Effects of Enalapril Versus Losartan on Regression of Volume Overload–Induced Cardiac Hypertrophy in Rats

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Background  The role of nonhemodynamic cardiac trophic mechanisms differs not only between different models of cardiac hypertrophy but also within the same model for development versus maintenance of cardiac hypertrophy. Our previous studies pointed to a major role for the renin-angiotensin system (RAS) as a cardiac trophic stimulus in the remodeling of the heart in response to volume overload by aortocaval shunt or minoxidil treatment.

Methods and Results  In the present study, we evaluated the effects of blockade of the RAS by the angiotensin-converting enzyme inhibitor enalapril and the angiotensin II receptor blocker losartan on left ventricular (LV) and right ventricular mass and LV dilation in relation to changes in central hemodynamics during the maintenance of minoxidil and aortocaval shunt–induced cardiac hypertrophy. Both blockers similarly decreased LV end-diastolic pressure (LVEDP) and LV peak systolic pressure, whereas cardiac output remained unchanged in both models of volume overload. This suggests a major contribution of improved LV performance and decreased afterload to the decrease in cardiac preload by the two blockers rather than decreased venous return. Both blockers reversed LV hypertrophy in parallel to their effects on LVEDP in both models of volume overload. In minoxidil-treated rats, the extent of reversal in LV mass and dilation by the two blockers was similar to “spontaneous regression” after discontinuation of minoxidil treatment.

Conclusions  These results indicate that in contrast to the development phase of cardiac hypertrophy, the RAS does not contribute to the maintenance of volume overload–induced cardiac hypertrophy in these two models via direct cardiac trophic effects. The RAS, however, maintains cardiac hypertrophy indirectly by contributing to the persistence of high filling pressures. (Circulation. 1994;90:484–491.)

Key Words  • aorta • minoxidil • angiotensin • hypertrophy • hemodynamics

The involvement of the renin-angiotensin system (RAS) in remodeling of the heart differs between different models of pressure overload–induced cardiac hypertrophy and may differ within the same model for development versus maintenance of cardiac hypertrophy. For example, the angiotensin-converting enzyme inhibitor (ACEI) quinapril did not prevent development of cardiac hypertrophy after ascending aorta banding. In contrast, quinapril started 6 weeks after aortic banding caused regression of cardiac hypertrophy similar to removal of the ascending aorta constriction. On the other hand, after abdominal aorta banding above the renal arteries, the ACEI ramipril and enalapril, in doses that did not affect cardiac afterload, did prevent the development and also caused complete regression of cardiac hypertrophy.

The role of the RAS in the cardiac remodeling in response to cardiac volume overload has been studied only to a very limited extent. In vitro, acute stretch of cardiomyocytes results in increased expression of c-fos as the earliest nuclear marker of their hypertrophic response. Angiotensin II generated by the stretched cardiomyocytes appears to mediate this hypertrophic response. In vivo, cardiac volume overload may develop rapidly after opening of an aortocaval shunt or may develop more gradually, as in the case of chronic minoxidil treatment by a shift of circulating volume from the periphery to the central compartment and by sodium and volume retention. In both models, cardiac volume overload results in right ventricular (RV) hypertrophy and left ventricular (LV) eccentric hypertrophy. The ACEI enalapril did not prevent volume overload–induced cardiac remodeling in either model, despite decreasing cardiac preload and afterload. In contrast, similar decreases in cardiac load by the angiotensin II receptor blocker losartan resulted in prevention/attenuation of the remodeling of the heart by cardiac volume overload. These results are consistent with the concept that factors other than hemodynamic factors are involved in the development of cardiac hypertrophy in both models of cardiac volume overload.

The presence in the heart of an angiotensin II–forming enzyme resistant to ACEI and/or the low affinity of enalapril to cardiac tissue, both resulting in continuous generation of angiotensin II in the heart during enalapril treatment, may explain the different cardiac effects of enalapril versus losartan.

For either model of volume overload, the contribution of hemodynamic versus direct cardiac trophic effects of the RAS in the maintenance of cardiac hypertrophy has not yet been established. In rats with aortocaval shunt for 3 weeks, short-term (1-week) treatment with losartan and captopril decreased LV mass similarly by about 12.5%, suggesting that the RAS still plays a role. During the maintenance of minoxidil-
induced cardiac hypertrophy, effects of blockers of the RAS have not been assessed at all.

In the present study, we therefore assessed the role of hemodynamic versus direct trophic effects of the RAS by chronic treatment with two blockers of the RAS, enalapril and losartan, during the maintenance phase of volume overload–induced cardiac hypertrophy. Effects of the blockers on volume overload–induced changes in cardiac morphology were evaluated in relation to their effects on cardiac and peripheral hemodynamics. Two models of volume overload (ie, aortocaval shunt or chronic minoxidil treatment) were studied to address the general paradigm of cardiac volume overload rather than possible model-specific mechanisms. Both enalapril and losartan were used to assess whether changes in cardiac hypertrophy for both blockers reflect only the new balance between cardiac mass and hemodynamic load or may indicate different effects on the cardiac RAS, as suggested by the prevention experiments. To assess the relative role of the RAS versus other trophic mechanisms in the maintenance of minoxidil-induced cardiac hypertrophy, the effects of the blockers were compared with the changes in cardiac morphology and hemodynamics after discontinuation of minoxidil.

Methods

Animals

Male Wistar rats, 200 to 225 g, were obtained from Charles River Breeding Laboratories. Rats were housed two per cage in a climatized room (24°C) of the animal care unit, kept on a 12-hour light-dark cycle, and given food (Purina rat chow, 120 µmol Na/g food) and water ad libitum. After an acclimatization period of at least 3 days, the rats were randomized into the above-mentioned two treatment groups: control (n=72), aortocaval shunt (n=48), or minoxidil (n=88; 120 mg/L of drinking water). Abdominal aortocaval shunt was produced by using an 18-gauge disposable needle (Becton-Dickinson) as described by Ruzicka et al. This technique has the advantages of a very low surgical mortality (<2% in the present study) and a high reproducibility regarding the level of volume overload and resulting changes in cardiac morphology. Sham-operated animals serving as controls were subjected to the same surgical procedure, with the exception of puncture of the aorta and the inferior vena cava. Animals were weighed on the day of randomization, weekly thereafter, and on the day of hemodynamic assessments.

Study Protocols

Time Course of Spontaneous Regression of Minoxidil-Induced Cardiac Hypertrophy

Five weeks after the start of minoxidil treatment, when changes in cardiac anatomy are fully established, 8 minoxidil rats and 6 control rats were subjected to the assessment of central hemodynamics and cardiac morphology as described below. At the same time, the minoxidil was discontinued in 16 rats and continued in the remaining 16 rats. The effect of discontinuation of minoxidil on central hemodynamics and cardiac morphology was assessed at 2 and 5 weeks after discontinuation of minoxidil. These two time points were chosen to take into account the time course of development of cardiac changes in this model and the regression of pressure overload–induced cardiac morphology.

Effects of the ACEI Enalapril and Angiotensin II Receptor Blocker Losartan on Hemodynamics and Cardiac Morphology

Five weeks after the shunt/sham surgery or start of minoxidil treatment, each of the three above-mentioned groups of rats (ie, control, shunt, and minoxidil) was further randomized into three different subgroups (n=16 per group): no treatment, losartan (40 mg/kg per day by gastric gavage), or enalapril (250 mg/L of drinking water). After 5 weeks of such regimens, 8 rats of each group were used for the assessment of cardiac output, blood pressure, and LV and RV weights. The remaining 8 rats of each group were used for assessment of central hemodynamics and cardiac morphology.

Cardiac Output

Cardiac output was assessed by the thermodilution technique as previously described by Yuan and Leenen. Briefly, under halothane/nitrous oxide/oxygen anesthesia, a PE-50 catheter was placed into the right atrium via the right jugular vein, and a PE-10 catheter was inserted into the left femoral artery for monitoring of blood pressure and heart rate. A thermistor (outer diameter, 0.64 mm) was advanced into the aortic arch via the left carotid artery and connected to a cardiac output computer (Cardiotherm-500) through a Cardiomax-II-R Interface and Probe Selector (Columbus Instruments). The rats were permitted to recover for 4 hours from anesthesia and surgical procedure. After a 30-minute acclimatization period, 200 µL of 5% dextrose at room temperature (21°C to 22°C) was injected into the right atrium as the thermal tracer indicator. This procedure was repeated, and the mean of two readings of the tracings and cardiac output data was used for the calculations of the following parameters: mean arterial pressure (MAP) equal to diastolic pressure plus pulse pressure divided by 3; cardiac index (CI) equal to cardiac output divided by body weight; stroke volume index (SVI) equal to cardiac output divided by heart rate divided by body weight; and total peripheral resistance index (TPRI) equal to MAP/CI.

Central Hemodynamics

On the day of the study, rats were anesthetized with halothane/nitrous oxide/oxygen, and a PE-50 catheter (Clay Adams) filled with heparinized saline (100 IU/mL) was inserted into the LV via the right common carotid artery and into the right atrium via the right external jugular vein. Catheters were exteriorized on the necks of the animals. After a 4-hour recovery period, LV end-diastolic pressure (LVEDP), LV peak systolic pressure (LVSPS), and right atrial pressure (RAP) were assessed as described by Fields et al. The heart rate was calculated from the curve of LVSPS and LVEDP recorded at a paper speed of 10 mm/s. Resting hemodynamics were assessed in conscious, unrestrained rats after a 30-minute acclimatization period.

Cardiac Morphology

After the assessment of central hemodynamics, under pentobarbital anesthesia the chest cavity was opened, and the heart was arrested in diastole by intravenous injection of 1 mol/L KCl, rapidly excised, and placed into ice-cold saline to remain in diastole and for removal of the blood. After removal of the atria and large vessels, the ventricles were blotted dry, and the RV was dissected along its septal insertion from the rest of the ventricular mass. LV long axis (apex-base distance) and LV and RV wet weights were assessed. Then the mass of the LV was divided by two transverse cuts at one third and two thirds of the length. The middle slice of the LV was used for the assessment of the LV wall thickness and internal diameters as previously described. LV and RV dry weights were determined after the tissue was dried in an oven at 37°C for 72 hours.

Statistical Analysis

Results are expressed as mean±SEM. Differences between groups at a given treatment period were evaluated by ANOVA and Duncan's multiple-range test. Linear regression analysis was used to study relations between variables. Possible differ-
TABLE 1. Time Course of Changes in Hemodynamics, Cardiac Morphology, and Hematocrit in Response to Discontinuation of Minoxidil After 5 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>5 Weeks</th>
<th>7 Weeks</th>
<th>10 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.6±0.6</td>
<td>0.0±0.6</td>
<td>0.3±0.6</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>4.1±0.8*</td>
<td>3.5±0.9*</td>
<td>2.5±0.7*</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>1.0±0.9</td>
<td>0.4±0.5†</td>
</tr>
<tr>
<td><strong>LVSP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>130±6</td>
<td>130±4</td>
<td>125±7</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>120±4</td>
<td>115±6</td>
<td>116±5</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>126±6</td>
<td>127±7</td>
</tr>
<tr>
<td><strong>LV wall thickness, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.63±0.01</td>
<td>2.66±0.01</td>
<td>2.67±0.01</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>2.71±0.01*</td>
<td>2.73±0.01*</td>
<td>2.74±0.01*</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>2.69±0.01*†</td>
<td>2.67±0.01†</td>
</tr>
<tr>
<td><strong>LV internal diameter, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.22±0.03</td>
<td>4.33±0.01</td>
<td>4.28±0.02</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>4.86±0.02*</td>
<td>5.03±0.02*</td>
<td>5.03±0.01*</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>4.66±0.03†</td>
<td>4.37±0.02†</td>
</tr>
<tr>
<td><strong>WTH/Radius</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.25±0.01</td>
<td>1.23±0.01</td>
<td>1.25±0.01</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>1.11±0.01*</td>
<td>1.08±0.01*</td>
<td>1.09±0.01*</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>1.16±0.01†</td>
<td>1.22±0.01†</td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>44±1</td>
<td>45±1</td>
<td>45±1</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>36±1*</td>
<td>36±1*</td>
<td>36±1*</td>
</tr>
<tr>
<td>Minoxidil discontinued</td>
<td>...</td>
<td>43±1†</td>
<td>45±1†</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; LVEDP, LV end-diastolic pressure; LVSP, LV peak systolic pressure; and WTH, wall thickness. Values are mean±SEM (n=6 to 8 per group).

*P<.05 vs control.
†P<.05 for discontinued minoxidil vs minoxidil.

ferences between regression lines were evaluated as described by Smith and Choi. Differences were considered statistically significant if P<.05.

Results

Hemodynamic Changes

After 10 weeks of treatment with minoxidil (Tables 1 and 2) or an aortocaval shunt (Table 2), LVEDP and RAP were still significantly increased compared with controls. Discontinuation of minoxidil at 5 weeks returned LVEDP to normal within 2 weeks (Table 1). Enalapril and losartan did not affect LVEDP and RAP of control rats. However, both drugs decreased LVEDP and RAP of minoxidil-treated rats and of rats with an aortocaval shunt to (near) normal levels (Table 2). Both minoxidil and aortocaval shunt caused modest decreases in LVSP ([P:NS], Tables 1 and 2) and MAP ([P<.05 for shunt], Table 3). Enalapril and losartan decreased LVSP of minoxidil-treated rats and shunt rats to levels similar to those observed in control rats (Table 2). In contrast, both drugs decreased MAP of minoxidil-treated rats and shunt rats to values below those of control rats (Table 3). There were no differences in heart rate between the different groups at 10 weeks (data not shown). Cardiac index and stroke volume were increased by 20% after 10 weeks of aortocaval shunt or minoxidil treatment (Table 3). Neither enalapril nor losartan significantly changed cardiac index in control, shunt, or minoxidil-treated animals. Total peripheral resistance index (inclusive shunt) was significantly decreased in shunt rats (Table 3). Enalapril and losartan did not further decrease total peripheral resistance index in animals with an aortocaval shunt. In minoxidil-treated rats, total peripheral resistance index was significantly decreased and dropped further when either enalapril or losartan was added (Table 3).

LV and RV Weights

Aortocaval shunt and minoxidil increased LV weight by 50% and 22%, respectively, at 10 weeks (Fig 1; Table 4). Discontinuation of minoxidil after 5 weeks of treatment resulted in a substantial decrease in LV weight at 7 weeks, and LV weight had returned to normal at 10 weeks (Fig 1). In control rats, both enalapril and losartan decreased LV weight by about 10% (Table 4).
Enalapril decreased LV weight of shunt rats somewhat less (P<.05) than losartan compared with untreated shunt animals, and the remaining hypertrophy in enalapril- and losartan-treated shunt rats was +41% and +32% compared with their respective treated control rats (Table 4). In minoxidil-treated rats, enalapril and losartan decreased LV weight similarly back to the level of untreated control rats. However, neither blocker reversed the LV weight to the extent of their respective treated controls, i.e., LV weight of rats on minoxidil treated with enalapril or losartan remained to a small but significant extent increased compared with the respective treated control group (Table 4).

Aortocaval shunt and minoxidil treatment increased RV weight by 68% and 24%, respectively (Table 4).

After discontinuation of minoxidil at 5 weeks, RV weight had substantially decreased at 7 weeks, and at 10 weeks it remained increased by only 6% (P<.05) compared with control rats (Fig 1). Neither enalapril nor losartan changed RV weight in control rats. However, both drugs significantly reduced RV hypertrophy induced by aortocaval shunt compared with untreated shunt rats (Table 4). However, in both enalapril- and losartan-treated shunt rats, RV weight remained significantly increased compared with their respective treated control rats. Neither enalapril nor losartan affected RV hypertrophy induced by minoxidil (Table 4).

There were no differences in percent dry weight of LV and RV between the groups at 10 weeks (data not shown).

### Table 2. Effects of Enalapril vs Losartan (From 5 to 10 Weeks) on Changes in Cardiac Hemodynamics Induced by Minoxidil or Aortocaval Shunt at 10 Weeks

<table>
<thead>
<tr>
<th>Control</th>
<th>Control+enalapril</th>
<th>Control+losartan</th>
<th>Shunt</th>
<th>Shunt+enalapril</th>
<th>Shunt+losartan</th>
<th>Minoxidil</th>
<th>Minoxidil+enalapril</th>
<th>Minoxidil+losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP, mm Hg</td>
<td>RAP, mm Hg</td>
<td>LVPSP, mm Hg</td>
<td>LVEDP, mm Hg</td>
<td>RAP, mm Hg</td>
<td>LVPSP, mm Hg</td>
<td>LVEDP, mm Hg</td>
<td>RAP, mm Hg</td>
<td>LVPSP, mm Hg</td>
</tr>
<tr>
<td>0.0±0.2</td>
<td>−0.2±0.4</td>
<td>123±5</td>
<td>0.5±0.3</td>
<td>0.0±0.3</td>
<td>108±7*</td>
<td>0.2±0.2</td>
<td>−0.8±0.4</td>
<td>92±6*</td>
</tr>
<tr>
<td>6.4±1.2*</td>
<td>2.5±0.4*</td>
<td>112±3</td>
<td>3.0±0.6†</td>
<td>0.8±0.5†</td>
<td>101±6</td>
<td>2.0±0.5††</td>
<td>0.6±0.4††</td>
<td>93±4†</td>
</tr>
<tr>
<td>4.5±0.8*</td>
<td>1.2±0.4*</td>
<td>114±4</td>
<td>1.2±0.6†</td>
<td>0.1±0.1</td>
<td>98±3†</td>
<td>1.0±0.4††</td>
<td>0.8±0.3††</td>
<td>95±3††</td>
</tr>
</tbody>
</table>

LVEDP indicates left ventricular end-diastolic pressure; RAP, right atrial pressure; and LVPSP, left ventricular peak systolic pressure. Values are mean±SEM (n=6 to 8 per group).

*P<.05 vs control.
†P<.05 for minoxidil or shunt+treatment vs minoxidil or shunt untreated.
‡P<.05 for minoxidil or shunt+treatment vs control+treatment.

### Table 3. Effects of Enalapril vs Losartan (From 5 to 10 Weeks) on Changes in Cardiac Output, Stroke Volume, and Total Peripheral Resistance Induced by Minoxidil Treatment or Aortocaval Shunt at 10 Weeks

<table>
<thead>
<tr>
<th>CI, mL·min⁻¹·kg⁻¹</th>
<th>SVI, mL·beat⁻¹·kg⁻¹</th>
<th>TPRI, mm Hg·min⁻¹·kg⁻¹</th>
<th>MAP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>282±10</td>
<td>0.66±0.02</td>
<td>0.37±0.01</td>
</tr>
<tr>
<td>Control+enalapril</td>
<td>279±11</td>
<td>0.69±0.04</td>
<td>0.34±0.02</td>
</tr>
<tr>
<td>Control+losartan</td>
<td>260±7</td>
<td>0.62±0.02</td>
<td>0.36±0.02</td>
</tr>
<tr>
<td>Shunt</td>
<td>340±11*</td>
<td>0.80±0.02*</td>
<td>0.27±0.02*</td>
</tr>
<tr>
<td>Shunt+enalapril</td>
<td>325±7†</td>
<td>0.76±0.02</td>
<td>0.26±0.01†</td>
</tr>
<tr>
<td>Shunt+losartan</td>
<td>344±15†</td>
<td>0.82±0.04†</td>
<td>0.23±0.01†</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>337±8*</td>
<td>0.84±0.02*</td>
<td>0.29±0.01*</td>
</tr>
<tr>
<td>Minoxidil+enalapril</td>
<td>351±6†</td>
<td>0.87±0.02†</td>
<td>0.22±0.01††</td>
</tr>
<tr>
<td>Minoxidil+losartan</td>
<td>338±4†</td>
<td>0.86±0.05†</td>
<td>0.25±0.01††</td>
</tr>
</tbody>
</table>

CI indicates cardiac index; SVI, stroke volume index; TPRI, total peripheral resistance index; and MAP, mean arterial pressure. Values are mean±SEM (n=6 to 8 per group).

*P<.05 vs control.
†P<.05 for minoxidil or shunt+treatment vs minoxidil or shunt untreated.
‡P<.05 for minoxidil or shunt+treatment vs minoxidil or shunt untreated.
Aortocaval shunt and minoxidil increased the LV long axis by 18% and 11%, respectively (Table 5). The LV long axis normalized within 5 weeks after discontinuation of minoxidil (data not shown). In rats on minoxidil, enalapril and losartan decreased the LV long axis to the level of treated and untreated control rats (Table 5). In shunt rats, both blockers decreased the LV long axis compared with untreated shunt rats but not to the level of treated and untreated control rats (Table 5).

Aortocaval shunt increased the LV (major) internal diameter by 19% at 10 weeks. Minoxidil resulted in an increase in LV internal diameter by 17% (Tables 1 and 5). The increase in LV internal diameter reversed by 50% within 2 weeks after discontinuation of minoxidil and had nearly normalized at 5 weeks. Both enalapril and losartan decreased the LV internal diameter in control rats, in shunt rats, and in minoxidil-treated rats. However, in both shunt and minoxidil groups, LV internal diameter remained significantly elevated compared with untreated and treated control rats (Table 5).

Aortocaval shunt and minoxidil caused small (P<.05) increases in LV wall thickness at 10 weeks (Table 5).
When minoxidil was discontinued at 5 weeks, LV wall thickness returned toward normal within the following 2 to 5 weeks (Table 1). Enalapril and losartan decreased LV wall thickness in control rats, in shunt rats, and in minoxidil-treated rats (Table 5). However, in both shunt and minoxidil-treated rats, LV wall thickness still remained increased compared with their treated controls (Table 5).

As a result of the above-mentioned remodeling of the LV in response to aortocaval shunt or minoxidil, the ratio of LV wall thickness to radius significantly decreased in minoxidil-treated and shunt rats. This ratio returned to normal after discontinuation of minoxidil (Table 1). Enalapril and losartan somewhat increased (P<0.05) this ratio when given to control rats (as a result of a larger decrease in LV internal diameter than in LV wall thickness). Enalapril or losartan added to minoxidil-treated or shunt rats partially reversed this ratio toward normal. However, in both enalapril- and losartan-treated shunt or minoxidil groups, the ratio of LV wall thickness to radius remained significantly lower than in untreated or treated controls (Table 5).

**Hematocrit**

Minoxidil significantly decreased hematocrit at 5 weeks. Hematocrit remained at this level at 7 and 10 weeks of treatment. Discontinuation of minoxidil at 5 weeks resulted in a gradual increase in hematocrit to normal (Table 1).

**Body Weight**

Minoxidil significantly increased body weight after 10 weeks of treatment. When minoxidil was discontinued at 5 weeks, body weight returned to normal (compared with control rats) within 2 weeks (data not shown). In minoxidil-treated rats, both enalapril and losartan treatment normalized body weight compared with the control group, but in both groups body weights remained significantly higher than in the respective treated control rats (Table 4). Aortocaval shunt did not affect body weight at 10 weeks. In shunt rats, enalapril and losartan caused only minor decreases in body weight similar to those observed in control rats (Table 4).

**Discussion**

The present study has two major findings: (1) In both models of volume overload–induced cardiac hypertrophy, losartan and enalapril reduced LV weight similarly and in parallel to their effects on LVEDP, (2) The effects of the two blockers on LV mass and LV dilation in minoxidil-treated rats are similar in magnitude to spontaneous regression of minoxidil-induced cardiac changes.

**Cardiac Morphology and Hemodynamics During Chronic Aortocaval Shunt or Minoxidil Treatment**

Cardiac remodeling in response to cardiac volume overload by aortocaval shunt or chronic minoxidil treatment occurs mostly within the first 3 to 5 weeks with no or minimal changes during subsequent weeks (see References 5 through 8, 17 through 19, and the present study). In both models, once the new balance between cardiac load and cardiac mass has been established, the LVEDP appears to remain relatively stable,5,18,20 presumably until heart failure develops, resulting in a further rise in LVEDP.21

The extent of cardiac hypertrophy is correlated with the degree of cardiac volume overload in both models (Fig 2). However, significantly more LV hypertrophy for a given increase in LVEDP was found in rats with aortocaval shunt than in rats on minoxidil (Fig 2). These data are consistent with a modulation of the hypertrophic response of the LV to volume overload by nonhemodynamic trophic stimuli such as the RAS or the sympathetic nervous system. Possible changes in cardiac sympathetic activity after aortocaval shunt have not yet been assessed. Both plasma and cardiac renin activity increase shortly after an aortocaval shunt is opened, and we recently showed that the remodeling of the heart by volume overload appears to be potentiated by the RAS.4 Less pronounced and delayed increases in plasma and cardiac renin activity4 during the development of minoxidil-induced cardiac hypertrophy6 may explain a less pronounced hypertrophic response to similar volume overload in this model. Thus, the extent of modulation of the hypertrophic response to volume overload appears to be a function of the renin activity.
overload by humoral stimuli may differ between models of cardiac volume overload. Alternatively, the rapid increase in volume load by opening of an aortic caval shunt may cause more hypertrophy than the more gradual increase caused by minoxidil.

After discontinuation of minoxidil treatment at 5 weeks, the LVEDP normalized within 2 weeks. This decrease in LVEDP probably resulted in part from a decrease in circulating volume, as suggested from the decrease in body weight and increase in hematocrit to control levels. The decrease in cardiac volume load was accompanied by regression of most of the minoxidil-induced increases in RV and LV mass and remodeling of the dilated LV toward the pattern of untreated rats within 5 weeks.

Effects of the ACEI Enalapril and the Angiotensin II Receptor Blocker Losartan on Cardiac Morphology in Relation to Cardiac Hemodynamics

In agreement with findings by Qing and Garcia,9 in shunt rats both blockers decreased LVEDP to close to normal. This decrease in LVEDP may be caused by natriuretic effects,13,22 reducing the volume expansion caused by a shunt,9 venodilation,13 and a decrease in cardiac afterload. Since angiotensin II (probably chronically increased, as assessed from plasma renin activity5) may negatively affect diastolic relaxation,23 improved diastolic relaxation by the two blockers may also participate in their effects on LVEDP. However, since cardiac output showed no or minor decreases compared with untreated shunt rats, a decrease in venous return does not appear to contribute to the blockers’ effect on LVEDP. A persistent increase in cardiac output at lower filling pressures as well as less LV dilation (see below) might therefore reflect the drug-induced decreases in cardiac afterload and/or improvement of LV systolic and diastolic performance. Both blockers caused only small decreases in total peripheral resistance and blood pressure, confirming the minimal dependence of total peripheral resistance and blood pressure on angiotensin II during the chronic phase of aortic caval shunt.5,24 Overall, there were no major differences in the effects of the two blockers on hemodynamics.

In rats with an aortic caval shunt, both blockers reversed LV hypertrophy in parallel to their effects on LVEDP (Fig 2). A nearly normalized LV wall thickness by the two blockers probably reflects the decrease both in LV filling pressures and in cardiac afterload. The two blockers also similarly decreased LV dilation, as reflected in decreases in LV long axis and in LV internal diameter. The extent of regression of RV hypertrophy by either blocker was similar to their effects on LV mass. The partial regression of LV and RV hypertrophy probably reflects that cardiac load remained somewhat increased. However, we cannot exclude that longer treatment would result in further regression.

In minoxidil-treated rats, both blockers normalized LVEDP. Venodilation13 and normalization of the intravascular volume expansion induced by minoxidil (as suggested from body weight) as well as a decrease in blood pressure may contribute to the decrease in LVEDP. Cardiac output, however, remained at the same level as in rats on minoxidil alone. Thus, the decrease in cardiac afterload, and therefore improved emptying of the LV, and possible effects on LV diastolic function by the two blockers (see above), rather than decrease in venous return, appear to cause the decrease in LVEDP.

In minoxidil-treated rats, both blockers returned both LV mass and dimensions (LV long axis and internal diameter) to close to normal. The somewhat larger decrease in blood pressure by enalapril versus losartan (Table 3) may explain the slightly more pronounced decrease in LV weight by enalapril than anticipated from its effect on LVEDP. Five weeks of treatment by either blocker reversed LV hypertrophy and dilation to a similar extent, as observed in rats 5 weeks after discontinuation of minoxidil (Fig 1). There is therefore no evidence for other trophic mechanisms playing a major role in the maintenance of minoxidil-induced LV hypertrophy. Nei-
ther blocker, however, significantly reduced RV hypertrophy. This may be related to a persisting increase in load of the RV in terms of minoxidil-induced increase in pulmonary artery pressure.25

In prevention experiments, enalapril decreased cardiac preload but did not prevent the cardiac remodeling of the LV in response to cardiac volume overload by aortocaval shunt or minoxidil treatment.5,6 Losartan had similar or less pronounced effects on LVEDP but, in contrast to enalapril, prevented/attenuated volume overload–induced changes in cardiac morphology in both models.5,6 We postulated5,6 that despite ACE inhibition by enalapril, angiotensin II continued to be generated in the heart, acting as a cardiac trophic stimulus mediating or involved in the cardiac remodeling. These differences between the two blockers, however, do not persist in the maintenance phase in these two models of cardiac volume overload. Both blockers decreased LV mass in parallel with their effect on cardiac preload. Thus, the RAS appears to act as a mediator of the hypertrophic response to the acute increase in hemodynamic load (and thus stretch of cardiomyocytes) in vitro and probably in vivo but no longer in the chronic phase of volume overload–induced hypertrophy. On the other hand, in both models of cardiac volume overload, hemodynamic effects of the RAS appear to continue to play a major role in determining filling pressures of the heart and thereby the maintenance of cardiac hypertrophy.

In conclusion, in both models of volume overload–induced cardiac hypertrophy, enalapril and losartan reversed LV hypertrophy in parallel to their effects on LVEDP. Thus, in contrast to the development phase, it appears that the RAS does not continue as a cardiac trophic stimulus for the maintenance of cardiac hypertrophy induced by aortocaval shunt and minoxidil treatment but indirectly maintains cardiac hypertrophy by contributing to the persistence of high filling pressures.

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