

# Effects of Treatment Type on Vertebral Heart Size in Dogs With Myxomatous Mitral Valve Disease

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## ABSTRACT

The effect of treatment protocols including either pimobendan or ramipril on vertebral heart size (VHS) in dogs with class II-III (Scandinavian-modified NYHA system) congestive heart failure (CHF) due to myxomatous mitral valve disease (MMVD) was assessed. Radiographs from 42 dogs were analysed with 21 randomized to pimobendan and 21 to ramipril. VHS was measured prior to treatment at inclusion (Month 0) and at Months 1, 3, and 6. The least square means for the individual treatment groups showed that, for the pimobendan group, a reduction in VHS at Months 1 and 3 of treatment

was observed with an increase at Month 6. In the ramipril group, an increase in VHS occurred at Months 1, 3, and 6. A difference in the treatment group least square means was demonstrable after 1 month of treatment and persisted for the remainder of the study period. Treatment with pimobendan led to lower VHS than treatment with ramipril. The clinical relevance of the changes observed in this study is as yet unclear and needs further investigation. However, it can be speculated that a reduction in VHS is a positive outcome and pimobendan would appear to be more beneficial than ramipril in this respect.

## INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the single most common cardiac disease

of dogs and is particularly prevalent in small breed dogs, but the etiology is still uncertain. Many studies have been published on various aspects of the pathogenesis of this disease.<sup>1,2</sup> As a consequence of this disease, there is an initial decrease in systemic blood flow due to a significant amount of the stroke volume flowing back from the left ventricle (LV) into the left atrium (LA). Cardiac and peripheral compensatory mechanisms are activated to increase heart rate and increase fluid retention; combined, these mechanisms cause volume overload, which results in dilation and eccentric hypertrophy.<sup>3</sup> This dilation and eccentric hypertrophy is partially due to dissolution of the collagen weave and remodeling of the extracellular matrix. There is rearrangement of myocardial fibers in association with the addition of new sarcomeres resulting in lengthening of the cardiomyocytes.<sup>4,5</sup>

Treatment of dogs with congestive heart failure (CHF) secondary to MMVD with protocols involving either angiotensin-converting enzyme inhibitors (ACEi) or pimobendan have been shown to reduce morbidity and mortality.<sup>6-11</sup>

Thoracic radiography is considered to be one of the most important diagnostic tools in the investigation and diagnosis of CHF in dogs. Information regarding status of the pulmonary circulation and the amount of oedema in the lungs can be obtained; additionally, the size and shape of the heart can be determined and give important information regarding the type and severity of disease. There are a variety of subjective and semi-quantitative methods of assessing heart size, and the preferred method at present is the vertebral heart scale.<sup>12</sup>

Comparison of heart size and vertebral length was first investigated by Buchanan and Bucheler<sup>12</sup> as good correlations were known to exist between body length and heart weight.<sup>13</sup> This led to the vertebral scale system used to measure canine and feline heart size in radiographs, where the cardiac dimensions in the lateral projection are scaled against the thoracic vertebral column. The mean canine vertebral heart size (VHS) value in the initial study was 9.7v (SD = 0.5)

with a “clinical” range of 8.5–10.5v suggested. Further studies have shown a need for breed-specific VHS values as several breeds had mean VHS values approximately 1v higher than 9.7v.<sup>14</sup> VHS has also been used to assess progressive cardiomegaly in spontaneous disease in dogs,<sup>12</sup> pacing induced experimental heart failure,<sup>15</sup> growth in dystrophin-deficient cats,<sup>16</sup> hypoadrenocorticism,<sup>17</sup> postoperative patent ductus arteriosus,<sup>18,19</sup> and postoperative mitral annuloplasty.<sup>20</sup>

The aim of the present study was to use VHS as an objective evaluation of heart size over time in 2 groups of dogs with heart failure caused by MMVD, comparing the effect of pimobendan and ramipril.

## MATERIALS AND METHODS

The radiographs used for this study were from a prospective, randomised, single-blind, parallel-group design trial.<sup>8</sup> Forty-two sets of radiographs were available from the 43 dogs that had completed that study. Radiographs were taken of each dog prior to treatment (Month 0) and over the 6-month treatment period (Months 1, 3, and 6) with a treatment protocol including furosemide and either pimobendan or ramipril in dogs with class II-III (Scandinavian-modified NYHA system) CHF due to MMVD. The minimum effective dose of furosemide was prescribed at all times. Digoxin was also prescribed, if needed, for the treatment of supraventricular tachyarrhythmias. No concomitant treatment with other inodilator drugs, other ACEis, or vasodilators occurred.

For the purpose of assessment of VHS, the following protocol was used. VHS was measured at each of the time points (0, 1, 3 and 6 months) using the system proposed by Buchanan and Bucheler.<sup>12</sup> The radiographs were first randomised using SAS Version 8.2 via the RANUNI function prior to the VHS being calculated. A RCVS diploma holder in veterinary radiography (EM), who was blinded to the treatment group to reduce bias then assessed the VHS from each of the radiographs. The length of the heart was measured from the ventral border of the left main stem bronchus to the most ventral contour of the cardiac apex. The width was

measured perpendicular to the long axis at the maximal short axis distance in the central third region. The length and width of the heart were individually recorded as the number of vertebrae from the cranial edge of T4 and estimated to the nearest 0.1 of a vertebra. The sum of the length and width gave the VHS.

Of the 42 dogs radiographs assessed, 40 provided at least 1 on-treatment assessment. In order to account for missing VHS values at Months 3 and 6, a last observation carried forward (LOCF) technique was used. This ensured that there were 40 dogs included in each of the Month 1, 3, and 6 analyses. Analysis of covariance (ANCOVA) was performed on the change from Month 0 to each of the Month 1, 3, and 6 assessments, with the Month 0 VHS being fitted as a covariate and treatment as a factor in the model. From the analysis, least square (LS) treatment means (adjusted for the Month 0 VHS) were calculated along with the difference in the LS means. The clinical aspects of this study were reported by Smith et al.<sup>8</sup>

## RESULTS

VHS was measured in 42 client-owned dogs with 21 randomised to receive pimobendan and 21 to receive ramipril; of these, 40 provided at least 1 on-treatment assessment (21, pimobendan; 19, ramipril). Twenty-six (60%) of the dogs were male and 17 (40%) were female. The mean (SE) age of the dogs was 10.1 (0.39) years. The majority of the dogs were Cavalier King Charles spaniels (58%).

The LS means for the individual treatment groups showed an initial reduction for the pimobendan group over the first month of treatment; by Month 3, a smaller reduction was observed; and by Month 6, a slight increase in VHS was observed. For the ramipril group, an initial increase was observed over the first month of treatment; this continued to increase at Month 3, and a further small increase was observed by Month 6 (Table 1 and Figure 1).

The difference between the treatment group LS means was relatively constant over the 6-month treatment period ranging

from 0.563 at Month 1 to 0.476 at Month 6. The difference between treatments at Months 1 and 3 were statistically significant ( $P < 0.05$ ), with the difference at Month 6 approaching statistical significance ( $P = 0.064$ ). There was no evidence of any departure from normality.

## DISCUSSION

This study demonstrated that pimobendan resulted in a reduction in VHS in clinically affected dogs with MMVD. Furthermore, the differences in LS means showed that treatment with pimobendan leads to lower VHS than treatment with ramipril, particularly over the first 3 months of treatment.

The VHS of the ramipril group increased at Months 1 and 3, and remained the same at Month 6 whereas the pimobendan group VHS decreased at Month 1 and increased from then to Month 3 but still remained below the original baseline. The initial mean VHS in the pimobendan group was similar to that at the end of the study. In this study, the difference in the vertebral heart scores between the groups was not reflected in the previously published echocardiographic data, with no statistical differences in any of the echocardiographic parameters measured between the 2 groups.<sup>8</sup>

The clinical significance, if any, of these findings is unknown, but it can be speculated that a reduction in cardiac size is a positive outcome of treatment and pimobendan would appear to be more beneficial than ramipril in this respect. Indeed, in the study by Kvarn et al<sup>21</sup> looking at the effects of enalapril on time to developing CHF in asymptomatic MMVD, cardiomegaly was a risk factor for developing CHF. In the situation where CHF has been controlled, the effect of controlling subsequent development of cardiomegaly on outcome is unknown. In the current study, the difference in VHS, while statistically significant, might be regarded as relatively small; further studies would be needed to ascertain whether even these small changes have a beneficial effect on disease progression, clinical outcome, and survival.

However, Lombard et al<sup>10</sup> similarly found that VHS was reduced in dogs with

**Table 1.** ANCOVA Results for Change in VHS.

Assessment	Statistic	Pimobendan	Ramipril
Month 1	N	21	19
	LS Mean <sup>1</sup>	-0.206	0.357
	Diff LS Means (Ram-Pim) <sup>2</sup>	0.563	
	95% CI <sup>3</sup>	(0.143, 0.984)	
	P-value <sup>4</sup>	0.010*	
Month 3	N	21	19
	LS Mean <sup>1</sup>	-0.031	0.524
	Diff LS Means (Ram-Pim) <sup>2</sup>	0.554	
	95% CI <sup>3</sup>	(0.061, 1.048)	
	P-value <sup>4</sup>	0.029*	
Month 6	N	21	19
	LS Mean <sup>1</sup>	0.054	0.530
	Diff LS Means (Ram-Pim) <sup>2</sup>	0.476	
	95% CI <sup>3</sup>	(-0.028, 0.981)	
	P-value <sup>4</sup>	0.064	

<sup>1</sup>Least square (LS) mean for change from Month 0 in VHS (adjusted for Month 0 VHS).

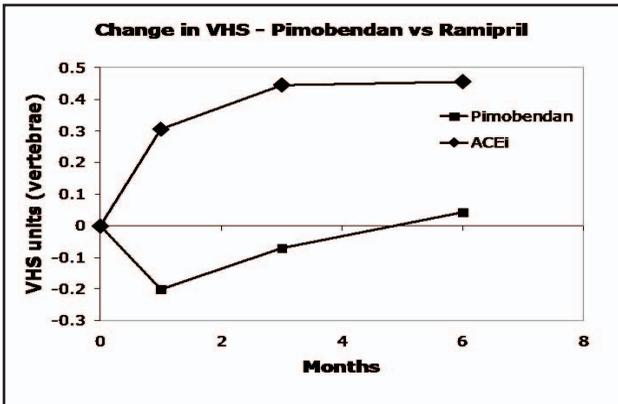
<sup>2</sup>Difference in least square means (ramipril minus pimobendan).

<sup>3</sup>95% confidence interval for the difference in the least square means.

<sup>4</sup>P-value from the ANCOVA F-test.

\*Statistically significant at the 2-sided 5% level.

**Figure 1.** LOCF Months on treatment compared to VHS change.



MMVD treated with pimobendan, whilst it increased in dogs treated with benazepril in the first 56 days of their study, during which period, significant differences were also identified with regard to clinical outcomes and survival. Furthermore, Vollmar et al<sup>11</sup>

have reported initial findings in Irish Wolfhounds with asymptomatic dilated cardiomyopathy which suggest that left ventricular reverse remodelling (LVRR) was observed in a higher percentage of pimobendan treated cases and normalization of LV measurements lasted longer than in benazepril and metildigoxin treated dogs. The findings with pimobendan were associated with a lower incidence of therapy failure, suggesting that decreasing heart size is associated with an improvement in prognosis.

The VHS of sequential radiographs of a dog with mitral valve disease have been reported by Buchanan and Bucheler.<sup>12</sup> A 21% increase in vertebral heart score over a 3.5-year period was found. The absolute M-mode echocardiographic measurements were reported not to reflect the extent of heart enlargement as well as the VHS method over the final 2.5-year period. In fact, echocardiography failed to identify any change in dimensions, whereas the VHS increased by 16%. The reason for this difference is the presumption that echocardiographic measurements represent only a single dimension (mainly short axis), whereas the VHS method identifies change in 2 dimensions. Other considerations are that differences in volume loading of the left ventricle and atrium are not the reason for the observed differences in the vertebral heart scores. Another possible explanation is a change in volume of the right side of the heart, not measured on echocardiography, which is included in the vertebral heart score measurement, is responsible for the difference.

The only other reference correlating VHS and echocardiographic parameters was an experimental dog study that used rapid ventricular pacing to cause varying degrees of cardiomegaly.<sup>15</sup> In that study, the VHS seemed to

correlate well with both echocardiographic and electrocardiographic parameters, but there was no attempt made to indicate which method of assessing cardiac size was the most accurate. The contrast between these results and those obtained by the present study and by Buchanan and Bucheler<sup>12</sup> could be simply explained by the difference in the initiating cause of the cardiomegaly (rapid ventricular pacing vs naturally occurring myxomatous mitral valve disease).

The mechanisms of development of cardiomegaly in mitral regurgitation are not completely understood. It has been characterized by an absence of fibrosis and by dissolution of the fine collagen weave. In a study by Dell'italia et al,<sup>4</sup> volume-overload cardiac hypertrophy due to experimentally created mitral valve regurgitation was shown to be unaffected by treatment with ramipril. In the group of dogs not treated with ramipril, a focal loss of the collagen fibre weave surrounding the individual myocytes and myocyte bundles in the left ventricle was observed, with a more diffuse loss of the collagen weave noted in the group treated with ramipril. Perry et al<sup>5</sup> demonstrated that treatment with AT1 receptor blocking agent during the early adaptive phase (at the onset of mitral regurgitation) further weakened the collagen weave thereby offsetting any beneficial effect on LV size that might be produced by vasodilation. In addition to these actions of ACEis and AT1 receptor blockers on the LV interstitium, it is possible that a similar deleterious effect is present in prolapsing mitral leaflets.<sup>22</sup> Dissolution of the collagen weave could be one of the factors that cause the increase in VHS in the ramipril-treated dogs.

It has been shown in an experimental study using myocardial infarction in the dog that ACEis decreased progressive ventricular dilation,<sup>23</sup> but in other studies, an increase in LV end diastolic dimensions and LA diameter in dogs receiving enalapril was observed.<sup>24</sup> Again, the discrepancy in the findings between this study, the study by Haggstrom et al,<sup>24</sup> and those with experimentally induced CHF can be attributed to the different characteristics of the underlying cardiac insult. In the study by Haggstrom

et al,<sup>24</sup> the different effects of the 2 treatments on LV end diastolic dimensions and LA diameter may have been caused by hypotension and increased heart rate in dogs receiving hydralazine.<sup>25</sup> An increased heart rate, shown in the hydralazine group, causes shortening of the diastolic filling period, decreasing the ventricular diastolic volume. In the present study, no difference in heart rate was observed between the different groups. Another reason for the increase in VHS in the ramipril group could be because of the antagonism of the angiotensin II positive inotropic effects.<sup>26, 27</sup>

Pimobendan has been shown to have positive inotropic effects in dogs with experimentally induced CHF due to calcium sensitisation rather than phosphodiesterase III inhibition and in this study, a reduction in LV volume in dogs receiving pimobendan was observed.<sup>28</sup> The positive inotropic effects of the pimobendan may be a possible explanation for the reduction in VHS seen in the pimobendan group. Though statistical significance has been observed, some consideration should be given as to whether the differences observed between the groups are clinically significant.

The limitations of this study include the fact that in the original study,<sup>8</sup> a statistically significant difference was present in the mean mobility and demeanor scores for the 2 treatment groups at baseline, with the ramipril group having worse scores. Since these scores were both significantly predictive of an adverse heart failure outcome, those dogs treated with ramipril may have had more advanced disease at baseline than those treated with pimobendan. The number of dogs enrolled was relatively low and the analysis is post-hoc and therefore potentially biased. Three analyses have been produced and hence the type I error rate is inflated; no adjustment for multiplicity has been performed (ie, the more analyses you do the more likely you are to get a significant *P*-value just by chance).

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