Left Ventricular Hypertrophy With Exercise and ACE Gene Insertion/Deletion Polymorphism
A Randomized Controlled Trial With Losartan

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Background—Local cardiac renin-angiotensin systems may regulate left ventricular (LV) hypertrophic responses. The absence (deletion [D]) of a 287-bp marker in the ACE gene is associated with greater myocardial ACE levels and exercise-related LV growth than is its presence (insertion [I]), an effect potentially mediated through either increased activity of the cellular growth factor angiotensin II on the angiotensin type 1 (AT₁) receptor or increased degradation of growth-inhibiting kinins. We sought to confirm ACE genotype–associated exertional LV growth and to clarify the role of the AT₁ receptor in this association.

Methods and Results—One hundred forty-one British Army recruits homozygous for the ACE gene (79 DD and 62 II) were randomized to receive losartan (25 mg/d, a subhypotensive dose inhibiting tissue AT₁ receptors) or placebo throughout a 10-week physical training program. LV mass, determined by cardiac magnetic resonance, increased with training (8.4 g, \( P=0.0001 \) overall; 12.1 versus 4.8 g for DD versus II genotype in the placebo limb, \( P=0.022 \)). LV growth was similar in the losartan arm: 11.0 versus 3.7 g for DD versus II genotypes (\( P=0.034 \)). When indexed to lean body mass, LV growth in the II subjects was abolished, whereas it remained in the DD subjects (−0.022 versus 0.131 g/kg, respectively; \( P=0.0009 \)).

Conclusions—ACE genotype dependence of exercise-induced LV hypertrophy is confirmed. Additionally, LV growth in DD (unlike II) subjects is in excess of the increase in lean body mass. These effects are not influenced by AT₁ receptor antagonism with the use of losartan (25 mg/d). The 2.4-fold greater LV growth in DD men may be due to the effects of angiotensin II on other receptors (eg, angiotensin type 4) or lower degradation of growth-inhibitory kinins. (Circulation. 2001;103:226-230.)

Key Words: hypertrophy ■ myocardium ■ genetics ■ angiotensin ■ exercise

Local cardiac renin-angiotensin systems may regulate left ventricular (LV) hypertrophy,1,2 which is itself associated with increased cardiovascular mortality and morbidity.3 The absence (deletion [D]) of a 287-bp marker in the ACE gene4 is associated with greater myocardial ACE levels5 and exercise-related LV growth6 than is its presence (insertion [I]), potentially through either increased activity of the cellular growth factor angiotensin II7,8 on the angiotensin type 1 (AT₁) receptor8 or increased degradation of growth-inhibiting kinins.9

We sought to confirm ACE genotype–associated exertional LV growth and to clarify the role of the AT₁ receptor in this association.

Methods

Subjects
Healthy normotensive white male army recruits were studied with appropriate ethics committee approval and informed consent. ACE genotype was determined (3-primer polymerase chain reaction amplification as previously described10). In a prospective parallel-arm, double-blind, randomized, placebo-controlled trial, ACE gene homozygotes were randomized to receive (compliance-witnessed) 25 mg losartan or placebo daily throughout a 10-week training period. At the start and end of training, height, weight, and blood pressure (mean of 3 measurements, 1 minute apart, 20 minutes supine) were recorded, and MRI was performed.

Magnetic Resonance Scanning
As previously described,11 10-mm ECG-gated short-axis cardiac images (single breath holding, 0.5 T; Figure 1) were obtained, and LV mass was determined by multiplying myocardial tissue volume (Simpson’s rule, single observer blind to subject data) by myocardial tissue–specific density (1.05 g/cm³). Chamber volumes were calculated by summing end-diastolic and end-systolic endocardial areas in each slice.

In addition, forty 10-mm-thick noncontiguous transaxial signal-averaged spin-echo image slices of the whole body (echo time 40 ms,
repetition time 500 ms, field of view 45×45 cm, and 40-mm intergap distance) were obtained, adipose tissue volume was quantified (automated threshold technique, ie, averaging adjacent slice values by the Cavalieri method), fat mass was obtained through multiplication by fat-specific density (0.95 g/m²), and lean body mass was calculated by subtracting adipose tissue mass from total body mass.

**Statistical Calculations**

The standard deviation of cardiac magnetic resonance (CMR) LV mass measurements in pilot studies was 8.9 g. Thus, 30 subjects in each group (II and DD, placebo or losartan) yielded 95% power to detect a 5% change in LV mass (8.35 g given past data) with 95% confidence

Data were analyzed for those who completed training at the first attempt. Baseline and follow-up values were compared by the paired Student t test, and between-group changes were compared by unpaired t tests and ANOVA (Statview 5.0, SAS Institute). A value of P<0.05 was considered statistically significant. Results are shown as mean±1 SD, unless otherwise stated.

**Results**

One thousand two hundred forty-eight recruits were screened. Genotype distribution (332 DD [27%], 615 ID [49%], and 301 II [24%]) was in Hardy-Weinberg equilibrium. Two hundred twelve homozygous individuals continued in the study (age, height, weight, pulse, and blood pressure were similar by genotype and treatment [Table 1]). One hundred forty-one recruits (79 DD and 62 II) completed training, of whom 66 had taken losartan (38 DD and 28 II), and 75 had taken placebo (41 DD and 34 II). Baseline physical characteristics (age 19.7±6.5 years, height 175.2±12.3 cm, weight 66.2±12.3 kg, pulse rate 66.2±6.5 bpm, and systolic and diastolic blood pressure 117.4±11.7/66.0±10.5 and 117.6±12.0/65.5±10.4 mm Hg, respectively) and LV mass (184.2±24.9 g) did not differ between those who completed and those who dropped out of training (P>0.05 by ANOVA for all parameters). In those who completed training, pretraining and posttraining blood pressures were similar (systolic/diastolic blood pressure 117.4±11.7/66.0±10.5 and 117.6±12.0/65.5±10.4 mm Hg, P=0.85 and P=0.55 for systolic and diastolic values, respectively) in all groups. Resting pulse rates fell with training (65.8±12.5 versus 63.6±10.4 bpm, respectively; P=0.023) but were also similar between groups.

The increase in LV mass associated with training (mean±SE 8.4±1.2 g overall, P<0.0001; 8.8±1.6 g, P<0.0001 in those taking placebo; Table 2) was lower among those of the II genotype (4.3±1.8 g, P=0.020 overall; 4.8±2.4 g, P=0.057 in the placebo group) than of the DD genotype (11.6±1.5 g, P<0.0001 overall; 12.1±2.0 g, P<0.0001 for placebo; P=0.002 and P=0.022 for comparison with those of II genotype, respectively). Losartan had no effect on LV mass increase: for DD genotype, 11.0±2.1 g; for II genotype, 3.7±2.7 g (P=0.69 and P=0.75, respectively, compared with placebo in each genotype group).

The ratio of LV mass to lean body mass was calculated in a subset of recruits (n=117, 52 II and 65 DD). Baseline values were similar in all groups (3.11±0.48 g/kg; P=0.16) and were increased with training by 0.063±0.023 g/kg (2.4%, P=0.008) and 0.057±0.033 g/kg (2.1%, P=0.09) in the treatment and placebo arms, respectively. The modest LV growth in II subjects was completely attenuated when indexed to lean mass (−0.022±0.047 g/kg [−0.5%], P=0.55 for placebo) but remained for DD subjects (0.131±0.029 g/kg [4.6%, P=0.0001 overall; 0.143±0.042 g/kg [4.7%, P=0.002 for placebo]); P values were 0.0009 and 0.009 for comparison with those of the II genotype, respectively. Losartan had no effect on the change in LV mass index within either genotype (DD 0.120±0.041 g/kg; II −0.011±0.048 g/kg; P=0.70 and 0.81, respectively, compared with placebo).

Overall, because recruit LV end-diastolic volume rose with little change in end-systolic volume, stroke volume increased (LV end-diastolic volume 108.2±24.7 to 114.7±26.5 mL, P=0.0004; LV end-systolic volume 34.2±10.3 to 35.9±11.0 mL, P=0.030; and LV stroke volume 73.9±16.9 to 78.8±19.0 mL, P=0.0005; Table 3). Because of a fall in resting pulse rate, cardiac output was unchanged (4.78±1.33 versus 4.99±1.23 L/min for baseline versus follow-up, respectively; P=0.72). Right ventricular volumes showed the same pattern (RV end-diastolic volume 130.6±25.5 to 139.5±28.2 mL, P<0.0001; RV end-systolic volume 57.1±14.4 to 60.9±15.0 mL, P=0.0004; and RV stroke volume 73.6±16.0 to 78.5±17.5 mL, P<0.0001). Neither genotype nor treatment group influenced volume parameters, although there was a nonsignificant trend for losartan to attenuate volume increases.

**Discussion**

We have confirmed the ACE genotype effect on LV growth. Furthermore, it has been suggested that LV mass is normally proportional to skeletal muscle mass and that the former
should thus be indexed for the latter. When this is done, the small II genotype–associated increase in LV mass is completely attenuated, whereas the LV growth in DD subjects persists, suggesting that the LV growth in DD subjects is in excess of the increase in lean body mass, whereas the small change in II subjects is proportional to it.

These findings were independent of 25 mg/d losartan, a dose chosen for sustained biological, yet minimal hypotensive, effect. Such doses inhibit the pressor response to angiotensin II, uricosuric, and alter plasma renin activity. The minor hypotensive effects seen in hypertensive patients are probably absent in normal subjects and minimal even at doses of 100 mg/d. Any hypotensive action would have tended toward a false-positive effect on LV growth, which was not observed in any event. Nonetheless, a small biological effect of losartan on the LV growth response was missed. Post hoc analysis demonstrates an 80% power to detect a 2.6% reduction in LV growth by losartan and a 95% power to detect a change of 4.8%. However, the nearly 3-fold difference in growth effect between genotypes was scarcely affected by losartan treatment. In keeping with rodent data, the present study does not support a nonpressor effect of the AT1 receptor on cardiac growth. ACE genotype might thus influence LV growth through increased levels of angiotensin II on the angiotensin type 4 receptor (the angiotensin type 2 receptor may modulate antiproliferative effects) or through the reduced levels of growth-inhibitory kinins, which are degraded by ACE.

Our previous study showed a greater hypertrophic response for DD subjects than was observed in the present study (42 versus 12.1 g). However, echocardiographic methodology uses cardiac dimensions and an assumed geometric shape to calculate LV mass through equations derived from postmortem examinations of individuals of diverse age and LV mass range (age 23 to 82 years, LV mass 96 to 625 g). Such a “best-fit” model for a mixed population of ages may have their place, it may be less applicable to serial prospective studies of LV growth in small samples. Moreover, exercise produces very specific LV morphological changes that may distort calculated LV mass. Such distortions (and any errors in measurement) will be cubed during calculation of LV mass. Thus, compared with CMR, M-mode echo overestimates LV mass (and hence, the prospective change in mass). Finally, repeated echocardiographic mass measurements have poorer reproducibility than do CMR measurements (standard deviation of the difference between successive CMR LV mass estimates being ≥20% of the mean). Repeated measures may thus overamplify detected changes. Thus, although echocardiographic measures of mass may have their place, it may be less applicable to serial prospective studies of LV growth in small samples. By contrast, CMR measures mass directly, removing any error associated with volume changes or ventricular shape.

Training intensity (specifically, resistance exercise) was reduced after the first study. Cardiac growth responses are influenced by exercise intensity and type, leading to large variations in LV mass in those participating in different sports and with different prospective training schemes. Even modest training changes (such as the addition of handgrip exercises to running) may alter cardiac growth stimuli or responses. Given the substantial ACE genotype–training

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**TABLE 1. Baseline Parameters for 141 Subjects With Paired Data Sets**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Drug</th>
<th>n</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Change</th>
<th>Increase</th>
<th>P (Paired t Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD</td>
<td>Placebo</td>
<td>41</td>
<td>185.0±4.2</td>
<td>197.1±4.2</td>
<td>12.1±2.0</td>
<td>6.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>38</td>
<td>178.1±4.1</td>
<td>189.0±3.6</td>
<td>11.0±2.1</td>
<td>6.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>II</td>
<td>Placebo</td>
<td>34</td>
<td>186.1±3.8</td>
<td>190.9±4.1</td>
<td>4.8±2.4</td>
<td>2.6%</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>28</td>
<td>189.0±4.5</td>
<td>192.6±4.4</td>
<td>3.7±2.7</td>
<td>2.0%</td>
<td>0.18</td>
</tr>
<tr>
<td>P (ANOVA)</td>
<td>Genotype</td>
<td>0.16</td>
<td>0.75</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug</td>
<td>0.62</td>
<td>0.52</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI indicates body mass index; BP, blood pressure.
TABLE 3. Cardiac Volume Data Before and After Training for 141 Subjects

<table>
<thead>
<tr>
<th></th>
<th>DD Genotype</th>
<th></th>
<th>II Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=41)</td>
<td>Losartan (n=38)</td>
<td>Placebo (n=34)</td>
</tr>
<tr>
<td>Baseline</td>
<td>Follow-Up</td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>110.6±26.0</td>
<td>117.4±27.5†</td>
<td>103.9±22.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>106.3±23.1</td>
</tr>
<tr>
<td>LV ESV, mL</td>
<td>34.7±10.6</td>
<td>37.0±11.5</td>
<td>31.9±8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34.1±10.3</td>
</tr>
<tr>
<td>LV SV, mL</td>
<td>74.8±18.1</td>
<td>80.6±19.7*</td>
<td>72.0±15.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72.1±15.6</td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>132.1±25.9</td>
<td>143.1±27.9†</td>
<td>125.6±24.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>129.0±22.5</td>
</tr>
<tr>
<td>RV ESV, mL</td>
<td>57.7±14.5</td>
<td>62.2±15.4*</td>
<td>54.4±12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56.2±14.0</td>
</tr>
<tr>
<td>RV SV, mL</td>
<td>74.4±16.4</td>
<td>80.8±17.3†</td>
<td>71.4±15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72.7±15.3</td>
</tr>
</tbody>
</table>

Values are mean±SD. EDV indicates end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; and RV, right ventricular. Differences between changes in losartan and placebo groups for each genotype did not reach statistical significance.

*P<0.05, †P<0.001, and ‡P<0.01 from baseline by paired t test.

environment interaction, it is likely that changes in the training stimulus will interact with genotype to produce differences in the nature and scale of the phenotypic response.

Proposed ACE genotype dependence of LV growth conflicts with some cross-sectional studies. However, the cardiac renin-angiotensin system probably transduces growth stimuli and is not a cause of LV hypertrophy in itself. Diverse environmental hypertrophic stimuli may create sufficient “white noise” to mask modest individual-effect gene-environment interactions in cross-sectional studies.42

Limitations of the Study
A higher dose of losartan might have influenced LV growth whether through a hypotensive effect or not.43 Furthermore, we studied no heterozygous group, because our aim was to confirm an ACE genotype association with LV growth and to explore the potential role of the AT1 receptor in such genotype dependence. We specifically did not set out to explore the potential additive or synergistic effects of the presence of ≥ 1 allele, an investigation that was beyond the scope of the present study.

Acknowledgments
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