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RESEARCH ARTICLE

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Effect of Single-dose Pimobendan on Echocardiographic Parameters in Healthy New Zealand White Rabbits

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ABSTRACT

keeping rabbits as pets and their use in laboratory research increased the need for studying heart diseases and treatments in rabbits. Pimobendan is one of the most common medications used in cardiac diseases and is anecdotal in rabbits. The first step toward the approval of pimobendan in rabbits is assessing the potential for beneficial effects on cardiac function through echocardiographic functional parameters.This study aimed to determine the effects of pimobendan on echocardiographic parameters. Eleven rabbits were included in this study. Echocardiographic examinations were performed before and after pimobendan administration for each rabbit. The LV morphological and functional parameters were compared between study time points. Pimobendan resulted in changes in several echocardiographic variables in the rabbits, including FS and an increase in EF, SV, LVPWs, and LA end-systolic ($p = 0.0001$, $p = 0.0001$, $p = 0.0284$, $p = 0.0272$, and $p = 0.0007$, respectively). Moreover, LVIDs and end-systolic volume decreased ($p = 0.0343$ and $p = 0.038$). The changes in some parameters were not significant, such as LVIDd, LVPWd, end-diastolic volume, LA max, Mitral annulus diameter, and LA/Ao. FS, which indicates an increase in the power of heart contraction and consequently an improvement in heart function, increased in this study after pimobendan administration. Therefore, it can be concluded that pimobendan improves cardiac functions. Further studies are required to investigate whether pimobendan has similar effects in rabbits with cardiac diseases.

Keywords

Echocardiography, Pimobendan, Rabbits, Cardiac function

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Abbreviations

LVIDs: Left ventricular internal diameter end-systole

LVIDd: Left ventricular internal diameter end-di-

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Introduction

Heart disease in rabbits can result in CHF, characterized by an excess of fluid volume resembling the signs of left-sided failure, such as pulmonary edema and pleural effusion, as well as the signs of right-sided failure, including abdominal effusion, hepatomegaly, and splenomegaly. The initial symptoms of heart disease include reduced activity, weight loss, alterations in eating patterns, and breathing difficulties.

Pimobendan, a benzimidazole pyridazinone medication, has demonstrated significant advantages in CHF, preclinical DCM, and preclinical degenerative valve disease in dogs [1, 2]. Pimobendan is used to treat dogs with CHF secondary to DCM. It has positive inotropic and vasodilatory effects via phosphodiesterase 3-inhibition and calcium sensitization [1]. It has other effects, such as increasing coronary blood flow, positive effects on myocardial oxygen consumption, and satisfactory effects on myocardial compliance [2].

Rabbits have been widely used as animal models to study various cardiac diseases, namely endocarditis and cardiomyopathies [3, 4]. The most common types of cardiovascular disease in rabbits include myocarditis, arteriosclerosis, and cardiomyopathy. Electrocardiograms [5, 6], blood pressure measurements, and echocardiograms [7, 8] can be used for diagnostic purposes in rabbits. The extra-label use of pimobendan in rabbits with CHF has garnered a lot of attention in the past decade. The positive inotropic effect of the medicine has been reported in rabbits without any negative impacts on morbidity and mortality [9].

In 2020, Ozawa et al. evaluated the pharmacokinetics of oral pimobendan administrated to healthy New Zealand White rabbits. According to their findings [10], the half-life of pimobendan was 3.54 ± 1.32 h, the plasma concentrations were detected for up to 24 hours, and desmethyl pimobendan, which is the active metabolite of pimobendan, was detectable for 24-36 h [10].

The present study was designed to address the knowledge gap by investigating the echocardiographic effects of pimobendan administered orally to healthy New Zealand White rabbits.

Abbreviations Cont'd

astole
LVPWs: Left ventricular posterior wall end-systole
LVPWd: Left ventricular posterior wall end-diastole
IVSs: Interventricular septum end-diastole
IVSd: Interventricular septum end-systole
EDV: End-diastolic volume
ESV: End-systolic volume
EF: Ejection fraction
SV: Stroke volume
FS: Fractional shortening
LA max: Left atrium maximum dimension
LA min: Left atrium minimum dimension
MVA max: Mitral valve maximum area
MVA min: Mitral valve minimum area
LA/Ao: Left atrium to Aorta ratio
CHF: Cardiac heart failure
DCM: Dilated cardiomyopathy
LV: Left ventricle
LA: Left atrium

Results

Pimobendan caused a significant increase in SV, EF, FS, LVPWs, and the minimum size of LA compared to the pre-drug group ($p < 0.05$), whereas LVIDs and ESV decreased significantly ($p = 0.0343$ and $p = 0.038$, respectively). No significant change was observed in some parameters, including LVIDd, LVPW thickness in diastole (LVPWd), EDV, LA max, Mitral annulus diameter, and LA/Ao (Figure 1,2).

Table 1 summarizes the changes from the base time (before administration) up to 3 h after the oral administration of pimobendan.

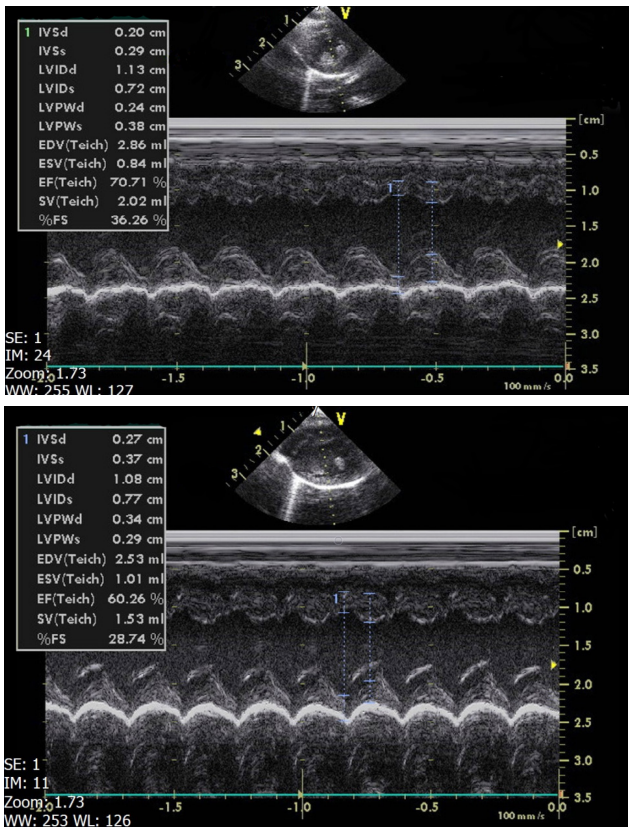

Figure 1.
Echocardiographic parameters in a rabbit before (lower image) and 3 hours after (upper image) the oral administration of pimobendan at 0.3 mg/kg

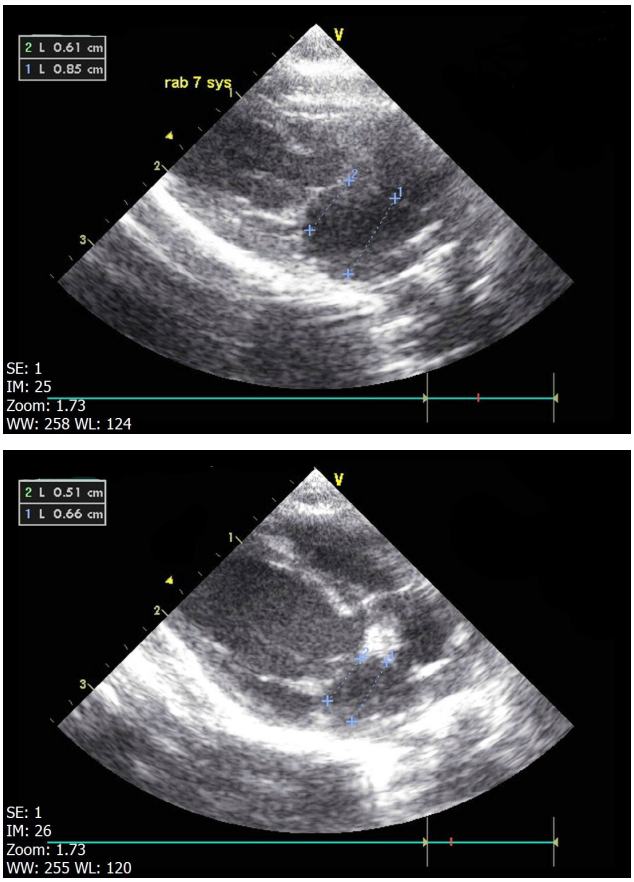

Figure 2.
Left atrium size and mitral annulus diameter during systole (upper image) and diastole (lower image)

Table 1.
Comparison of echocardiographic parameters before and after pimobendan administration

Variables	Pre-drug	Post-drug	*p*-value
IVSd	0.23 ± 0.02	0.22 ± 0.01	0.2158
IVSs	0.31 ± 0.01	0.32 ± 0.01	0.1388
LVIDd	1.05 ±0.01	1.09 ± 0.02	0.2537
LVIDs	0.74 ±0.02	0.73 ± 0.02	0.0343
LVPWd	0.29 ± 0.01	0.29 ± 0.01	0.4537
LVPWs	0.28 ± 0.01	0.30 ± 0.01	0.0007
EDV	2.36 ± 0.58	2.61 ± 0.13	0.2632
ESV	0.92 ± 0.16	0.89 ± 0.05	0.038
FS%	29.4 ± 0.64	32.95 ± 0.76	0.0001
EF%	60.99 ± 0.47	65.94 ± 0.99	0.0001
SV	1.4 ± 0.26	1.71 ± 0.09	0.0284
LA max	0.76 ± 0.02	0.78 ± 0.01	0.2736
LA min	0.57 ± 0.01	0.60 ± 0.01	0.0272
MVA max	0.52 ± 0.01	0.53 ± 0.01	0.7082
MVA min	0.46 ± 0.02	0.47 ± 0.01	0.3111
LA/Ao	1.12 ± 0.02	1.12 ± 0.02	0.7919

Discussion

This study found results about the effects of pimobendan on the LV function of healthy adult rabbits. The LV function increase by pimobendan was confirmed by some echocardiographic LV variables.

There was no significant change in LVID during diastole, while LVID during systole decreased after 3 h. Pimobendan had the same impact in a study on dogs with asymptomatic mitral valve disease and another research on beagle dogs [11, 12]. Moreover, in studies conducted by Boswood et al. and Haggstrom et al. on dogs with myxomatous Mitral valve disease both LVIDd and LVIDs decreased. In another investigation by Kinel et al. (2021) on dogs with Mitral valve disease, pimobendan only reduced the size of LV during diastole [13–15].

The LV posterior wall was slightly increased during systole. This finding was found in two studies by Yata et al. on healthy dogs and healthy cats [1, 2]. The main cavity of the heart is LV and the blood in LV is pumped in the aorta to deliver oxygenated blood to all body tissues. Therefore, a rise in LVPW can interfere with the ability of the heart to pump blood in the aorta. However, the increase in LVPWs in this study was very mild and remained in the normal range of LV posterior wall thickness in rabbits. As a result, it did not have destructive effects on the LV function.

The FS reflects the LV systolic function. Our study showed increased left ventricular FS after pimobendan administration, which means a rise in LV function. Left ventricular FS has been used in veterinary medicine [16] and humans [17] to assess LV systolic function. Prior studies have shown increased left ventricular FS in other animals. For example, a study evaluated cardiovascular effects after a single dose of pimobendan in healthy cats. The same result was found by Ro et al. after the oral administration of a pimobendan-pentoxifylline mixture in dogs [1, 18]. Changes in some echocardiographic parameters that indicate systolic function, such as the increase in FS and decrease in LVIDs, indicate the positive inotropic effect of pimobendan in rabbits.

In the current study, we observed a reduction in ESV after 3 h, but there was no significant change in the blood volume at the end of diastole. This finding is similar to that of Sengklab et al. (2022) [12]. Many studies of M-mode in veterinary medicine, showed a strong relationship between cardiac volume measurements (ESV and EDV) and cardiac output (19). In the present study, SV rose after 30 min of pimobendan administration. Despite the lack of change in cardiac output, it can be concluded that pimobendan can augment cardiac output, thereby improving cardiac function in diseases, such as heart failure in which cardiac output decreases. In similar studies on

dogs, different results had been found; SV increased after pimobendan administration in dogs with DCM, while in another study there was no change in SV in dogs with Mitral regurgitation [20, 21]. While SV rose after pimobendan administration in some studies on dogs, there was no change in SV in other research on dogs with Mitral valve regurgitation [20, 21].

The EF, as the gold standard index in evaluating LV, significantly increased after taking pimobendan. It depends on preload, afterload, and heart contractility. In patients with CHF, it can be reduced, which means the heart pumps less than before. With a significant increase in EF in our study, it can be concluded that pimobendan can be used in rabbits with CHF or any other diseases that can decrease EF. Similar results were found in an investigation on 24 dogs with Mitral valve disease [11] and another study on dogs with DCM treated with pimobendan [20].

There are a few studies about LA size after pimobendan administration. We observed that left atrial size at the end of the diastole increased slightly after 30 min and did not change since then. However, a study on dogs with cardiomyopathy showed that pimobendan did not cause a change in the size of the LA [22]. In addition, in a study on the left ventricular function of myxomatous Mitral valve disease in dogs treated with pimobendan, a similar result was obtained, and no change in the size of the LA was reported [23]. Pimobendan had similar effects in a study on the effects of pimobendan on left atrial transport function in cats [24].

Considering the discrepancy in the findings concerning the effects of pimobendan on LA in rabbits, further research is required. The reason for increasing the size of the LA in our study was not found.

Conclusion

Echocardiographic results after pimobendan administration indicated that pimobendan has useful effects on LV function in healthy rabbits. Further evaluations are needed to find out whether pimobendan is effective in rabbits with cardiac disease.

Materials and Methods

Ethical statement

Islamic Azad University, Karaj Branch approved all the procedures used in the current study for the care and treatment of animals (IR.IAU.K.REC.1401.018).

Animals

Eleven White New Zealand rabbits (24-30 weeks old and weighing 2.1 ± 0.3 kg) were purchased from the Pasteur Institute of Iran (Tehran, Iran) for this study. All the rabbits were adopted under supervision after the experiments were finished.

Medication

Pimobendan (0.3 mg/kg, Vetmedin 5 mg chewable tablet, Boehringer Ingelhei, Germany) was dissolved in distilled water and administered orally [10]. The medication dosage was calculated according to the weight of each rabbit, and an appropriate amount of powdered pimobendan, depending on the weight of each animal, was separately dissolved in 1 cc of water and gently administered from the corner of their mouth.

Echocardiography protocol

Echocardiography was carried out under spontaneous respiration, and without any anesthesia. It was performed by a single board-certified radiologist using a GE Vivid 7 ultrasound machine equipped with a phased-array (S10) probe (5-10 MHz). To obtain the right parasternal window, rabbits were positioned in the right lateral recumbency, and an ultrasound probe was placed on the cranial aspect of the thoracic wall, which had been shaved before, through a gap in the echocardiography table.

For a short axis view from the right parasternal, M-mode imaging was made at the level of the papillary muscles. Measurements of IVSs, IVSd, LVIDs, LVIDd, left ventricular free wall in systole (LVFWs), and in diastole (LVFWd) were performed. The right parasternal short-axis view with M-mode was used for measuring the aortic and left atrial diameters at the level of the aortic valve. M-mode parameters were measured by the leading-edge method of the American Society of Echocardiography. Left ventricular EF and FS were calculated by the following formulas:

$FS = [(LVIDd - LVIDS) / LVIDd] \times 100$

$EF = (SV / EDV) \times 100$

$SV = EDV - ESV$

Study design

Rabbits were healthy based on physical, radiologic, echocardiographic, and hematologic examinations.

Chest radiography for possible respiratory disorders was obtained for all subjects. The animals were fed with water and pellet. They were housed in steel cages at temperatures of 21°C-24°C, with a 12:12 h light-dark cycle.

Each rabbit went through five echocardiographic examinations. On day 0 the first examination was performed, and 1 hour apart possible valvular blood regurgitation and thickening were checked by color Doppler and M-mode imaging. The third examination, the baseline, was done on day 1; the fourth and fifth evaluations were completed 30 min and 3 h after a single dose of pimobendan was administered, respectively [26]. The planning of the echocardiographic assessment time depended on a pharmacokinetics investigation of pimobendan in rabbits [10].

Statistical analysis

To compare the echocardiographic data in pre-drug and post-drug conditions, the average records were collected during three quantitative assessments of pre-drug. The records were investigated between time points using SAS-9.2 software. In this research, the primary descriptive statistics of the data and the primary statistical distributions of the data were obtained and investigated. To examine the normal distribution of data and variance independence, the Kolmogorov-Smirnov test was performed at a statistical level of 5%. Moreover, an analysis of variance was performed.

The mean values and standard deviations for each experimental group, including the pre-drug, 30 min post-drug, and 3 hours post-drug, for each parameter extracted, and comparisons between the means were performed by Duncan's multiple range test. The coefficient of variation, mean value, and total standard deviation with the level of significance were calculated. Differenc-

es at $p < 0.05$ were considered significant.

Authors' Contributions

Ariana Askari Ghalehi, Ali Moradganjeh, Vria Tohidi, and Ali Roustaei conceived and planned the experiments. Ariana Askari Ghalehi, and Ali Roustaei carried out the experiments. Ariana Askari Ghalehi planned and carried out the simulations. Ariana Askari Ghalehi and Ali Roustaei contributed to sample preparation. Ariana Askari Ghalehi contributed to the interpretation of the results. Ali Moradganjeh took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Competing Interests

The authors declare that there is no conflict of interest.

References

1. Yata M, McLachlan AJ, Foster DJR, Hanzlicek AS, Beijerink NJ. Single-dose pharmacokinetics and cardiovascular effects of oral pimobendan in healthy cats. Journal of Veterinary Cardiology. 2016 Dec 1;18(4):310–25. Doi: 10.1016/j.jvc.2016.07.001.

2. Yata M, McLachlan AJ, Foster DJR, Page SW, Beijerink NJ. Pharmacokinetics and cardiovascular effects following a single oral administration of a nonaqueous pimobendan solution in healthy dogs. J Vet Pharmacol Ther. 2016;39(1):45–53. Doi: 10.111/JVP.12243.

3. Yanni AE. The laboratory rabbit: An animal model of atherosclerosis research. Lab Anim [Internet]. 2004 Jul 23 [cited 2022 Aug 4];38(3):246–56. Doi: 10.1258/002367704323133628.

4. Gava FN, Zacché E, Ortiz EMG, Champion T, Bandarra MB, Vasconcelos RO, et al. Doxorubicin induced dilated cardiomyopathy in a rabbit model: An update. Res Vet Sci. 2013;94(1):115–21. Doi: 10.1016/j.rvsc.2012.07.027.

5. Lord B, Boswood A, Petrie A. Electrocardiography of the normal domestic pet rabbit. Veterinary Record [Internet]. 2010 Dec 1 [cited 2022 Aug 4];167(25):961–5. Doi: 10.1136/vr.c3212.

6. Turner Giannico A, Ayres Garcia DA, Lima L, de Lara FA, Corona Ponczek CA, Shaw GC, et al. Determination of Normal Echocardiographic, Electrocardiographic, and Radiographic Cardiac Parameters in the Conscious New Zealand White Rabbit. J Exot Pet Med. 2015;24(2):223–34. Doi: 10.1053/j.jepm.2015.04.013.

7. Harvey L, Knowles T, Murison PJ. Comparison of direct and Doppler arterial blood pressure measurements in rabbits during isoflurane anaesthesia. Vet Anaesth Analg. 2012;39(2):174–84. Doi: 10.1111/j.1467-2995.2011.00685x.

8. Sato K, Chatani F, Sato S. Circadian and short-term variabilities in blood pressure and heart rate measured by telemetry in rabbits and rats. J Auton Nerv Syst. 1995;54(3):235–46. Doi: 10.1016/0165-1838(95)00016-Q.

9. Hagemeijer F. Calcium sensitization with pimobendan: pharmacology, haemodynamic improvement, and sudden death in patients with chronic congestive heart failure. Eur Heart J [Internet]. 1993[cited 2022];14(4):551–66. Doi: 10.1093/eurheartj/14.4.551.

10. Ozawa SM, Guzman DSM, Hawkins MG, Diao SM, Masri AE, Gunther-Harrington CT, et al. Pharmacokinetics of pimobendan following oral administration to New Zealand White rabbits (Oryctolagus cuniculus). Am J Vet Res [Internet]. 2022 [cited 2022];83(4):356–63. Doi: 10.2460/ajvr21.03.0032.

11. Ouellet M, Bélanger MC, DiFruscia R, Beauchamp G. Effect of pimobendan on echocardiographic values in dogs with asymptomatic mitral valve disease. J Vet Intern Med. 2009;23(2). Doi: 10.111/j.1939-1676-2008.0239.x.

12. Saengklub N, Boonyarattanasoonthorn T, Kijtawornrat A, Chantasart D. Preliminary Bioequivalence of an Oral Pimobendan Solution Formulation with Reference Solution Formulation in Beagle Dogs. Vet Sci. 2022;9(3). Doi: 10.3390/vetsci9030141.

13. Klein S, Nolte I, Rumstedt K, Sehn M, Raue JF, Weiner F, et al. The effect of treatment with pimobendan in dogs with preclinical mitral valve disease – a placebo-controlled double-blinded crossover study. BMC Vet Res. 2021;17(1). Doi: 10.1186/s12917-021-03014-5.

14. Häggström J, Boswood A, O'Grady M, Jöns O, Smith S, Swift S, et al. Longitudinal analysis of quality of life, clinical, radiographic, echocardiographic, and laboratory variables in dogs with myxomatous mitral valve disease receiving pimobendan or benazepril: The QUEST study. J Vet Intern Med. 2013;27(6). Doi: 10.1111/jvim.12181.

15. Boswood A, Gordon SG, Häggström J, Wess G, Stepien RL, Oyama MA, et al. Longitudinal Analysis of Quality of Life, Clinical, Radiographic, Echocardiographic, and Laboratory Variables in Dogs with Preclinical Myxomatous Mitral Valve Disease Receiving Pimobendan or Placebo: The EPIC Study. J Vet Intern Med. 2018;32(1). Doi: 10.1111/jvim.14885.

16. Serres F, Chetboul V, Tissier R, Poujol L, Gouni V, Carlos Sampedrano C, et al. Comparison of 3 ultrasound methods for quantifying left ventricular systolic function: Correlation with disease severity and prognostic value in dogs with mitral valve disease. J Vet Intern Med. 2008;22(3). Doi: 10.1111/J.1939-1676.2008.0097.x.

17. Tissot C, Singh Y, Sekarski N. Echocardiographic evaluation of ventricular function-for the neonatologist and pediatric intensivist. Vol. 6, Frontiers in Pediatrics. 2018. Doi: 10.3389/fped.2018.00079.

18. Ro W Bin, Song DW, Kim KH, Jeong SH, Kang MH. Pharmacokinetics and pharmacodynamics of pimobendan-pentoxifylline liquid mixture after oral administration in dogs. Journal of Veterinary Clinics. 2019;36(3). Doi:10.17555/jvc.2019.06.36.3.159.

19. Uehara Y, Takahashi M, Koga M. Determination of cardiac output by echocardiography. Journal of Veterinary Medical Science. 1995;57(3). Doi: 10.1292/jvms.57.401.

20. Sergeev D, Kovalev S, Trushkin V, Vasilev R, Nikitina A, Kiselenko P, et al. Use of high doses of pimobendan in animals with dilated cardiomyopathy. The FASEB Journal. 2021;35(S1). Doi: 10.1096/FASEBJ.2021.35.S1.01489.

21. Kanno N, Kuse H, Kawasaki M, Hara A, Kano R, Sasaki Y. Effects of pimobendan for mitral valve regurgitation in dogs. Journal of Veterinary Medical Science. 2007;69(4). Doi: 10.1292/JVMS.69.373.

22. Abbott-Johnson K, Pierce KV, Roof S, Del Rio CL, Hamlin R. Acute Effects of Pimobendan on Cardiac Function in Dogs With Tachycardia Induced Dilated Cardiomyopathy: A Randomized, Placebo-Controlled, Crossover Study. Front Vet Sci. 2021;8:646437. doi: 10.3389/fvets.2021.646437.

23. Sarcinella F, Neves J, Maddox TW, Hodgkiss-Geere HM, Bode EF, Dukes-Mcewan J. Effect of pimobendan on left atrial function in dogs with preclinical myxomatous mitral valve disease. Open Vet J. 2019;9(4):375–83. Doi: 10.4314/ovj.v9i4.16.

24. Kochie SL, Schober KE, Rhinehart J, Winter RL, Bonagura JD, Showers A, et al. Effects of pimobendan on left atrial transport function in cats. J Vet Intern Med. 2021;35(1). Doi: 10.111/jvim.15976.

25. Boon, J.A. In: Boon, J.A., editor. Two-dimensional and M-mode Echocardiography for Small Animal Practitioner. 2nd ed. John Wiley and Sons Inc., New York, United states. 2016. Doi: 10.1002/9781119028574

26. Kost LV, Glaus TM, Diana A, Baron Toaldo M. Effect of a single dose of pimobendan on right ventricular and right atrial function in 11 healthy cats. J Vet Cardiol. 2021;37:52-61. Doi: 10.1016/j.jvc.2021.08.006.

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