SUBACUTE ECHOCARDIOGRAPHIC EFFECTS OF ACE INHIBITORS IN THE DOGS WITH SEVERE MITRAL REGURGITATION

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Abstract

The effects of the angiotensin converting enzyme inhibitors benazepril (B), enalapril (E), and ramipril (R) on the function, geometry, and dimensions of the left ventricle (LV) in the dogs with naturally acquired severe mitral regurgitation (MR) were evaluated by echocardiography. Thirty-two dogs, aged 8-16 years and weighing 10-12 kg, with fractional shortening (FS) >50% were included into the study. Benazepril (0.5mg/kg/d), enalapril (0.5mg/kg/d), and ramipril (0.5mg/kg/d) were administered orally to B, E, and R groups, respectively. Furosemide (2mg/kg/d) was administered orally for conventional heart failure therapy. Physical, radiographic, electrocardiographic, and echocardiographic examinations were performed before treatment and on day 7 after the treatment. A decrease in the left ventricle end diastolic diameter (LVEDd) in groups E and R and in end diastolic volume (EDV) in group E was considerable during the subacute period (P<0.05). The stroke volume (SV) significantly decreased in groups E and R (P<0.01), whereas group B dogs had a mild decrease (P<0.05). FS and ejection fraction (EF) that were higher before treatment decreased significantly in all groups after the treatment (P<0.001). Differences in SV, FS, and EF were not statistically significant between groups. It was detected that LV was remodelled as a result of the effects of enalapril and ramipril on LVEDd and also EDV was decreased by enalapril. Furthermore, it was observed that these ACE inhibitors were effective on geometry, dimensions, and functions on LV of the dogs with severe MR, and enalapril was found to be the most effective agent, followed by ramipril and benazepril.

Key words: dog, mitral regurgitation, benazepril, enalapril, ramipril.

Mitral regurgitation (MR) caused by myxomatous degeneration of the mitral valve leaflets and associated structures, is the most common cardiovascular disease identified in dogs (13, 24). The disease is frequently found in older dogs and small breeds (3). Although the aetiology of the disease is ascertained, there is a substantial information concerning factors influencing the disease development, such as genetic factors, collagen abnormalities, breed predilection, stress, hypertension, hypoxia, prior viral and bacterial infections, and a variety of endocrine abnormalities (13, 19, 24). The diagnosis of MR is commonly based on case description, history, and physical examination findings. Echocardiography identifies the abnormal valve anatomy and ventricle enlargement (16). Chronic degenerative mitral valve disease (CVD) causes thickening of the mitral valve leaflets and the subsequent volume load associated with MR causes left ventricular (LV) and atrial dilatation, LV wall and septal hypertrophy, elevated parameters of function, and hyperkinetic LV wall and interventricular septal motion (5, 8, 13).

Blockade of the renin-angiotensin system with angiotensin converting enzyme (ACE) inhibitors has showed to modulate adverse LV remodelling and beneficially alter haemodynamic and clinical status in dogs with heart failure (10, 20, 23). The studies in humans and dogs with MR have suggested that therapy with ACE inhibitors prevents progressive worsening of MR and LV dilatation (10, 15, 17, 23). In addition, the studies, which tested ACE inhibitors for the prevention of MR or for the reduction of the severity of the existing regurgitation, demonstrated acute or long-term effects (11, 15, 21, 23). However, the effects of ACE inhibitors in dogs with MR are controversial. Because some dogs have a dramatic response or no response or mild to moderate improvement, clinical impression to ACE inhibitors can be quite various (7, 17, 27). The hypothesis that subacute therapy with ACE inhibitors, such as benazepril, enalapril, and ramipril have beneficial effects on the function, geometry, and dimensions of LV in the dogs with naturally acquired MR, was tested in present study.
Material and Methods

Study design. The medical records of dogs examined between January 2000 and April 2007 were reviewed. Sixty-two dogs with chronic mitral regurgitation diagnosed by echocardiography were detected in these records. Their body weight was between 10 and 12 kg. The presence of a cough or exercise intolerance and systolic heart murmur (V/VI or VI/VI), and the identification of a severe degree of MR and LV fractional shortening (FS) more than 50% by 2-D and M-mode echocardiographic examination were the criteria that was considered as suitable for inclusion to the study.

The criteria that excluded dogs from the study were the presence of myocardial disease of any aetiology; systemic or congenital disease, or both; multivalvular disease, acquired cardiovascular disorders that affect the mitral valve, FS less than 50% in miniature, toy, or large breed dogs. According to the criteria, 32 dogs were selected for this study. They consisted of 25 males and 7 females and aged 8-16 years. The dogs were randomly divided into three groups as benazepril-treated (B), enalapril-treated (E), and ramipril-treated (R).

Study protocol and drug administration. Within group B, 10 dogs received benazepril tablets at a daily dose of 0.5 mg/kg b.w. Enalapril tablets at a dose of 0.5 mg/kg/d were given to 20 dogs in group E and ramipril tablets at a dose of 0.25 mg/kg/d were given to 10 dogs in group R. All the drugs were administered for 7 d. A conventional therapy for heart failure (furosemide 10 mg/kg/d) was applied to all the dogs. Before and after the medication, the dogs underwent clinical examination, 12-lead electrocardiography, chest X-ray, and echocardiography (2-D and M-mode). The examination and all the measurements and calculations were evaluated by two observers.

Echocardiography and measurements. In accordance with the techniques described, records of 2-D and M-mode echocardiograms were obtained from right parasternal short-axis and long-axis views at the level of the chordae tendineae with the dogs positioned in a right lateral recumbence (2, 26). The echocardiographic images were obtained with SDU-350A echocardiography device and micro-convex transducer of 3.5-5.0 MHz. After a complete 2-dimensional examination of the dogs, LV diastolic and systolic diameters were assessed on M-mode measurement as recommended by the American Society of Echocardiography. The examinations were performed in conscious, unseated dogs. Left ventricular end-diastolic diameter (LVEDd) and left ventricular end-systolic diameter (LVEDs) were obtained according to M-mode measurements as previously described (2, 22). The FS percentage was calculated using the following formula: [(LVEDd - LVEDs)/ LVEDd] x 100. The end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using the Teichholz method: EDV= [7x (EDD)^3]/(2.4+EDD) and ESV= [7x (EDS)^3]/(2.4+EDS). Stroke volume (SV) and ejection fraction (EF, %) were calculated according to the formula: SV=(EDV–ESV) and EF%=[(EDV-ESV)/EDV] x 100 (13, 24).

Statistical analysis. The student’s t-test was used for a comparison of changes from a baseline of such parameters as LVEDd, LVEDs, FS, EDV, ESV, SV, and EF. The treatment effects were compared between groups and within groups using a two-way repeated-measures analysis of variance (ANOVA). Values of P<0.05 were considered to be statistically significant. Data were presented as mean ± SD.

Results

None of the dogs used in the study had other disease associated with severe MR and all of them had a systolic murmur (V/VI and/or VI/VI) obtained in the left cardiac apex. Clinical characteristics and measurements of the LV dimensions and functions at baseline were similar in all the groups and the differences of baseline data were not statistically significant. The comparison of the results before and after ACE inhibitors therapy performed in dogs with severe MR is presented in Table 1.

At the end of the 7-d treatment, LVEDd and LVEDs decreased in all groups. While the left ventricle end diastolic diameters were markedly declined, there were no significant differences between the left ventricle end systolic diameters. The decline of LVEDd was significant in the dogs receiving enalapril and ramipril (P<0.05). FS (>53%), which was higher before the treatment decreased significantly during the 7-d period in three groups (P<0.001).

Although the left ventricle EDV and ESV decreased in all the dogs after the treatment, a decrease in EDV was statistically significant only in group E (P<0.05). SV was markedly declined in three groups. E and R dogs showed significant differences in SV (P<0.01), whereas group B dogs showed a mild difference (P<0.05). Ejection fraction decreased significantly in all the groups after the treatment (P<0.001). No significant differences in SV, FS%, and EF% were detected between the groups, but the drugs induced a considerable effect on these parameters.

The left atrial volume equal or larger than left ventricular volume, thickening of inferior and posterior leaflets of the mitral valve, mitral posterior and inferior leaflets moving towards the left atrial space during systole, opening the leaflets during systole, contact of inferior leaflet of the mitral valve to the interventricular septum, and ineffective contraction of LVPW were detected by a pre-treatment echocardiographic examination. A decrease in myocardial contractibility of LVPW was obvious in post-treatment echocardiographic evaluation. There was no significant decrease in myocardial contractibility of the interventricular septum (Fig. 1). In addition, it was detected that the left ventricle was remodelled as a result of the effects of enalapril and ramipril on LVEDd and enalapril decreased diastolic stroke volume.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Group B (n=10) Before</th>
<th>Group B (n=10) After</th>
<th>Group E (n=12) Before</th>
<th>Group E (n=12) After</th>
<th>Group R (n=10) Before</th>
<th>Group R (n=10) After</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDd (mm)</td>
<td>41.7±2.2</td>
<td>33.2±2.4*</td>
<td>41.6±0.89</td>
<td>32.2±0.81*</td>
<td>41.4±1.7</td>
<td>31.6±1.9*</td>
</tr>
<tr>
<td>LVEDs (mm)</td>
<td>19.5±1.0</td>
<td>18.6±1.1*</td>
<td>18.8±0.41</td>
<td>18.1±0.56*</td>
<td>19.2±1.0</td>
<td>19.0±1.1*</td>
</tr>
<tr>
<td>FS (%)</td>
<td>53.1±0.58</td>
<td>39.8±1.4***</td>
<td>54.7±1.2</td>
<td>40.5±1.5***</td>
<td>53.7±1.1</td>
<td>40±0.93***</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>118.1±13.1</td>
<td>77.9±11.8*</td>
<td>115±5.1</td>
<td>67.7±3.7*</td>
<td>95.3±4.2</td>
<td>67.1±9.0*</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>26±3.8</td>
<td>24.5±9.0*</td>
<td>23.7±1.3</td>
<td>22±0.96*</td>
<td>23.7±2.8</td>
<td>23.2±2.8*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>93.6±10.4</td>
<td>51.9±8.1*</td>
<td>91±4.0</td>
<td>44.9±3.9**</td>
<td>91.6±8</td>
<td>43.9±6.3**</td>
</tr>
<tr>
<td>EF (%)</td>
<td>79±0.59</td>
<td>66±1.4***</td>
<td>80.8±1.3</td>
<td>65.1±3.3***</td>
<td>79.6±0.93</td>
<td>65±1.2***</td>
</tr>
</tbody>
</table>

* P<0.05, ** P<0.01; *** P<0.001; ns: non-significant

B - benazepril-treated dogs, E - enalapril-treated dogs, R - ramipril-treated dogs, LVEDd - left ventricular end-diastolic diameter, LVEDs - left ventricular end-systolic diameter, FS - fractional shortening, EDV - end-diastolic volume, ESV - end-systolic volume, SV - stroke volume, EF - ejection fraction.

Fig. 1. M-mode and 2D echocardiograms obtained from right parasternal long-axis views: A - 2-D image of thickening of the mitral valve leaflet and M-mode image of no closure of the mitral valve leaflets during systole from an echocardiogram of a dog in group B. B - M-mode images of hyperkinetic left ventricle and interventricular septal wall motion and 2D image of left atrial space more echogenic than left ventricular space from an echocardiogram of a dog in group R. C - hyperkinetic wall motion and contact of inferior leaflet of the mitral valve to the interventricular septum shown in pre-treatment echocardiogram of a dog in group E. D - a decrease in left ventricular diameter and myocardial contractility of the left ventricular posterior wall shown in post-treatment echocardiogram of a dog in group E. IVS - interventricular septum, CT - chordae tendineae, LV - left ventricle, LA - left atrium, MV - mitral valve, LVPW - posterior wall of left ventricle.
Discussion

The valvular lesions characteristic for CVD are caused by an acquired chronic structural degeneration of the atrioventricular valves. The disease occurs also due to disturbances of the heart muscle, destruction of connective tissue, and consequently, an enlargement of the left ventricle and cardiac infarct. Most commonly, the mitral leaflets and corresponding chordae tendineae are affected (9). Small breed dogs are sensitive to mitral regurgitation due to CVD. The prevalence of the illness is 10% within an appropriate dog population of five- to eight-year-old animals and increases with age (1, 3, 4). The dogs included into this study were of small breeds. Several studies have shown that the age is a major determinant of prevalence of CVD in various dog populations (4, 5, 9).

CVD of mitral valve regurgitation may lead to left atrioventricular volume overload, pulmonary oedema, atrial dilatation, arrhythmias, and occasionally to myocardial failure and pulmonary hypertension in advanced heart disease (1). In this study, pulmonary oedema, and left atrioventricular volume overload, severe systolic murmur, and atrial dilatation were found in the dogs by clinical, radiographic, and echocardiographic evaluations and also supraventricular arrhythmias were detected in most of the dogs by electrocardiography.

Echocardiography permits a confirmation of the diagnosis, a statement of disease severity, the probable cause, as well as an evaluation of the process. Additionally, the size and pumping function of the left ventricle can be reliably determined with the help of the echocardiography. MR, to a lesser degree, does not induce any apparent changes in the indices of cardiac size or function. As the regurgitation increases due to progressive valvular lesions, the left atrium expands to buffer the regurgitant volume. The left ventricle compensates the loss of forward stroke volume by increasing its end diastolic volume. This causes an increased force of contraction according to the Frank-Starling mechanism. The resistance to ventricular emptying is reduced in MR, causing a more complete emptying of the chamber (12, 14). When compared to healthy dogs with the same body weight (19), LVEDd, LVEDs, EDV, ESV, and SF were calculated as higher pre-treatment echocardiographic parameters of the dogs in this study. There was also a severe MR detected clinically and by echocardiography in the dogs examined.

There were three major findings of this study. First: benazepril, enalapril, and ramipril significantly reduced cardiac contractility and ejection fraction after treatment. Second: ACE inhibition reduced cardiac sizes. While this reduce was insignificant in LVEDs, LVEDd significantly decreased in the groups E and R. Therefore, ACE inhibitors used in this study prevented progressive ventricular dilatation and it was detected that the left ventricle was remodelled in the short period. Third: in spite of a significant reduction in cardiac contractility and sizes in preload in group E, no alteration were detected in the afterload. It could be explained by ventricular wall stress. However, a reduction in stroke volume was significant in all the groups.

ACE inhibitors are potent vasodilators reducing volume load to the heart, as shown in the previous human and animal studies (15, 17, 23). The effects of ACE inhibitors, such as benazepril, enalapril, and ramipril were compared in the present study. It was reported in a study performed on the dogs with experimentally induced MR that Lisinoprilin had a decreasing effect on preload but not afterload (17). It was reported also that ibersertan, angiotensin receptor blocker did not improve LV remodelling and functions in the dogs with subacute MR induced by chordal disruption (20). However, it was suggested that a decrease in LV volume and volume overload occurred in the children under long-term treatment with cilazapril and enalapril (15). In this study, it was found that enalapril had a decreasing effect on the preload and SV without alteration occurring in the left ventricle ESV. With the effect of angiotensin II, left ventricular end diastolic volume increases by filling excessive amount of blood in diastole. This leads to left ventricular remodelling and destruction of the left ventricular geometry resulting in left ventricular enlargement and deposition of papillary muscles of mitral valve leaflets from a closure line. Thus, the mitral valves cannot close completely and mitral regurgitation occurs (3, 20).

Therapeutic effects of benazepril, enalapril, and ramipril on decreasing left ventricular end diastolic dimensions and left ventricular volume in the dogs with severe MR were shown in this study. Another parameter playing a role in mitral regurgitation, is the difference in the pressures of the left ventricle and left atrium. This potency helps complete closure of mitral valves during systole (12). In this study, no alteration in left ventricular ESV was detected.

These findings are the short-term effects of benazepril, enalapril, and ramipril. Studies made on the long-term effect of ACE inhibitors showed a therapeutic effect on the left ventricular function by decreasing the end systolic volume (7, 10, 15, 17, 23). It has been shown that our findings are related with results of cited above studies. However, the limitation of this study was the small number of dogs in groups and the remodelling of the heart using other techniques as doppler echocardiography would be more helpful in the evaluation.

In addition to the standard therapy in dogs with heart failure caused by MR, ACE inhibitors had been demonstrated to be both efficacious and safe (7, 10, 23, 25). Ramipril, enalapril, and benazepril are hydrolysed by the liver. Maximum haemodynamic effect starts just 3, 6, 7, and 12 h after the application and this effect lasts 24 h in ramipril and enalapril, whereas effect of benazepril lasts longer than 24 h (18). In this research, the effect of ramipril, and enalapril on decreasing LVEDd and EDV in subacute period could be due to time of maximum haemodynamic effect. Similarly, a mild decrease in SV occurred in group B and a significant decrease occurred in groups E and R. FS and
EF that were higher before treatment, decreased significantly in all the groups after the treatment with ACE inhibitors. No significant differences in SV, FS, and EF were detected between the groups and the drugs showed considerable effects on these parameters. It was found that LV was remodelled as a result of the effects of enalapril and ramipril on LVEDV and also EDV was decreased by enalapril. Furthermore, it was observed that these ACE inhibitors were effective on geometry, dimensions, and functions of LV of the dogs with severe MR and enalapril was found to be the most effective agent, followed by ramipril and benazepril.

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