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# Clinical and cardiologic assessment of Anatolian shepherd dogs with asymptomatic degenerative mitral valve disease

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ABSTRACT

Degenerative mitral valve disease (DMVD) is the leading cause of cardiac disease and heart failure in the dog. Advanced age, breed and male gender are well-known risk factors for DMVD. The incidence of the disease in German Shepherds seems to be noteworthy. Early diagnosis of DMVD is related to the identification of a left apical systolic murmur, characteristic of MR in a dog. Dogs with DMVD had a low frequency of arrhythmias compared to other cardiac conditions. The goal of the study was (i) to evaluate the age and gender incidences of the asymptomatic Anatolian Shepherd Dogs (ASHs) with DMVD and, (ii) to investigate the importance of its clinical, radiological, electrocardiographic (ECG) findings and the correlations of those with some echo cardio logical measurements. 35 healthy ASHs (control group) and 38 ASHs with DMVD (experimental group) were used as the materials. The severity of cardiac disease was classified according to the American College of Veterinary Internal Medicine (ACVIM) consensus statement. Thirty two dogs (84.2%) were males and 6 dogs (15.8%) were females in the experimental group. The median age, the intensity of heart murmur and the severity of mitral regurgitation (MR) of the B2 dogs were bigger ($p < 0.05$) than that of the B1 dogs. There was a positive correlation ($P<0.05$) between age and mitral valve lesions (MVLs). The clinical examination assessed by cardiac auscultation (murmur) was not correlated to MVLs, VHS, ECG findings and ARJ/LAA ($P>0.05$). The intensity of murmur was correlated to left ventricle to aorta ratio (LA/Ao) and it was not correlated ($P>0.05$) to MVLs, vertebral heart scale (VHS), ECG findings and regurgitant jet area to LA area ratio (ARJ/LAA). The correlations between ECG findings and VHS, along with, LA/Ao and ARJ/LAA were positive ($P <0.05$). In conclusion, aging and male gender may have a significant impact on DMVD progression in ASHs. Assessment of higher murmur in group B2 might be related to the progressive severity of the illnesses. The prevalence of arrhythmia was low in asymptomatic ASHs with DMVD. P-mitrale was noteworthy.



## 1. Introduction

Anatolian Shepherd dog, which is a popular breed in Turkey, is a large, rugged and powerful livestock guardian. DMVD is the leading cause of cardiac disease in dogs throughout the world (Bonagura and Schober, 2009; Borgarelli et al., 2012; Terzo et al., 2009). Its prevalence has been found to be associated with breed, age and body size (Bernay et al., 2010; Borgarelli et al., 2004; Petric, 2015). Older small-breed dogs are predisposed (Petric, 2015). However, less is known about the disease prevalence in large breeds. The incidence of the disease in German Shepherds seems to be noteworthy (de Madron, 1992; 1998). Advanced age and male gender are well known risk factors for DMVD (Chetboul and Tissier, 2012; Connell et al., 2012; Garncarz et al., 2013; Terzo et al., 2009). Jones and Zook (1965) reported that DMVD is an age dependent disease. Males predominated in most of the studies (Pedersen and Häggström, 2000; Serfass et al., 2006; Thrusfield et al., 1985; Petric, 2015).

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The disease progresses through various stages (A to D) in dogs. Stage B is the non-symptomatic period of DMVD which is characterized by stage B1 and stage B2 (Turgut, 2017). There is no evidence of cardiac enlargement in stage B1 dogs, however stage B2 dogs have cardiac enlargement to compensate for the volume load (Bonagura and Schober, 2009; Häggström et al., 2009; McGinley et al., 2007). Nevertheless, even at the asymptomatic compensated stage (stage B), DMVD may still cause problems by complicating elective surgical interventions, such as dental care, and by causing anxiety for the owner (Häggström et al., 2009).

The clinical, radiological, ECG findings along with the changes evident by integrated echocardiographic studies should be considered in the diagnosis and assessing the severity of DMVD, even in the asymptomatic compensated stage of the disease. Cardiac murmur, cardiomegaly, supraventricular and ventricular arrhythmias and, MVLs and MR are common findings in the disease (Borgarelli and Buchanan, 2012; Borgarelli et al., 2004; Buchanan and Bücheler, 1995; Connell et al., 2012; Ljungvall et al., 2014).

Studies focused on a particular breed can give some additional information about the diseases. There is no information about DMVD and its clinical importance in the Anatolian Shepherd dogs (ASHs). This study was aimed (i) to evaluate age and gender incidences of the disease and, (ii) to assess the importance of the clinical, radiological, ECG findings and the correlations of those with some echo cardio logical measurements in ASHs with a symptomatic DMVD.

## 2. Materials and methods

### 2.1. Animals

The medical records of ASHs which were brought to the Small Animal Hospital of the Faculty of Veterinary Medicine of Selçuk University between June 2015 and December 2017 were reviewed. A total of 38 ASHs affected by DMVD was used as the experimental group. The control group was consisted of 35 healthy ASHs. All the ASHs had been presented for a cardiology consultation both for the identification of a heart murmur and for the evaluation of the cardiovascular system or for the regular checkup purpose.

### 2.2. Study design

The severity of cardiac disease was classified according to the ACVIM consensus statement (Matos and Glaus, 2010). VHS and echocardiographic LA/Ao ratio were the criteria to differentiate between class B1 and B2. Eighteen dogs from the experimental group which had both VHS scores >10.5 and LA/Ao ratios >1.7 were classified as stage B2 (enlarged atrium and ventricle), whereas 20 dogs from the experimental group which had both VHS scores ≤10.5 and LA/Ao ratios ≤1.7 were classified as stage B1 (normal cardiac size). Inclusion criteria in the experimental group were the recognition of mitral valve leaflet thickening and/or mitral valve prolapse (MVP) and the determination of mitral regurgitation (MR) in echo graphic examination. The control dogs were normal according to the all cardiologic examinations findings. Exclusion criteria in the control group were the detection of concomitant non-cardiac diseases or cardiac diseases other than DMVD. A physical examination, ECG study, chest radiography and blood pressure (BP) measurements were performed in each ASHs of both the experimental and the control groups.

### 2.3. Clinical and cardiologic examination

The intensity of cardiac murmurs was evaluated according to Levine's classification (Ware, 2011). The systolic and diastolic BPs of each dog was measured with an oscillometric technique (Ware, 2011). All the radiographs were examined for the cardiac silhouette, pulmonary parenchyma, and vessels. The VHS of each dogs were measured and the grade of cardiac enlargement was classified according to the VHS method (Buchanan and Bücheler, 1995). The ECGs were performed using a standard 6 lead ECG (Vet ECG Electrocardiograph VE-300 Vega Group), with the dog in right lateral recumbence, and the ECG recordings were analyzed (Martin, 2007). Electrocardiographic variables based on the followings: sinus arrhythmia, as a RR interval >180% longer than the previous RR interval; P-mitrale as a P duration> 0.04 sn (Turgut, 2017).

Each dog had standard 2-D, M-mode, and color flow Doppler echo graphic examinations. Transducer arrays of 4-7 MHz were used (SUIU, CZXL-43C). The examinations were performed in conscious and unsedated dogs. Right parasternal and left apical echocardiographic examinations were performed in accordance with techniques described by Turgut (2017). The presence of MVL and MVP was evaluated by 2-D examination. Mitral valve lesions were graded as (1) fibrotic, (2) fibrotic+nodular, (3) fibrotic+nodular+chordate tendinea involvement and (4) MVP associated with mitral valve leaflet thickening. The LA/Ao was obtained from the right parasternal short-axis view in 2-D mode (Rishniw and Erb, 2000). The mitral valve insufficiency jet (%) was evaluated, and its severity was subjectively assessed using the left apical four-chamber view. The MR was classified as mild, moderate or severe if the maximal ratio of the ARJ/LAA; <%20, %20-40, >%50, respectively (Turgut, 2017).

### 2.4. Statistical methods

Apart from the age, all values are reported as the mean±SE. Data (control, B1 and B2 groups) was evaluated with ANOVA and Tukey. Date for the age was evaluated with Kruskal-Wallis and Mann-Whitney U test. Independent sample t-test was used to compare the auscultation findings, the

echocardiographic grading of mitral valve lesions and the qualitative echocardiographic grading of mitral regurgitation (ARJ/LAA) from the two groups (Group B1 and Group B2). To examine univariate associations between the parameters, Pearson correlation test was used (SPSS 19.0). Statistical significance level was set P<0.05.

## 3. Results

### 3.1. Clinical and cardiologic examination findings

Thirty-two dogs (84.2%) were males and 6 dogs (15.8%) were females in the experimental group. 23 dogs (65,7%) were males and 12 dogs (34,3%) were females in the control group (Fig. 1).

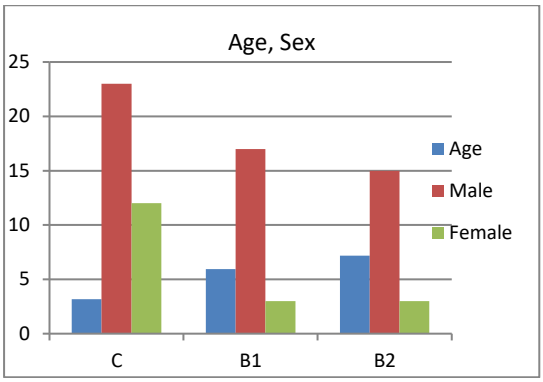


**Fig. 1:** Proportion of age and gender (male, female) of the control dogs, the B1 dogs and the B2 dogs

There was no statistically significant difference among the B1 dogs, the B2 dogs and the control dogs concerning with the body weight or heart rate (HR) (Table 1).

**Table 1:** Clinical, cardiologic and echocardiographic examination findings in the control and the experimental (B1, B2) groups of dogs

| Parameters | Control group (n= 35) | Experimental group | | P |
|---|---|---|---|---|
| | | B1 (n=20) | B2 (n=18) | |
| Age (years) (median and interquartile) (range) | 3.94 and 2.35 (1-7)[c] | 5.67 and 4.57 (3-9)[b] | 7.42 and 6.43 (4-8,5)[a] | P<0.05 |
| Sex | 23 male; 12 female | 17 male; 3 female | 15 male; 3 female | |
| Weight (kg) (mean and range) | 44.6±1.38 (32-63) | 40.2±2.19 (27.5-54) | 43.6±2.35 (28.5-54) | |
| Sinus rhythm | 35 (100%) | 19 (95%) | 10 (56%) | |
| Sinus arrhythmia | — | 1 (5%) | 2 (11%) | |
| P-mitrale | — | — | 6 (33%) | |
| BP findings | | | | |
| Systolic (mean and range) | 10.5±2.95 (9,5-14,0) | 10.4±1.20 (8.9-13.4) | 11.2±3.33 (8.7-12.6) | |
| Diastolic (mean and range) | 8.5±0.95 (6.5-9.0) | 7.4±1,20 (6.9-8.4) | 7.2±2.33 (6.9-9.6) | |
| ECG findings | 1±0[b] | 1.05±0.05[b] | 1.78±0.22[a] | P<0.05 |
| HR (beats/min) (mean and range) | 105±3,95 (65-140) | 105±4.20 (70-140) | 113±3.33 (80-140) | |
| No murmur | ND | 4 (20%) | 1 (6%) | |
| Grade I-II/VI murmur | ND | 13 (65%) | 10 (55%) | |
| Grade III-IV/VI murmur | ND | 3 (15%) | 7(39%) | |
| Auscultation findings | ND | 2.40±0.22 | 3.22±0.22 | P<0.05 |
| VHS | 9.74±0,06 (9.10-10.50)[c] | 10.30±0.09 (9.00-10.50)[b] | 10.90±0.05 (10.60-11.50)[a] | P<0.05 |
| MVLs | ND | 2.30±0.30 | 2.67±0.24 | |
| LA/Ao (mean and range) | 1.20±0.03 (0,69-1.58)[c] | 1.44±0.04 (1.10-1.70)[b] | 1.80±0.03 (1.73-2.10)[a] | P<0.05 |
| ARJ/LAA | ND | 1±0 | 1.72±0.14 | P<0.001 |

ARJ/LAA, regurgitant jet area to LA area ratio; MVLs, mitral valve lesions; HR, heart rate; BP, blood pressure (a, b, and c: Different letters show significant differences on the same row)

The median age in the control dogs (median and interquartile: 3.94 and 2.35; range 1-7 years) was significantly lower (p<0.05) than the B1 dogs (median and interquartile: 5.67 and 4.57; range 3-9 years) and the B2 dogs (median and interquartile: 7.42 and 6.43; range 4–8.5). The median age of the B2 dogs was bigger (p <0.05) than that of the median age of the B1 dogs (Table 1 and Fig. 1). On the physical examination, sixteen (80%) of the B1 dogs had left-apical holosystolic murmurs (13 with grade I-II/VI; 3 with grade III-IV/VI) and 4 (20%) had no an auscultable murmur. Seventeen (94.4 %) of the B2 dogs had left-apical holosystolic murmurs (10 with grade I-II/VI; 7 with grade III-IV/VI) and 1 (5.6%) had no an auscultable murmur (Table 1). The B2 dogs presented more often with a detectable heart murmur and more frequently with a high intensity heart murmur (grade III-IV/VI), when it was compared with the B1 dogs (p < 0.05) (Table 1 and Fig. 2).

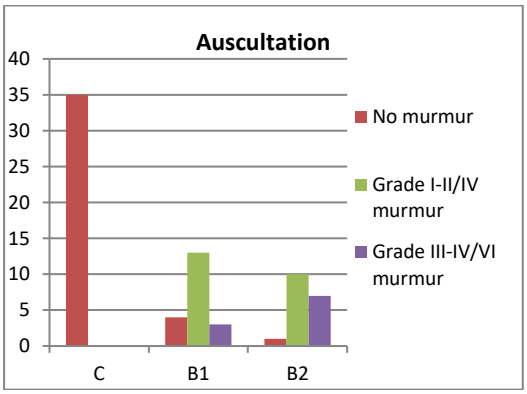


**Fig. 2:** Proportion of cardiac auscultation findings (no murmur, grade I-II, grade III-IV) of the control dogs, the B1 dogs and the B2 dogs

The control dogs were in sinus rhythm. 19 of the B1 dogs (95%) had a normal sinus rhythm on a screening ECG while 1 of them (5%) had a sinus arrhythmia. 10 of the B2 dogs (56%) had a normal sinus rhythm while the other 2 of the dogs (11%)

had sinus arrhythmia, and remaining 6 dogs (33%) had P-mitrale (Table 1 and Fig. 3).

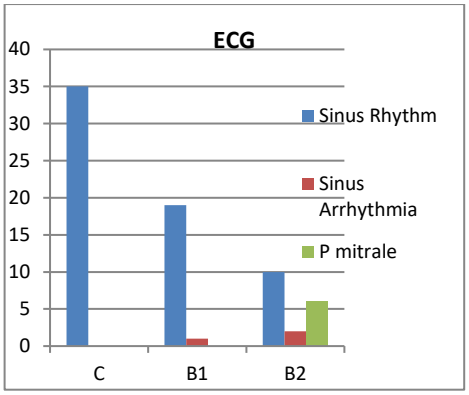


**Fig. 3:** Proportion of ECG findings (sinus rhythm, sinus arrhytmia and P mitrale) of the control dogs, theB1 dogs and theB2 dogs

Important differences (p< 0.05) was found between the B2 dogs and the B1 dogs concerning with the frequency of ECG findings (sinus rhythm, sinus arrhythmia and P-mitrale; Table 1). The pulmonary parenchyma and vessels were all normal in thoracic radiographies in the both groups of dogs (B1, B2). However, VHS was significantly bigger (p < 0.05) in B2 group of dogs compared with B1 dogs and healthy control dogs (mean 10.9 for B2 group, 10.3 for B1 group and 9.74 for control dogs; Table 1).

Systolic and diastolic BPs determined by oscillometric method of all the ASD used in this study, were within normal reference values (systolic BP <180 mm Hg and diastolic BP >60 mm Hg). There was no statistically significant difference among the B1 dogs, the B2 dogs and the control dogs concerning with BP (Table 1).

### 3.2. Echocardiographic findings

According to the ranging of MVLs, there was no difference (p >0.05) between the B2 dogs and the B1 dogs (Table 1). The median LA/Ao was significantly higher (p < 0.05) in B2 dogs compared with B1 dogs and Control dogs (1.80, 1.44 and 1.20 respectively). The difference between B2 Group and B1 Group (Table 1) was also significant (p < 0.05). On the color flow Doppler examination, the B1 dogs consisting of 20 dogs (100 %) had mild MR (< 20%), whereas in the B2 dogs consisting of18 dogs; 6 had mild, 11 had moderate and 1 had severe MR. Therefore, the severity of MR was higher (p <0.001) in the B2 dogs than the B1 dogs (Table 1).

### 3.3. Bivariate analyses

There was a positive correlation (P<0.05) between the age and MVLs (Table 2).

The clinical examination assessed by cardiac auscultation (murmur; Table 3) was not correlated to MVLs, VHS, ECG findings and ARJ/LAA (P>0.05).

**Table 2:** Pearson correlations test with age in the B2 dogs and theB1 dogs

| Variable | Pearson test | *P* value |
|---|---|---|
| Murmur | 0.399 | 0.013 |
| VHS | 0.087 | 0.604 |
| MVL | 0.372 | 0.021* |
| ECG findings | 0.315 | 0.054 |
| LA/Ao | 0.125 | 0.454 |
| ARJ/LAA | 0.289 | 0.078 |

VHS, vertebral heart scale; LA/Ao, left atrial to aortic root ratio; ARJ/LAA, regurgitant jet area to LA area ratio; MVL, mitral valve lesions (* shows significant correlations)

**Table 3:** Pearson correlations test with murmur in the B2 dogs and the B1 dogs

| Variable | Pearson test | *P* value |
|---|---|---|
| MVL | 0.211 | 0.204 |
| VHS | 0.315 | 0.054 |
| ECG findings | 0.108 | 0.517 |
| LA/Ao | 0.302 | 0.035* |
| ARJ/LAA | 0.084 | 0.615 |

VHS, vertebral heart scale; LA/Ao, left atrial to aortic root ratio; ARJ/LAA, regurgitant jet area to LA area ratio; MVL, mitral valve lesions (* shows significant correlations)

The cardiac auscultation (murmur) was correlated to LA/Ao. The correlations between ECG findings and VHS, along with, LA/Ao and ARJ/LAA (Table 4) were positive (P <0.05).

**Table 4:** Pearson correlations test with ECG findings in the B2 dogs and the B1 dogs

| Variable | Pearson test | *P* value |
|---|---|---|
| MVL | 0.176 | 0.292 |
| VHS | 0.342 | 0.035* |
| LA/Ao | 0.325 | 0.047* |
| ARJ/LAA | 0.461 | 0.004** |

VHS, vertebral heart scale; LA/Ao, left atrial to aortic root ratio; ARJ/LAA, regurgitant jet area to LA area ratio; MVL, mitral valve lesions (* and ** show significant correlations)

## 4. Discussion

In dogs, the prevalence and severity of the DMVD have been reported to be closely age dependent (Bernay et al., 2010; Borgarelli and Buchanan, 2012; Buchanan, 1977). Two comprehensive studies, carried out by Whitney (1974) and Kogure (1980), have demonstrated that the structural changes in canine mitral valves were an age dependent process. In the present study, it was determined that the median age of the B2 dogs was bigger (P<0.05) than that of the B1 dogs (Table 1 and Fig. 1). This age distribution in ASHs suggested that the structural changes in mitral valves might be an age dependent process because MVLs were more severe in the B2 group (Table 1). There was a positive correlation between MVLs and age (Table 2). However, the sequence of events and the time course should be investigated with longitudinal studies in ASHs with DMVD.

Risk factors such as male gender are also important in the development of DMVD in dogs (Hyun, 2005). The diseases in males develop at a younger age and progress rapidly from mild to severe (Pedersen and Häggström, 2000; Pedersen et al., 1999a; Serfass et al., 2006; Thrusfield et al., 1985).

In this study, the gender distribution in the experimental group shows an imbalance favor to the male (Table 1 and Fig. 1). For these reasons, DMVD in ASH may be interpreted as a gender dependent disease.

Early diagnosis of DMVD is related to the identification of a left apical systolic murmur, characteristic of MR in a dog (Gordon et al., 2017). In the early stage of the DMVD, the patients may have no detectable clinical signs. Nevertheless, progression of the MVLs causes more insufficiency in the coaptation of the leaflets, more regurgitation of blood back into the LA, and more dilation of the LV and mitral annulus. As a result of these, mitral systolic murmurs occur (Connell et al., 2012; Häggström et al., 2009). On physical examination in this study, 16 (80 %) of the B1 dogs had left-apical holosystolic murmurs (13 with grade I-II/VI; 3 with grade III-IV/VI) and 4 (20%) had no an auscultable murmur. 17 of the B2 dogs (94,4%) had left-apical holosystolic murmurs (10 with grade I-II/VI; 7 with grade III-IV/VI) and 1 (5,6%) had no an auscultable murmur (Table 1 and Fig. 2). So, 5 ASHs (4 in Group B1, 1 in Group B2) with echocardiographic evidence of DMVD did not have murmurs. Although the finding of systolic murmur is a good indicator of the disease, it has been stated that the dogs with mild disease might not have a murmur, despite the echocardiographic evidence of MVLs and MR (Garncarz et al., 2013; Pedersen et al., 1999a). In a study on Norfolk terriers with DMVD (32), 44% of the dogs did not have an auscultable murmur, which is higher than previous reports in which 23% of CKCS with a greater than 10% MR jet area did not have a murmur on physical examination (Pedersen et al., 1999b; Trafny et al., 2012). Many factors, such as background noise or heart rate, stress level and chest conformation may be the reason of this. Assessment of higher murmur in group B2 might be related to the progressive severity of the illnesses. It has been reported that the severity of DMVD in dogs was well associated with lower serum serotonin concentrations and higher LA/Ao which causes low serotonin concentrations (Ljungvall et al., 2014; Petric, 2015). The positive correlation between the cardiac auscultation (murmur) and LA/Ao (Table 3) can explain this result.

Lopez-Alvarez et al. (2014) stated that dogs with DMVD had a low frequency of arrhythmias compared to other cardiac conditions, with 19% of dogs showing some form of ectopic activity but only 1.6% of dogs developing atrial fibrillation in the course of their disease. This confirms the general suspicion that DMVD is a disease with a low prevalence of arrhythmia occurrence. In this study, 19 of B1 dogs (95%) had a normal sinus rhythm on a screening ECG, while 1 of the dogs (5%) had a sinus arrhythmia. However, 10 of the B2 dogs (56%) had a normal sinus rhythm on a screening ECG while the other 2 of the dogs (11%) had sinus arrhythmia, and remaining 6 dogs (33%) had P-mitrale. Significant difference ($p<0.05$) was found between the B2 dogs and the B1dogs concerning the frequency of ECG findings (sinus rhythm, sinus arrhythmia and P-mitrale; Table 1 and Fig. 3). Sinus arrhythmia is common in healthy dogs without any clinical significance. Sinus arrhythmia results from cardiac vagal function reflecting respiratory-circulatory interactions. It is also possible to observe sinus arrhythmia in dogs with MR (Turgut, 2017). It has been reported that in early stages of DMVD, sinus arrhythmia was often present, but during progression to CHF, tachycardia usually developed and the sinus arrhythmia ceased because of compensatory increase in sympathetic tone (Rasmussen et al., 2011; 2012). Determination of sinus arrhythmia in 3 dogs of the experimental group (1 in the B1, 2 in the B2 groups) may also indicate the early stages of DMVD. Six dogs (33%) in the B2 dogs had P-mitrale (prolonged P wave >0.04 sec) in this study (Fig. 3). LA is affected directly by increased ventricular filling pressure and resistance across the mitral valve, or volume overload due to MR (Chirife et al., 1975; Ware, 2011). The dogs having P-mitrale in this study had also LA enlargement (LA/Ao>1.7), and ECG findings were positively correlated ($p<0.05$) to VHS, LA/Ao and ARJ/LAA (Table 4). These results can support the development of P-mitrale in the B2 dogs.

## 5. Conclusion

In conclusion, the results of the present study showed that aging and male gender might have a significant impact on DMVD progression in ASHs. Assessment of higher murmur in group B2 might be related to the progressive severity of the illnesses. The prevalence of arrhythmia was low in asymptomatic ASHs with DMVD. P-mitrale was noteworthy.

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## Compliance with ethical standards

## Conflict of interest

The authors declare that they have no conflict of interest.

## Ethical approval

This study was approved by Ethic committee of Faculty of Veterinary Medicine, University of Selcuk (Permit number: 2012/053).

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

## References

Bernay F, Bland JM, Häggström J, Baduel L, Combes B, Lopez A, and Kaltsatos V (2010). Efficacy of spironolactone on survival

in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. Journal of Veterinary Internal Medicine, 24(2): 331-341. https://doi.org/10.1111/j.1939-1676.2009.0467.x **PMid:20102506**

Bonagura JD and Schober KE (2009). Can ventricular function be assessed by echocardiography in chronic canine mitral valve disease?. Journal of Small Animal Practice, 50(s1): 12-24. https://doi.org/10.1111/j.1748-5827.2009.00803.x **PMid:19765216**

Borgarelli M and Buchanan JW (2012). Historical review, epidemiology and natural history of degenerative mitral valve disease. Journal of Veterinary Cardiology, 14(1): 93-101. https://doi.org/10.1016/j.jvc.2012.01.011 **PMid:22386588**

Borgarelli M, Zini E, D'Agnolo G, Tarducci A, Santilli RA, Chiavegato D, and Häggström J (2004). Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. Journal of Veterinary Cardiology, 6(2): 27-34. https://doi.org/10.1016/S1760-2734(06)70055-8

Buchanan JW (1977). Chronic valvular disease (endocardiosis) in dogs. Advances in Veterinary Sciences and Comparative Medicine, 7: 75-106.

Buchanan JW and Bücheler J (1995). Vertebral scale system to measure canine heart size in radiographs. Journal of The American Veterinary Medical Association, 206: 194-194.

Chetboul V and Tissier R (2012). Echocardiographic assessment of canine degenerative mitral valve disease. Journal of Veterinary Cardiology, 14(1): 127-148. https://doi.org/10.1016/j.jvc.2011.11.005 **PMid:22366573**

Chirife R, Feitosa GS, and Frankl WS (1975). Electrocardiographic detection of left atrial enlargement: Correlation of P wave with left atrial dimension by echocardiography. Heart, 37(12): 1281-1285. https://doi.org/10.1136/hrt.37.12.1281

Connell PS, Han RI, and Grande-Allen KJ (2012). Differentiating the aging of the mitral valve from human and canine myxomatous degeneration. Journal of Veterinary Cardiology, 14(1): 31-45. https://doi.org/10.1016/j.jvc.2011.11.003 **PMid:22364720 PMCid:PMC3307912**

de Madron E (1992). Primary acquired mitral insufficiency in adult large breed dogs. In the 10th American College Veterinary İnternal Medicine Forum (ACVIM Forum), San Diego, USA: 608-609.

de Madron E (1998). Unusual aspects of mitral valve disease in the dog. In the 16th American College Veterinary İnternal Medicine Forum (ACVIM Forum), San Diego, USA: 116-118.

Garncarz M, Parzeniecka-Jaworska M, Jank M, and Łój M (2013). A retrospective study of clinical signs and epidemiology of chronic valve disease in a group of 207 Dachshunds in Poland. Acta Veterinaria Scandinavica, 55(1): 52-58. https://doi.org/10.1186/1751-0147-55-52 **PMid:23844824 PMCid:PMC3723884**

Gordon SG, Saunders AB, and Wesselowski SR (2017). Asymptomatic canine degenerative valve disease: Current and future therapies. Veterinary Clinics: Small Animal Practice, 47(5): 955-975. https://doi.org/10.1016/j.cvsm.2017.04.003 **PMid:28669433**

Häggström J, Höglund K, and Borgarelli M (2009). An update on treatment and prognostic indicators in canine myxomatous mitral valve disease. Journal of Small Animal Practice, 50(s1): 25-33. https://doi.org/10.1111/j.1748-5827.2009.00800.x **PMid:19765217**

Hyun CB (2005). Mitral valve prolapse in cavalier King Charles spaniel: A review and case study. Journal of Veterinary Science, 6(1): 67-73. https://doi.org/10.4142/jvs.2005.6.1.67 **PMid:15785126**

Jones TC and Zook BC (1965). Aging changes in the vascular system of animals. Annals of the New York Academy of Sciences, 127(1): 671-684. https://doi.org/10.1111/j.1749-6632.1965.tb49434.x

Kogure K (1980). Pathology of chronic mitral valvular disease in the dog. Japanese Journal of Veterinary Science, 42(3): 323-335. https://doi.org/10.1292/jvms1939.42.323 **PMid:7218618**

Ljungvall I, Rishniw M, Porciello F, Ferasi L, and Ohad DG (2014). Murmur intensity in small-breed dogs with myxomatous mitral valve disease reflects disease severity. Journal of Small Animal Practice, 55(11): 545-550. https://doi.org/10.1111/jsap.12265 **PMid:25213440**

Lopez-Alvarez J, Boswood A, Moonarmart W, Hezzell MJ, Lotter N, and Elliott J (2014). Longitudinal electrocardiographic evaluation of dogs with degenerative mitral valve disease. Journal of Veterinary Internal Medicine, 28(2): 393-400. https://doi.org/10.1111/jvim.12311 **PMid:24494591 PMCid:PMC4857969**

Martin M (2007). Small animal ECGs: An introductory guide. 2nd Edition, Blackwell Publishing Ltd, Hoboken, USA.

Matos JM and Glaus TM (2010). Medical treatment of canine heart failure. European Journal of Companion Animal Practice, 20(2): 171-176.

McGinley JC, Berretta RM, Chaudhary K, Rossman E, Bratinov GD, Gaughan JP, and Margulies KB (2007). Impaired contractile reserve in severe mitral valve regurgitation with a preserved ejection fraction. European Journal of Heart Failure, 9(9): 857-864. https://doi.org/10.1016/j.ejheart.2007.05.013 **PMid:17594913**

Pedersen D, Lorentzen KA, and Kristensen BØ (1999a). Echocardiographic mitral valve prolapse in cavalier King Charles spaniels: Epidemiology and prognostic significance for regurgitation. Veterinary Record, 144(12): 315-320. https://doi.org/10.1136/vr.144.12.315 **PMid:10212505**

Pedersen HD and Häggström J (2000). Mitral valve prolapse in the dog: A model of mitral valve prolapse in man. Cardiovascular Research, 47(2): 234-243. https://doi.org/10.1016/S0008-6363(00)00113-9

Pedersen HD, Häggström J, Falk T, Mow T, Olsen LH, Iversen L, and Jensen AL (1999b). Auscultation in mild mitral regurgitation in dogs: observer variation, effects of physical maneuvers, and agreement with color doppler echocardiography and phonocardiography. Journal of Veterinary Internal Medicine, 13(1): 56-64. https://doi.org/10.1111/j.1939-1676.1999.tb02166.x **PMid:10052065**

Petric AD (2015). Myxomatous mitral valve disease in dogs-An update and perspectives. Macedonian Veterinary Review, 38(1): 13-20. https://doi.org/10.14432/j.macvetrev.2014.11.026

Rasmussen CE, Falk T, Zois NE, Moesgaard SG, Häggström J, Pedersen HD, and Olsen LH (2012). Heart rate, heart rate variability, and arrhythmias in dogs with myxomatous mitral valve disease. Journal of Veterinary Internal Medicine, 26(1): 76-84. https://doi.org/10.1111/j.1939-1676.2011.00842.x **PMid:22151356**

Rasmussen CE, Vesterholm S, Ludvigsen TP, Häggström J, Pedersen HD, Moesgaard SG, and Olsen LH (2011). Holter monitoring in clinically healthy Cavalier King Charles Spaniels, Wire-haired Dachshunds, and Cairn Terriers. Journal of Veterinary Internal Medicine, 25(3): 460-468. https://doi.org/10.1111/j.1939-1676.2011.0707.x **PMid:21418322**

Rishniw M and Erb HN (2000). Evaluation of four 2-dimensional echocardiographic methods of assessing left atrial size in dogs. Journal of Veterinary Internal Medicine, 14(4): 429-435.

https://doi.org/10.1111/j.1939-1676.2000.tb02252.x **PMid:10935894**

Serfass P, Chetboul V, Sampedrano CC, Nicolle A, Benalloul T, Laforge H, and Tissier R (2006). Retrospective study of 942 small-sized dogs: Prevalence of left apical systolic heart murmur and left-sided heart failure, critical effects of breed and sex. Journal of Veterinary Cardiology, 8(1): 11-18. https://doi.org/10.1016/j.jvc.2005.10.001 **PMid:19083332**

Terzo E, Di Marcello M, Mcallıster H, Glazier B, Lo Coco D, Locatelli C, and Brambilla PG (2009). Echocardiographic assessment of 537 dogs with mitral valve prolapse and leaflet involvement. Veterinary Radiology and Ultrasound, 50(4): 416-422. https://doi.org/10.1111/j.1740-8261.2009.01559.x

Thrusfield MV, Aitken CGG, and Darker PGG (1985). Observations on breed and sex in relation to canine heart valve incompetence. Journal of Small Animal Practice, 26(12): 709-717. https://doi.org/10.1111/j.1748-5827.1985.tb02199.x

Trafny DJ, Freeman LM, Bulmer BJ, MacGregor JM, Rush JE, Meurs KM, and Oyama MA (2012). Auscultatory, echocardiographic, biochemical, nutritional, and environmental characteristics of mitral valve disease in Norfolk terriers. Journal of Veterinary Cardiology, 14(1): 261-267. https://doi.org/10.1016/j.jvc.2011.10.002 **PMid:22364691**

Turgut K (2017). Klinik kedi ve köpek kardiyolojisi. Nobel Tıp Kitabevleri, Istanbul, Turkey.

Ware W (2011). Cardiovascular disease in small animal medicine. CRC Press, Boca Raton, USA. https://doi.org/10.1201/b15177

Whitney JG (1974). Observations on the effect of age on the severity of heart valve lesions in the dog. Journal of Small Animal Practice, 15(8): 511-522. https://doi.org/10.1111/j.1748-5827.1974.tb06529.x **PMid:4469562**