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Evaluation of response to combination therapy with enalapril and torasemide in dogs with mitral valve disease#

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Abstract

The present study was carried out with the objective of evaluating the response to a combination therapy of enalapril and torasemide in dogs with mitral valve disease (MVD). Dogs diagnosed with stage C of MVD as per the American College of Veterinary Internal Medicine guidelines were included in the study. Treatment was initiated with enalapril at 0.5 mg/kg BID and torasemide at 0.2 mg/kg OD orally on 0th day. Detailed clinical examination with special reference to the cardiovascular system including measurement of blood pressure, radiographic, electrocardiographic and echocardiographic parameters of the animals were performed on 0th and 30th day of treatment. The treatment was well tolerated by all the animals. Amelioration of clinical signs with a noticeable reduction in cough was noticed in all the animals. On 30th day of treatment, a significant decrease was noticed in the vertebral heart score and left ventricular internal diameter during diastole and a non-significant decrease was noticed in left atrium to aortic root ratio, left ventricular internal diameter during systole, with a considerable reduction in severity of mitral regurgitation. Post- treatment clearing of lung fields was noticed in dogs with radiographic evidence of pulmonary oedema on 0th day. In addition to this, ventricular premature complexes noticed in three animals pre- treatment was not noticed post treatment.

Keywords: *Mitral valve disease, Enalapril, Torasemide*

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Mitral valve disease (MVD) is the most common acquired cardiac disease in dogs representing 75 per cent of all cardiac cases (Haggstrom *et al*., 2009). The disease commonly affects small breed dogs with an occurrence of over 90 per cent in dogs above 13 years and 58 per cent in dogs above 9 years of age. (Abbott, 2008). Along with other senile changes in the body, the valve leaflets also undergo degeneration, thickening and deformation (Revathi *et al*., 2020). Long standing valvular insufficiency leads to volume overload of left atrium (LA) and left ventricle (LV). The increased pressure overload on LA as a result of increased end-diastolic volume in LV inhibits pulmonary venous drainage leading to pulmonary congestion. If left untreated, it can develop to LV dysfunction and congestive heart failure (CHF). Reducing cardiac workload, improving clinical conditions from CHF, retarding cardiac remodelling from neurohormonal response from heart failure and reducing complications from heart failure are the basic strategies for treating MVD. Loop diuretics are the corner stone of treatment of CHF in dogs since they relieve congestion by reducing intravascular hydrostatic pressure thus alleviating the clinical signs associated with it (Atkins and Haggstrom, 2012). Werner *et al.* (2010) attributed the beneficial effects of angiotensin converting enzyme inhibitors (ACE-I) in MVD to the favourable haemodynamic situation by vasodilatation, counteracting fluid retention and blunting the cardiac remodelling.

Materials and methods

The dogs presented to Teaching Veterinary Clinical Complex, Mannuthy with clinical signs suggestive of cardiac diseases such as exercise intolerance, cough, dyspnoea, abnormal cardiac sounds on auscultation and ascites were screened and ten dogs diagnosed with MVD based on two dimensional, M mode and colour Doppler echocardiography were selected for the study (Group I). Echocardiographic evidence of MVD included mitral valve irregularities like mitral valve nodularity, thickening and prolapse, LA dilatation (Left atrium to aortic root ratio $\geq$1.6), LV dilatation, mitral regurgitation with normal to reduced E point to septal separation (EPSS) and a normal to elevated ejection fraction (EF) and fractional shortening (FS) (Boon, 2011). Six apparently healthy adult dogs brought for vaccination or health check-up served as the control (Group II). The selected animals were subjected to detailed clinical examination including blood pressure measurement, radiography, electrocardiography and detailed echocardiographic examination. The radiographs were examined and vertebral heart score (VHS) was calculated based on the procedure described by Buchanan and Bucheler (1995) in left lateral radiographic view. Animals of group I were subjected to a combination therapy with enalapril at 0.5 mg/kg BID and torasemide at 0.2 mg/kg OD orally for one month. The statistical comparison of parameters of animals in group I and II were done using independent t test and that of group I on 0^{th} and 30^{th} day by paired t test using computer software Statistical Package for Social Sciences (SPSS), version 24.0.

Results and discussion

The major presenting complaints of animals in group I were exercise intolerance (80 per cent), cough (70 per cent), dyspnoea (60 per cent), lethargy (60 per cent), syncope (40 per cent), oedema of body parts (30 per cent), inappetence (10 per cent) and recumbency (10 per cent). Similar findings were reported by Unny (2014). A better quality of life with amelioration of clinical signs was evident in the animals post treatment and a noticeable reduction in cough was reported by all owners. The cardiac remodeling effect of enalapril, reduction in congestion by the diuretic action of torasemide or a combination of both might have contributed to the decrease in intensity of cough. Hind limb oedema exhibited by one animal persisted even after the treatment, which on further examination was found to be due to the lymphatic obstruction associated with microfilariosis. An animal that was presented as recumbent remained so even after treatment. Cardiac cachexia was evident in that case.

The predominant finding of sinus rhythm (four animals) in electrocardiography in the present study coincided with the findings of Beaumier *et al*. (2018). The lower prevalence of

sinus arrythmia (one animal) recorded in this study corroborate well with the findings of Rosa *et al*. (2019) and might be due to the increased sympathetic and decreased parasympathetic control occurring in advanced MVD. Wide P wave (P-mitrale) indicative of LA enlargement in MVD was recorded in two animals in this study pre-treatment and was not recorded post-treatment. This might be due to the reduction in LA dimension with decrease in preload.

A significant ($p<0.05$) increase in the QT interval of animals in group I (0.204 ± 0.007 sec) was observed before treatment when compared to group II (0.173 ± 0.012 sec) (Table 1). Similar findings were made by Bruler *et al.* (2018) and it might be indicative of damage to ventricular musculature. Ventricular premature complexes (VPC) were recorded in three animals with moderate to severe MVD (Fig. 1) similar to the findings of Aiswariya *et al*. (2019) and this was corrected by combination therapy (Fig. 2). The increased wall stress and resultant chamber dilatation served as foci for re-entrant arrythmias as suggested by Crosara *et al*. (2010). Right bundle branch block (BBB) was recorded in one dog in this study pre and post treatment (Fig. 3). As BBB can occur without any apparent cardiac diseases and no changes were noticed in ECG post-treatment, it might be associated with an anatomic disruption or neurological disturbance in the conducting bundle.

Significant ($p<0.05$) increase noticed in the systolic and diastolic blood pressure of animals in group I when compared to group II is in agreement with the findings of Unny (2014). This finding was likely caused by the vasoconstrictive effect of angiotensin II, aldosterone and norepinephrine. Antihypertensive effect of enalapril was not effective in reducing blood

Table 1. Mean QT interval of animals in group I and II

Parameter	Period	Group I Mean ± SE	Group II Mean ± SE	t value	p value
QT interval (sec)	Day 0	0.204 ± 0.007	0.173 ± 0.012	2.31*	0.035
	Day 30	0.196 ± 0.011			
	t value	0.801			
	pvalue	0.443			

* Significant at 5 per cent level

Table 2. Blood pressure values of animals in group I and II

Parameter	Period	Group I (Mean ± SE)	Group II (Mean ± SE)	t value	p value
Systolic BP (mmHg)	Day 0	169.2 ± 7.39	139.17 ± 5.15	2.87*	0.012
	Day 30	172.5 ± 9.58			
	t value	0.375			
	p value	0.716			
Diastolic BP (mmHg)	Day 0	101 ± 4.56	83.33 ± 4.01	2.63*	0.019
	Day 30	95.1 ± 5.34			
	t value	0.828			
	p value	0.429			

* Significant at 5 per cent level

Table 3. Vertebral heart score of animals in group I and II

Parameter	Period	Group I (Mean ± SE)	Group II (Mean ± SE)	t value	p value
VHS	Day 0	10.68 ± 0.35	10.13 ± 0.26	1.09	0.292
	Day 30	10.2 ± 0.25			
	t value	2.69*			
	p value	0.025			

* Significant at 5 per cent level

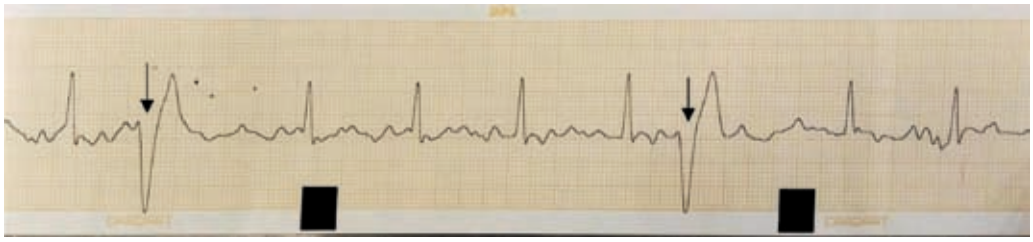

Fig. 1. Lead II ECG of a dog showing VPC pre-treatment (speed :- 50mm/sec, sensitivity :- 10mm = 1mV)

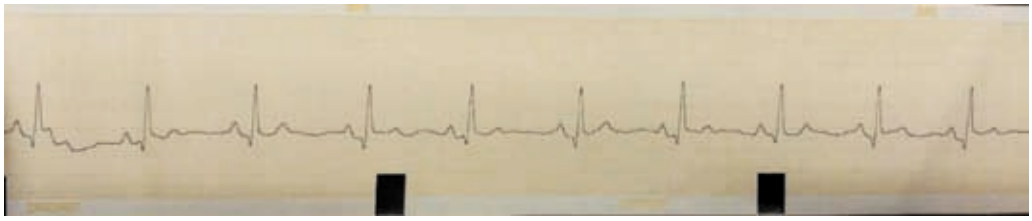

Fig. 2. Lead II ECG of the same dog showing normal sinus rhythm post-treatment (speed :- 50mm/sec, sensitivity :- 10mm = 1mV)

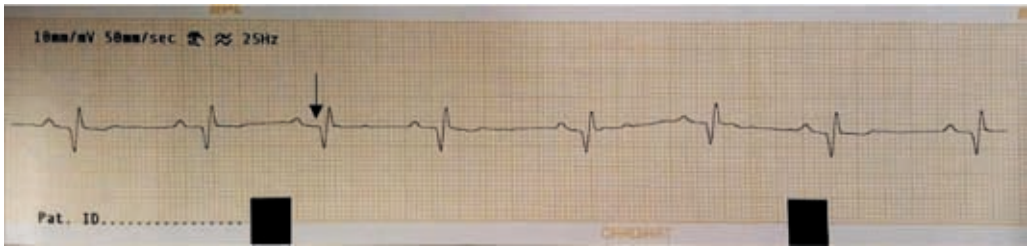

Fig. 3. Lead II ECG of a dog showing right BBB (speed :- 50 mm/sec, sensitivity :- 10mm = 1mV)

pressure. This is supported by the findings of Lefebvre *et al*. (2007) who reported that ACE-I had mild hypotensive effect in dogs. The mean blood pressure values are given in Table 2.

A significant ($p<0.05$) decrease in the VHS of animals in group I was observed on 30th day (10.2 ± 0.25) when compared to 0th day (10.68 ± 0.35), while no significant difference was observed between animals in group I on 0th day and group II (10.13 ± 0.26) (Table 3). Kim *et al*. (2017) reported increase in VHS with disease progression. So the significant decrease noticed in VHS post treatment in this study was indicative of improvement in condition.

Dillon *et al*. (2012) reported that the volume overload resulting in increased end diastolic wall pressure and thus end diastolic wall stress, was the triggering event for the structural and geometrical changes of heart associated with MVD. The radiographic findings in the present study included LA and LV enlargement, dorsal displacement of trachea, carina and left mainstem bronchus and dilated pulmonary veins which commensurate with the findings of Guglielmini (2003). Cardiogenic pulmonary oedema observed in three cases in the present study was defined by the presence of pulmonary venous congestion and unstructured interstitial pattern or alveolar pattern on radiograph as suggested by Borgarelli *et al.* (2021). There was a reduction in the pulmonary oedema post-treatment which was evident by the clearing of lung fields.

The echocardiographic changes included mitral leaflet thickening in seven cases (Fig. 4), leaflet tip nodularity in three Labrador dogs, chordae tendineae thickening with subsequent rupture in one case and systolic leaflet prolapse into LA in two cases.

The left atrium to aortic root ratio (LA: Ao) of animals in group I (1.82 ± 0.12) on 0th day, which was significantly ($p<0.05$) higher than animals of group II (1.48 ± 0.03), showed

a non-significant (p>0.05) decrease on 30th day (1.68 ± 0.07). This can be attributed to the preload reduction by the use of ACE-I and diuretic which further reduced the LA pressure leading to beneficial atrial remodelling.

The M mode echocardiographic parameters are given in Table 4.

No significant difference (p>0.05) in the end-diastolic thickness was observed between the animals of group I on 0th and 30th days and group II. This is in agreement with the findings of Borgarelli *et al.* (2007) who reported that rise in diastolic stress with volume overload of valvular regurgitation led to the serial replication of sarcomeres, which increased myocyte length instead of increasing wall

Table 4. M mode echocardiographic parameters of animals in group I and II

Variable	Period	Group I (Mean ± SE)	Group II (Mean ± SE)	t value	p value
End diastolic wall thickness(cm)	Day 0	0.88 ± 0.04	0.94 ± 0.06	0.81	0.431
	Day 30	0.98 ± 0.06			
	t value	1.594			
	p value	0.145			
LVIDd (cm)	Day 0	3.45 ± 0.28	3.79 ± 0.23	0.828	0.422
	Day 30	3.19 ± 0.24			
	t value	2.335*			
	p value	0.044			
LVIDs (cm)	Day 0	2.07 ± 0.22	2.55 ± 0.13	1.586	0.135
	Day 30	1.92 ± 0.18			
	t value	1.438			
	p value	0.184			
EF (%)	Day 0	70.1 ± 3.54	61.33 ± 2.51	1.75	0.102
	Day 30	71.8 ± 2.65			
	t value	1.176			
	p value	0.27			
FS(%)	Day 0	39.9 ± 2.98	32.67 ± 1.86	1.747	0.103
	Day 30	40.2 ± 2.27			
	t value	0.209			
	p value	0.839			
EPSS (mm)	Day 0	2.71 ± 0.46	3.91 ± 0.43	1.74	0.102
	Day 30	3.06 ± 0.39			
	t value	1.468			
	p value	0.176			

* Significant at 5 per cent level

Table 5. Pulsed wave Doppler echocardiographic findings of animals in group I and II

Parameter	Period	Group I (Mean ± SE)	Group II (Mean ± SE)	t value	p value
E wave velocity (m/s)	Day 0	0.95 ± 0.08	0.82 ± 0.06	1.12	0.278
	Day 30	0.81 ± 0.04			
	t value	2.146			
	p value	0.06			
A wave velocity (m/s)	Day 0	0.54 ± 0.04	0.41 ± 0.03	2.45*	0.028
	Day 30	0.47 ± 0.02			
	t value	1.577			
	p value	0.149			

* Significant at 5 per cent level

thickness.No significant difference (p>0.05) in left ventricular internal diameter during diastole (LVIDd) was observed between animals of group II and group I on 0th day while a significant decrease (p<0.05) was noticed in animals of group I after treatment. Angiotensin II is involved in increase in LV end diastolic volume by excessive filling during diastole and ACE-I by its inhibitory action on renin angiotensin aldosterone system (RAAS) together with the diuretic action of torasemide, might have led to beneficial cardiac remodelling.

The left ventricular internal diameter during systole (LVIDs) of animals in group I before treatment and group II showed no significant difference (p>0.05). Similar findings were made by Petric (2015) who reported that normal LVIDs was seen in case of chronic MVD, unless in the late stage of disease where the systolic function was affected resulting in systolic dilatation. The LVIDs of animals of group I showed a mild decrease post-treatment, similar to the observations of Bakirel *et al.* (2008). This might be indicative of the preservation of normal systolic function.

A non-significant (p>0.05) increase in the value of EF and FS was observed in animals of group I on 0th day compared to group II. Mitral regurgitation resulted in increased preload, which combined with decreased afterload and increased sympathetic tone resulted in a LV hyperdynamic state with elevated EF and FS (Bonagura and Schober, 2009). No significant difference (p>0.05) in the value of animals in group I were observed pre and post- treatment.

The E point to septal separation values showed no significant difference (p>0.05) between animals of group I before and after treatment and group II.

The pulsed wave Doppler echocardiographic findings are given in Table 5. The mean transmitral E wave velocity of animals in group I on 0th day, 30th day and group II were 0.95 ± 0.08, 0.81 ± 0.04 and 0.82 ± 0.06 m/sec, respectively. No significant difference (p>0.05) was noticed between the value of animals in group I on 0th day and group II, and within the animals in group I on 0th and 30th days. Although transmitral E wave velocity is used in identifying diastolic dysfunction and elevated LV filling pressure, the assessment is difficult since they have opposite effects on the value, which may give a pseudonormal value.

Transmitral A wave velocity of animals in group I on 0th day (0.54 ± 0.04 m/sec) was statistically greater (p<0.05) than that of group II (0.41 ± 0.03 m/sec). This was in agreement with the findings of Petrus *et al.* (2018). This might indicate a diastolic dysfunction as with mild diastolic dysfunction, more ventricular filling occurs late in diastole, thus increasing the A wave velocity as reported by Bonagura and

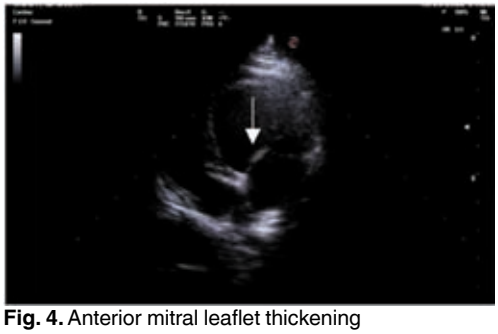

Fig. 4. Anterior mitral leaflet thickening

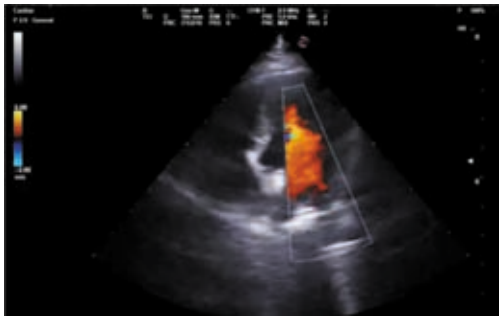

Fig. 5. Pre-treatment colour Doppler echocardiographic image of a dog showing moderate mitral regurgitation

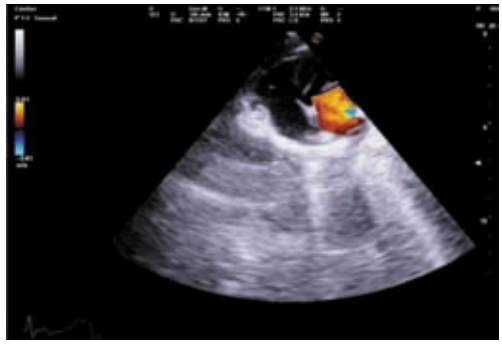

Fig. 6. Post-treatment colour Doppler image of the samedog showing reduction in severity of mitral regurgitation

Schober, (2009). Transmitral A wave velocity of animals in group I before and after treatment (0.47 ± 0.02 m/sec) remained almost similar.

Severe mitral regurgitation (>50 per cent) was observed in two cases, followed by moderate regurgitation (30-50 per cent) in four cases (Fig. 5) and mild regurgitation (<30 per cent) in four cases. Mild tricuspid regurgitation was noticed in three cases. A marked reduction in the severity of mitral regurgitation was observed post treatment (Fig. 6). It is consistent with the findings of Bakirel *et al*. (2008). It might be due to the preload reduction and beneficial cardiac remodelling from the combined effect of enalapril and torasemide.

Conclusion

A significant decrease was noticed in the VHS and LVIDd and a non-significant decrease was noticed in LVIDs and LA: Ao ratio post-treatment in group I animals. This might be due to the beneficial cardiac remodeling effect with the combined preload reduction of enalapril and torasemide. A considerable reduction in the severity of mitral regurgitation was also evident. The post-treatment clearing of lung field in animals with radiographic evidence of pulmonary oedema before treatment might be associated with the relief of congestion by diuretic action of torasemide. The combination therapy with enalapril and torasemide is successful in the management of MVD in dogs.

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Conflict of interest

The authors declare that they have no conflict of interest.

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