The End-systolic Wall Stress/End-systolic Volume Index Ratio for Systolic Function in Anatolian Shepherd Dogs with Stage B2 Degenerative Mitral Valve Disease [1]

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Abstract
This study was performed to evaluate the end-systolic wall stress/end-systolic volume index ratio (ESWS/ESV-I) for LV systolic function in Anatolian shepherd dogs (ASHs) with stage B2 degenerative mitral valve disease (DMVD). Thirty-eight adult ASHs (20 B1 dogs and 18 B2 dogs) and 30 weight-matched adult healthy ASHs (control group) were used as subjects. There was no overlap for the ESWS/ESV-I ratio (0.83±0.03, range: 0.61-1.09 for B2 dogs, 1.34±0.05, range: 1.11-1.89 for B1 dogs, 2.17±0.0 range: 1.91-3.02 for the control dogs) among the groups. ESWS/ESV-I ratio (≤1.09) in ASHs with stage B2 DMVD may play a developmental role in left ventricular remodelling and risk factor for development of systolic dysfunction.

Keywords: Anatolian shepherd dog, Degenerative mitral valve disease, Echocardiography, End-systolic wall stress/end-systolic volume index ratio, Systolic function indices

INTRODUCTION
The most common heart diseases causing heart failure (HF) in dogs is degenerative mitral valve disease (DMVD) [1,2]. Dogs in stage B2 may be days away from developing congestive heart failure (CHF), or may never develop CHF in their life time [2]. Systolic function is not easy to evaluate in DMVD because of decreased afterload, increased preload.

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and enhanced sympathetic tone \[3,4\]. Therefore, systolic function indices, such as fractional shortening (FS), end-systolic volume index (ESV-I) and E point septal separation (EPSS) remain high or no change during the compensated state of chronic mitral regurgitation (MR), despite reduced myocardial functioning \[3\].

Many authors have advocated the use of different parameters in dealing with wall stress to better define left ventricular function in humans. Alter et al.\[6\] suggested that elevated end-diastolic wall stress (EDVS) was a strong predictor of systolic and diastolic dysfunction. Clerfond et al.\[7\] informed that end-systolic wall stress (ESWS) was an independent predictor of LV remodelling and post-discharge HF after that end-systolic wall stress (ESWS) was an independent function in humans. Carabello et al.\[8\] suggested that elevated in dealing with wall stress to better define left ventricular systolic function and operative risk in human patients with chronic, symptomatic MR.

End systolic volume (ESV) is independent of preload and has been shown to vary linearly with afterload. Afterload has been approximated by measuring either end-systolic pressure or ESWS \[3\]. The importance of ESWS/ESV-I ratio has been approximated by measuring either end-systolic and diastolic dysfunction. ESWS/ESV-I ratio might be helpful in assessing left ventricular systolic function and operative risk in human patients with chronic, symptomatic MR.

### MATERIAL and METHODS

#### Legal Conformity and Ethics Statement

Ethical approval was received from the Faculty of Veterinary Medicine of Selçuk University (permit number 2012/053).

#### Animals

This retrospective study used 38 adult (age: median 5.87 (3-9) years; weight: 41±3.29 (28-55) kg gender: 31 males, 7 females) ASHs with DMVD (experimental group) and 30 weight-matched, adult (age: median 5.17 (2-9) years; weight: 40±6.33 (27-52) kg gender: 25 males, 5 females), healthy ASHs (control group) as subjects. All the ASHs had extra-cardiac disease based on history, physical examination, and a chemistry profile was excluded.

The presence of ticked valve leaflets and/or prolapsed and the identification of MR was inclusion criteria in the experimental group. The control dogs had no symptoms of heart disease showing normal blood pressure, chest radiography, ECG, and echocardiographic findings. Dogs with any medical treatment for mitral valve disease or that had extra-cardiac disease based on history, physical examination, and a chemistry profile was excluded.

The degree of heart disease was classified according to the ACVIM consensus statement \[9\], according to radiographic and echocardiographic heart size. In order to differentiate class B animals as B1 and B2, the vertebral heart scale (VHS) and echocardiographic left atrial/aortic root (LA/Ao) ratio were performed. From the experimental group, 18 dogs had both VHS scores >10.5 vertebrae and LA/Ao ratios >1.7 (stage B2), whereas 20 had both VHS scores ≤10.5 vertebrae and LA/Ao ratios ≤1.7 (stage B1).

#### Echocardiography

Transthoracic echocardiographic examinations (2-D, M-mode and Doppler) were performed in all dogs according to the techniques described by Turgut \[3\]. Transducer arrays of 4-7 MHz were used (SUIU, CZXL-43C).

The regurgitant jet area signal to the LA area (ARJ/LAA) and the LA/Ao ratio were classified as described by Turgut \[3\]. M-mode measurements including EPSS, LV end-diastolic diameter (Ded), end-systolic diameter (Des), IVSed and LV posterior wall thickness in end-systole (PWhes) were obtained according to the leading-edge-to-leading-edge method. The FS, end-diastolic volume (EDV), ESV and stroke volume were calculated using the Teichholz method using the software program of the echocardiogram. The EDV, ESV and cardiac output values were indexed for body surface area. This was in order to obtain the EDV-I, ESV-I and the cardiac index (CI).

### Study Design and Clinical Examination

A clinical examination, an electrocardiography (ECG) (Vet ECG Electrocardiograph VE-300, Vega Group) study, thoracic radiography for VHS determination \[3\] and arterial blood pressure (BP, systolic and diastolic) measurements using oscillometric technique (DynaPulse DP 5200A Pathway Pulse Dynamic NIBP Monitor, Pulse Metric Inc., USA) \[3\] were done in each ASH for both the experimental and control groups. The intensity of cardiac murmurs was evaluated according to Levine's classification \[3\], NT-proBNP concentrations (CardioPet, NT-proBNP, IDEXX, Westbrook, ME) were measured by enzyme immunoassay (EIA).

Each dog was examined using a standard 2-D, M-mode, and colour-flow Doppler imager.

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ESWS = (PxDs) × 1.35/PWhs; where ESWS is left ventricular wall stress (g/cm²) at end-systole, P is the systolic BP (mmHg), Ds and PWhs are the left ventricular internal dimension and posterior wall thickness (cm) at end-systole, respectively, and 1.35 is a conversion factor (mmHg to g/cm²). Thus, the determination of ESWS and ESV-I allowed for calculation of the ESWS/ESV-I ratio.

**Statistical Methods**

All data (control, B1, and B2 groups) were evaluated by a homogeneity test (Kolmogrov-Smirnov Z) to determine the data distributions. The values for FS, EPSS, NT-proBNP and LA/Ao were evaluated using Mann-Whitney U test, because of the data’s nonparametric distribution. Values for FS, EPSS, NT-proBNP and LA/Ao are reported as the mean ± SE. The values for VHS, ESV-I, CI, EDV-I, the IVSd/LVd ratio and the ESWS/ESV-I ratio were evaluated using a One-way ANOVA and Tukey post hoc test (SPSS 19.0). The values for VHS, ESV-I, CI, EDV-I, the IVSd/LVd ratio and the ESWS/ESV-I ratio are reported as the mean ± SE. The statistical significance level was set at P<0.05.

**RESULTS**

On the physical examination, 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 auscultable murmur. 17 (94.4%) of the B2 dogs had left-apical holosystolic murmurs (13 with grade I-II/VI; 3 with grade III-IV/VI) and 4 (20%) had no auscultable murmur.

The left ventricular systolic function parameters (FS, ESV-I, EPSS, NT-proBNP, VHS, LA/Ao, IVSd/LVd and ESWS/ESV-I ratio) were evaluated using a statistical approach. In our study, FS, ESV-I, CI showed a significant difference, especially in the B2 dogs (Table 1). However, there was some overlap for FS (29-45% for the control dogs, 31-48% for B1 dogs and 45-51% for B2 dogs) (Table 1), for the ESV-I (5.6-30.16 mL/m² for the control dogs, 13.69-42.59 mL/m² for the B1 dogs, 22.37-36.23 mL/m² for the B2 dogs (Table 1), for CI (2907-6399 mL/min/m² for the control dogs, 1267-5285 mL/min/m² for the B1 dogs, 2112-4304 mL/min/m² for the B2 dogs) among the groups, and these indexes did not manage to separate the groups (Table 1). This might be the result of decreased afterload, increased preload and sympathetic tone. For these reasons, we think that FS, ESV-I and CI are thought to be less sensitive indicators of systolic function in asymptomatic ASHs with DMVD, which is in agreement with previous studies [10,12]. All these results may demonstrate that there seemed to be

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group (n = 30)</th>
<th>Experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (pmol/L) (median and range)</td>
<td>759±47 (250-2050)</td>
<td>1588±212 (900-4650)</td>
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<tr>
<td>VHS vertebrae (mean and range)</td>
<td>9.7±0.06 (9.10-10.50)</td>
<td>10.3±0.09 (9.00-10.50)</td>
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<tr>
<td>LA/Ao (median and range)</td>
<td>1.20±0.03 (0.69-1.58)</td>
<td>1.44±0.04 (1.10-1.70)</td>
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<tr>
<td>FS (%) (median and range)</td>
<td>35.00 (29-45)</td>
<td>44.50 (31-48)</td>
</tr>
<tr>
<td>ESV-I (mL/m²) (mean and range)</td>
<td>17.1±1.3 (5.84-30.16)</td>
<td>27.6±2.35 (13.69-42.59)</td>
</tr>
<tr>
<td>CI (mL/min/m²) (mean and range)</td>
<td>4352±186 (2907-6399)</td>
<td>3227±226 (1267-5285)</td>
</tr>
<tr>
<td>EPSS (mm) (median and range)</td>
<td>3.70 (2.00-6.50)</td>
<td>3.40 (2.30-7.00)</td>
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<tr>
<td>EDV-I (mL/m²) (mean and range)</td>
<td>55.7±2.4 (29.9-78.1)</td>
<td>52.2±3.6 (31.4-73.7)</td>
</tr>
<tr>
<td>IVSd/LVd (mean and range)</td>
<td>0.27±0.007 (0.22-0.33)</td>
<td>0.28±0.008 (0.22-0.33)</td>
</tr>
<tr>
<td>ESWS/ESV-I ratio (mean and range)</td>
<td>2.17±0.0 (1.91-3.02)</td>
<td>1.34±0.05 (1.11-1.89)</td>
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</table>

**DISCUSSION**

Many studies have provided important information on the natural progression of stage B2 DMVD and reported factors that can be used to identify which stage B2 dogs have higher versus lower risks of developing CHF [14,15]. The results of studies on the effect of volume overload caused by DMVD on left ventricular function are controversial [5,4,8]. In our study, FS, ESV-I, CI showed a significant difference, especially in the B2 dogs (Table 1). However, there was some overlap for FS (29-45% for the control dogs, 31-48% for B1 dogs, 45-51% for B2 dogs) (Table 1), for the ESV-I (5.6-30.16 mL/m² for the control dogs, 13.69-42.59 mL/m² for the B1 dogs, 22.37-36.23 mL/m² for the B2 dogs (Table 1), for the CI (2907-6399 mL/min/m² for the control dogs, 1267-5285 mL/min/m² for the B1 dogs, 2112-4304 mL/min/m² for the B2 dogs) among the groups, and these indexes did not manage to separate the groups (Table 1). This might be the result of decreased afterload, increased preload and sympathetic tone. For these reasons, we think that FS, ESV-I and CI are thought to be less sensitive indicators of systolic function in asymptomatic ASHs with DMVD, which is in agreement with previous studies [10,12]. All these results may demonstrate that there seemed to be
preserved systolic function and a hyper-dynamic phase of the heart in the B1 and B2 dogs.

Chamber enlargement may lead to increased peak systolic wall stress (by the Law of La Place), which causes wall thickening of a sufficient magnitude to normalise the systolic stress [3]. Suzuki et al. [13], have also reported that relative wall thickness was not a factor in determining asymptomatic dogs with Class I DMVD and healthy dogs.

Increased ESWS in LV volume overload causes mainly chamber enlargement, and eccentric hypertrophy. ESWS probably gives more accurate prediction when determining afterload than using pressure alone, because it deals with filling conditions, BP, wall thickness and curvature radius [7]. Clerfond et al. [7] informed that ESWS was an independent estimator of LV remodelling and post-discharge HF after MI. When we consider ESV-I, dogs with ESV-I values >30 mL/m² indicate impaired systolic function [3]. In our study, ESV-I was high in the B2 dogs (>30 mL/m²) (Table 1). For this reason we thought ESWS/ESV-I would be useful in evaluating systolic function. Carabello et al. [8] studied patients with symptomatic, chronic, severe MR to determine which hemodynamic and angiographic factors might be prognostic of surgical outcome. They found that the ESWS/ESV-I ratio was more sensitive than EF or other hemodynamic variables in predicting surgical outcome in symptomatic patients with chronic MR. In our study, the mean ESWS/ESV-I ratio was lower (P < 0.05) in the B2 dogs (0.83 ± 0.03, range: 0.61-1.09) when compared with B1 dogs (1.34 ± 0.05, range: 1.11-1.89) and control dogs (2.17 ± 0.0 range: 1.91-3.02). The difference between the B2 dogs and the B1 dogs was also significant (P < 0.05). There was no overlap for the ESWS/ESV-I ratio among the groups, and the ESWS/ESV-I ratio did separate the groups alone (Table 1, Fig. 2). All the ESWS/ESV-I ratios were ≤1.09 for the B2 group. This may indicate that the ESWS/ESV-I ratio is more accurate in assessing left ventricular function. Thus, the B2 dogs, who had a median FS of 46.50% (range: 45-51%), had a significantly lower ESWS/ESV-I ratio (≤1.09) than both control dogs and B1 dogs, indicating left ventricular function. The level of...
NT-proBNP secreted predominantly from the ventricle is elevated in response to cardiac remodelling \[^{14,15}\]. In our study, NT-proBNP levels (the B2 dogs: 2985±218 pmol/L (1250-4300 pmol/L), the B1 dogs: 1588±212 pmol/L (900-4650 pmol/L) and the control dogs: 759±47 pmol/L (250-2050 pmol/L) were irrespectively correlated with ESWS/ESV-I ratio \[^{Table 1}\]. These results could be the reason of synthesis and secretion of NT-proBNP induced by the elevation of left ventricular ESWS in the B1 and the B2 dogs. It may suggest that the echocardiography-based approach could be improved through the determination of BNP.

Our results highlight that ESWS/ESV-I ratio (≤1.09) in ASHs with stage B2 DMVD may result in left ventricular remodelling and a risk factor in the development of systolic dysfunction; in other words, it may be to foresee the transition from asymptomatic to a symptomatic DMVD in dogs.

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**REFERENCES**


