

Enalapril in the Asymptomatic Patient with Chronic Valvular Disease

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One of the most frequent dilemmas we face in cardiac patients is what to do with the older, small breed dog with a murmur of mitral regurgitation from chronic valvular disease that is otherwise asymptomatic for cardiac disease. As valvular disease progresses along its inexorable path toward congestive heart failure, we strive to provide some therapy that will alter the course of this disease.

Enalapril, the only angiotensin-converting enzyme inhibitor (ACEI) approved for use in dogs in this country, is one drug that is potentially promising for this purpose.

ACEI and the Asymptomatic Dog

Human studies have shown benefit from the use of ACEI in all stages of heart failure secondary to myocardial failure including Class I and II in which congestion (pulmonary edema) is not present. This is fairly easy to extrapolate to dogs with dilated cardiomyopathy (DCM). In fact, a retrospective study showed increased survival in asymptomatic Dobermans with DCM treated with one of three different ACEI. Therefore, ACEI are warranted as therapy in asymptomatic DCM.

The harder question then has been: what about ACEI in asymptomatic canine mitral valve disease? Is there either an increase in time to development of congestive heart failure or in overall survival time when dogs with asymptomatic mitral regurgitation are treated with ACEI? Two recent studies (relatively large-scale, in veterinary terms) have addressed just this issue.

The first of these trials to be completed and published is the Scandinavian Veterinary Enalapril Project (SVEP). Two hundred twenty-nine Cavalier King Charles Spaniels (CKCS) with murmurs of mitral regurgitation but no congestive heart failure were enrolled in the 4-year study. One hundred seven of these dogs had radiographic signs of cardiomegaly at entry. Dogs were treated with either enalapril (0.25-0.5mg/kg *q.d.*, average 0.38mg/kg) or placebo. Ninety-eight dogs reached the endpoint of congestive heart failure. There was no detectable difference in time to development of heart failure in dogs receiving enalapril versus dogs receiving placebo, even when only those dogs with cardiomegaly at entry (and therefore potentially more advanced disease) were evaluated. This led the authors to conclude, "This study failed to show any preventive effect of enalapril for developing congestive heart failure (CHF)."

The second study is the Veterinary Enalapril Trial to Prove Reduction in Onset of Failure (VETPROOF). Results of this study are not yet published, but preliminary results were presented at the ACVIM Forum in 2002. One hundred twenty-four dogs with echocardiographically confirmed valve disease, radiographic and echocardiographic evidence of severe left atrial enlargement, but no pulmonary edema were enrolled in the study. Numerous breeds were represented, but all dogs were <22kg in body weight. Dogs were randomized to treatment with either enalapril at 0.5mg/kg *PO q.d.* or placebo. Endpoint was the

development of congestive heart failure. Dogs treated with enalapril remained in the study longer than dogs receiving placebo, and there was a trend toward increased time to onset of heart failure, though this did not reach statistical significance. The benefit appeared to be modest.

In evaluating the results of these studies, one must look at the study limitations. In the SVEP trial, one could certainly argue that the results are only valid for the breed studied, the CKCS. We know that Cavaliers develop mitral regurgitation at an earlier age and with a very high prevalence as compared to other breeds, so perhaps their disease is also different in its response to ACE inhibition. Also, the average daily dose of enalapril in SVEP (0.38mg/kg) is lower than that used in the enalapril studies in dogs with congestive heart failure. VETPROOF did include multiple breeds and the dose of enalapril was higher (0.47mg/kg average dose). Both studies suffer from a lack of adequate statistical power. Though these are large-scale studies in veterinary terms, the number of patients enrolled is only adequate to show very large differences in outcome. Modest benefit, as is suggested in the VETPROOF trial, is very difficult to prove statistically without much larger studies. Because the entry criteria for the VETPROOF study required significant left atrial enlargement in the enrolled patients and the SVEP trial did not, the patients enrolled in VETPROOF tended to have more advanced disease than those in SVEP. This may have accounted for the trend toward increased time to CHF detected in VETPROOF that was not apparent in SVEP.

Now that we have the results of these trials at hand, do we know the answer as to whether or not ACEI are indicated in asymptomatic mitral valve disease? If the benefit expectations are high, then the answer is no. However, if a modest benefit is sufficient to meet treatment expectations, then the answer remains perhaps...

How We Use Enalapril in Our Practice

It is relatively clear from these two studies that enalapril is not the wonder drug we long for that will delay the onset of congestive heart failure by years in chronic valvular disease. It is also relatively clear that its usefulness early in the course of disease, before the onset of significant cardiac enlargement, is minimal. Initiation of enalapril therapy at this point could condemn an owner to years of treatment with a relatively expensive drug that can have significant side effects with little to be gained. Therefore, we evaluate our patients with suspected valvular disease with the purposes of confirming the disease process (i.e. ruling out other cardiac conditions such as myocardial failure) and assessing the degree of cardiac enlargement. This is best accomplished with the combination of an echocardiogram and thoracic radiographs. We also measure blood pressure in every patient with chronic valvular disease.

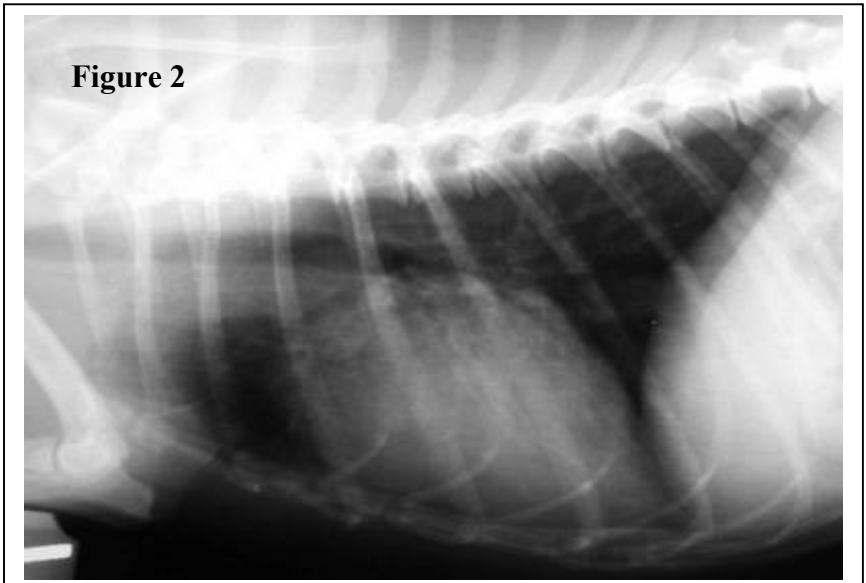
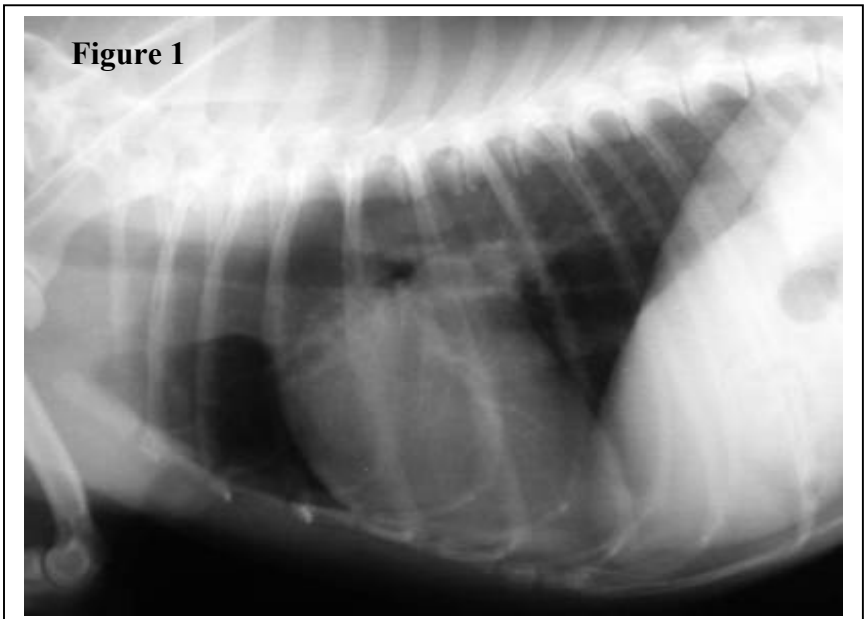
If a patient with valvular disease is hypertensive (blood pressure repeatedly greater than 170 mmHg systolic), it is placed on enalapril and the dose is adjusted to achieve normotension while monitoring renal function. If a normotensive animal has mild (**Figure 1**) or moderate heart enlargement (**Figure 2**), we follow heart size radiographically every 6 -12 months. Once a normotensive animal develops severe heart enlargement, even when

asymptomatic, it is our practice to initiate enalapril therapy. Renal function and blood pressure are assessed before and 1-2 weeks following initiation to treatment. Our belief in doing this is that while we are unlikely to lengthen this animal's life by years, we often fight for months once an animal develops CHF. If monotherapy with enalapril can buy us a few months of these animals' lives before we are fighting symptoms with multiple drugs, it is probably worthwhile.

References:

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