Effects of Long-Term Monotherapy With Eplerenone, a Novel Aldosterone Blocker, on Progression of Left Ventricular Dysfunction and Remodeling in Dogs With Heart Failure

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Background—In heart failure (HF), aldosterone has been implicated in the formation of reactive interstitial fibrosis, a maladaptation that contributes to left ventricular (LV) remodeling. Eplerenone is a novel selective aldosterone blocker. The present study examined the effects of long-term monotherapy with eplerenone on the progression of LV dysfunction and remodeling in dogs with chronic HF.

Methods and Results—HF was produced in 14 dogs by intracoronary microembolizations that were discontinued when LV ejection fraction (EF) was between 30% and 40%. Two weeks after the last embolization, dogs were randomized to 3 months of oral therapy with eplerenone (10 mg/kg twice daily, n=11) or no therapy at all (control, n=7). Hemodynamic measurements were made just before randomization and were repeated at the end of 3 months of therapy. In control dogs, LV end-diastolic and end-systolic volume increased significantly (62±4 versus 68±4 mL, P<0.001, and 38±3 versus 47±3 mL, P<0.001, respectively), and EF decreased significantly (38±1% versus 31±2%, P<0.001). In contrast, end-diastolic volume, end-systolic volume, and EF remained unchanged during the 3 months of treatment in eplerenone-treated dogs. LV end-diastolic wall stress increased significantly in control dogs but decreased significantly in eplerenone-treated dogs. Compared with control, eplerenone was associated with a 28% reduction in cardiomyocyte cross-sectional area, a 37% reduction of volume fraction of reactive interstitial fibrosis, and a 34% reduction of volume fraction of replacement fibrosis.

Conclusions—Our results indicate that long-term therapy with eplerenone prevents progressive LV dysfunction and attenuates LV remodeling in dogs with chronic HF. (Circulation. 2002;106:2967-2972.)

Key Words: heart failure ■ hemodynamics ■ remodeling
tinted when LV ejection fraction (EF) was 30% to 40%. Microembolizations were performed during cardiac catheterization under general anesthesia and sterile conditions. Anesthesia consisted of a combination of intravenous injections of xylazine (0.5 mg/kg), diazepam (0.17 mg/kg), and sodium pentobarbital (150 to 250 mg to effect). The present study was approved by the Henry Ford Hospital Institutional Animal Use and Care Committee and conformed to the “Position of the American Heart Association on Research Animal Use.”

**Study Protocol**

Two weeks after the last microembolization, dogs underwent a prerandomization left and right heart catheterization. One day later, dogs were randomized to 3 months of oral therapy with eplerenone (10 mg/kg twice daily, n = 7) or no therapy at all (control, n = 7). Final hemodynamic and angiographic measurements were made at the end of 3 months of therapy. While under anesthesia, the dog’s chest was opened, the heart was removed, and tissue was prepared for biochemical and histological evaluations.

**Hemodynamic and Angiographic Measurements**

Hemodynamic and angiographic measurements were made during cardiac catheterizations at baseline, 1 day before initiation of therapy, and at the end of 3 months of therapy. Aortic and LV pressures were measured with catheter-tip micromanometers (Millar Instruments). Mean pulmonary artery pressure was measured with a fluid-filled catheter in conjunction with a Perceptor DT pressure transducer (Boston Scientific). Peak LV rate of change in pressure during isovolumic contraction (+dP/dt) and relaxation (−dP/dt) and end-diastolic pressure were measured from the LV pressure waveform. The time constant of isovolumic relaxation, τ, was calculated as described previously.

Left ventriculograms were obtained after completion of the hemodynamic measurements, with the dog placed on its right side, and recorded on 35-mm cine film at 30 frames/second during the injection of 20 mL of contrast material (RENO-M-60, Squibb). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the LV. LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF were calculated as described previously. Global indexes of LV shape were used to quantify changes in chamber sphericity. LV shape was quantified from angiographic silhouettes as the ratio of the major to minor axes at end diastole and end systole. Venous blood samples were obtained before and 3 months after initiation of therapy for measurement of plasma concentrations of Na+, K+, blood urea nitrogen (BUN), and creatinine.

**Echocardiographic Measurements**

Echocardiograms were performed with a Hewlett-Packard model 77020A ultrasound system with a 3.5-MHz transducer and recorded on a VHS recorder. The thickness of the intraventricular septum and LV posterior wall was determined by M-mode echocardiography, summed, and averaged to obtain a single representative measure of LV wall thickness. The end-diastolic LV major and minor semiaxes at the midwall were measured from 2D echocardiograms with the apical 4-chamber view. LV end-diastolic circumferential wall stress was calculated as described previously.

**Histological and Morphometric Assessments**

From each heart, 3 transverse slices (~3 mm thick), 1 each from the basal, middle, and apical thirds of the LV, were obtained. For comparison, tissue samples from 7 normal dogs were prepared in an identical manner. From each slice, transmural tissue blocks were obtained and embedded in paraffin blocks. From each block, 6-μm-thick sections were prepared and stained with Gomori trichrome to identify fibrous tissue. The volume fraction of replacement fibrosis, namely, the proportion of scar tissue to viable tissue in all 3 transverse LV slices, was calculated as the percent total surface area occupied by fibrous tissue by use of computer-based video densitometry (MOCHA, Jandel Scientific). LV free-wall tissue blocks were obtained from a second midventricular transverse slice, mounted on cork with Tissue-Tek embedding medium (Sakura), and rapidly frozen in isopentane precooled in liquid nitrogen and stored at -70°C until used. Cryostat sections were prepared and stained with fluorescein-labeled peanut agglutinin (Vector Laboratories Inc) after pretreatment with 3.3 U/mL neuraminidase type V (Sigma Chemical Co) to delineate the myocyte border and the interstitial space, including capillaries. Sections were double stained with rhodamine-labeled Griffonia Simplicifolia lectin I (GSL-I) to identify capillaries. Ten radially oriented microscopic fields (magnification ×100, objective ×40, and ocular 2.5) were selected from each tissue sample for analysis. Fields that contained scar tissue (infarcts) were excluded. Average myocyte cross-sectional area was calculated by computer-assisted planimetry. Volume fraction of interstitial fibrosis was calculated as the percent total surface area occupied by interstitial space minus the percent total area occupied by capillaries. Capillary density was calculated as the number of capillaries per square millimeter.

**TaqMan Analysis and Zymography**

RNA was extracted and purified from frozen LV tissue with the RNeasy Midi Kit (Qiagen, Inc) followed by DNA removal with DNase (Qiagen, Inc). Primers and probes for basic fibroblast growth factor (bFGF) were designed with Primer Express software supplied with the 7700 Sequence Detection System and synthesized by Applied Biosystems. Target gene results were normalized to the housekeeping gene cyclophilin. Purified RNA (200 ng of total) was added to a reverse transcription-polymerase chain reaction mix that contained the following: 12.5 μL of 2X One-Step PCR Master Mix without uracil-N-glycosylase, 0.625 μL of a 40X MultiScribe and RNase Inhibitor Mix, 0.625 μL of 20 μmol/L forward primer, 0.625 μL of 20 μmol/L reverse primer, 0.5 μL of 5 μmol/L TaqMan probe, and 0.125 μL of DNAse/RNase-free water. Reactions were analyzed in duplicate in the 7700-Sequence Detector with the following protocol: 30 minutes at 48°C (reverse transcription), 10 minutes at 95°C (inactivation of reverse transcriptase and polymerase activation), 40 cycles of 15 seconds at 95°C (denaturation), and 1 minute at 60°C (annealing). Zymography was performed as described previously. Gelatinase activity was analyzed by densitometry, and activity is represented as optical density.

**Data Analysis**

Intragroup comparisons were made between measurements obtained before initiation of therapy and measurements made after 3 months of therapy. For these comparisons, a Student’s paired t test was used, and a probability ≤0.05 was considered significant. To ensure that all study measures were similar at baseline and at the time of randomization, intergroup comparisons were made with a t statistic for 2 means. To assess treatment effect, the change (Δ) in each measure from before treatment to after treatment was calculated for each group. To determine whether significant differences were present between groups, a t statistic for 2 means was used, with P ≤0.05 considered significant. Differences in electrolytes, BUN, creatinine, bFGF, gelatinase activity, and histomorphometric measures were examined with ANOVA, with a set at 0.05, and pairwise comparisons were made with the Student-Neuman-Keuls test, with P ≤0.05 considered significant. All data are reported as mean ± SEM.

**Results**

Baseline data for both groups are shown in Table 1. There were no differences in any of the baseline parameters between eplerenone and controls. Similarly, there were no differences between groups in any of the parameters obtained before treatment (Tables 2 and 3).

**Measurements in Control Dogs**

Control dogs manifested a significant decrease in LV EF, accompanied by a significant increase in EDV and ESV.
Increase in LV chamber sphericity. LV end-diastolic wall stress increased significantly. Both LV end-diastolic and end-systolic axes ratios decreased significantly after 3 months of follow-up.

### Table 2. Hemodynamic and Angiographic Measurements in Control Dogs Before (Pretreatment) and After 3 Months of Follow-Up (Posttreatment)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>81 ± 4</td>
<td>81 ± 3</td>
<td>0.63</td>
</tr>
<tr>
<td>Mean AoP, mm Hg</td>
<td>92 ± 4</td>
<td>108 ± 7</td>
<td></td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>8 ± 0</td>
<td>8 ± 1</td>
<td></td>
</tr>
<tr>
<td>EDV, mL</td>
<td>53 ± 4</td>
<td>61 ± 6</td>
<td></td>
</tr>
<tr>
<td>ESV, mL</td>
<td>24 ± 2</td>
<td>27 ± 3</td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>54 ± 1</td>
<td>56 ± 1</td>
<td></td>
</tr>
<tr>
<td>Peak LV + dp/dt, mm Hg/s</td>
<td>1976 ± 58</td>
<td>2334 ± 121</td>
<td></td>
</tr>
<tr>
<td>Peak LV − dp/dt, mm Hg/s</td>
<td>1949 ± 78</td>
<td>2281 ± 157</td>
<td></td>
</tr>
<tr>
<td>Mean PA, mm Hg</td>
<td>12.6 ± 1.5</td>
<td>11.9 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>τ, ms</td>
<td>30 ± 3</td>
<td>29 ± 2</td>
<td></td>
</tr>
<tr>
<td>LV ED axis ratio</td>
<td>1.52 ± 0.06</td>
<td>1.48 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>LV ES axis ratio</td>
<td>1.79 ± 0.12</td>
<td>1.89 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>LV ED wall stress, g/cm²</td>
<td>27 ± 1</td>
<td>31 ± 7</td>
<td></td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>9.8 ± 0.3</td>
<td>9.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>23.9 ± 1.1</td>
<td>26.3 ± 1.1</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Hemodynamic and Angiographic Measurements Obtained Before (Pretreatment) and After 3 Months of Treatment With Eplerenone (Posttreatment)

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>87 ± 4</td>
<td>83 ± 4</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean AoP, mm Hg</td>
<td>94 ± 7</td>
<td>99 ± 8</td>
<td>0.54</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>15 ± 1</td>
<td>9 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>73 ± 5</td>
<td>72 ± 5</td>
<td>0.51</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>46 ± 3</td>
<td>45 ± 4</td>
<td>0.77</td>
</tr>
<tr>
<td>Peak LV + dp/dt, mm Hg/s</td>
<td>1861 ± 140</td>
<td>1990 ± 131</td>
<td>0.06</td>
</tr>
<tr>
<td>Peak LV − dp/dt, mm Hg/s</td>
<td>1564 ± 146</td>
<td>1989 ± 145</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean PA, mm Hg</td>
<td>11.6 ± 0.4</td>
<td>14.0 ± 1.1</td>
<td>0.043</td>
</tr>
<tr>
<td>τ, ms</td>
<td>34 ± 2</td>
<td>29 ± 2</td>
<td>0.08</td>
</tr>
<tr>
<td>LV ED axis ratio</td>
<td>1.31 ± 0.03</td>
<td>1.38 ± 0.03</td>
<td>0.060</td>
</tr>
<tr>
<td>LV ES axis ratio</td>
<td>1.42 ± 0.05</td>
<td>1.49 ± 0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>LV ED wall stress, g/cm²</td>
<td>58 ± 7</td>
<td>33 ± 6</td>
<td>0.003</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>8.9 ± 0.2</td>
<td>9.0 ± 0.1</td>
<td>0.296</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>26.7 ± 1.0</td>
<td>27.5 ± 1.5</td>
<td>0.179</td>
</tr>
<tr>
<td>Na⁺, mmol/L</td>
<td>148 ± 1</td>
<td>147 ± 0</td>
<td>0.172</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>4.9 ± 0.2</td>
<td>5.0 ± 0.1</td>
<td>0.882</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.0</td>
<td>0.356</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>25 ± 2</td>
<td>22 ± 2</td>
<td>0.158</td>
</tr>
</tbody>
</table>

Body weight increased slightly but significantly, and LV wall thickness tended to decrease, but the change was not significant. There were no differences in Na⁺, K⁺, BUN, and creatinine between before and after treatment.

### Measurements in Eplerenone-Treated Dogs

LV EF, EDV, and ESV remained unchanged in eplerenone-treated dogs during the 3 months of the treatment. There was a small but clinically insignificant increase in mean pulmonary artery pressure. Peak LV + dp/dt increased but was not statistically significant. Peak LV − dp/dt increased significantly and was associated with a decrease in τ. No differences were noted in LV end-diastolic or end-systolic axes ratios, which indicates prevention of progressive increase in LV sphericity. Eplerenone therapy resulted in a significant decrease of LV end-diastolic wall stress. Body weight, LV wall thickness, and Na⁺, K⁺, BUN, and creatinine did not change between before and after treatment.

### Comparisons of Treatment Effect

Intragroup comparisons of the changes between pretreatment and posttreatment measurements are shown in Table 4. Compared with control dogs, eplerenone had no effect on heart rate or mean aortic pressure. LV EF and peak LV + dp/dt were significantly higher in dogs treated with eplerenone. ESV, EDV, and LV end-diastolic pressure were also significantly lower in dogs treated with eplerenone than in controls. Peak LV − dp/dt was significantly higher in dogs treated with eplerenone and was associated with a significant reduction in τ. Both end-diastolic and end-systolic axes ratios were significantly higher in eplerenone-treated dogs than in control dogs. Compared with control, eplerenone therapy...
TABLE 4. Comparison of Change From Before Treatment to After Treatment in Hemodynamic and Angiographic Measurements Between the 2 Study Groups (Treatment Effect)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Eplerenone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>4±9</td>
<td>−4±6</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean AuP, mm Hg</td>
<td>1±6</td>
<td>5±8</td>
<td>0.68</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>−1±1</td>
<td>−6±1</td>
<td>0.002</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>6±1</td>
<td>−1±2</td>
<td>0.003</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>9±1</td>
<td>−1±2</td>
<td>0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>−7±1</td>
<td>1±1</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak LV +dP/dt, mm Hg/s</td>
<td>−324±81</td>
<td>129±56</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak LV −dP/dt, mm Hg/s</td>
<td>−299±87</td>
<td>424±92</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean PA, mm Hg</td>
<td>−0.6±2.0</td>
<td>−2.43±1.0</td>
<td>0.417</td>
</tr>
<tr>
<td>t, ms</td>
<td>6±1</td>
<td>−5±2</td>
<td>0.002</td>
</tr>
<tr>
<td>LV ED axis ratio</td>
<td>−0.12±0.02</td>
<td>0.07±0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ES axis ratio</td>
<td>−0.22±0.03</td>
<td>0.08±0.04</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ED wall stress, g/cm²</td>
<td>14±5</td>
<td>−25±5</td>
<td>0.001</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>−0.5±0.3</td>
<td>0.1±0.1</td>
<td>0.084</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>−1.1±0.4</td>
<td>−0.8±0.5</td>
<td>0.711</td>
</tr>
<tr>
<td>Na⁺, mmol/L</td>
<td>2±32</td>
<td>−1±1</td>
<td>0.930</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>−0.2±1.0</td>
<td>0.0±0.2</td>
<td>0.851</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.0±0.2</td>
<td>0.0±0.0</td>
<td>0.790</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>−1±5</td>
<td>−3±2</td>
<td>0.668</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

resulted in a significant decrease of LV end-diastolic wall stress (Table 4). There were no significant differences in body weight, heart weight to body weight ratio, LV wall thickness, or Na⁺, K⁺, BUN, or creatinine between the control and eplerenone-treated groups. Heart weight to body weight ratio tended to be higher in the control group than in the treatment group, but the difference was not significant (8.1±0.5 versus 7.5±0.3 g/kg).

Histomorphometric findings are shown in Table 5. Cardiac myocyte cross-sectional area, a measure of cell hypertrophy, volume fraction of interstitial fibrosis, and volume fraction of replacement fibrosis were all significantly lower in eplerenone-treated dogs than in controls, whereas capillary density was significantly higher. Treatment with eplerenone significantly inhibited gelatinase activity (Figure 1) and significantly increased transcription of bFGF (Figure 2).

Discussion

The study results demonstrate that long-term aldosterone receptor blockade with eplerenone prevents progressive LV dysfunction and remodeling in dogs with moderate HF. Eplerenone prevented progression of LV systolic dysfunction, as evidenced by improvement in LV EF and peak +dP/dt, as well as progression of LV diastolic dysfunction, as evidenced by improvement of peak LV −dP/dt, τ, and LV end-diastolic wall stress compared with controls. Eplerenone also attenuated the progressive increase in LV size and LV chamber sphericity and attenuated replacement fibrosis. At the cellular level, eplerenone attenuated interstitial fibrosis and cardiomyocyte hypertrophy and increased capillary density. These findings suggest that eplerenone may be beneficial in the treatment of patients with chronic HF.

Previous studies examining the effects of aldosterone receptor antagonists in HF produced controversial results regarding the cardioprotective actions of these drugs. Bauersachs et al. found that spironolactone in combination with the ACE inhibitor trandolapril restored endothelial function in rats with HF, whereas spironolactone alone had no effect. However, in the RALES trial, spironolactone reduced the incidence of mortality by 30%. The majority of these patients were also taking ACE inhibitors (95%); therefore, the improved survival was clearly attributable to the addition of

Figure 1. Gelatinase activity after 3 months of therapy or follow-up. Values are mean±SEM. *P<0.01 vs normal, †P<0.01 vs heart failure. OD indicates optical density units.

Figure 2. TaqMan analysis quantifying bFGF mRNA. Values are mean±SEM. *P<0.01 vs normal, †P<0.01 vs HF.
spironolactone. Although it is generally assumed that inhibiting the formation of angiotensin II with ACE inhibitors will also suppress the formation of aldosterone, recent studies in patients with hypertension or HF have demonstrated that escape of aldosterone occurs despite treatment with ACE inhibitors.1–4

Aldosterone has been implicated in myocardial interstitial and perivascular fibrosis,1,15 and has been suggested to mediate baroreceptor dysfunction14 and prevent the reuptake of norepinephrine by myocardial nerve terminals.17 It was previously suggested that spironolactone acts on the central nervous system to regulate fluid volume.18 Spironolactone also decreases sympathetic drive and improves baroreflex function in HF.18 Volume unloading may explain the mechanism by which aldosterone receptor antagonists exert their beneficial effects. In the present study, eplerenone did not alter body weight, electrolytes, BUN, or creatinine, which suggests that regulation of fluid volume did not play a primary role in its cardioprotective actions.

Aldosterone and angiotensin II can stimulate excessive accumulation of collagen within the cardiac interstitium, a structural abnormality that can lead to LV diastolic dysfunction and ultimately systolic dysfunction. Brilla et al19 demonstrated that spironolactone prevents the development of interstitial fibrosis in hypertensive rats and in normotensive rats given intravenous aldosterone. Delyani et al20 also reported that eplerenone attenuates the development of ventricular remodeling and reactive but not reparative fibrosis after myocardial infarction in rats. In the present study, the volume fraction of reactive interstitial fibrosis was significantly reduced in dogs treated with eplerenone compared with control. Correspondingly, dogs treated with eplerenone exhibited a decrease in LV end-diastolic pressure and a decrease in LV end-diastolic wall stress suggestive of reduced myocardial stiffness. This argues in favor of improved diastolic function, a concept supported by the present study.

Eplerenone decreased gelatinase activity and increased the transcription of bFGF. Matrix metalloproteinases 2 and 9 are both gelatinases that have been shown to be upregulated in HF.21 The decrease in gelatinase activity with eplerenone may account for the decrease in interstitial fibrosis. The possibility exists that eplerenone only appeared to cause an increase in capillary density as a result of attenuating the development of fibrosis. However, dogs treated with eplerenone also increased bFGF, which can promote angiogenesis.22–25 Thus, the increase in capillary density associated with eplerenone treatment may have been due in part to the upregulation of bFGF.

In the present study, early, long-term therapy with eplerenone prevented progressive LV shape changes, specifically increased LV chamber sphericity. In patients with dilated cardiomyopathy, a more spherical LV chamber was shown to be associated with higher end-systolic wall stress, abnormal distribution of fiber shortening, more severely depressed contractility at rest, blunted response to exogenous catecholamine, and poor long-term survival.9,26–28 The development of functional mitral regurgitation in patients with HF and in experimental animal models of HF has also been attributed in part to increased LV chamber sphericity.29 These factors could also have contributed to the observed beneficial effects of eplerenone in this canine model of HF.

In conclusion, the results of the present study indicate that chronic monotherapy with eplerenone prevents progressive LV systolic and diastolic dysfunction and attenuates LV chamber remodeling in dogs with moderate HF.

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