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Evaluation of Quadruple Therapy (Pimobendan, Benazepril, Furosemide, Spironolactone) for the Treatment of Dilated Cardiomyopathy (DCM) in Dogs

Ashi. R. Krishna[1]*, K. Jeyaraja[2], R. Ramprabhu[2], S. Eswari[3], Mohamed Shafiuzama[4], and S. Kavitha[5]

Department of Veterinary Clinical Medicine, Madras Veterinary College, Chennai 600007, Tamil Nadu.

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Abstract

Dilated cardiomyopathy is a common cardiac disease which affects larger breeds of dogs. The present study evaluated the occurrence of DCM in 10 dogs, its treatment and the treatment response. Ten dogs presented to the Medicine Outpatient unit of Madras Veterinary College Hospital presented with the clinical signs suggestive of DCM formed the study group. The animals were undergone general clinical examination, complete haematology, serum biochemistry, electrocardiography, thoracic radiography and echocardiography. Treatment was initiated with oral pimobendan, benazepril, diuretics and cardiac supportives. The cases showed substantial improvement after three months of treatment.

Keywords: Dilated cardiomyopathy, dogs, systolic function, echocardiography

Dilated cardiomyopathy is characterized by dilatation of either left or both the ventricles with the impairment of systolic function (Cobb, 1922). Idiopathic DCM is commonest form and is one of the major causes of death in Dobermans (Cheng *et al.,* 2012). Large and giant breed dogs have historically been affected with dilated cardiomyopathy (DCM), which is linked to a known genetic defect or recognized inheritance pattern in particular breeds (Martin *et al.,* 2009; Oyama *et al.,* 2009; Meurs *et al.,* 2012 and Simpson *et al.,* 2016). Starting in 1995, it was discovered that dietary taurine insufficiency in dogs-most frequently in American Cocker Spaniels, Golden Retrievers, and Newfoundlands, but also in other breeds-was linked to a nutritional type of DCM (Kramer *et al.,* 1995 and Kittleson *et al.,* 1997). The cases are diagnosed based on the clinical signs and echocardiography. Other diagnostics which aids in diagnosis of DCM include thoracic radiography and electrocardiography. The objective of the present study was to identify, evaluate and manage DCM in dogs with quadruple therapy.

Materials and Methods

About 10 dogs presented to the Medicine Outpatient unit of Madras Veterinary College Hospital with the signs suggestive of DCM formed the study group. The cases were diagnosed based on clinical signs, general clinical examination, complete hemogram, serum biochemistry, thoracic radiography (Buchanan and Bucheler, 1995), electrocardiography (Jeyaraja *et al*., 2015) and echocardiography (Boon, 2011). Echocardiographic evaluation was carried out with the Aeroscan CD 25 ultrasound system with a phased array probe (2 – 6 Hz) to get the 2-D (Fig 1), M – mode(Fig 2 &3), spectral Doppler (Fig 4 & 5) and Tissue Doppler images (Fig 6) according to the recommendations made by Boon(2011). Once confirmed, the cases were treated with oral pimobendan (0.25 mg/kg BID), benazepril (0.25 mg/kg BID), diuretics (lasilac-

**Corresponding author*: Email : ashikrishna18@gmail.com
[1]Ph.D. Scholar, Dept. of Veterinary Clinical Medicine, Madras Veterinary College, Chennai, 600007
[2]Professor, Dept. of Veterinary Clinical Medicine, Madras Veterinary College, Chennai, 600007
[3]Professor and Head, Center for Stem Cell Research and Regenerative Medicine, Madras Veterinary College, Chennai, 600007
[4]Professor and Head, Dept. of Veterinary Surgery and Radiology, Madras Veterinary College, Chennai, 600007
[5]Professor and Head, Dept. of Veterinary Clinical Medicine, Madras Veterinary College, Chennai, 600007

tone @ 1 mg/kg TID) & cardiac supportives (strongbeat @ 1tab/10kg BID). Antiarrhythmic medication included Tab. Diltiazem @ 1.5 mg/kg TID & Tab.Digoxin @ 0.003 mg/kg BID for atrial fibrillation.

Results and Discussion

Hematology and serum biochemistry

Haemato-biochemical parameters did not show significant changes. This was in accordance with the findings of Martin *et al.* (2010).But this was in contrary to the reports by Jeyaraja *et al*. (2015) who reported significant decrease of hemoglobin (Hb), packed cell volume, red cell volume, total protein and a significant increase in white blood cell count, blood urea nitrogen, creatinine and potassiumin DCM affected groups when compared to healthy group. Similarly Srivastava *et al*. (2015) also reported a significant decrease in Hb, PCV, RBC count in DCM affected cases compared to that of healthy ones. As per the authors the decline in the Hb, PCV and RBC was attributed to cardio-renal syndrome that develops in DCM affected dogs and the anemia developed which in turn can worsen the congestive heart failure (CHF). The absence of changes in the present study might be due to the absence of comorbid conditions.

Thoracic radiography

An increased VHS was noted on day 0 (12.70±0.21). As a response to treatment a significant reduction ($P<0.0001^*$) in VHS was noted byday 90 (11.10±0.27).Other changes observed in the X ray included cardiomegaly (100 %),

Fig 1 : L_A/A_o ratio

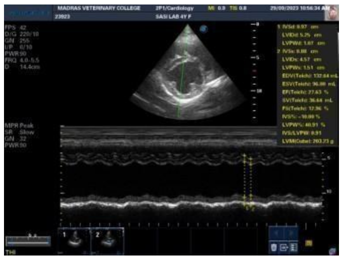

Fig 2 : M mode measurements at the level of chordae tendinae

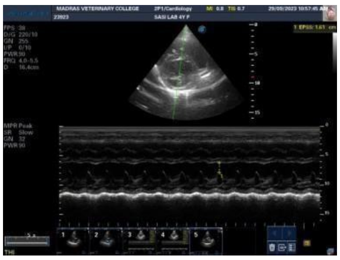

Fig 3 : Measurement of EPSS

Fig 4: Pulse wave Doppler measuring mitral E and A velocity

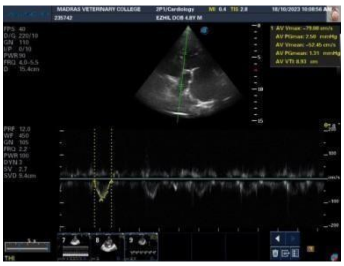

Fig 5: Pulse wave Doppler measuring aortic velocity

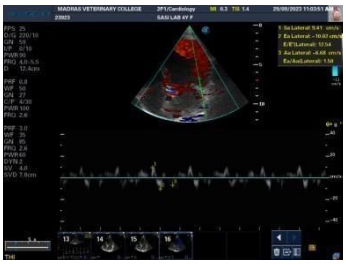

Fig 6: Tissue Doppler measuring myocardial velocities.

pulmonary edema (40 %) and pleural effusion (30 %)on day 0, which got resolved by day 90 as a response to treatment. This was in accordance with the findings of Martin *et al*. (2009) who reported cardiomegaly and congestive signs suchas pulmonary edema and pleural effusion in dogs with DCM. Similarly Jeyaraja *et al*. (2015) also recorded a significant increase of vertebral heart scores in DCM affected dogs(12.51 ± 0.41) compared to control (10.78 ± 0.03) group. They also reported cardiomegaly in 100 %, pulmonary edema in 80 %, and pleural effusion in 20 % of the cases with DCM. The significant decline in the VHS and resolution of changes in X ray during therapy can be considered as a positive response to treatment. The reduction in VHS might have occurred due to the decrease in the dimensions of cardiac chambers in a response to the treatment. Similar to the present study Haggstrom *et al*. (2013) also reported a reduction in VHS in dogs with mitral valve disease treated by pimobendan. The resolution of pulmonary edema might be a result of response to diuretics as they are reportedly effective in managing pulmonary edema due to volume overload (Purvey and Allen, 2017) which acts through reduction of preload on the heart and reducing further congestion in pulmonary vasculature. The complete resolution of pleural effusion was achieved through reduction of systemic and pulmonary venous pressure over a period of3 months of treatment.

Electrocardiography

There was a significant ($P<0.0001^*$) reduction in heart rate by day 90 (115.0±4.53) when compared to day 0 (177.0±4.95). The electrocardiographic changes in dogs with DCM included sinus tachycardia (70 %), atrial fibrillation (AF) (20 %) and reduced amplitude of QRS complex (10 %). Atrial fibrillation was the most common arrhythmia observed in dogs with DCM. Similarly Sisson and Thomas (1995) observed atrial fibrillation and ventricular premature complex as the common arrhythmias in dogs with DCM. Effective heart rate control was noticed in all the cases of atrial fibrillation treated with Tab. Diltazem and Tab. Digoxin. Diltiazem is a calcium channel blocker as well as class IV antiarrhythmic agent that slows AV conduction whereas digoxinexhibits its antiarrhythmic effect through sympathetic inhibition and parasympathomimetic effects (Wess and Torti, 2018).

Echocardiography

The Mean ± S.E values of two dimensional, M mode and pulse wave Doppler echocardiography values in day 0 and day 90 are given in Table3. Highly significant increase in the mean ± S.E values of LVIDd, LVIDs, EPSS and LA/Ao ratio were noticed in day 0 compared to day 90.Highly significant decrease in the mean ± S.E values of EF and FS was noticed in day 0 compared to day 90. Similar findings were reported by Jeyaraja *et al.* (2019) and Haritha *et al*. (2020). As per Wess (2022) the measurement of left ventricular systolic dysfunction and left ventricular volume overload are necessary to detect typical features of DCM. Increased left ventricular end systolic chamber diameter or end systematic volume, reduced FS or EF along with increase in endpoint to septal separation are to be considered for diagnosing left ventricular systolic dysfunction.

The Mean ± S.E values of LVIDd, LVIDs, EPSS and LA/Ao showed a significant reduction by day 90 as a response to treatment. Similarly Summerfield *et al.* (2012) also reported reduction in left ventricular size in both systole and diastole in Dobermans with DCM treated by pimobendan. Suzuki *et al.* (2011) and Bosswood *et al*. (2016) also reported reduction in left atrial diameter, overall heart size and left atrial pressure in dogs with mitral valve disease (MVD) treated by pimobendan. The authors also reported that the pimobendan was effective in reducing LV diameters in systole and diastole and improved systolic and diastolic function. Haggstrom *et al*. (2013) also reported a reduction in left atrial size, ventricular systolic and diastolic dimensions in dogs with MVD treated by pimobendan. Similarly Kanno *et al.* (2007) also reported reduction in LA/Ao ratio in dogs with MVD treated by pimobendan.

The Mean ± S.E values of EF and FS showed significant increase by day 90 as a response to treatment. This was in accordance with the findings of Bell *et al*. (2016) and Yata *et al*. (2016). According to the authors pimobendan has been shown to increase fractional shortening

Table I : Mean ± S.E values of two dimensional, M mode and pulse wave Doppler echocardiography values

Echocardiographic parameters	Mean Values ± SE*		t- value	p- value
	Day 0(n=10)	Day 90(n=10)		
LVIDd (cm)	6.41±0.2290	5.23 ± 0.2633	5.74	0.0003*
LVIDS (cm)	5.22±0.2204	3.93 ± 0.2687	5.52	0.0004*
EF (%)	35.37±2.1904	52.16 ± 3.1161	6.42	0.0001*
FS (%)	16.65±1.3888	28.79 ± 1.7899	6.59	0.0001*
HR (bpm)	150.70±5.4996	112.00 ± 5.7310	7.17	0.0001*
L_A/A_O	2.41 ± 0.2471	1.53 ± 0.0839	3.42	0.0076*
EPSS (cm)	2.05 ± 0.2100	0.83 ± 0.0672	6.42	0.0001*
MV E (m/s)	129.93 ± 6.6839	89.08 ± 5.5103	4.31	0.0020*
MV A (m/s)	49.96 ± 4.1048	48.59 ± 2.7378	0.37	0.7229^{ns}
E/A	2.71 ± 0.2014	1.64 ± 0.2313	4.14	0.0025*
AV (m/s)	96.22 ± 10.5757	128.92 ± 6.3350	3.09	0.0129*
E/E’	11.47±1.187	5.676±0.3851	4.647	0.0012*

* SE - Standard error, * - Significant at (P < 0.05), ^{ns} - Non - significant

in healthy dogs with peak effects between two and five hour after oral dosing. Similarly Abbott-Johnson *et al*. (2021) also reported improved systolic function in dogs with DCM treated by pimobendan. Sergeev *et al.* (2021) also reported increase in EF and FS in dogs with DCM treated by pimobendan. According to Kanno *et al.* (2007) there was an increase in EF and FS in dogs with mitral valve disease treated by pimobendan.

Significant increase in the mean ± S.E values of Mitral valve peak E-velocity, E/A ratio and E/E’ ratio was observed in day 0when compared to day 90. Whereas the mean ± S.E values of aortic velocity (AV) was found to be significantly decreased by day 0 when compared to day 90. Similar findings were reported by Jeyaraja *et al.* (2015).

As per Jeyaraja *et al.* (2015) in normal animals, peak E-velocity indicates rapid ventricular filling and peak A represents secondary atrial contractions. But in DCM cases, rapid heart rate will result in the overlapping of two phases resulting in super imposed waveforms (heart rates > 125 bpm). The increased mitral E-velocity might be secondary to increased atrial pressure or volume. Therefore the decreased mitral E velocity and E/A ratio by day 90 can be considered as a positive response to the treatment as according to Suzuki *et al.* (2011) and Bosswood *et al*. (2016) pimobendan has been shown to reduce left atrial pressure.

As per Jeyaraja *et al.* (2015) the reduced aortic velocity in DCM might be due to systolic failure. There was a significant increase in aortic velocity by day 90 as a response to treatment. This was in accordance with the findings of Bell *et al*. (2016) and Yata *et al*. (2016). According to the authors pimobendan has been shown to increase aortic flow velocity. The improved aortic velocity might be due to the increased cardiac output as a response to treatment with pimobendan (Sandez *et al.,* 2023).

Significant increase in E/Ea ratio was observed in day 0 when compared to day 90. This indicates diastolic dysfunction in dogs with DCM.E/Ea ratio was used to diagnose diastolic dysfunction in dogs which is similar to E/A ratio in conventional Doppler. However, the latter is not able to gradeor identify the pseudonormalisation phenomenon. Grading of diastolic dysfunction was also proposed using E/Ea with 8-11 as mild, 11.1-15 as moderate and greater than 15 as severe (Aparna, 2021). Diastolic dysfunction in DCM is attributed to cellular changes in myocardium which include myocyte degeneration, fibrosis and necrosis contributing to the ventricular remodelling (Gasparini *et al*., 2020) with resultant loss of elastic recoil, slower relaxation and impaired filling from ventriculardilatation itself (Little, 2005). The reduction in E/Ea ratio by day 90 can be considered as a response to treatment as pimobendan has been shown to improve diastolic dysfunction as reported by Suzuki *et al.* (2011) and Bosswood *et al*. (2016). As per Summerfield *et al.* (2012) pimobendan has been shown to reduce preload, afterload, cardiac size and filling pressures together with positive inotropic support and vasodilatory effects in Dobermans with preclinical DCM and therefore might have improved diastolic function. According to MacDonald (2009) pimobendan has reduced diastolic filling pressure and improved diastolic function. According to Sotillo *et al.* (2023) both angiotensin II and aldosterone contributed to myocardial fibrosis and therefore and Angiotensin converting enzyme inhibitor like benazepril might have decreased the myocardial fibrosis and remodeling.

Primary management of DCM aims to improve the cardiac contractility as well as blocking the neuro-humoral response and reducing the preload. Currently the medications suggested for management of DCM included angiotensin converting enzyme inhibitors, ionodilator, diuretics, antiarrhythmic therapies and cardiac supportives. The changes observed in dogs with DCM included increased left ventricular dimensions, impaired systolic and diastolic functions. Upon treatment with quadruple therapy (pimobendan, furosemide, spironolactone and benazepril) the left ventricular dimensions were reduced, systolic and diastolic functions were improved.

Conclusion

The present study evaluated the therapeutic efficacy of quadruple therapy (pimobendan, furosemide, spironolactone and benazepril) for the management of DCM in dogs and was found to be effective in reducing the left ventricular dimensions and improving systolic and diastolic functions in dogs with DCM.

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References

Abbott-Johnson, K., Pierce, K.V., Roof, S., Rio, C.L.D. and Hamlin, R. (2021). Acute Effects of Pimobendan on Cardiac function in Dogs with Tachycardia Induced Dilated Cardiomyopathy: a randomized, Placebo-Controlled, crossover study. Front. Vet. Sci. 8: 1-12.

Aparna, G.P.(2021). Pulsed tissue doppler imaging (tdi) in the assessment of left ventricular function in dogs with acquired heart disease. M.V.Sc thesis, Tamil Nadu Veterinary and Animal Sciences university, Chennai.

Bell, E.T., Devi, J.L., Chiu, S., Zahra, P. and Whittem, T. (2016). The pharmacokinetics of pimobendan enantiomers after oral and intravenous administration of racemate pimobendan formulations in healthy dogs. *J. Vet. Pharmacol. Ther.* **39** : 54–61.

Boon, J.A.(2011). Veterinary echocardiography. 2nd edn. John Wiley & Sons. United Kingdom. pp 139-205.

Boswood, A., Häggström, J., Gordon, S.G., Wess, G., Stepien, R.L., Oyama, M.A., Keene, B.W., Bonagura, J., MacDonald, K.A., Patteson, M., Smith, S., Fox, P.R., Sanderson, K., Woolley, R., Szatmári, V., Menaut, P., Church, W.M., O'Sullivan, M.L., Jaudon, J.P., Kresken, J.G., Rush, J., Barrett, K.A., Rosenthal, S.L., Saunders, A.B., Ljungvall, I., Deinert, M., Bomassi, E., Estrada, A.H., Fernandez Del Palacio, M.J., Moise, N.S., Abbott, J.A., Fujii, Y., Spier, A., Luethy, M.W., Santilli, R.A., Uechi, M., Tidholm, A. and Watson, P. (2016). Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study—a randomized clinical trial. *J. Vet. Intern. Med.* **30**(6) :1765–1779.

Buchanan, J.W. and Bucheler, J. (1995). Vertebral scale system to measure canine heart size in radiographs. *J. Am. Vet. Med. Assoc*. **206** : 194-199.

Cheng, K., Malliaras, K., Li, T.S., Sun, B., Houde, C., Galang, G., Smith, J., Matsushita, N. and Marbán, E. (2012). Magnetic enhancement of cell retention, engraftment and functional benefit after intracoronary delivery of cardiac-derived stem cells in a rat model of ischemia/reperfusion. *Cell Transplant*. **21**: 1121–1135.

Cobb.M.A. (1992). Idiopathic dilated cardiomyopathy: advances in aetiology, pathogenesis and management. *J. Small Anim. Pract*. **33**: 113-118.

Gasparini, S., S. Fonfara, S. Kitz, U. Hetzel and A. Kipar. (2020). Canine dilated cardiomyopathy: diffuse remodeling, focal lesions, and the involvement of macrophages and new vessel formation. *Vet. Pathol*. **57**(3) : 397-408.

Häggström, J., Boswood, A., O'Grady, M., Jöns, O., Smith, S., Swift, S., Borgarelli, M., Gavaghan, B., Kresken, J.G., Patteson, M. and Åblad, B.(2013). 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.* **27**(6): 1441-1451.

Haritha, G.S., S.K.Kumar and A.V.V.V. Kumar. (2020). Management of dilated cardiomyopathy with enalapril and losartan. *Adv. Anim. Vet. Sci*.**8**(7) : 777- 781.

Jeyaraja, K., A. Arun, Y.S. Hamsa, P.S.L. Sesh and A.P. Nambi. (2015). Diagnostic evaluation of dilated cardiomyopathy in Labrador Retrievers. *Int. J. Adv. Res*. **3**(12) : 628-655.

Jeyaraja, K., Yamini, S.H. and Chandrasekaran, D. 2019. A Retrospective Analysis of Dilated Cardiomyopathy in Labrador Retrievers. *J. Anim. Res.* **9**(5) : 707-714.

Kanno, N., Kuse, H., Kawasaki, M., Hara, A., Kano, R. and Sasaki, Y. (2007). Effects of pimobendan for mitral valve regurgitation in dogs. *J. Vet. Med. Sci*. **69** : 373–377.

Kittleson, M.D., Keene, B., Pion, P.D. and Loyer, C.G. (1997). Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American Cocker Spaniels with decreased plasma taurine concentration. *J. Vet. Intern. Med*. **11**(4) : 204-211.

Kramer, G.A., Kittleson, M.D., Fox, P.R., Lewis, J. and Pion, P.D. (1995). Plasma taurine concentrations in normal dogs and in dogs with heart disease. *J. Vet. Intern. Med*. **9**(4) : 253-258.

Little, W.C.(2005). Diastolic dysfunction beyond distensibility: adverse effects of ventricular dilatation. *Circulation*. **112**(19) : 2888-2890.

Martin, M.W.S., Stafford, Johnson, M.J. and Celona, B. (2009). Canine dilated cardiomyopathy: a retrospective study of signalment, presentation and clinical findings in 369 cases. *J. Small Anim. Pract*. **50**(1) : 23-29.

Martin, M.W.S, .Stafford, M.J., Strehlau, G and King, J.N. (2010). Canine dilated cardiomyopathy: a retrospective study of prognostic findings in 367 clinical cases *J. Small Anim. Pract*. **51** : 428–436.

Meurs, K.M., Lahmers, S., Keene, B.W., White, S.N., Oyama, M.A., Mauceli, E. and Lindblad-Tohet, K. (2012). A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman pinscher. *Hum Genet*. **131**(8) : 1319-1325.

Oyama, M.A., Chittur, S.V. and Reynolds, C.A. (2009). Decreased triadin and increased calstabin2 expression in Great Danes with dilated cardiomyopathy. *J. Vet. Intern. Med*. **23**(5) : 1014-1019.

Purvey, M. and Allen, G. (2017). Managing acute pulmonary oedema. *Aust. Prescr*. **40**(2) : 59.

Sández, I., Redondo, J.I., Donati, P.A. and Gómez, J.(2023). Haemodynamic Effects of Pimobendan during General Anaesthesia in Healthy Senior Dogs: A Prospective, Randomised, Triple-Blinded, Placebo-Controlled Clinical Study. *Animals* **13**(13) : 2110.

Sergeev, D., Kovalev, S., Trushkin, V., Vasilev, R., Nikitina, A., Kiselenko, P., Konoplev, V. and Tuvargiev, A.(2021). Use of high doses of pimobendan in animals with dilated cardiomyopathy. *The FASEB Journal* : **35**(S1).

Simpson, S., Dunning, M.D., Brownlie, S., Patel, J., Godden, M., Cobb,M., Mongan, N.P. and Rutland, C.S. (2016). Multiple genetic associations with Irish Wolfhound dilated cardiomyopathy. Bio. Med. Res. Intl. 2016 : 1-14.

Sisson, D.D. and Thomas, W.P. (1995). Myocardial disease. In: Textbook of Veterinary Internal Medicine 4th edn.,Ed: S.J. Ettinger, W.B. Saunders, Philadelphia. pp 99-1005.

Srivastava, M., A. Ahuja, R.D. Velhankar, D.K. Bihani, A. Chahar, R.V. Gaikwad, H. Dhadich, S.K. Kashyap, S. Kacchawaha and P. Khangal.(2015). Cardiorenal syndrome in dilated cardiomyopathy of dogs. *Ind. Jour. Can. Pract*. **7**(2) : 94.

Summerfield, N.J., Boswood, A., O'Grady, M.R., Gordon, S.G., Dukes McEwan, J., Oyama, M.A., Smith, S., Patteson, M., French, A.T., Culshaw, G.J. and Braz Ruivo, L. (2012). Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman pinschers with preclinical dilated cardiomyopathy (The PROTECT Study). *J. Vet. Intern. Med.* **26**(6) : 1337-1349.

Suzuki S, Fukushima R, Ishikawa T, Hamabe L, Aytemiz D, and Huai-Che H. (2011) The effect of pimobendan on left atrial pressure in dogs with mitral valve regurgitation. *J. Vet. Intern. Med.* 25(6) : 1328–1333.

Wess, G. and M. Torti.(2018). Arrhythmias in canine cardiomyopathies and valvular heart disease. In. Guide to canine and feline electrocardiography, 1st end., Ed: Willis, R., Oliveira, P. and Mavropoulou, A., John Wiley & Sons Ltd, Oxford, United Kingdom pp 285-300.

Wess, G, (2022). Screening for dilated cardiomyopathy in dogs. *J. Vet. Cardiol*. **40** : 51-68.

Yata, M., McLachlan, A.J., Foster, D.J., Page, S.W. and Beijerink, N.J. (2016). Pharmacokinetics and cardiovascular effects following a single oral administration of a non-aqueous pimobendan solution in healthy dogs. *J. Vet. Pharmacol. Ther.* **39** : 45–53.