Relative Effects of $\alpha_1$-Adrenoceptor Blockade, Converting Enzyme Inhibitor Therapy, and Angiotensin II Subtype 1 Receptor Blockade on Ventricular Remodeling in the Dog

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**Background**
Progressive ventricular remodeling after myocardial damage is associated with a poor prognosis. Optimal prevention of the histopathological processes involved in remodeling requires a more complete understanding of the mechanisms involved in initiating and maintaining these structural changes. Since the sympathetic nervous system and the renin-angiotensin system may be involved in the remodeling process, the structural effects of pharmacological inhibitors have been evaluated in a canine model of localized myocardial injury resulting from transmyocardial DC shock.

**Methods and Results**
The study comprised two protocols run in series. In protocol 1, zofenopril (Z), a converting enzyme inhibitor (CEI), prevented the increase in left ventricular mass (LVM) and end-diastolic volume (LVV) observed in the control group (C) at 16 weeks (Z: LVM, 69.8±3.4 g; LVV, 54.4±2.7 mL; P=.0001; C: LVM, 68.4±3.2 g; LVV, 56.6±3.0 mL; P=.0003). Terazosin, an $\alpha_1$-adrenoceptor antagonist, failed to prevent remodeling at 16 weeks despite continued receptor blockade. In protocol 2, the antiremodeling effect of full-dose CEI therapy with ramipril was confirmed. Low-dose ramipril that exerted no hemodynamic effect failed to prevent remodeling (LVM, 89.7±4.6 to 105.7±3.4 g, P=.01; LVV, 61.8±3.8 to 76.8±3.3 mL, P=.002). An angiotensin II subtype 1 receptor blocker also failed to prevent the increase in LVM or LVV (LVM, 89.7±4.6 to 109.7±5.3 g, P=.0001; LVV, 66.0±1.9 to 78.4±3.6 mL, P=.007).

**Conclusions**
High-dose CEI therapy can prevent progressive structural changes resulting from localized myocardial damage induced by DC shock. The failure of $\alpha_1$-adrenoceptor blockade and angiotensin II subtype 1 blockade to attenuate remodeling argues against an important direct role for norepinephrine acting through $\alpha_1$-receptors or angiotensin II acting through the type 1 receptor in the remodeling process in this model. (Circulation. 1994;90:3034-3046.)

**Key Words**
- angiotensin
- ventricles
- pharmacology
- receptors, adrenergic, alpha
- myocardium

**Ventricular Remodeling**
Ventricular remodeling after myocardial infarction is characterized by chamber dilation and an increase in mass of surviving viable myocardium.1-4 These structural changes are the result of several distinct pathological processes including infarct expansion,5,6 myocyte hypertrophy,7,8 myocyte slippage,9 and growth of the cardiac interstitium.4 Although remodeling occurring early after infarction may be an appropriate compensatory response to preserve ventricular function,10 recent observations have suggested that the long-term process has a deleterious effect on prognosis.11-13 Attempts to inhibit these structural changes thus have been the focus of recent clinical studies.4,11,14,15

The mechanisms initiating and contributing to progression of left ventricular (LV) remodeling have not been fully identified. The load on the LV wall resulting from intracavitary pressure and radius of curvature undoubtedly plays a role,6 but hormonal, autocrine, and paracrine factors also may be involved.16-19 Some pharmacological agents, predominantly angiotensin-converting enzyme (ACE) inhibitors, have exhibited a favorable effect on remodeling in clinical and experimental studies,1,4,11,14,15,20,21 but the mechanism of this effect is not clear.

Norepinephrine17,22-26 and angiotensin II19,27,28 are known stimulants of myocardial hypertrophy and also may play a role in growth of the cardiac interstitium.18,29,30 Since the sympathetic nervous system and the renin-angiotensin system are activated in the setting of acute myocardial infarction,31 it is attractive to postulate that these hormones may contribute to remodeling after myocardial damage and that inhibition of these effects might attenuate the process. Indeed, $\alpha_1$-adrenoceptor blockade has been shown to inhibit norepinephrine-mediated myocyte hypertrophy,29 and ACE inhibitors are effective in preventing remodeling in experimental and clinical studies.1,4,11,15,21

We used a canine model of localized myocardial necrosis to explore the time course and structural changes in the myocardium during remodeling.3,15,20,33 We have previously described the natural history of this process, which is characterized by an early increase in mass of the uninvolved myocardium associated by 16 weeks with considerable global LV dilatation.3 The present studies were undertaken to explore the effect of specific...
inhibitors of the actions of norepinephrine and angiotensin II on structural changes during the first 16 weeks after myocardial damage. Since inhibitors of these systems also tend to reduce blood pressure and ventricular load, hemodynamic monitoring at trough drug effect was used to gain insight into the magnitude of the chronic load reduction associated with the interventions.

**Methods**

**Myocardial Damage**

Discrete transmural necrosis on the anteroapical surface of the left ventricle of the dog was produced by transmyocardial DC shock. Mongrel dogs were anesthetized with sodium pentobarbital, intubated, and prepared for the transmyocardial DC shock procedure after baseline hemodynamic measurements were made in the awake state. Animals were placed in the right lateral position. A small area of the left chest over the maximal precordial impulse was shaved. A pigtail catheter was placed across the aortic valve and then advanced 1 to 2 cm to distance it from conduction tissue at the base of the heart. A premeasured soft metallic guide wire was then passed through the catheter with approximately 5 mm of wire extended beyond the catheter tip into the LV cavity. One electrode paddle was placed on the shaved area of the left chest, and the second electrode was connected to the proximal end of the guide wire that had been placed in the left ventricle. Shocks of 80 J were delivered at 25- to 60-second intervals to a total of one shock per kilogram of body weight. This protocol was previously determined to produce a moderate-sized area of transmural necrosis involving 17±6% of the LV myocardium. Heart rhythm was monitored electrocardiographically throughout the DC shock procedure. Each shock of 80 J was invariably followed by a rhythm disturbance. Usually this was a short run of nonsustained ventricular tachycardia that did not result in hemodynamic compromise. The next shock was delayed until hemodynamic parameters were stable. Rarely, cardioversion (80-J shock) was needed to break ventricular tachycardia when it was associated with low blood pressure. In these situations, this "therapeutic" cardioversion was counted as one of the individual shocks for that dog. Temporary bradycardia/arrhythmias occasionally occurred but generally did not persist and rarely required therapy. A brief period of hypotension, occasionally associated with bradycardia/arrhythmias, often followed an individual shock. After the completion of the shock procedure, the guide wire and catheter were removed, and hemostasis was achieved at the puncture site by pressure. The procedure usually took 30 to 45 minutes.

**Experimental Protocols**

This study was divided into two separate protocols. All experiments were performed in accordance with the guidelines of the University of Minnesota Animal Research Committee.

**Protocol 1**

Thirty-four adult mongrel dogs subjected to DC shock-induced myocardial damage were studied. Three animals did not survive the procedure. Surviving animals (mean weight, 17.1±1.1 kg) were randomly assigned within 24 hours to a control group (n=15), to treatment with the ACE inhibitor zofenopril (n=7), or to treatment with the α1-adrenergic blocking agent terazosin (n=9). Treatment was initiated the day after the DC shock procedure and continued for 16 weeks. It was elected to have a larger number of animals in the control group in order to confirm the reproducibility of structural changes in this model. All animals underwent baseline magnetic resonance imaging (MRI) and hemodynamic studies before transmyocardial DC shock. These studies were repeated 1 and 16 weeks after myocardial damage. Medications were withheld on the morning of hemodynamic studies at 1 and 16 weeks.

Zofenopril, a sulfhydryl group-containing ACE inhibitor that exhibits a sustained 24-hour effect on blood pressure in experimental animals, was given once daily in a morning dose of 10 mg. Terazosin was also given in a daily morning dose of 10 mg. The efficacy of the terazosin dose in attenuating the hypertensive response to phenylephrine was confirmed in 2 normal dogs before this study.

At the end of the 16-week study period, 5 terazosin-treated animals underwent phenylephrine challenge while on therapy using incremental infusion rates between 50 and 200 μg/min while mean arterial pressure was monitored. This challenge was performed at the same time of day as hemodynamic studies approximately 24 hours after drug dosing. Terazosin therapy was then discontinued, and 1 week later, the phenylephrine challenge was repeated at the same time of the day using the same protocol. This procedure was performed to confirm that chronic therapy with terazosin resulted in effective long-term α1-adrenoceptor blockade. No pharmacological test of the inhibiting effect of zofenopril was performed. At the end of the 16-week study period, most of the dogs were entered into other studies that precluded gross examination of the heart at the end of this protocol.

**Protocol 2**

Protocol 2 was started after the completion of protocol 1. Thirty-six adult mongrel dogs were studied. As in protocol 1, all underwent baseline MRI 1 week before the creation of LV damage. Baseline resting hemodynamic values were obtained before DC shock. Twenty-four hours after the induction of myocardial damage, 32 dogs (mean weight, 20.4±0.6 kg) were assigned to one of four different groups: a control group (n=7), which received no therapy; a group treated with ramipril 10 mg BD (n=8); a group treated with low-dose ramipril 1.25 mg BD (n=10); and a group assigned to therapy with DUP 532 (n=9), an AT1-receptor blocking agent. Two dogs did not survive DC shock (procedural mortality of 5.6%) and 2 additional animals developed complete heart block as a result of DC shock and did not continue in this protocol. Pharmacological therapy was continued for a period of 16 weeks. Hemodynamic measurements and MRI scans, separated by a period of 24 to 48 hours, were repeated at 2 and 16 weeks after DC shock. During the 16-week protocol, dogs from all four groups were treated in a similar manner with respect to diet and activity level. At the end of this study period, the majority of these animals were reassigned to other studies.

Ramipril is a non-sulfhydryl-containing prodrug that is rapidly hydrolyzed after absorption to ramiprilat, its active metabolite. The nonhemodynamically effective dose of this ACE inhibitor was determined by analyzing the response of mean arterial pressure and pulmonary capillary pressure over a 5-hour period to ramipril 2.5 mg, 1.25 mg, and 0.625 mg. This dose-ranging pilot study was performed on 4 normal adult mongrel dogs, each of which received all the above doses on different days. Ramipril 1.25 mg was the largest dose that did not significantly reduce mean arterial or pulmonary wedge pressure. At the end of the 16-week study period, an angiotensin I challenge was performed in control dogs and in groups receiving ramipril 10 mg BD or 1.25 mg BD to define the degree of converting enzyme inhibition. A catheter was placed in the femoral artery under sedation (Innovar 2 mL) and local anesthetic. Angiotensin I was given as an intravenous bolus in the following doses: 0.025, 0.05, 0.1, and 0.3 μg/kg. The peak systolic blood pressure response was noted after each bolus injection. Blood pressure values were allowed to return to control levels before subsequent bolus injections were given. The angiotensin I challenge was repeated 7 days after discontinuation of therapy.

Angiotensin II subtype 1 receptor blockade was achieved using the compound DUP 532 (Dupont Pharmaceutical Co), a noncompetitive blocker of this receptor. DUP 532 is a close
analogue of the competitive AT₁-receptor antagonist DUP 753 except for a carboxyl group at the 5' position of the imidazole ring. The dose of 15 mg/kg BID was chosen on the basis of preliminary data demonstrating 90% inhibition of the systemic pressor response to angiotensin II (0.1 μg/kg IV bolus) in the dog. Angiotensin II challenge was performed during the study period using DUP 532 to define the degree of receptor inhibition. These studies were performed at baseline, before the institution of therapy, and at the 2- and 16-week time points after myocardial damage. Angiotensin II challenges were carried out during the morning approximately 16 hours after the last dose of the drug. The angiotensin II challenge was performed in the same manner as the angiotensin I challenge described above. The bolus doses of angiotensin II used were 0.025, 0.05, 0.1, and 0.3 μg/kg.

**Magnetic Resonance Imaging Studies**

Magnetic Resonance Imaging (MRI) was used to assess LV mass and volume. The accuracy of this method has been documented previously at this institution and at other centers. MRI studies were performed within 1 week before transmyocardial shock and repeated at the intermediate time point of 1 week (protocol 1) or 2 weeks (protocol 2) and 16 weeks after this procedure. Sodium pentobarbital general anesthesia was used for these procedures (200-mg IV bolus with continuous infusion of 2 mg/min). Animals were intubated but not ventilated during the MRI study.

A magnet with a field strength of 1.0-T unit was used for imaging in protocol 1. Gated short-axis paracoronal spin-echo views of the heart were obtained at a repetition time of 300 milliseconds as determined by the dog's heart rate and an echo time of 30 milliseconds. These views were obtained 40 milliseconds after the ECG R wave to approximate end diastole. Six slices, each 1 cm in width with no interslice gap, were required to image the heart from base to apex. The damaged area could be identified as a thin scar on the anterolateral wall on the image at 16 weeks and on autopsy specimens. To measure the surface area of each slice, epicardial and endocardial LV edges were traced using a computer-assisted light pen. LV mass measurement in each slice was calculated using a commercially available software package (Siemens). The total area enclosed by the endocardium was subtracted from that enclosed by the epicardium. The resultant figure was multiplied by the slice depth of 1 cm to calculate volume and then by 1.05 (specific gravity of myocardium) to calculate the mass of each slice. The total LV mass was thus computed by adding together the individual mass measurements of all slices. The LV volume of each slice was represented by the volume enclosed by the endocardium. The total LV volume was computed by adding together the volumes of all slices. At the time of initiation of protocol 2, the MRI method had changed. Magnet strength had been upgraded to 1.5 T. To increase signal-to-noise ratio, an 18-cm Helmholz coil was used. All of the imaging sequences were synchronized to the ECG signal obtained from leads placed on the shaved skin surface of the dog. Scout images were taken in the axial plane with an ultrafast gradient echo sequence (TurboFlash). The parameters for this sequence were TR/TE/angle of 6 milliseconds/3 milliseconds and 8 degrees, respectively, and a matrix of 128×256 within a field of view of 250 mm. The delay after the inversion pulse was kept to a minimum, 15 milliseconds, resulting in a bright blood signal and a hypointense myocardium. From axial scout images, a long axis was obtained. The short-axis orientation was aligned perpendicular to the main axis of the left ventricle. Aside from providing assistance in defining the short-axis plane, the TurboFlash sequence also provided information on how many short-axis cine sequences (described below) were needed to image the myocardium from apex to base. The short-axis TurboFlash images covered the heart from apex to base using a slice thickness of 10 mm with no interslice gap.

After completion of the TurboFlash sequence, a gradient echo (FISP) cine sequence was performed to provide images from which the calculations of ventricular mass and volume were made. To improve the contrast of the cine images, a contrast agent (gadolinium-DPTA) was administered intravenously at the FDA-approved dose (0.1 mg/kg). This contrast agent enhances the blood, thus giving better wall definition. The parameters for the FISP sequence were TR/TE/angle of 30 milliseconds/10 milliseconds/60 degrees, respectively, with a matrix of 128×256 within a field of view of 250 mm. A section thickness of 10 mm with no interslice gap was used with short-axis images obtained from the apex to base. Each myocardial level took approximately 5 minutes to image, depending on heart rate. This protocol provided high signal-to-noise movie-like images of the heart.

LV mass and volume were calculated from end-diastolic images as in protocol 1. To calculate LV ejection fraction (LVEF), the end-systolic image was defined by scrolling through the images obtained at each tissue level (separated by 30-millisecond intervals) and noting the one with the smallest ventricular cavity. Once identified, the LVEF was calculated in a standard fashion by subtracting the total end-systolic volume of the ventricle from the total end-diastolic volume and dividing the resultant figure by the end-diastolic volume.

Mass and volume measurements were made by two of the authors, who were unaware of the treatment status of the dogs at the time of analysis. Intraobserver error and interobserver error for these individuals has been estimated previously to be less than 3 g for mass and less than 3 mL for volume in canine hearts. A further analysis of LV remodeling was performed in both protocols by assessing wall thickness and chamber diameter. Septal, anterior, lateral, and posterior wall thickness was measured at end diastole in all animals in each group in the third short-axis slice from the base of the heart. This slice was chosen because it was located in the midventricle and did not include the scar at the apex. Chamber diameter was also measured at this level from the endocardium of the septum to the endocardium of the lateral wall and from the endocardium of the anterior wall to the endocardium of the posterior wall. The chamber diameter to wall thickness ratio (d:h) was derived as an index of diastolic wall stress by dividing the mean.
of the two values for chamber diameter by the mean of the four regional measurements of wall thickness.

To ascertain whether any early structural change in the myocardium represented inflammatory fluid, T2 relaxation times were obtained during the baseline MRI study and repeated at the 1-week study in 6 control dogs in protocol 1. This parameter reflects the rate at which nuclei lose coherence with each other after the application of radiofrequency pulses.37 Alteration in the T2 relaxation time reflects change in tissue fluid content.37 This parameter was assessed in three randomly chosen areas remote from the scar tissue using a method previously described from this center.38 The mean of the values was then calculated.

### Statistical Methods

ANOVA was used to determine if changes in parameters within or between the treated or control groups were statistically significant. Based on the results of the ANOVA, intergroup and intragroup comparisons were made using paired and unpaired t tests. The obtained P values were interpreted using the modified Bonferroni method.39

The response of mean arterial pressure to phenylephrine was assessed using a repeated two-factor ANOVA (terazosin, phenylephrine). Data are expressed as mean±1 SD.

### Results

#### Protocol 1

Thirty-one dogs were randomized to the three treatment arms, but 2 dogs in the control group died during the first week of follow-up, 1 unexpectedly and 1 related to a complication of a procedure. The data on these 2 animals are not reported. There were no other deaths during follow-up.

#### Remodeling at 16 Weeks

The control group displayed a significant increase in LV end-diastolic volume (56.6±3.0 to 71.9±2.4 mL, \( P=.0003 \)) and mass (68.4±3.2 to 91.4±2.9 g, \( P=.0001 \)) at the end of the 16-week period of observation compared with baseline values (Table 1). Terazosin did not significantly alter the remodeling process at 16 weeks compared with dogs in the control group. At this time point, LV mass had increased significantly compared with baseline (66.6±2.6 to 80.9±3.1 g, \( P=.0007 \)), as had end-diastolic volume (54.6±3.7 to 74.3±3.6 mL, \( P=.0017 \)). The absolute change in mass and volume was similar in the terazosin and control groups (Fig 1). The zofenopril-treated group exhibited an insignificant increase in LV mass and no change in mass at 16 weeks. At this time point, the absolute increase in end-diastolic volume was significantly less in the zofenopril group compared with the control group, and there was significant inhibition of the increase in ventricular mass (Fig 1).

### Early Structural Changes

By 1 week after DC shock, the control group exhibited a significant increase in LV mass but not in ventricular volume (Table 1). This early change in mass was inhibited, as expected, by zofenopril, but also appeared to be inhibited by terazosin (Table 1 and Fig 1). The increase in mass observed in the control group was significantly greater than the mass change observed in either of the drug-treated groups. Neither of the drug-treated groups exhibited a significant increase in ventricular volume at 1 week. The reproducibility of the structural changes in the control group in protocol 1 is demonstrated in Fig 2.

### Wall Thickness, Chamber Diameter, Wall Stress, and \( T_2 \) Relaxation

Changes in wall thickness and chamber diameter from baseline in protocol 1 are displayed in Table 2 and are consistent with the mass and volume data. Regional wall thickness and chamber diameter were similar at baseline in the three groups. Wall thickness increased significantly in the septal, lateral, and pos-

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**Table 1.** Left Ventricular Mass and Volume Measurements at Baseline, 1 Week, and 16 Weeks After Transmymyocardial DC Shock

<table>
<thead>
<tr>
<th></th>
<th>LV Mass, g</th>
<th>LV Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( C )</td>
<td>( T )</td>
</tr>
<tr>
<td>Baseline</td>
<td>68.4±3.2</td>
<td>66.6±2.6</td>
</tr>
<tr>
<td>1 wk</td>
<td>81.8±3.6*</td>
<td>67.4±2.5†</td>
</tr>
<tr>
<td>16 wk</td>
<td>91.4±2.9*</td>
<td>80.9±3.1*</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; \( C \), control group; \( T \), terazosin-treated animals; and \( Z \), zofenopril-treated animals.

\( *P<.025 \) compared with baseline; \( †P<.025 \) compared with control. Values are mean±1 SEM.
terior regions in the control group at 1 week after myocardial damage. The increase of 0.8±0.4 mm in the anterior region almost attained statistical significance. Unchanged chamber diameter during this period resulted in a decrease in the regional d:h ratio. By 16 weeks, the control dogs exhibited a reduction in wall thickness in all four regions compared with the 1-week values and increased chamber diameter resulting in a significant increase in the d:h ratio compared with baseline (+0.6±0.2, P=.02). Wall thickness and chamber diameter did not change significantly during the period of observation in the zofenopril group. Wall thickness was unchanged at 1 week in the terazosin group but was reduced significantly in three regions by 16 weeks as the chamber diameter increased. As in the control group, the increase in the d:h ratio at 16 weeks was statistically significant (+1.03±0.1, P=.001).

$T_2$ relaxation times did not change in the control group (n=6) between baseline and 1 week after shock (29±4 versus 27±4 milliseconds, P=NS), indicating the absence of significant tissue edema that otherwise could have contributed to the early increase in mass (Table 3). This parameter was assessed in three areas remote from the damaged zone where increased wall thickness had been documented.

### Table 3. $T_2$ Relaxation Times at Baseline and 1 Week in 6 Control Dogs After Transmyocardial DC Shock in Protocol 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline, ms</th>
<th>1 Week, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>29±4</td>
<td>27±4</td>
</tr>
</tbody>
</table>

### Hemodynamic Data

The hemodynamic values for all three groups in protocol 1 at baseline, 1, and 16 weeks are shown in Table 4. The control group demonstrated a modest but significant increase in PCWP at 1 week compared with baseline (8±1 to 12±1 mm Hg, P=.01). At 16 weeks, there was a further elevation in PCWP (16±1 mm Hg, P=.0001) and a significant increase in PAP (17±1 to 24±1 mm Hg, P=.0001) and RAP (5±1 to 9±1 mm Hg, P=.0002) compared with baseline.

Drug-treated dogs were studied 24 hours after the previous drug dose. No hemodynamic effects were noted in the terazosin-treated group at 1 week. This group, however, demonstrated a reduction in SV (46±3 to 34±2 mL, P=.02) and an increase in HR (75±6 to 106±6 beats per minute, P=.001) at 16 weeks compared with baseline. No significant change in arterial pressure was noted in the terazosin group at either time period. This group also demonstrated a trend in PCWP, PAP, and RAP similar to that in the control group, but the increments did not achieve statistical significance. There was no significant difference over time in hemodynamic variables between the terazosin and control groups.

The zofenopril group displayed no alteration of any hemodynamic parameters during the observation pe-

### Table 2. Baseline Values and Changes at 1 Week and 16 Weeks After Myocardial Damage for Wall Thickness and Chamber Diameter in the Control, Zofenopril, and Terazosin Groups

<table>
<thead>
<tr>
<th></th>
<th>Interventricular Septum, mm</th>
<th>Anterior Left Ventricular Wall, mm</th>
<th>Lateral Left Ventricular Wall, mm</th>
<th>Posterior Left Ventricular Wall, mm</th>
<th>Septal to Lateral Chamber Diameter, mm</th>
<th>Anterior to Posterior Chamber Diameter, mm</th>
<th>Diameter to Wall Thickness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.6±0.2</td>
<td>8.2±0.2</td>
<td>7.7±0.2</td>
<td>8.2±0.2</td>
<td>38.2±0.8</td>
<td>37.8±0.6</td>
<td>4.57±0.08</td>
</tr>
<tr>
<td>1 wk</td>
<td>+1.3±0.4*</td>
<td>+0.8±0.4</td>
<td>+1.2±0.2*</td>
<td>+1.2±0.3*</td>
<td>-0.1±0.7</td>
<td>+0.3±0.7</td>
<td>-0.27±0.1*</td>
</tr>
<tr>
<td>16 wk</td>
<td>0.3±0.4</td>
<td>-0.1±0.2</td>
<td>+0.5±0.3</td>
<td>+0.5±0.4</td>
<td>+4.1±0.8*</td>
<td>+4.1±0.9*</td>
<td>+0.60±0.2*</td>
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<tr>
<td><strong>Zofenopril</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3±0.4</td>
<td>8.1±0.3</td>
<td>8.0±0.5</td>
<td>7.5±0.3</td>
<td>39.3±1.1</td>
<td>37.4±1.2</td>
<td>4.23±0.1</td>
</tr>
<tr>
<td>1 wk</td>
<td>-0.7±0.4</td>
<td>+0.5±0.3</td>
<td>-0.6±0.3</td>
<td>-0.7±0.3</td>
<td>+0.6±0.7</td>
<td>+0.3±0.5</td>
<td>+0.29±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>-0.5±0.4</td>
<td>+0.6±0.2</td>
<td>+0.6±0.6</td>
<td>-0.2±0.4</td>
<td>+0.3±0.9</td>
<td>+0.1±0.6</td>
<td>+0.02±0.2</td>
</tr>
<tr>
<td><strong>Terazosin</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>8.7±0.3</td>
<td>9.0±0.3</td>
<td>9.0±0.4</td>
<td>8.8±0.3</td>
<td>38.6±1.3</td>
<td>36.4±1.0</td>
<td>4.23±0.1</td>
</tr>
<tr>
<td>1 wk</td>
<td>-0.4±0.2</td>
<td>-0.2±0.3</td>
<td>-0.4±0.2</td>
<td>-0.4±0.4</td>
<td>+0.2±0.6</td>
<td>-0.4±0.5</td>
<td>+0.16±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>-0.7±0.2</td>
<td>-0.7±0.1*</td>
<td>-0.7±0.2*</td>
<td>-0.7±0.2*</td>
<td>+4.7±1.2*</td>
<td>+5.6±0.8*</td>
<td>+1.03±0.1*</td>
</tr>
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</table>

*P<.025 compared with own baseline value.
period. There was a significant hemodynamic difference between the control and zofenopril groups over the 16-week period. At 16 weeks, PCWP in the zofenopril group (9±1 versus 16±1 mm Hg, *P=.0005) was significantly lower than in the control animals. Arterial pressure was not significantly altered by zofenopril; there was a trend toward a reduction in this parameter at 1 week but not at 16 weeks.

**Phenylephrine Challenge**

The mean arterial pressure response to phenylephrine on and off terazosin therapy is shown in Fig 3. Terazosin significantly reduced the arterial pressure response to phenylephrine (*P=.0025). These data indicate that terazosin, despite the lack of a sustained effect on remodeling, maintained a persistent vascular α1-adrenoceptor blockade with no evidence of pharmacological tolerance.

**Protocol 2**

Thirty-two dogs survived DC shock and were randomized to treatment groups. Two did not survive the DC shock procedure, and 2 developed complete heart block and were excluded from further analysis.

**LV Mass and Volume**

LV mass and LV end-diastolic volume were similar in the four groups at baseline (Table 5). In the control group, there was a mean increase of 8.5±3.3 g (*P=.04) in LV mass between baseline and 2 weeks after LV damage. In those receiving low-dose ramipril, a similar mean change of 5.9±2.4 g (*P=.04) was noted, and in dogs assigned to treatment with DUP 532, there was a mean increase of 8.0±2.9 g (*P=.03). These three groups demonstrated a further and similar increase in LV mass at 16 weeks, with a total change of 20.2±1.6 g (*P=.0001), 15.9±3.6 g (*P=.01), and 20.6±4.9 g (*P=.003), respectively. The increase in end-diastolic volume at 2 weeks achieved statistical significance only in the DUP 532 group (6.85±2.4 mL, *P=.02). At 16 weeks, the increase in volume in the DUP 532 group (12.4±3.4 mL, *P=.007) and the low-dose ramipril group (15.0±4.0 mL, *P=.002) was significant and was similar to that in the control group (10.8±2.4 mL, *P=.004).

Dogs randomized to high-dose ramipril exhibited no significant change in LV mass or end-diastolic volume during the 16-week study period. The changes in mass at 2 weeks and in mass and volume at 16 weeks were significantly less than that observed in the control, DUP 532, and low-dose ramipril groups.

LV ejection fraction was similar among the four groups at baseline (Fig 4). In the control group, there was a reduction in the ejection fraction over the 16-week follow-up period (57±2% to 48±3%, *P=.05). A similar finding was observed in dogs treated with DUP 532 (58±3% to 46±2%, *P=.002). There was also a trend toward a reduction in ejection fraction in dogs receiving low-dose ramipril (56±2% to 49±3%, *P=.08). A nonsignificant increase in ejection fraction was noted in those treated with high-dose ramipril (52±2% to 59±3%, *P=.14), and at the end of the study period, ejection fraction was significantly greater in this group compared with control animals (59±3% versus 48±3%, *P=.02), those treated with low-dose ramipril (59±3% versus 49±3%, *P=.04), and those treated with DUP 532 (59±3% versus 46±2%, *P=.006).

Mean wall thickness increased significantly between baseline and 2 weeks in all groups except the high-dose ramipril group (Table 6). This observation, along with the lack of significant change in chamber diameter during this period, is consistent with the overall mass and volume changes already described. At 16 weeks, chamber diameter had increased significantly in all groups except the high-dose ramipril group, with little further change in wall thickness. This resulted in a significant increase in the d:h ratio in the control,

<table>
<thead>
<tr>
<th>Hemodynamic Variable</th>
<th>Baseline</th>
<th>1 Week</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>T</td>
<td>Z</td>
</tr>
<tr>
<td>Ao, mm Hg</td>
<td>96±3</td>
<td>96±3</td>
<td>99±2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>8±1</td>
<td>11±1</td>
<td>11±1</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>17±1</td>
<td>18±1</td>
<td>19±1</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>5±1</td>
<td>8±1</td>
<td>6±1</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.97±0.3</td>
<td>3.37±0.3</td>
<td>3.18±0.3</td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>93±6</td>
<td>75±6</td>
<td>90±2</td>
</tr>
<tr>
<td>SV, mL</td>
<td>43±2</td>
<td>46±2</td>
<td>36±3</td>
</tr>
</tbody>
</table>

*C indicates control group; T, terazosin-treated animals; and Z, zofenopril-treated animals. Abbreviations for hemodynamic variables as in text.

*p=.025 compared with baseline; †p=.025 compared with control.
Table 5. Values for Left Ventricular Mass and End-diastolic Volume in All Groups at Baseline, 2 Weeks, and 16 Weeks After Myocardial Damage

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ramipril 10 mg BID</th>
<th>Ramipril 1.25 mg BID</th>
<th>DUP 532</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM, g</td>
<td>87.3±4.1</td>
<td>89.1±4.4</td>
<td>89.7±4.6</td>
<td>89.0±4.6</td>
</tr>
<tr>
<td>LVV, mL</td>
<td>68.9±5.3</td>
<td>66.4±2.9</td>
<td>61.8±3.8</td>
<td>66.0±1.9</td>
</tr>
<tr>
<td>2 wk LVM, g</td>
<td>95.8±5.3</td>
<td>88.9±5.5</td>
<td>95.7±5.2</td>
<td>97.0±3.4</td>
</tr>
<tr>
<td>2 wk LVV, mL</td>
<td>73.7±4.7</td>
<td>63.9±3.6</td>
<td>63.6±3.9</td>
<td>72.9±2.9</td>
</tr>
<tr>
<td>16 wk LVM, g</td>
<td>107.5±4.3*</td>
<td>92.1±7.0†</td>
<td>105.7±3.4*</td>
<td>109.7±5.3*</td>
</tr>
<tr>
<td>16 wk LVV, mL</td>
<td>79.7±4.1*</td>
<td>67.2±2.4†</td>
<td>76.8±3.3*</td>
<td>78.4±3.6*</td>
</tr>
</tbody>
</table>

LVM indicates left ventricular mass; LVV, left ventricular volume.

*P<.025 compared with baseline; †P<.025 compared with control, Ramipril 1.25 mg BID, and DUP 532.

low-dose ramipril, and DUP 532 groups. No significant change in wall thickness, chamber diameter, or d:h ratio was noted in the high-dose ramipril group. The increase in the d:h ratio at 16 weeks in the control group was significantly different from the change in the high-dose ramipril group (0.35 versus 0.03, P=.02) but not different from the DUP 532–treated group (0.35 versus 0.15, P=.14) or the low-dose ramipril group (0.35 versus 0.25, P=.51).

**Hemodynamic Results**

In the control animals, a small but significant increase in PCWP was noted between baseline and 16-week measurements (7±1 to 12±1 mm Hg, P=.01) (Table 7). There was a similar trend in PAP (14±1 to 18±2 mm Hg, P=.04) and RAP (4±1 to 7±1 mm Hg, P=.07). MAP was not significantly changed.

A similar trend in PCWP was noted in those animals treated with low-dose ramipril (9±1 to 11±1 mm Hg, P=.05), and PAP in this group also tended to rise. Arterial pressure was not altered in this group or in the DUP 532 group. Dogs assigned to high-dose ramipril displayed a reduction in MAP at 2 weeks after myocardial damage (89±4 to 78±3 mm Hg, P=.03) and at the 16-week time point (89±4 to 80±3 mm Hg, P=.06). No other hemodynamic change was noted in this group.

Intergroup comparisons revealed no significant differences between groups at baseline except for HR, which was significantly higher in dogs randomized to high-dose ramipril. At 2 weeks after DC shock, MAP in this group was significantly less than in the DUP 532 group (78±3 versus 93±4 mm Hg, P=.005), the low-dose ramipril group (78±3 versus 89±3 mm Hg, P=.02), and the control group (78±3 versus 86±3 mm Hg, P=.04). At the end of the 16-week study period, MAP remained significantly less in those treated with high-dose ramipril compared with control dogs (80±3 versus 91±3 mm Hg, P=.01) and those treated with low-dose ramipril (80±3 versus 92±2 mm Hg, P=.005) and DUP 532 (80±3 versus 92±4 mm Hg, P=.03). At this time point, PCWP was significantly less in those treated with high-dose ramipril compared with the control group (7±1 versus 12±1 mm Hg, P=.001), low-dose ramipril (7±1 versus 11±1 mm Hg, P=.02), or DUP 532 group (7±1 versus 10±1 mm Hg, P=.02).

**Plasma Renin Activity**

PRA rose insignificantly at 2 weeks compared with baseline in the group receiving low-dose ramipril.

Table 6. Values for Mean Wall Thickness, Chamber Diameter, and Diameter to Wall Thickness Ratios in All Groups at Baseline, 2 Weeks, and 16 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Wall Thickness, mm</th>
<th>Chamber Diameter, mm</th>
<th>Diameter to Wall Thickness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.4±0.1</td>
<td>39.6±0.4</td>
<td>4.7±0.1</td>
</tr>
<tr>
<td>2 wk</td>
<td>8.7±0.2*</td>
<td>40.0±0.3</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>8.5±0.1</td>
<td>43.2±0.5*</td>
<td>5.1±0.1*</td>
</tr>
<tr>
<td>Ramipril (standard dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.4±0.1</td>
<td>40.1±0.6</td>
<td>4.8±0.1</td>
</tr>
<tr>
<td>2 wk</td>
<td>8.3±0.1</td>
<td>40.0±0.4</td>
<td>4.8±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>8.3±0.1</td>
<td>40.1±0.4†</td>
<td>4.8±0.1†</td>
</tr>
<tr>
<td>Ramipril (low dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.5±0.2</td>
<td>39.8±0.5</td>
<td>4.7±0.1</td>
</tr>
<tr>
<td>2 wk</td>
<td>8.8±0.2*</td>
<td>40.0±0.4</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>8.6±0.1</td>
<td>42.1±0.5*</td>
<td>4.9±0.1*</td>
</tr>
<tr>
<td>DUP 532</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6±0.2</td>
<td>40.4±0.3</td>
<td>4.7±0.1</td>
</tr>
<tr>
<td>2 wk</td>
<td>8.8±0.2*</td>
<td>41.0±0.3</td>
<td>4.7±0.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>8.8±0.1*</td>
<td>42.6±0.7*</td>
<td>4.9±0.1*</td>
</tr>
</tbody>
</table>

*P<.025 compared with baseline; †P<.05 compared with control.

Fig 4. Bar graph shows left ventricular ejection fraction (LVEF) at baseline (BL) and 16 weeks after myocardial damage in the control and treated groups in protocol 2.
TABLE 7. Values for Hemodynamic Variables in All Groups at Baseline, 2 Weeks, and 16 Weeks After Myocardial Damage

<table>
<thead>
<tr>
<th>Hemodynamic Variable</th>
<th>Baseline</th>
<th>2 Weeks</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Ao, mm Hg</td>
<td>90±3</td>
<td>89±4</td>
<td>92±2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>7±1</td>
<td>9±2</td>
<td>9±1</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>14±1</td>
<td>16±1</td>
<td>16±1</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>4±1</td>
<td>5±1</td>
<td>5±1</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.4±0.4</td>
<td>4.1±0.2</td>
<td>3.5±0.3</td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>65±7</td>
<td>91±7‡</td>
<td>76±7</td>
</tr>
<tr>
<td>SV, mL</td>
<td>52±3</td>
<td>44±5</td>
<td>47±2</td>
</tr>
</tbody>
</table>

A indicates control group; B, ramipril 10 mg BID group; C, ramipril 1.25 mg BID group; and D, DUP532 group. Hemodynamic variables are defined in text.

(1.8±0.4 to 4.0±1.1 ng/mL per hour, $P = .09$) (Table 8). A similar but nonsignificant trend was noted in the dogs treated with high-dose ramipril (3.0±0.9 to 11.9±4.1 ng/mL per hour, $P = .07$) and in the DUP 532 group (1.9±0.4 to 9.3±3.6 ng/mL per hour, $P = .07$). At 16 weeks, all values had returned toward baseline and were not significantly different from those obtained before the initiation of therapy.

**Angiotensin I Challenge**

To determine the degree of ACE blockade by the two doses of ramipril, angiotensin I challenge was performed on 6 control dogs, 6 dogs taking high-dose ramipril, and 7 dogs taking low-dose ramipril. These studies were performed at the end of the 16-week study period. In the dogs treated with low-dose ramipril (Fig 5A), the arterial pressure response to the higher bolus doses of angiotensin I was significantly inhibited. In those treated with high-dose ramipril (Fig 5B), the response to all four doses of angiotensin I was significantly inhibited. Fig 5C displays the relative increase in MAP in response to increasing boluses of angiotensin I in the 2 ramipril-treated groups while on therapy. The graph demonstrates that the increase in MAP to each dose of angiotensin I was significantly greater in the animals assigned to therapy with low-dose ramipril than high-dose ramipril. When ramipril was discontinued, the response to angiotensin I was similar in all three groups (Fig 5D).

**Angiotensin II Challenge**

To determine if there was significant AT₁-receptor blockade, angiotensin II challenge was performed on 7 dogs from the group receiving DUP 532. This analysis was performed at baseline, before the initiation of therapy, and at 2 and 16 weeks after DC shock. When performed while on therapy, the angiotensin II challenge was carried out approximately 16 hours after the last dose of the drug. Therapy with DUP 532 was associated with a significant attenuation of the increase in arterial pressure in response to bolus injections of angiotensin II (Fig 6). While it appears that some AT₁-blocking activity may be lost with chronic therapy, inhibition of the systemic pressor response was still statistically significant at 16 weeks when compared with baseline and not statistically different from the degree of inhibition at 2 weeks. These data suggest that there was persistent peripheral vascular AT₁-receptor blockade by DUP 532.

**Discussion**

Structural changes that occur in the myocardium after ventricular damage are referred to as ventricular remodeling and consist of a change in shape of the ventricle associated with an increase in ventricular chamber size as well as an increase in mass of the surviving myocardial tissue.1-9 The process of ventricular remodeling is initiated immediately after myocardial damage and can progress in the absence of overt symptoms of LV dysfunction.1,2,21 Several distinct pathological processes may contribute to these structural changes. Expansion of the necrotic zone5,6 and eccentric hypertrophy7,8 and/or slippage9 of myocytes may result in chamber dilation. An increase in ventricular mass could reflect concentric and/or eccentric hypertrophy of myocytes7,8 and/or growth of the cardiac interstitium.4 The model used in these studies to induce myocardial mass and ventricular volume increase is unique.3,32 It imposes neither an early pressure load nor a measurable early volume load on the ventricle. The localized wall motion abnormality in the region of the scar would be expected to alter chamber geometry, particularly during systole, but the mechanism stimulating this remodeling process, which may be similar to that after acute moderate-sized myocardial infarction, remains elusive. Since LV ejection fraction falls and plasma norepinephrine is elevated in this model,3 it appears to mimic the syndrome of asymptomatic LV dysfunction, which was studied in two recent clinical trials.40,41

**Table 8. Plasma Renin Values (ng/mL per hour) in All Four Groups at Baseline, 2 Weeks, and 16 Weeks After Myocardial Damage**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.0±0.9</td>
<td>1.8±0.4</td>
<td>1.9±0.4</td>
</tr>
<tr>
<td>2 wk</td>
<td>2.9±0.4</td>
<td>11.9±4.1</td>
<td>4.0±1.1</td>
</tr>
<tr>
<td>16 wk</td>
<td>1.5±0.2</td>
<td>3.0±0.8</td>
<td>1.8±0.4</td>
</tr>
</tbody>
</table>

Group A: control; group B, ramipril 10 mg BID; group C, ramipril 1.25 mg BID; and group D, DUP532.
dogs and 5 with postshock LV dilation to evaluate the LV pressure-volume relation. Volume loading was carried out under pentobarbital anesthesia using rapid intravenous infusions of 0.9% saline. Two-dimensionally guided M-mode echocardiography was used to monitor the short axis of the left ventricle at the level of the papillary muscles in 8 of these dogs (4 normal, 4 post-DC shock). PCWP was monitored from a catheter in the pulmonary artery. Initial PCWP in these anesthetized dogs was <5 mm Hg. During saline infusion, PCWP increased to 30 mm Hg in both normal and left ventricle–damaged dogs. As shown in Fig 7, the modest increase in echocardiographic chamber diameter in the normal dogs could not account for the increased chamber volume observed in 4 myocardial-damaged dogs whose PCWP at 1 and 16 weeks after shock averaged only 12 and 16 mm Hg, respectively. In the remodeled ventricles, volume expansion produced barely perceptible changes in ventricular chamber size. Estimation of LV volume by the MRI method used in these studies in 2 dogs (one normal, one post-DC shock) during fluid challenge confirmed these echocardiographic findings. In 1 normal dog, LV volume increased from 56.8 to 61.5 mL as the PCWP rose from 5 to 30 mm Hg. The other dog had LV remodeling as a result of DC shock. A rise
in PCWP from 5 to 30 mm Hg in this dog resulted in a 5.5-mL increase in LV volume from 72.0 to 77.5 mL. Thus, the volume increase in this model results from remodeling and cannot be attributed to an augmentation of preload.

We have previously reported an early increase in myocardial mass in this model.3,4,19,21 The stimulus for this early structural change is unclear. Since the LV volume increase at this early time point is small, inconsistent, and not statistically significant and since an estimate of diastolic wall stress was actually reduced at 7 days, it is difficult to ascribe the mass increase to a compensatory response to an increase in chamber volume or diastolic wall stress, mechanisms thought to play a significant role in initiating remodeling.21 The index of wall stress used in this study does not take into account LV pressure and simply reflects the association between chamber diameter and wall thickness. However, when measured at end diastole, as in this study, this index is probably a reasonable guide to diastolic load. The influence on systolic load of a wall motion abnormality and possible enhanced contractile force of remote myocardium was not assessed.

Trophic hormones as well as load have been implicated in the process of ventricular mass increase and could play a role in chamber dilation as a result of elongation of myocytes.17,19,22,28 Angiotensin II and norepinephrine stimulate myocyte growth and fibroblast activity in vitro.22,28 In vivo studies have shown that ACE inhibitor therapy attenuates myocardial growth.1,4,11,14,15,21 The studies support a role for angiotensin II in ventricular growth, but they do not exclude the possibility that other effects of ACE inhibitor therapy, such as reduced degradation of bradykinin, may be important in the attenuation of remodeling.

Animal experiments support a role for norepinephrine in myocardial growth. Zierhut and Zimmer26 demonstrated that norepinephrine directly stimulates cardiac hypertrophy, even when the hemodynamic effects of the α₁-adrenoceptor agonist were negated by verapamil. Furthermore, preliminary data from the rat myocardial infarct model have shown that α₁-adrenoceptor blockade can attenuate early postinfarction myocyte hypertrophy.32 However, Cooper and colleagues42 demonstrated that α- and β-blockade did not attenuate the increase in right ventricular mass observed in cats after banding of the pulmonary artery.

The present experiments were designed to explore a possible role for norepinephrine and angiotensin in the LV remodeling process that follows localized myocardial damage. Two ACE inhibitors, one sulfydryl containing and one a nonsulfydryl compound, were effective in preventing both mass increase and chamber dilation over a 16-week postinjury period. In contrast, the α₁-adrenoceptor blocker terazosin was ineffective by 16 weeks, although it did inhibit the early mass increase during the first week. Failure of a chronic effect of terazosin on ventricular remodeling probably cannot be attributed to tachyphylaxis, since the phenylephrine dose-response curve remained significantly shifted to the right during chronic therapy. These data suggest that norepinephrine may be involved through α₁-adrenoceptor stimulation in the early remodeling in this model but that long-term structural changes occur despite α₁-receptor inhibition. On the contrary, ACE inhibitors are effective in blocking both the early and long-term process.

The second protocol in these studies was designed to further elucidate the mechanism of ACE inhibitor effect on remodeling. Since load reduction, decreased angiotensin II formation, and increased kinin production all may accompany ACE inhibitor therapy, studies were performed with the angiotensin receptor antagonist DUP 532 as well as with low-dose ramipril that was ineffective in lowering arterial pressure. The latter strategy was based on the results of previous studies in a rat aortic coarctation model in which ramipril or enalapril inhibited LV hypertrophy in a low dose that exerted no blood pressure–lowering effect.33,44 Although the mechanism of this action was not clarified in those studies, a direct hormonal effect was considered.43,44 The failure of low-dose ramipril to interfere with the remodeling process in our canine model provides little mechanistic insight. Although it indicates that a higher dose of an ACE inhibitor is needed for therapeutic efficacy in this model, it does not allow separation of the influence of load, angiotensin II, or kinins on the process.

Angiotensin II receptor blockade by DUP 532 did not attenuate ventricular remodeling. These findings are at some variance with those of Raya and colleagues,45 who demonstrated that DUP 753, a competitive AT₁-receptor antagonist, inhibited chamber enlargement in the rat after myocardial infarction. Several factors could account for the differences between these two studies. First, MAP tended to fall in rats assigned to DUP 753,45 whereas we observed no effect of DUP 532 on MAP in our canine model. The differing effects on arterial pressure may be explained by the fact that PRA is not consistently increased in the canine model of DC shock, whereas with the large infarcts studied by Raya and colleagues (>40% of the LV myocardium), it is likely that PRA was elevated. AT₁-receptor blockers tend to have no significant effect on arterial pressure when PRA is not increased,46 although it is of interest that these
agents produce a dose-dependent increase in renin activity. Second, different species and models used in these two studies may explain the difference in response to AT1-receptor blockade. Few data are available on the distribution and type of angiotensin II receptors in the myocardium, but preliminary studies suggest that subtype I receptors are present in the canine heart. It is possible that the distribution of myocardial AT1-receptors differs in the rat and dog.

We recognize that the dose of DUP 532 could have been inadequate in these studies. However, pilot data demonstrated that 15 mg/kg BID of DUP 532 provides a 90% inhibition of the systemic pressor response to angiotensin II administered at a dose of 0.1 μg/kg. Data gathered during the study suggest that less complete inhibition of the vascular response was achieved, but the angiotensin II challenge studies were performed approximately 16 hours after the last dose of DUP 532 and therefore may underestimate the extent of receptor blockade. Implicit in these statements is the assumption that inhibition of the systemic pressor effect of angiotensin II reflects blockade of the AT1-receptor on the cardiac myocyte. There are no data to support this important assumption. Despite these uncertainties, the data raise the likelihood that the effectiveness of ACE inhibition in this model is mediated not primarily through the AT1-receptor.

Two other potential mechanisms, not addressed by this study, need to be considered as possible explanations for our findings. It is possible that the direct trophic effect of angiotensin II might be mediated by an upregulated AT2-receptor rather than by the AT1-receptor. A selective AT2-blocker was not used in our study. It is of interest that preliminary data in the rat coarctation model demonstrate that there is a relative increase in the ratio of AT2 to AT1-receptors in LV hypertrophy. However, little is known regarding the functional properties of the AT2-receptor. Preliminary data suggest a role in fibroblast function. Moreover, a recent study by Janiak and colleagues demonstrated that blockade of AT2-receptor inhibits vascular intimal proliferation after endothelial injury to the same extent as that observed with ACE inhibitor therapy. Whether the AT2-receptor plays a similar role in the myocardial response to acute injury remains unknown.

ACE inhibition is well known also to inhibit bradykinin degradation. Bradykinin, like other endogenous vasodilators that act through the production of nitric oxide and the intracellular second messenger cGMP, may have antiproliferation effects unrelated to load reduction. In support of this hypothesis are data demonstrating that the addition of a bradykinin antagonist to ACE inhibitor therapy results in loss of the usual ACE inhibitor antiremodeling effect after intimal injury. Preliminary data from the rat coarctation model demonstrate that a bradykinin antagonist blocks the antihypertrophic effect of ramipril. Therefore, it is possible, although not yet proved, that the antiremodeling effect of ACE inhibitor therapy may be related to an increment in bradykinin. Analysis of the effect of a bradykinin antagonist on the antiremodeling action of an ACE inhibitor compound in this model would provide important data on this question.

These studies were not designed to quantitate the load-reducing effect of these vasodilator interventions. Hemodynamic measurements were made only on two occasions during therapy and were performed at the trough effect of the drug in order to assess chronic changes rather than acute pharmacological actions. The modest arterial pressure reduction noted in response to the two ACE inhibitors could have contributed to the antiremodeling effect but is unlikely to have been the sole mechanism. The rise in pulmonary capillary pressure in the untreated and ineffectively treated dogs may be a result and not necessarily a cause of the remodeling process. The effectiveness of the ACE inhibitors in preventing the progressive rise may therefore be a marker for the favorable effects on structure and not a pharmacological action of the drugs.

Although analysis of the effect of remodeling on LV function was not a major focus of this study, LV ejection fraction did decline modestly over the 16-week period in the control group, and this decline was prevented by ACE inhibition. A further indirect index of ventricular function was obtained from analysis of wall stress. An index of diastolic wall stress was computed by analyzing the ratio of chamber diameter to wall thickness at end diastole. A more precise estimation of wall stress was not possible because hemodynamic measurements were obtained at different times and under different anesthetic conditions from the MRI measurements. Nonetheless, analysis of the d:h ratio suggests that wall stress increased in all groups except the high-dose ramipril group (Table 2), further supporting the concept that attenuation of ventricular remodeling is accompanied by a reduction in wall stress. The response of the remodeled and remodeling-inhibited ventricles to exercise stress must be studied in order to evaluate the long-term effects in this model.

The morphometric correlates of remodeling and its inhibition in this model were not addressed in this study. Accordingly, the relative contribution of myocyte hypertrophy or shape change and growth of the cardiac interstitium to the remodeling process are unclear. However, the major end points of these studies were the changes that occurred in ventricular mass and volume, parameters that we5,20 and others35,36 have shown can be very accurately assessed by MRI. Ongoing and future studies will address the morphometrics of remodeling in this model.

Summary

The data from this study confirm previous observations from this laboratory that ventricular remodeling occurs after transmyocardial DC shock and that these structural changes are associated with a modest reduction in LV systolic function. Despite attenuating the early mass increase, α1-adrenergic blockade was ineffective in preventing long-term remodeling in this model. Conversely, two converting enzyme inhibitors were effective in preventing remodeling. The failure of low-dose ramipril and AT1-receptor blockade to inhibit remodeling suggests that angiotensin II acting through the AT1-receptor may not be critical for the remodeling process, although load reduction from ACE inhibition may contribute to the antiremodeling effect.

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