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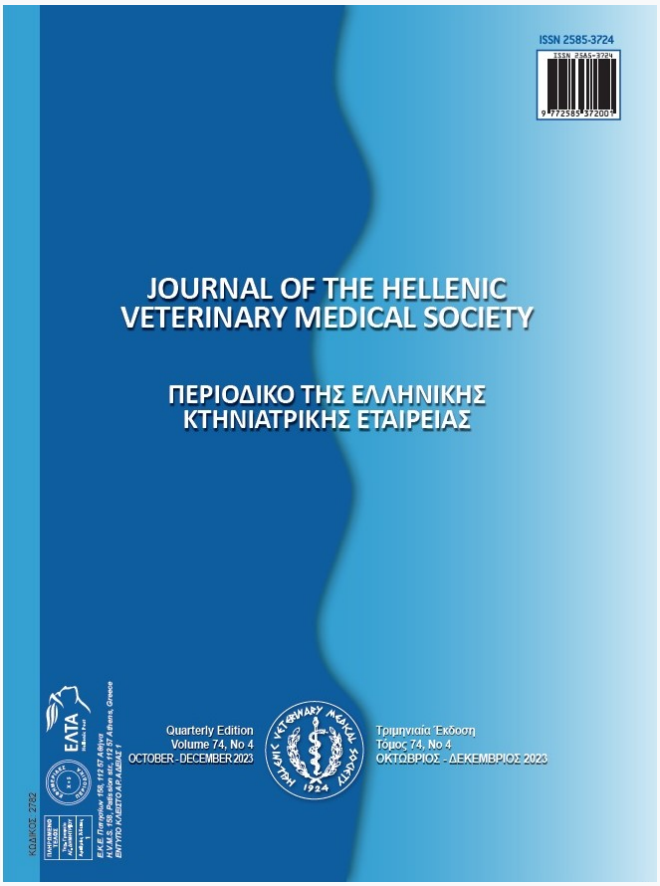

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Research article
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Effect of pimobendan on TAPSE in dogs with cardiac valvular disease

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ABSTRACT: Many caridac and pulmonary disease affect right heart functions. Therefore, clinical examination of it's systolic function has recently became important in humans, whereas it has been largely overlooked in dogs. So that in this research, the effects of pimobendan on right ventricular fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), and systolic functions were analyzed in detail by echocardiography. For this purpose, 40 cases of mitral and/or tricuspid valve disease (group II) and 10 healthy dogs (group I) were included in the study. Echocardiographic examinations were repeated after giving of pimobendan (0.2 mg/kg x2 for 1 week) to groupII (group III). In the echocardiographic examinations, the values EF, EPSS, RV-Area D, RV-Area S, IVSd, IVSs, LVPWs, MV E, and MV A showed statistically significant differences between the groups. Also, we found that TAPSE was lower in group II (1.29 cm) than in group I (2.25 cm) ($P<0.001$), and after treatment with pimobendan, TAPSE was increased (1.41 cm). RVFAC also decreased in the patient group, and this value increased after treatment with pimobendan, as did TAPSE, but these changes weren't statistically significant. Therefore, we concluded that right ventricular functions should be carefully monitored in patients with various heart diseases for better diagnosis, treatment, and prognosis.

***Key words*:** dog;echocardiography; pimobendan; tapse; tricuspid

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INTRODUCTION

Many diseases such as arrhythmogenic right ventricular cardiomyopathy (ARVC), mitral valve disease(MVD), aortic valve disease, dilated cardiomyopathy (DCM), and pulmonary hypertension (PH) also affect right heart functions (Morita et al., 2019; Voelkel et al., 2006). In addition, approximately 30% of patients with left cardiac disorder have right ventricle (RV) systolic function disorders due to primary mitral valve regurgitation (Dini et al., 2007; Le Tourneau et al., 2013).Therefore, clinical evaluation of the RVis very critical for diagnosis and prognosis (Chapel et al., 2018; Morita et al., 2019). However, in both human and veterinary cardiology, the function of the RV has not been as well studied as that of the left ventricle (LV) (Chapel et al., 2018; Lance et al., 2015). Therefore, noninvasive techniques such as echocardiography that let determination of RV disorders are critical (Visser et al., 2015a,2015b).

Recently, indices such as right ventricular ejection fraction (RVEF), right ventricular fractional area change (RVFAC), and tricuspid annular plane systolic excursion (TAPSE), which measure and calculate RV function, have been used clinically to detect RVdisorders and to monitor disease progression. In humans, a TAPSE <16 mm indicates RV systolic dysfunction and unfavorable prognosis (Cunningham et al., 2018; Kjaergaard et al., 2009). Therefore, evaluation of the RV provides important information regarding both RV systolic function and prognosis of mitral regurgitation (Dini et al., 2007; LeTourneau et al., 2013).

TAPSE is usually measured with M-mode and 2D echocardiography, this measurement represents the displacement of the tricuspid annulus toward the apex of the RV (Pariaut et al., 2012).When evaluating TAPSE, disadvantages such as the angle of acquisition and misalignment of the cursor, are eliminated (Visser, 2017a,2018a).

RVFAC measured from the longitudinal and transverse components of RV contraction also relates to the percent change in RV chamber area between end-diastole and end-systole (Mauritz et al., 2012; Lee et al., 2018; Vitarelli and Barilla, 2014). RVFAC correlates with RVEF and has prognostic value in PH and heart failure (Ghio et al., 2000).

Pimobendan is described as a new cardiac drug called an “inodilator” because it has both positive inotropic and vasodilatory effects (Van Meel and Diederen, 1989). Pimobendan may increase cardiac output (CO) and contractility of the heart muscle and cause a decrease in preload and after load (Suzuki et al., 2011). Pimobendan prolongs survival in patients with MVD and DCM(Lombard et al., 2006; O’Grady et al., 2008; Smith et al., 2005).

Therefore, in this research, the effects of pimobendan, used to treat dogs with mitral and tricuspid regurgitation, on RVFAC, TAPSE,RV diastolic and RV sistolic functions were studied in detail by echocardiography.

MATERIAL AND METHODS

The study was performed in 10 healthy dogs (group I), 40 sick dogs with mitral and/or tricuspid valve disease (group II), and these 40 dogs treated with pimobendan for1 week (0.2 mg/kg b. w., peros, BID) (Vetmedin®, Boehringer Ingelheim) (group III). The average age of healthy and patient groups were mean±SD4.5±2.5 and9.4±3 years, respectively. All studies were performed after obtaining the consent of the patient owner and in compliance with animal welfare with the permission of the Ethics Committee of our faculty with meeting resolution of March 13, 2020 and number 11.

Echocardiographic examinations were performed with the SIUI Apogee 3500V Veterinary Digital Color Doppler Ultrasound Imaging Device and the SI Multifrequency P3F14C Cardiac Phased Array Probe (1.7-4 MHz frequency) with optimal gain (0-100 dB), depth (1,6-30,8 cm) and pulse repetition frequency (0,25-25 KHz) (Shantou Institute of Ultrasonic Intstruments, China). Echocardiographic examinations of the dogs participating in the study was evaluated in accordance with the technique(Thomas et al., 1993). LA/Ao ratio and pulmonic arter doppler measurements on right parasternal herat base2-D images, IVS (interventricular septal thickness), LVID (left ventricular inner dimension), LVPW (left ventricular posterior wall thickness) systolic and diastolic measurements on right parasternal short axis M-Mode images were determined and FS% (fractional shortening) and EF% (ejection fraction) measurements were calculated with Teicholz formula by machine automotically (Teicholz et al., 1976). Pulmonic artery Doppler measurements were made on the right parasternal heart base image. Mitral inflow measurements were performed in the AP4C (apical four chamber) image, Ao Doppler measurements in the AP5C (apical five chamber) image, and tricuspid inflow measurements in the AP4C image. The following measurements were performed

to assess RV functions: TAPSE in the image acquired with the cursor parallel to the RV and through the tricuspid annulus using M mode in AP4C, RVFAC by video recording with measurements of RV diastolic area (RV-Area D) and RV sistolic area (RV-Area S) inthe AP4C window, pulsed tissue Doppler measurements of the lateral tricuspid annulus using tissue doppler imaging (TDI) (Figure 1, 2) (Cunningham et al., 2018; Visser et al., 2015b; Visser et al., 2018b).

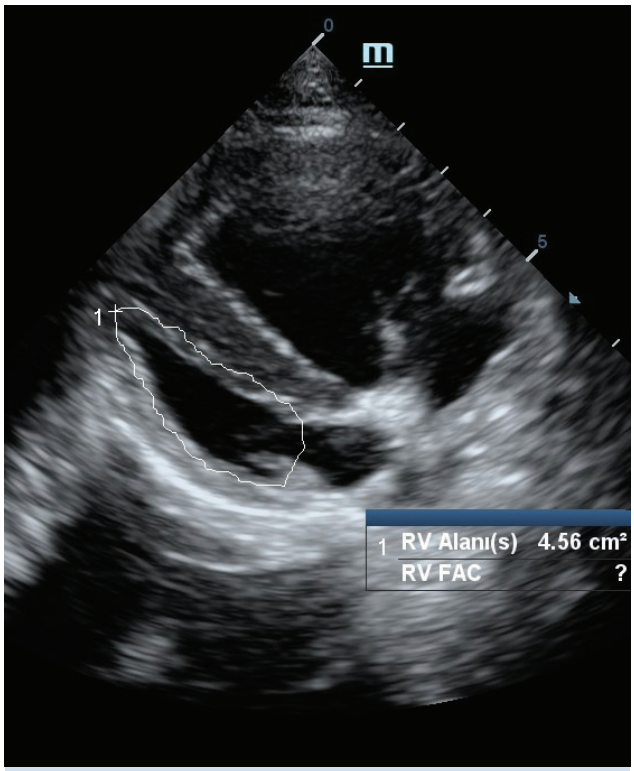

Figure 1: Representative echocardiographic image for the measurement of right ventricular sistolic area in apical 4-chamber view.

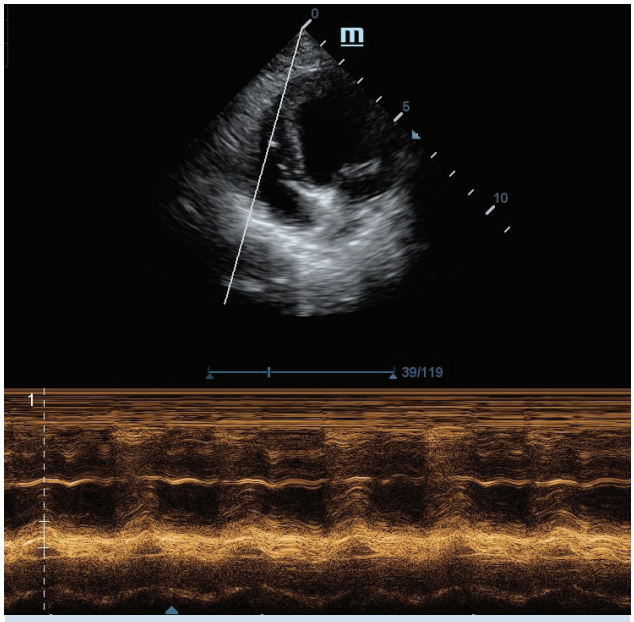

Figure 2: Representative echocardiographic image for the measurement of TAPSE in apical 4-chamber view.

The SPSS statistical software package (version 28 Windows, IBM Corporation, NY) was used for statistical analyses. For all analyses performed, a $P<0.05$ was considered statistically significant. The Shapiro-Wilk test was applied to determine whether the data sets were normally distributed, and the normally distributed variables were expressed as mean and standard deviation. When it was determined that there was a normal distribution, an independent Student t-test was performed using the one-way ANOVA method to compare Group I - II and Group II - III. Homogeneity of variance was checked with Levene's test. The relationship between age and TAPSE, RV-Area D, and RV-Area S was evaluated using the Pearson correlation coefficient.

RESULTS

In our study, the healthy dogs belonged to the Pomeranian (4), Golden Retriever (3), Pug (2), and Doberman Pinscher (1) breeds, while the sick animals belonged to the Cavalier King Charles Spaniel (14), Pekingese (9), Golden Retriever (8), Terrier (4), French Bulldog (3), and Pomeranian (2) breeds. While most of the healthy dogs were younger than 3 years, the dogs with congestive heart failure were dogs older than 7 years. In the group of patients included in our study, 6 of the dogs had DCM, 18 had PH, and 16 had MVD and associated congestive heart failure (CHF).

In the echocardiographic examinations performed group II, the mean RV area-D was 6.24 cm^2, whereas in the healthy dogs it was 12.82 cm^2, and there was a statistically significant difference as a result of statistical comparison of the groups ($P<0.001$). Similarly, the mean RV-Area S was found to be 4.03 cm^2 in the group II and 7.58 cm^2 in the group I. Statistical comparison revealed a significant difference in RV-Area S measurements between the two groups ($P<0.001$). In the assessment of diastolic mitral valve velocity, statistically significant results were obtained between the patient and healthy groups in the measurements of E and A waves (MV E and MV A) (Table1). Also, a statistically significant increase in EF% value observed as a result of repeated echocardiographic examinations after the use of pimobendan ($P < 0.05$) (Table 2).

The mean value of TAPSE measurements evaluat-

Table 1: Echocardiographic parameters in healthy and sick dogs.

Parameter	Grup I	Grup II	Significancy
LA (cm)	2.18±0.72	2.37±0.82	Insignificant
AO (cm)	1.9±0.66	1.37±0.69	Insignificant
LA/AO	1.16±0.25	1.48±0.6	Insignificant
RV-Area (D) (cm^2)	12.82±4.98	6.24±4.17	Significant ***
RV-Area-(S) (cm^2)	7.58±3.54	4.03±2.74	Significant ***
RVFAC%	41.01±11.39	33.57±16.46	Insignificant
EPSS (cm)	0.75±20.68	0.55±0.26	Significant *
TAPSE (cm)	2.25±0.88	1.29±0.55	Significant ***
IVSd (cm)	1.78±0.78	0.87±0.35	Significant ***
LVIDd (cm)	2.71±1.5	3.78±1.64	Insignificant
LVPWd (cm)	0.76±0.22	1.81±0.7	Insignificant
IVSs (cm)	0.78±0.37	1.13±0.29	Significant **
LVIDs (cm)	2.16±0.88	2.43±1.41	Insignificant
LVPWs (cm)	1.59±0.68	1.1±0.51	Significant *
EF%	79.25±10.51	74.27±13.05	Insignificant
FS%	38.77±4.94	39.15±12.79	Insignificant
MV E (cm/sec)	113.37±16.6	86.03±26.64	Significant **
MV A (cm/sec)	104.98±32.29	60.59±19.8	Significant ***
MV E/A	1.34±0.25	1.53±0.49	Insignificant

Values are expressed as mean ± SD. Statistical sinificancy; *P<0.05, **P<0.01, ***P<0.001.

Table 2: Echocardiographic parameters in sick and treatment dogs.

Parameter	Grup II	Grup III	Sigificiancy
LA (cm)	2.37± 0.82	2.08±0.71	Insignificant
AO (cm)	1.73± 0.69	1.66±0.54	Insignificant
LA/AO	1.48±0.6	1.54±1.31	Insignificant
RV-Area (D)(cm^2)	6.24± 4.17	6.17±4.61	Insignificant
RV-Area (S)(cm^2)	4.03± 2.74	3.75±2.69	Insignificant
RVFAC%	33.57± 16.46	38.88±17.11	Insignificant
EPSS (cm)	0.55±0.26	0.48±0.19	Insignificant
TAPSE (cm)	1.29±0.55	1.41±0.5	Insignificant
IVSd (cm)	0.87±0.35	0.88±0.29	Insignificant
LVIDd (cm)	3.78±1.64	3.36±1.35	Insignificant
LVPWd (cm)	1.18±0.7	1.08±0.48	Insignificant
IVSs (cm)	1.13±0.29	1.17±0.34	Insignificant
LVIDs (cm)	2.43±1.41	2.01±1.11	Insignificant
LVPWs (cm)	1.1±0.51	1.07±0.41	Insignificant
EF%	74.27±13.05	79.95±11.59	Significant *
FS%	39.15±12.79	42.68±11.03	Insignificant
MV E (cm/sec)	86.03±26.64	84.79±31.21	Insignificant
MV A (cm/sec)	60.59±19.8	57.42±18.71	Insignificant
MV E/A	1.53±0.49	1.59±0.48	Insignificant

Values are expressed as mean ± SD. Statistical sinificancy; *P<0.05

ing RV function in the group II, to which the patients belonged, was reported as 1.29 cm. When the group I and II were compared, with a mean of 2.25 cm in group I,there was a statistically significant difference (P<0.001) (Table 1).There were also similar results between groups for RVFAC values, but these weren't statistically significant. There were moderate positiv correlations between TAPSE and RV-Area S and, between TAPSE and RV-Area D (r=0.46 and r=0.49 respectively, P<0.001) (Figure 3). But, there was't any statistically significant correlation between age and RV values.

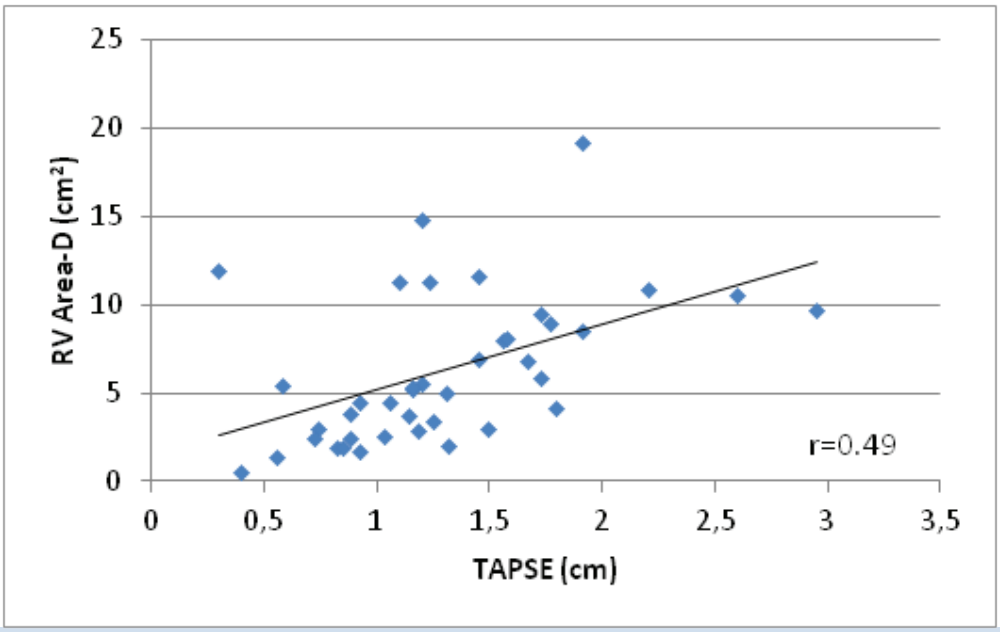

Figure 3: Correlation coefficient between TAPSE and RV Area-D in dogs with cardiac valvular disease.

DISCUSSION

Various cardiac and pulmonary or pulmonary vascular diseases cause RV failure in dogs (Morita et al., 2019; Voelkel et al., 2006). Therefore, clinical examination of the right ventricle is very crucial for diagnosis (Meluzin et al., 2005). Although cardiac magnetic resonance imaging is very useful for evaluation of RV, this method is time consuming, unsuitable for routine clinical practice, and costly (Smolarek et al., 2017). Therefore, echocardiographic examination is primarily preferred for right ventricular assessment because it is easily accessible and relatively inexpensive (Meluzin et al., 2005; Smolarek et al., 2017). Tricuspid or pulmonary valve regurgitation can be easily detected with Doppler echocardiography, noninvasive estimates of pulmonary arterial pressure (PAP) can be made, and right heart function and structure can be easily assessed, and prognosis can be determined along with disease follow-up (Morita et al., 2019). The prognostic significance of TAPSE, which is defined as a simple and reproducible parameter in the echocardiographic evaluation of RV function, has also been better understood recently, and therefore the related source parameters are proposed in the American and European guidelines (Ghio et al., 2001; Kaul et al., 1984).

Hsue and Visser(2020) emphasized that the LA/Ao ratio on echocardiography is more informative than other parameters for the diagnosis of left atrial enlargement. Borgarelli et al.(2015)reported that a LA/Ao >1.7 result was associated with a worse prognosis in dogs with PH due to myxomatous MVD. In our study, it was observed that the LA/Ao ratio was higher in sick dogs than in healthy dogs, but this difference was insignificant. It is thought that the reason for this is that all the cases in our patient group were not only dogs with enlargement of the left atrium or mitral valve regurgitation but also animals with various cardiac defects such as right ventricular failure and tricuspid regurgitation. In our study, it was found that there were statistically significant differences between groups in both EPSS values and left ventricular M-mode measurements, as reported by other investigators (Holler and Wess 2014; Koch et al., 1996). It has been suggested that the reason for this is the thickening of the left ventricular walls and mitral valves and the changes in heart size.

Damy et al. (2012)reported that TAPSE decreased in 1.547 patients with chronic heart failure. Pariaut et al. (2012)found that TAPSE decreased significantly in dogs with PH because of significant changes in right ventricular function. Also, various studies (Cunningham et al., 2018; Marthaet al., 2021; Sehgal et al., 2019)showed that the decrease in TAPSE value was directly proportional to the severity of heart disease and mortality rate. Similar to what the investigators reported, we found that dogs with heart disease had lower TAPSE than healthy dogs ($P<0.001$).

Visser et al. (2018b) observed significant changes

in RV systolic function indices echocardiographically in 80 healthy dogs after a single oral administration of pimobendan and atenolol (P<0.001). Similarly, Visseret al. (2015b)found a significant increase in TAPSE after the use of pimobendan in healthy dogs and reported that this increase was proportional to the absence of right ventricular myocardial injury. In our study, we found that there was a statistically significant decrease in TAPSE in dogs in the group with heart disease compared with the healthy group (P<0.001). In patients receiving pimobendan for 1 week, TAPSE increased, but this increase was insignificant (P>0.05). We hypothesise that, this is due to myocardial damage in sick dogs with an inadequate short-term response. Likewise, Sabbah et al. (1994) reported increased LV ejection fraction (EF) in dogs with LV dysfunction receiving Enalapril, Metoprolol, and Digoxin. In our study, we observed that the EF% value increased significantly in dogs with heart disease and we thought that this result was due to the inodilator effect of pimobendan.

Laster et al. (1994)found a statistical decrease in RVFAC reference in dogs with chronic occlusion of the right coronary artery attributable to decreased perfusion in the free wall of the RV. Vezzosi et al. (2018) in a study they performed in a total of 163 dogs with PH and 74 healthy dogs from 22 different breeds, found that the RVFAC value had no significant difference between the groups. In another study, Chapel et al.(2018)classified 36 dogs with myxomatous MVD as ACVIM stage B1, B2, or C, depending on the severity of the disease, and measured echocardiographic parameters of RV systolic function and reported that there was no significant correlation between RVFAC indices. A statistical decrease in the RVFAC reference value was observed in a dog with acute pulmonary thromboembolism (Morita et al., 2019). According to the data of our study, the RVFAC value was lower in the patient group than in the healthy group, but these changes weren't statistically significant. The reason for these different results may be due to the distribution of breed, age, body weight, and diseases of the animal population in the study.

Visseret al. (2015b)reported an increase in right ventricular function indices from baseline after a single administration of pimobendan in healthy dogs, particularly in RVFAC. After 1 week of pimobendan use, an increase in RVFAC values were observed in our patients, but it was not statistically significant. At the same time, statistically significant results were obtained in RV-Area D and RV-Area S values between the healthy dogs and the patient group. While both values decreased significantly in the sick dogs, no significant change was observed in the percentage of RVFAC. Despite the volume changes, it was concluded that the ventricular contractile response was not significantly impaired. In addition, it was found that there was no statistical difference between RV-Area D and RV-Area S values after the application of pimobendan in these patients.

CONCLUSION

In conclusion, we found a statistically significant decrease in TAPSE, RV-Area D, RV-Area S, and EPSS values and an insignificant decrease in RVFAC and EF% values in dogs in the heart disease group compared with the healthy group. Although there was an increase in TAPSE, RVFAC, and EF% values, only EF% value increased statistically significantly in patients receiving pimobendan for 1 week (P>0.05). We speculate that this is due to myocardial damage in sick dogs, which does not show sufficient response in the short term. However, long-term treatment with pimobendan may be more useful and improve survival in these patients.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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