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Heredity on the Cardiovascular System in Dogs: Mitral Valve Insufficiency and the King Charles Dog

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ABSTRACT

This review addresses the genetic basis of cardiovascular disease in dogs, with a particular focus on mitral valve insufficiency (MVI), which is common in the Cavalier King Charles Spaniel breed. MVI is a common degenerative heart disease, especially in small breed dogs, which progresses with age. Genetic predisposition plays a critical role in the pathogenesis of heart disease, and is also important for both early diagnosis and long-term treatment strategies. In the Cavalier King Charles Spaniel breed, polygenic inheritance and loci identification have been reported to be associated with early onset of the disease. In this study, the stages and clinical, echocardiographic and radiologic findings of MVI were detailed in line with the classification systems proposed by ISACH and ACVIM, and also modern diagnostic methods and clinical use of biomarkers were discussed. In addition, the contribution of proteomic research to the understanding of cardiac pathophysiology was emphasized and its relationship with platelet function and coagulation processes in heart failure was evaluated. In conclusion, it is suggested that further studies at the genetic and molecular level will provide innovative approaches in the fields of diagnosis, treatment and preventive medicine in veterinary cardiology practice.

INTRODUCTION

Cardiovascular diseases (CVDs) are serious health problems that affect animal welfare and their lifespan negatively. Understanding the genetic background of these diseases is essential for an effective treatment process. Recent studies have reported that genetic factors are the important risks for developing of heart diseases. This should be considered in the context of the One Health concept both for humans and animals.

Veterinary cardiologists have been studying genetic predisposition in CVDs since the 70s. The genetic prevalence of heart diseases is high in some specific dog species such as King Charles Spaniel, Dachshund, Cavalier. It has been known that understanding the genetic basis of CVDs can help in the treatment process. Particularly atrial fibrillation, mitral valve insufficiency (or mitral regurgitation, MVI) and subvalvular aortic stenosis have been interested more by researchers (Ontiveros and Stern, 2021; O'Brien et al., 2021; Arcuri et al., 2024).

Mitral valve insufficiency is accepted the major heart disease in dogs with the age that encountered in almost all breeds. It has been found more commonly in some breeds especially the Cavalier King Charles Spaniel and the Dachshund (O'Brien et al., 2021). Although some dogs have a rapid and early onset of the disease, many others live long periods without any clinical signs (Atkins et al., 2009; Meurs et al., 2018). In this review, in addition to a general overview of CVDs in dogs, studies on MVI and treatment which are frequently encountered especially in King Charles Spaniel dogs can be reviewed.

Genetic Etiology of CVDs in Dogs

CVDs involves a complex interplay of genetic, neurohormonal, inflammatory and biochemical changes in body. The heart valve diseases, MVI, chronic valve diseases and tricuspid valve insufficiency are the most important disease encountered in dogs. The age, sex, physiological condition and breed are important occurrences of these diseases (Ontiveros and Stern 2021; O'Brien et al., 2021; Arcuri et al., 2024). In addition, Cavalier King Charles Spaniels, Chihuahuas, Miniature Poodles, Miniature Pinchers and Whippets are considered as important dog breeds. Especially Cavalier King Charles

Spaniel dogs are more genetically predisposed to CVDs than other breeds. Importantly, MVI is one of the most crucial diseases for this breed.

Researchers have showed that polygenic inheritance is effective in the formation of MVI in Cavalier King Charles Spaniel dogs (O'Brien et al., 2021). The two locus on chromosomes 13 and 14 that are associated with the early onset of the MVI was reported. Researchers determined that especially in dogs over 8 years of age, this disease is more common (Borgarelli and Buchanan, 2012). However, in a postmortem study, it was shown that under MVI was found 35% in 5 years old of age Cavalier King Charles Spaniel dogs and 97% in dogs over 9 years of age (Whitney, 1974). Also, Beardow and Buchanan (1993), reported that mitral murmurs were determined in 9% of Cavalier King Charles Spaniel dogs under 1 year of age, 56% over 4 years of age and 100% over 10 years of age. Additionally, it was observed that MVI was higher in males than females as well as at an earlier age (Olsen et al., 2003).

Several classification systems have been categorized the severity of MVI in dogs. Earlier systems, especially the International Small Animal Cardiac Health Council (ISACH) scheme, dogs were classified into a four-class system (Classes I-IV) based on the clinical symptoms exhibited by dog. However, the American College of Veterinary Internal Medicine Cardiology Specialty consensus panel (ACVIM) has developed a more rigid system for some CVDs (Atkins et al., 2009; Keene et al., 2019; O'Brien et al., 2021).

Classification of CVDs and The Symptoms

ISACH has classified the CVDs in animals according to clinical, auscultation, radiologic and echocardiographic findings. The evaluations and modifications have been still made based on the same classification by the committee from teh date 1994 (ISACH 1994; Table 1).

Table 1. Classification of radiologic and echocardiographic findings of heart failure (modified from ISACH, 1994)

Class	Clinical Findings	Echocardiographic Findings	Radiological Findings
1. Asymptomatic heart failure	- No clinical symptoms. - Systolic murmur and arrhythmia - Weakening of systolic heart sounds	- No dilation in the left atrium and left ventricle.	- No pulmonary vein engorgement.
2. Moderate heart failure (asymptomatic)	- Exercise intolerance - Increased respiratory rate - Dyspnea - Cough	-Mild/moderate increase in internal diameters of the left atrium and left ventricle.	-Mild/moderate enlargement of the left atrium and left ventricle. - Thickening of the pulmonary veins is observed.
3. Severe heart failure	- Marked dyspnea - Marked ascites - Exercise intolerance - Hypoperfusion - Signs of cardiogenic shock	- Prominent left atrial dilation - Increased left ventricular volume - Eccentric hypertrophy observed - Hyperdynamic left ventricle detected - Increased end-systolic diameter	- Marked cardiomegaly - Dorsal deviation of the trachea - Increased pressure on the left main bronchus - Thickening in perihilar and caudodorsal lungs - Alveolar infiltration and changes in auscultation
4. End-stage heart failure	- Severe symptoms of congestive heart failure are observed.	- Enlargement and increased internal diameter of the left atrium and left ventricle - Significant decrease in myocardial function	- Severe cardiomegaly - Marked alveolar infiltration is detected.

As in humans in dogs and cats, heart failure can lead to impaired hemostasis. Also it has been reported that thrombus formation can occur due to platelet overwork (Smith et al., 2015). Circulatory insufficiencies in such organs (lung and brain) due to thromboembolism can cause the clinical pathological findings. The findings include peracute walking difficulties or paraplegia due to arterial thromboembolism, respiratory distress due to pulmonary embolism, syncope or seizures due to thrombus in the brain vessels. Therefore, using drugs which regulate the platelet activity in CVDs is accepted for both treatment and prophylaxis in humans as well as in animals (Wendy 2011; Smith et al., 2015). However, studies reported that while thromboembolism is a risk in hypertrophic cardiomyopathies in cats, there is a lower risk in heart failure in dogs (Smith et al., 2015).

Table 2. Classification of Heart Failure Findings according to the consensus panel of the American College of Veterinary Internal Medicine Cardiology Specialty (compiled from ACVIM)

Stage	Findings
Stage A	There is no audible heart murmur, but no obvious structural abnormality is found on examination, which would put the risk of developing heart failure above average.
Stage B	Dogs in Stage B show structural abnormalities. However, clinical signs of heart failure associated with mitral valve disease have never been observed.
Stage C	Mitral valve insufficiency is severe enough to cause current or past clinical signs of heart failure. Stage C includes all dogs with mitral valve insufficiency that have experienced an episode of clinical heart failure and are not resistant to standard heart failure treatment.
Stage D	Patients exhibit clinical signs of heart failure that are resistant to standard treatment used for Stage C heart failure.

Mitral Valve Insufficiency (Mitral Regurgitation, MVI) and Findings

Guidelines for the diagnosis and treatment of mitral valve disease in dogs were reported by the American College of Veterinary Internal Medicine Cardiology Specialty consensus panel (ACVIM) in 2009 (Atkins, 2009). However, new strategies for diagnostic, medical, surgical and dietary treatment recommendations have been more detailed and updated over the years (Table 2).

Mitral regurgitation is known as a leakage of the mitral valve during blood flow from the left ventricle to the left atrium due to deterioration of its structure (De Madron 2015; Abbott 2016). As the mitral valve is distrupted, the blood from the left ventricle cannot directed to the aorta, and thereby the blood passes into the left atrium. Accordingly, left atrium adaptation cannot be achieved due to the increasing blood volume and chordae tendineae rupture, which causes mitral regurgitation. Also, pulmonary edema and signs of left-sided congestive heart failure occur (Eriksson et al., 2010). Nevertheless, some other important findings of MVI include the increased left ventricular filling pressure, pulmonary hypertension and myocardial dysfunction (Keene et al., 2019). Compensatory mechanisms such as left ventricular hypertrophy, dilatation or increased neurohormonal system activity are initially seen as effective mechanisms to maintain hemodynamic pressure against mitral regurgitation. However, with the progression of the disease, collagen fiber accumulation and myocyte damage in the heart are existed. Also, as the disease progresses even death can be observed (Vereb et al., 2023).

The basic reason of MVI in dogs has been reported as degenerative mitral valve disease which especially encounters in small breeds (Chetboul et al., 2016). Additionally, the polygenic inheritance effective in the formation of MVI in Cavalier King Charles Spaniel dogs and two locus on chromosomes 13 and 14 are associated with the early onset of the disease are noticed (Madsen et al. 2011). Borgarelli and Buchanan (2012) found that age and sex especially in dogs over 8 years of age are effective in disease. In a postmortem study, it was determined that MVI can be found in 35% of Cavalier King Charles Spaniel dogs under 5 years of age, and 97% of dogs over 9 years of age (Whitney, 1974). Furthermore, Beardow and Buchanan (1993), presented the mitral murmurs detected in 9% of Cavalier King Charles Spaniel dogs under 1 year of age, 56% over 4 years of age, and 100% over 10 years of age. Also, some researchers showed the high incidence of MVI in males at an earlier age than females (Olsen et al., 2003). According to the ACVIM, the therapeutic approach for this disease is based on the latest consensus guidelines.

Diagnosis of Cardiovascular Diseases and Technologies Routine Analyses

Despite the new generation technologies, anamnesis and physical examination methods are the first important step for the diagnosis of a disease. The anamnesis should be evaluated together with the physical examination. The first steps towards diagnosis are checking the external appearance, auscultation, pulse measurement, respiratory examination, and listening to the heart. The most clinical findings in cardiovascular diseases are respiratory problems such as cough, difficulty breathing, tachycardia, weak pulse, weight loss and abdominal distension. Particularly in MVI, tachycardia, a systolic sound shorter than diastole, and the qualities of first and second sound are accepted other important auscultation findings.

Table 3. Echocardiography techniques (compiled from Fries et al., 2019; Tidholm et al., 2024)

Type of Echocardiography	Ability to Show Anatomical Structures	Sensitivity to Abnormal Blood Flow	Examination of Blood Flow	Measurement of Ventricular Functions
M-Mode Echocardiography	Limited	Not Sensitive	Abnormal valve motion Ventricular septal hypertrophy Dilation	Left ventricular function measurement
2-D Echocardiography	Very Good	Not Sensitive	Dilatation of great vessels	Ventricular ejection fraction
PW (Pulsed Wave) Doppler	None	Sensitive	Indirect	Blood flow velocity (aorta and valves)
Color Doppler	None	Sensitive	Direct	None
CW (Continuous Wave) Doppler	None	Sensitive	Blood flow velocity and pressure gradients	Blood flow velocity (aorta and valves)

Although the diagnosis of heart diseases cannot be diagnosed directly, the general condition of the heart, rhythm and cardiovascular disorders can be revealed by electrocardiography. Electrocardiography has been successful in the diagnosis of cardiac arrhythmias that has been used in animal and human health for many years (Table 3). However, along with electrocardiography, echocardiography is one of the best imaging methods in the diagnosis of heart diseases today. It has also been reported that important information about the contractile strength of the heart and diastolic heart failure can be provided by these methods (Fries et al., 2019; Klein et al., 2022; Tidholm et al., 2024). Echocardiography imaging formats are obtained in 2-D (two-dimensional) or M-Mode (Mobilization mode). Especially in in 2-D echocardiography, cardiac structures can be seen in the right and left parasternal long axis, short axis and apical acoustic windows (Figure 1, 2). Some researchers have reported that echocardiography is far from being a screening test because it requires expertise, and also is expensive (Fries et al., 2019; Tidholm et al., 2024).

Routine analyses of heart failure include complete blood count (erythrocyte, hemoglobin, hematocrit, leukocyte, platelet), serum-electrolytes (Na, K, Cl), creatinine, urea, aspartate aminotransferase (AST), CK-MB (Creatine Kinase-MB isoenzyme), lactate dehydrogenase (LDH) and alpha hydroxybutyrate-dehydrogenase (α-HBDH), which are isoenzymes of

creatine phosphokinase (CPK), and LDH/α-HBDH ratio. Although there is no blood test to diagnose heart failure definitively, there is strong evidence that circulating hormones and enzymes called as biomarkers, can detect heart failure. Initially, it was determined that while cardiac output, glomerular filtration ratio, urine output, venous oxygen pressure and serum sodium levels decreases, urea/creatine ratio and blood lactate levels increase (Baisan et al., 2016). It was reported that plasma norepinephrine levels also increase in all conditions that cause heart failure. Additionally, plasma levels of aldosterone and angiotensin II are increased besides the acid-base imbalance (do Carmo et al., 2024).

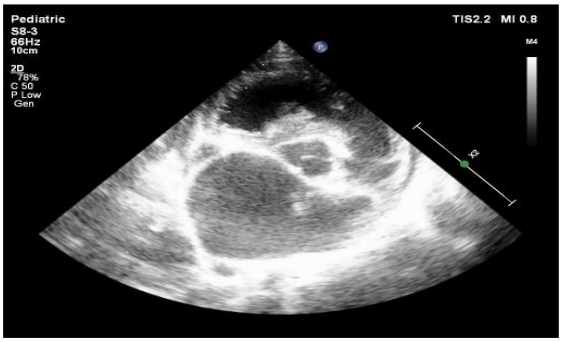

Figure 1. Echocardiographic mitral regurgitation in a Cavalier King Charles Spaniel dog with mitral valve insufficiency (right ventricle; Permissions of figures have been obtained from Bilgiçer and his veterinarians)

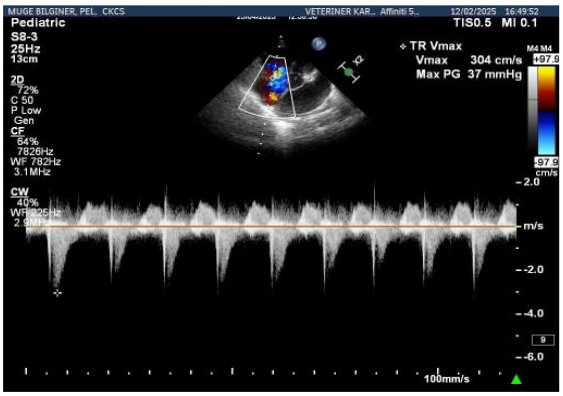

Figure 2. Echocardiographic mitral regurgitation in a Cavalier King Charles Spaniel dog with mitral valve insufficiency (mosaic image of the region of aortic narrowing on colour Doppler; Permissions of figures have been obtained from Bilgiçer and his veterinarians)

In recent years, neurohormonal biomarkers especially N-terminal-prohormone B-type natriuretic peptide (NT-proBNP) and cardiac Troponin I (cTnI) have gained an important role in small animal cardiology (Ljungvall et al., 2010; Oyama 2013). Brain Natriuretic Peptide (BNP) is secreted in the cavities and its production increases due to increasing pressure in heart failure. ProBNP is also a marker which reliefs in early diagnosis before symptoms appear in asymptomatic heart diseases. It is also important for the classification of respiratory and heart failure symptoms. It provides information about the prognosis of heart failure, and the evaluation of therapeutic responses (do Carmo et al., 2024). It has been reported that if the proBNP level is below 49 pmol/L in dogs, no heart failure is accepted with 80% accuracy (Boswood 2009; Oyama et al., 2008). According to genetic structure, it was observed that the genetic structure of NT-proBNP is different and can only be detected with special kits prepared for dogs (Oyama et al., 2008). It's also stated that the genetic structure of NT-proANP and NT-proBNP in cats is different from humans and can be detected with kits prepared for cats (Connolly et al., 2008). However, there is a room in examining biomarkers for heart diseases in dogs (Kim et al., 2018; Lee et al., 2018).

Proteomics Analysis: Protein analysis for the identification of a disease is incomparably more difficult than DNA analysis. While DNA consists of only four building blocks, natural proteins are made up of 20 different amino acids and the three-dimensional structure of the chain greatly influences the function of the protein. An organism has one genome but many proteomes. Protein is composed of the words Protein and Genome, which is the name given to the proteins expressed by the genome of an organism or tissue. Proteome analysis is an important technology that enable the determination of their structural properties and the disclosure of protein functions. Proteomics reveals the structures, localization, quantities, post-translational modifications and interactions of proteins with other molecules in a specific process. It's also defined as the technology of quantitative analysis of proteins in cells, tissues or body fluids under several conditions (Francois et al., 2025). There are five types of proteomics according to the purpose of the application; expression proteomics (which determines the proteins expressed from the cell or tissue), structural proteomics (determining the protein in three dimensions); functional proteomics (which examines the functions of proteins), chemoproteomics (which examines which small molecules interact with cells), and cell-map proteomics (determining protein-protein interaction and subcellular localization of proteins).

Platelet proteomics studies allow for the characterization and elaboration of basic biological behaviors in the organism that affect platelet hemostasis. Additionally, it authorises the determining the roles of platelets in disease and health conditions (Burkhart et al., 2014). In a study, significant changes in serum proteins were observed in dogs with Dilated Cardiomyopathy (DCM), and it was suggested that these proteins play an important role in DCM (Kocatürk et al., 2016). Regarding serum proteomics in dogs with heart failure, Locatelli et al. (2019), compared data from dogs with mitral valve disease (n=8) with a healthy control group (n=4); they found 8 significant proteins. In that study, compared to the control group, an increase in 1 protein and a decrease in 3 proteins were identified in class B2 patients; an increase in 8 proteins and a decrease in 8 proteins in class C patients; and an increase in 2 proteins and a decrease in 10 proteins in class D patients. Despite limited information on platelet proteomics studies in humans, any studies have been reported to examine heart failure and platelet proteomics together in dogs. In this context, it should be aimed to increase the ability of platelet proteomes to distinguish between healthy and diseased conditions, to address the pathophysiology of heart failure from different aspects, and to specificize the coagulation functions of platelet proteomes.

Despite the studies conducted with traditional methods in human and veterinary medicine, there is a need for molecular level studies to reveal the activation of the

coagulation system in heart diseases. It is thought that the activation of platelets, which play a primary role in coagulation, shows many morphological and functional changes. These changes are not fully revealed by the evaluation methods that may be effective in the emergence of this need. According to the technological developments, protein identification on serum and cells enables the identification of disease-health problems and obtaining new details (Burkhart et al., 2014).

Treatment of Cardiovascular Diseases

Improving The Cardiac Workload: Cardiovascular diseases primarily require the use of medications that reduce cardiac workload, including diuretics such as furosamide or thiazide, angiotensin-converting enzyme inhibitors such as enalapril or benezapril, and some important mixed vasodilators such as pimobendan.

1. Diuretic therapy: Furosemide is an important pharmacologic agent commonly used to reduce cardiogenic pulmonary edema observed in congestive heart failure. It works by inhibiting the absorption of electrolytes, especially Na and Cl, in the renal excretory. According to the ACVIM, furosemide is recommended at doses of 1 - 4 mg/kg as initial applications depending on the severity of clinical findings in dogs with congestive heart failure (Atkins et al. 2009; Keene et al., 2019).

2. Positive Inotrope Therapy: Positive inotropes should be used to maintain contractility in the heart. For this purpose, it is recommended to use pimobendan (0.25-0.5 mg/kg/day, orally), which is both a vasodilator and an inotrope and therefore called inodilator. Pimobendan is an orally active drug that combines calcium sensitizing properties on myofilaments with c-AMP and phosphodiesterase III inhibition properties. Pimobendan is chemically a pyridazone-benzimidazole derivative. It has positive inotropic effect, and pre- and afterload reduction ability to improve energy utilization in the heart (Chetboul et al., 2007; Oullet et al., 2009). Pimobendan is used orally in dogs at a standard dose of 0.2-0.3 mg/kg at 12-hour intervals (Oullet et al., 2009, Atkinson et al., 2009), while Fuentes et al. (2002), recommend a dose of 0.3-0.6 mg/kg once daily.

Another drug used for positive inotropic therapy is Benazepril. In a study, treatment with Benazepril and Pimobenden on congestive heart diseases of dogs, it was reported that an increase in partial contraction strength and left ventricular systolic internal diameter at the end of 15days. It was also determined that no change was observed in the ratio of left atrium to aortic root. However, it was observed that the long-term treatment of Pimobendan increased the systolic function but worsened mitral valve disease and caused specific lesions in mitral valves (Chetboul et al., 2007). The recommended dose of benazepril is 0.12 to 0.25 mg per pound orally once or twice daily in dogs.

3. Angiotensin Converting Enzyme Inhibitors: Angiotensin-converting enzyme inhibitors (ACE inhibitors) are the most commonly used drugs in human and canine cardiology for left-sided congestive heart failure and MVI. There have been several studies reported the usage of ACE to improve quality of life, exercise opportunities and life expectancy in patients with heart failure (Amberger et al., 2004; Chetboul et al., 2007). Enalapril is an important ACE inhibitor approved by the Food and Drug Administration (FDA) as clinically safe and effective in dogs (The IMPROVE Study Investigators 1995; Nakayama et al., 2007). The drug acts by eliminating the enzymes that convert angiotensin I to angiotensin II. Angiotensin II has a peripheral vasoconstrictor effect which increases the thirst and aldosterone excretion. It adversely affects vital circulation by causing an increase in blood pressure and peripheral vascular resistance in acute heart failure (Bilal, 2011). In a study in Cavalier King Charles Spaniel dogs with severe mitral heart failure, it was reported that plasma aldosterone level decreased significantly after 3 weeks of ACE administration, and had improving effects on aldosterone (COVE Study Group, 1995). The recommended dose for dogs is 0.25 - 0.5 mg/kg orally at intervals of 12 hours or 24 hours (Kvart et al., 2002).

Correcting Arrhythmia (if occur): Researchers determined that in patients with supraventricular tachycardia (atrial fibrillation, etc.), digoxin (0.005-0.008 mg/kg, PO) can be used alone or in combination with a calcium channel blocker such as diltiazem (1 mg/kg, 3x1, PO) (Borgarelli and Haggstrom, 2010).

Other Important Considerations in Treatment: One of the important considerations in the treatment phase is arterial thromboembolism. It is reported that the incidence of such these disorders in dogs with the course of heart disease is not common. Winter et al. (2012) mentioned that there was no heart disease occurred in any of the 26 dogs with thromboembolism. On the contrary, Lake-Bakaar et al. (2012), determined the aortic thrombosis that related to the heart in 6 of 31 dogs. These contradictory studies reported that the period of hemostasis course during thromboembolism should be determined, and anti-platelet drugs (clopidogrel, aspirin, etc.) should be used as in humans (Smith et al., 2015). The changes in the coagulation chain in these diseases was accepted important in the development of diagnosis, treatment and prophylaxis strategies in animals (Lake-Bakaar et al., 2012; Winter et al., 2012).

DISCUSSION AND CONCLUSION

In veterinary cardiology, genetic predisposition is important for early diagnosis of cardiac diseases and treatment approaches. In this review, the effects of genetic factors on cardiovascular disorders, especially in important dog breeds such as the Cavalier King Charles Spaniel, were discussed, and the role of genetic predisposition in common diseases such as mitral valve insufficiency was emphasized.

Researchers reported that mitral valve insufficiency most common acquired in small breed dogs (Atkins et al., 2009). It has been indicated that it is particularly observed with findings of mitral valve degeneration and valve insufficiency. In additionally, it is known that polygenic inheritance is effective in the development of MVI in the Cavalier King Charles Spaniel breed. There is a relationship between the loci located on the related chromosomes (13th and 14th), and the possibility of this disease occurring at an early age. Studies have shown that mitral valve regurgitation can be seen at an earlier age, and is more severe in males than females. It also emphasizes the critical role of genetic factors of the disease, and the fact that the disease becomes more prominent with age.

Although radiographic, electrocardiographic, and echocardiographic criteria are currently available for the diagnosis and grading of MVI, they are not always practical due to limited access to techniques such as echocardiography, the cost of examination, and the need

for specialist review. Therefore, researchers have begun to focus on electrocardiographic methods (Kim et al., 2020; Vezzosi et al., 2021; Seddigh Nia et al., 2022). Seddigh Nia et al. (2022), has been observed that rhythm-conduction problems and cardiac enlargements related to the mitral valve insufficiency can be diagnosed electrocardiographically quickly and easily, and thereby the disease can be followed. Vezzosi et al. (2021), used two radiographic measures for the valvular enlargement detection, and they reported that the methods can be criteria for stage of disease.

The use of advanced diagnostic methods in veterinary cardiology that supported by genetic testing and advanced imaging techniques such as echocardiography increases the possibility of early diagnosis. In addition, the dissemination of genetic analyses in veterinary practice may contribute to reducing the prevalence of the disease, and also to controlling genetic predisposition through selection programs. In conclusion, addressing the genetic aspects of cardiovascular diseases can make a big difference in diagnostic and therapeutic approaches. It is thought that future genetic and proteomic studies will expand the knowledge of veterinary medicine in this field, and contribute to the development of preventive strategies, especially for predisposed breeds.

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Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Concept: E.B., N.S., Design: E.B., N.S., Data Collection or Processing: E.B., N.S., Literature Search: E.B., N.S., Writing: E.B., N.S.

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