Brief Report

Effect of Treatment of Isolated Systolic Hypertension on Left Ventricular Mass

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Context.—Left ventricular (LV) hypertrophy is a common problem among elderly patients with isolated systolic hypertension (ISH), but the effect of treatment of ISH on LV mass is not known.

Objective.—To assess the ability of antihypertensive drug treatment to reduce LV mass in ISH.

Design.—Echocardiographic Substudy of the Systolic Hypertension in the Elderly Program (SHEP).

Patients.—A total of 104 participants at the St Louis SHEP site who had interpretable baseline echocardiograms, 94 of whom had 3-year follow-up echocardiograms.

Intervention.—The SHEP participants were randomized to placebo or active treatment with chlorthalidone (12.5-25 mg/d), with atenolol (25-50 mg/d) added if necessary to maintain goal blood pressure.

Main Outcome Measure.—Change in LV mass assessed by echocardiography.

Results.—Minimum follow-up was 3 years. In the active treatment group, 91% and 80% of subjects were receiving treatment with chlorthalidone alone by the end of years 1 and 3, respectively. The LV mass index was 93 g/m² in the active treatment group and 100 g/m² in the placebo group (P = .001). The LV mass index declined by 13% (95% confidence interval, −3% to −23%) in the active treatment group compared with a 6% increase (95% confidence interval, −3% to +16%) in the placebo group over 3 years (P = .01).

Conclusion.—Treatment of ISH with a diuretic-based regimen reduces LV mass.

THE REPORT of the final results of the Systolic Hypertension in the Elderly Program (SHEP) drew attention to the problem of isolated systolic hypertension and conclusively showed the value of treatment.1 In this landmark study there was a 36% reduction in total stroke incidence, the primary end point, among those randomly assigned to active antihypertensive treatment compared with the placebo control group. In addition to the blood pressure level, left ventricular hypertrophy (LVH) is a powerful and independent predictor of cardiovascular morbidity and mortality.2,6

Echocardiographically determined left ventricular (LV) mass is the most powerful risk factor for cardiovascular disease, yielding prognostic information beyond what is provided by traditional cardiovascular risk factors, including high blood pressure.2 We have reported the high prevalence of LVH in the SHEP echocardiographic cohort compared with age-matched normotensive controls,7 and preliminary results for the effect of treatment on LV mass.8,9 We now report the long-term effects of treatment with antihypertensive drugs on echocardiographic LV mass in this SHEP cohort.

Methods

Study Population.—The rationale, design, and eligibility criteria of SHEP have been previously described.10 Participants were at least 60 years of age, with an average systolic blood pressure of 160 mm Hg or greater and diastolic blood pressure lower than 90 mm Hg. Exclusion criteria were systolic blood pressure greater than 220 mm Hg; recent myocardial infarction or coronary artery bypass surgery; and history of stroke, renal insufficiency, alcohol abuse, or other serious coexisting conditions. Eligible volunteers were randomized in a double-blind manner to active antihypertensive drug treatment or placebo. A stepped-care program was used to achieve a goal of systolic blood pressure between 140 and 159 mm Hg, depending on the baseline average. Chlorthalidone was the step 1 drug, used in 2 progressive dosages (of 12.5 and 25 mg/d) if necessary to achieve the goal blood pressure. The step 2 drug (atenolol, 25-50 mg/d) was added if needed to achieve the goal blood pressure. Reserpine, 0.05 mg/d, was used if atenolol was contraindicated because of significant bradycardia, bronchospasm, or heart failure. Blood pressure was monitored at 1- to 3-month intervals, and clinical assessments of the participants were undertaken at annual visits, according to the SHEP protocol.1

Between March 1985 and September 1987, approximately 30 000 subjects 60 years of age and older underwent screening for SHEP eligibility in the St Louis metropolitan area. From this group, 397 were eventually entered into the study and were randomly assigned to drug or placebo. Beginning in May 1986, SHEP volunteers were asked to participate in the echocardiographic substudy, which was added to the usual SHEP protocol. Of the 104 individuals who agreed and who had interpretable baseline echocardiograms, 94 were available at 3 years of follow-up. These 94 participants who form the basis of this report were no different from the 4736 participants in the entire SHEP study with regard to age, race and sex ratios, baseline blood pressure, cholesterol level, history of diabetes, and cigarette smoking.
**Baseline Characteristics of the Echocardiographic Substudy Patients**

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment Group (n = 47)</th>
<th>Placebo Group (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71 (6)</td>
<td>70 (6)</td>
<td>.66</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>23/24</td>
<td>25/27</td>
<td>.59</td>
</tr>
<tr>
<td>White/black, No.</td>
<td>43/4</td>
<td>44/3</td>
<td>.50</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.86</td>
<td>1.88</td>
<td>.69</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71 (12)</td>
<td>70 (10)</td>
<td>.82</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>169 (11)</td>
<td>172 (13)</td>
<td>.13</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79 (8)</td>
<td>79 (8)</td>
<td>.91</td>
</tr>
<tr>
<td>Ventricular septum thickness, cm</td>
<td>1.07 (0.23)</td>
<td>0.99 (0.16)</td>
<td>.07</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>1.07 (0.28)</td>
<td>1.06 (0.24)</td>
<td>.88</td>
</tr>
<tr>
<td>Left ventricular end diastolic dimension, cm</td>
<td>4.95 (0.94)</td>
<td>5.02 (0.65)</td>
<td>.67</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>204 (67)</td>
<td>194 (52)</td>
<td>.43</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>109 (33)</td>
<td>102 (24)</td>
<td>.29</td>
</tr>
<tr>
<td>Left ventricular shortening fraction, %</td>
<td>59 (9)</td>
<td>49 (10)</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Values are mean (SD) unless otherwise indicated.

**Echocardiography.**—All echocardiographic studies were performed in standard, parasternal long- and short-axis views using a commercially available, high-resolution, phased-array system with a 2.25- or 3.5-MHz transducer and were recorded on 0.5-in videotape. Two-dimensional directed M-mode recordings of the left ventricle were made according to the recommendations of the American Society of Echocardiography.\(^1\) Digitized M-mode tracings were measured offline for an average of 5 cardiac cycles. Echocardiographic measurements were made without knowledge of the subjects’ randomization status. The LV mass was derived according to American Society of Echocardiography standards (LV Mass = 0.80 \(\times\) [LVEDD + VS + PW]) – LVEDD\(^3\), where LVEDD indicates LV end diastolic dimension; VS, ventricular septum thickness; and PW, posterior wall thickness) and indexed to body surface area to determine the LV mass index.

**Statistical Analysis.**—Data were analyzed by intention to treat. All values are reported as mean ± SD unless otherwise indicated. Analysis of variance for repeated measures was used to compare baseline and follow-up data in the active treatment and placebo groups. Analysis of variance with interaction plots was used to examine the effects of treatment assignment, baseline LV mass, age, sex, and total cholesterol level on LV mass at follow-up. The significance of any interaction was analyzed using the Scheffé F test. Multiple regression analysis was used to determine the independent effect of systolic and diastolic blood pressure on LV mass. P < .05 was considered statistically significant.

**Results**

Of the 94 participants available for follow-up at 3 years, 47 were in the active treatment group and 47 were in the placebo control group. The baseline characteristics of the active and placebo groups were similar (Table). By the end of years 1 and 3, respectively, 91% and 80% of patients in the active treatment group were receiving only the first-line drug, chlorthalidone; 18% were receiving atenolol in addition to chlorthalidone, while 2 participants were receiving reserpine at the end of year 3. Twenty-one participants were receiving additional antihypertensive therapy prescribed by their private physicians: 9 patients (17%) in the active treatment group vs 12 patients (25%) in the placebo group (P = .39). The following nonstudy drugs were used: calcium channel blockers in 9 patients (active, 5; placebo, 4), diuretics in 7 patients (active, 2; placebo, 5), angiotensin-converting enzyme inhibitors in 3 patients (active, 1; placebo, 2), and ß-blockers (active, 2). The average systolic and diastolic blood pressures from baseline through 3 years of follow-up are shown in Figure 1.

Reductions in both systolic and diastolic blood pressures occurred early in the active treatment group (within 6 months of the start of therapy) and were maintained throughout the 36-month follow-up period. The systolic and diastolic blood pressures were significantly lower in the active treatment group than in the placebo group at follow-up (systolic: 144 ± 15 vs 163 ± 21 mm Hg; P < .001; diastolic: 62 ± 8 vs 75 ± 9 mm Hg; P < .001).

Echocardiographic parameters were similar in the active treatment and placebo groups at baseline (Table). At follow-up, the body surface area remained unchanged. However, the LV mass index and ventricular septal thickness were significantly lower in the active treatment group than in the placebo group (LV mass index: 93 ± 28 vs 110 ± 26 g/m², P < .001; ventricular septal thickness: 1.02 ± 0.20 vs 1.17 ± 0.28 cm, P = .01).

Within-group analysis showed that the LV mass at follow-up was significantly lower in the active treatment group compared with baseline (93 ± 28 g at follow-up vs 104 ± 30 g, P = .04), while LV mass in the placebo group increased over the 3-year follow-up period (110 ± 26 g at follow-up vs 106 ± 24 g, P = .05). The wall thickness also decreased in the active treatment group compared with baseline: 1.02 ± 0.20 cm at follow-up vs 1.07 ± 0.23 cm at baseline (P = .69) for the ventricular septum and 0.93 ± 0.21 vs 1.07 ± 0.28 cm (P = .03) for the posterior wall, while the septal thickness increased in the placebo group: 1.17 ± 0.28 vs 0.99 ± 0.16 cm (P = .03). There was a nonsignificant reduction in the LV end diastolic dimension in the active treatment group compared with the placebo group at follow-up (4.72 ± 0.88 cm vs 4.94 ± 0.82 cm, P = .44).

The mean changes (with 95% confidence intervals [CIs]) in blood pressure and LV mass are shown in Figure 2. The active treatment group had a 24% reduction in systolic blood pressure (95% CI, −17% to −31%) and a 17% reduction in diastolic blood pressure (95% CI, −14% to −20%). For the placebo group, the mean systolic blood pressure reduction was −11% (95% CI, −2% to −20%) and the mean diastolic blood pressure reduction was −9% (95% CI, −5% to −14%). There was a 13% reduction in mass in the active treatment group (95% CI, −3% to −23%), compared with a 6% increase in LV mass in the placebo group (95% CI, −3% to +16%) (P = .01).

Change in systolic blood pressure was correlated with change in LV mass (r = 0.40, P < .003) by multivariate analysis, independent of treatment assignment, age, sex, and high blood cholesterol level. Change in diastolic blood pressure...
showed a weaker correlation with change in LV mass (r = 0.30, P < 0.04).

After controlling for change in blood pressure, there were no independent effects of treatment assignment (active treatment vs placebo), age, or cholesterol level on change in LV mass with treatment. Although men had higher LV mass at baseline and follow-up, both men and women in the active treatment group had lower LV mass at follow-up than those in the placebo group (men: 99 ± 20 vs 119 ± 23 g, P = 0.01; women: 86 ± 25 vs 98 ± 21 g, P = 0.09). Active treatment participants receiving chlorthalidone alone at dosages of 25 and 12.5 mg/d had follow-up LV mass index values of 87 ± 26 and 93 ± 31 g/m², respectively (P = 0.06), significantly lower than values in the placebo group (P = 0.001). Only 8 active treatment participants received atenolol, 50 or 22 mg/d, in addition to chlorthalidone; their LV mass index values at follow-up were 71 ± 18 and 106 ± 14 g/m², respectively (P = 0.67). Open-label treatment did not significantly affect LV mass in either the active treatment or placebo group. The LV mass index value for the 9 active treatment participants receiving open-label treatment was 89 ± 29 g/m², compared with 95 ± 28 g/m² for active treatment participants who did not receive open-label treatment (P = 0.75). The LV mass index for the 12 patients in the placebo group who received open-label treatment was 103 ± 24 g/m², compared with 112 ± 26 g/m² for placebo participants who did not receive open-label treatment (P = 0.36).

Comment

The antihypertensive treatment regimen, using chlorthalidone as sole therapy in 80% of the active treatment group, was effective in significantly lowering systolic blood pressure and decreasing LV mass compared with the placebo group. In the placebo group, LV mass increased over time, presumably reflecting the natural history of isolated systolic hypertension. The change in LV mass was significantly correlated with change in both systolic and diastolic blood pressures (r = 0.40 and r = 0.30, respectively) on multiple regression analysis. The reduction in LV mass in the active treatment group was due to an actual decrease in wall thickness; the decrease in LV end diastolic dimension (5%, compared with 2% in the placebo group), although small, was directionally compatible with an additional effect of diuretic agents to reduce LV chamber size and volume. The LV fractional shortening, an index of systolic function, remained unchanged despite significantly decreased LV mass, a finding consistent with previous studies of LV mass regression in treated hypertension, which showed preservation of systolic function despite a reduction in LV mass.12-15

The SHEP study demonstrated that reducing blood pressure among persons with isolated systolic hypertension is associated with a reduction in both morbidity and mortality associated with cardiovascular disease.1 One of the most striking beneficial effects of treatment was the relative risk of 0.46 for LV failure in the treatment group compared with the control group. To the extent that concentric LV hypertrophy is a risk factor for LV failure, our data are consistent with this finding. The various agents used to lower blood pressure among patients with hypertension may have differing effects on LV mass.16-18 The efficacy of a diuretic-based regimen on LV mass reduction is consistent with the findings of 2 multicenter trials of hypertension treatment in younger adults.19,20 This randomized study clearly shows that chlorthalidone therapy is effective in reducing LV mass in elderly patients with isolated systolic hypertension.

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References


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