Jong AM, Maass AH, Oberdorf-Maas SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. *Cardiovascular Research*. 2010; 89: 754-65.
- [39] Ward EE Jr. North Park Animal Hospital. 2012.
- [40] Waxman AS, Kornreich BG, Gould RA, Moise NS, Butcher JT. Interactions between TGF β 1 and cyclic strain in modulation of myofibroblastic differentiation of canine mitral valve interstitial cells in 3D culture. *Journal of Veterinary Cardiology*. 2012; 14: 211-21.
- [41] Boswood A. Valvular heart disease in the dog. *Veterinary Focus*. 2008;18(3): 25.
- [42] Atkins CE, Haggstrom J. Pharmacologic management of myxomatous mitral valve disease in dogs. *Journal of Veterinary Cardiology*. 2012; 14(1): 165-84.
- [43] Chandler ML. Safety: Sodium in Pet Foods. *Pet Food*. 2008; 23(3): 148-53.
- [44] Bernay F, Bland JM, Häggström J, et al. Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. *J Vet Intern Med*. 2010; 24: 331-41.
- [45] Jeunesse E, Woehrlé F, Schneider M, Lefebvre P. Effect of spironolactone on diuresis and urine sodium and potassium excretion in healthy dogs. *Journal of Veterinary Cardiology*. 2007; 9(2): 63-8.
- [46] Thomason JD, Rockwell JE, Fallaw TK, Calvert CA. Influence of combined angiotensin-converting enzyme inhibitors and spironolactone on serum K, Mg $^{2+}$, and Na concentrations in small dogs with degenerative mitral

- valve disease. *Journal of Veterinary Cardiology*. 2007; 9(2): 103-8.
- [47] Oyama M, Peddle GD, Reynolds CA, Singletary GE. Use of the loop diuretic torsemide in three dogs with advanced heart failure. *Journal of Veterinary Cardiology*. 2011; 13(4): 287-92.
- [48] Peddle GD, Singletary GE, Reynolds CA, Trafny DJ, Machen MC, Oyama MA. Effect of torsemide and furosemide on clinical, laboratory, radiographic and quality of life variables in dogs with heart failure secondary to mitral valve disease. *Journal of Veterinary Cardiology*. 2012; 14(1): 253-9.
- [49] Atkins CE. Advances in the Management of Canine Heart Failure. Proceedings of the Congreso Latinoamericano de Emergencia y Cuidados Intensivos LA-VECCS. 2010. Disponible en: [disponible http://www.laveccs.org/biblioteca/file/CHF%20Advances%2009%20LONG%20version.pdf](http://www.laveccs.org/biblioteca/file/CHF%20Advances%2009%20LONG%20version.pdf)
- [50] de Andrade J, Orton EC, Boon J, Nishimori CT, Olivaes C, Camacho AA. Partial external mitral annuloplasty in dogs with myxomatous mitral valve degeneration and heart failure: Outcome in 9 cases. *Journal of Veterinary Cardiology*. 2011; 13(3): 197-201.