

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

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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 with DMVD (experimental group; 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

## Evre B2 Dejeneratif Mitral Kapak Hastalığı Olan Anadolu Çoban Köpeklerinde Sistol-sonu Duvar Stresi/Sistol-sonu Hacim İndeks Oranı İle Sistolik Fonksiyonun Değerlendirilmesi

### Öz

Bu çalışma, evre B2 dejeneratif mitral kapak hastalığı (DMVD) olan Anadolu çoban köpeklerinde (ASHs) sistol-sonu duvar stresi/sistol-sonu hacim indeks oranı (ESWS/ESV-I) ile sistolik fonksiyonu değerlendirmek için yapıldı. Çalışmada, DMVD'li 38 yetişkin ASHs (deney grubu; 20 B1 köpek ve 18 B2 köpek) ve 30 yetişkin sağlıklı ASHs (kontrol grubu) kullanıldı. Gruplar arasında ESWS/ESV-I oranı için (B2 köpeklerinde: 0.83±0.03, aralık: 0.61-1.09, B1 köpeklerinde 1.34±0.05, aralık: 1.11-1.89, kontrol köpeklerinde 2.17±0.0 aralık: 1.91-3.02) bir örtüşme yoktu. Evre B2 DMVD'li ASH'lerde, ESWS/ESV-I oranı (≤1.09) sol ventrikül yeniden yapılanması ve sistolik disfonksiyon gelişiminde risk faktörü olarak rol oynayabilir.

**Anahtar sözcükler:** Anadolu çoban köpeği, Dejeneratif mitral kapak hastalığı, Ekokardiyografi, Sistol-sonu duvar stresi/Sistol-sonu hacim indeksi oranı, Sistolik fonksiyon endeksleri

## INTRODUCTION

The most common heart diseases causing heart failure (HF) in dogs is degenerative mitral valve disease (DMVD) <sup>[1,2]</sup>.

Dogs in stage B2 may be days away from developing congestive heart failure (CHF), or may never develop CHF in their life time <sup>[2]</sup>. Systolic function is not easy to evaluate in DMVD because of decreased afterload, increased preload



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and enhanced sympathetic tone<sup>[3,4]</sup>. 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<sup>[5]</sup>.

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.<sup>[6]</sup> suggested that elevated end-diastolic wall stress (EDVS) was a strong predictor of systolic and diastolic dysfunction. Clerfond et al.<sup>[7]</sup> informed that end-systolic wall stress (ESWS) was an independent predictor of LV remodelling and post-discharge HF after myocardial infarction (MI). Carabello et al.<sup>[8]</sup> suggested that the end-systolic wall stress/end-systolic volume index ratio (ESWS/ESV-I) might be helpful in assessing 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<sup>[3]</sup>. The importance of ESWS/ESV-I ratio and its applicability are unknown in dogs with DMVD. Our hypothesis is that ESWS/ESV-I ratio is related with ventricular function and thus provides a new criterion in determining LV remodelling and systolic function. It seemed logical to us to determine if the ESWS/ESV-I ratio would be higher (indicating relatively greater left ventricular shortening) or would be lower (indicating less shortening and thus relatively poorer left ventricular function). For this reason, our study aimed to assess the ESWS/ESV-I ratio for LV systolic function in Anatolian shepherd dogs (ASHs) with asymptomatic DMVD.

## **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 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.

### **Study Design and Clinical Examination**

A clinical examination, an electrocardiography (ECG) (Vet ECG Electrocardiograph VE-300, Vega Group) study, thoracic

radiography for VHS determination<sup>[3]</sup> and arterial blood pressure (BP, systolic and diastolic) measurements using oscillometric technique (DynaPulse DP 5200A Pathway Pulse Dynamic NIBP Monitor, Pulse Metric Inc., USA)<sup>[3]</sup> were done in each ASH for both the experimental and control groups. The intensity of cardiac murmurs was evaluated according to Levine's classification<sup>[3]</sup>. 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.

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<sup>[9]</sup>, 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<sup>[3]</sup>. 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<sup>[3]</sup>. M-mode measurements including EPSS, LV end-diastolic diameter ( $D_{ed}$ ), end-systolic diameter ( $D_{es}$ ),  $IVS_{ed}$  and LV posterior wall thickness in end-systole ( $PWh_{es}$ ) 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).

IVSd/LVd ratio; The IVSd/LVd ratio was determined by M-mode measurements from right parasternal long-axis 5-chamber view.

ESWS/ESV-I ratio; The ESWS is determined by the ratio of left ventricular internal dimension ( $D_{es}$ ) to the posterior wall thickness ( $PWh_{es}$ ):

ESWS =  $(Px D_{es}) \times 1.35 / PWh_{es}$ ; where ESWS is left ventricular wall stress ( $g/cm^2$ ) at end-systole, P is the systolic BP (mmHg),  $D_{es}$  and  $PWh_{es}$  are the left ventricular internal dimension and posterior wall thickness (cm) at end-systole, respectively, and 1.35 is a conversion factor (mmHg to  $g/cm^2$ ). 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 (Kolmogorov-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 median. 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  $\pm$  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 an auscultable murmur. 17 (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.

The left ventricular systolic function parameters (FS, ESV-I, EPSS and ESWS/ESV-I ratio), EDV-I, NT-proBNP, VHS, LA/Ao, IVSd/LVd and ESWS/ESV-I values in the control and the experimental (B1 and B2) groups of dogs are summarised in Table 1.

On the colour-flow Doppler examination, all 20 B1 dogs (100%) had mild MR ( $< 20\%$ ), whereas among 18 B2 dogs, 6 (33%) had mild, 11 (61%) had moderate (20-40%) (Fig. 1) and 1 (6%) had severe ( $> 50\%$ ) MR.

The mean ESWS/ESV-I ratio was ( $P < 0.05$ ) lower in the B2 dogs ( $0.83 \pm 0.03$ , range: 0.61-1.09) when compared with the B1 dogs ( $1.34 \pm 0.05$ , range: 1.11-1.89) and control dogs ( $2.17 \pm 0.0$ , range: 1.91-3.02). The difference between the B2 dogs and the B1 dogs (Table 1, Fig. 2) was also significant ( $P < 0.05$ ).

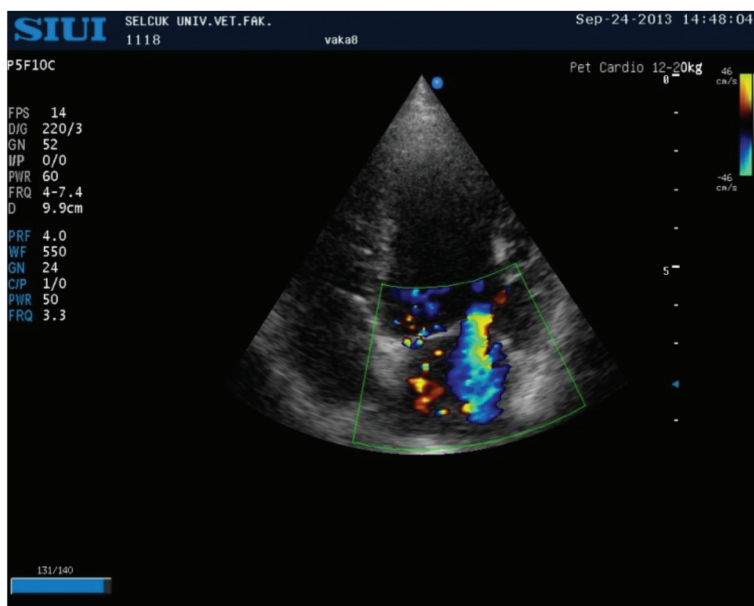
## DISCUSSION

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<sup>[10,11]</sup>. The results of studies on the effect of volume overload caused by DMVD on left ventricular function are controversial<sup>[2,4,8]</sup>. 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 the B1 dogs, 45-51% for the B2 dogs) (Table 1), for the ESV-I ( $5.84-30.16$  mL/m<sup>2</sup> for the control dogs,  $13.69-42.59$  mL/m<sup>2</sup> for the B1 dogs,  $22.37-36.23$  mL/m<sup>2</sup> for the B2 dogs) (Table 1), for the CI ( $2907-6399$  mL/min/m<sup>2</sup> for the control dogs,  $1267-5285$  mL/min/m<sup>2</sup> for the B1 dogs,  $2112-4304$  mL/min/m<sup>2</sup> 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<sup>[4,12]</sup>. All these results may demonstrate that there seemed to be

**Table 1.** NT-proBNP, VHS, LA/Ao, LV, FS, ESV-I, CI, EPSS, EDV-I, IVSd/LVd and ESWS/ESV-I ratio in the control and experimental groups of dogs

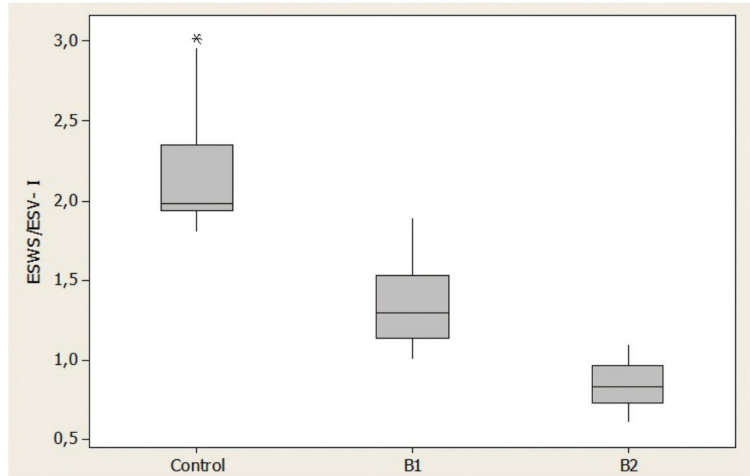
Parameters	Control group (n = 30)	Experimental group	
		B1 (n = 20)	B2 (n = 18)
NT-proBNP (pmol/L) (median and range)	759 $\pm$ 47 (250-2050) <sup>c</sup>	1588 $\pm$ 212 (900-4650) <sup>b</sup>	2985 $\pm$ 218 (1250-4300) <sup>a</sup>
VHS vertebrae (mean and range)	9.74 $\pm$ 0.06 (9.10-10.50) <sup>c</sup>	10.30 $\pm$ 0.09 (9.00-10.50) <sup>b</sup>	10.90 $\pm$ 0.05 (10.60-11.50) <sup>a</sup>
LA/Ao (median and range)	1.20 $\pm$ 0.03 (0.69-1.58) <sup>c</sup>	1.44 $\pm$ 0.04 (1.10-1.70) <sup>b</sup>	1.80 $\pm$ 0.03 (1.73-2.10) <sup>a</sup>
FS (%) (median and range)	35.00 (29-45) <sup>c</sup>	44.50 (31-48) <sup>b</sup>	46.50 (45-51) <sup>a</sup>
ESV-I (mL/m <sup>2</sup> ) (mean and range)	17.1 $\pm$ 1.39 (5.84-30.16) <sup>b</sup>	27.6 $\pm$ 2.35 (13.69-42.59) <sup>a</sup>	31.7 $\pm$ 1.0 (22.37-36.23) <sup>a</sup>
CI (mL/min/m <sup>2</sup> ) (mean and range)	4352 $\pm$ 186 (2907-6399) <sup>a</sup>	3227 $\pm$ 226 (1267-5285) <sup>a</sup>	3165 $\pm$ 157 (2112-4304) <sup>b</sup>
EPSS (mm) (median and range)	3.70 (2.00-6.50)	3.40 (2.30-7.00)	3.35 (2.50-4.40)
EDV-I (mL/m <sup>2</sup> ) (mean and range)	55.7 $\pm$ 2.4 (29.9-78.1) <sup>b</sup>	52.2 $\pm$ 3.6 (31.4-73.7) <sup>b</sup>	75.7 $\pm$ 2.2 (54.2-85.2) <sup>a</sup>
IVSd/LVd (mean and range)	0.27 $\pm$ 0.007 (0.22-0.33)	0.28 $\pm$ 0.008 (0.22-0.33)	0.27 $\pm$ 0.01 (0.23-0.33)
ESWS/ESV-I ratio (mean and range)	2.17 $\pm$ 0.0 (1.91-3.02) <sup>a</sup>	1.34 $\pm$ 0.05 (1.11-1.89) <sup>b</sup>	0.83 $\pm$ 0.03 (0.61-1.09) <sup>c</sup>

FS: fractional shortening; EF: ejection fraction; ESV-I: end-systolic volume index; EPSS: E point septal separation; EDV-I: end-diastolic volume index; CI: cardiac index; ESWS/ESV-I: end-systolic wall stress/end-systolic volume ratio; IVSd/LVd: interventricular septum thickness/left ventricular internal dimension ratio; <sup>abc</sup> Values with different character in each row are statistically different with  $P < 0.05$ .



**Fig 1.** Moderate mitral regurgitation jet in a B2 dog with DMVD

**Fig 2.** ESWS/ESV-I ratio distribution for the control dogs, B1 dogs, and B2 dogs. There was no overlap for the ESWS/ESV-I ratio among the groups, and the ESWS/ESV-I ratio did separate the groups alone



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<sup>[3]</sup>. Suzuki et al.<sup>[13]</sup>, 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<sup>[7]</sup>. Clerfond et al.<sup>[7]</sup> 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/m<sup>2</sup> indicate impaired systolic function<sup>[3]</sup>. In our study, ESV-I was high in the B2 dogs (>30 ml/m<sup>2</sup>) (Table 1). For this reason we thought ESWS/ESV-I would be useful in

evaluating systolic function. Carabello et al.<sup>[8]</sup> 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 ( $0.83 \pm 0.03$ , range: 0.61-1.09) when compared with B1 dogs ( $1.34 \pm 0.05$ , range: 1.11-1.89) and control dogs ( $2.17 \pm 0.0$  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  $\leq 1.09$  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 ( $\leq 1.09$ ) 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<sup>[14,15]</sup>. 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 ( $\leq 1.09$ ) 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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