Reduction of Left Ventricular Hypertrophy After Exercise and Weight Loss in Overweight Patients With Mild Hypertension

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Background: Hypertrophy and concentric remodeling of the left ventricle are important manifestations of hypertension that are associated with increased morbidity and mortality. Although lifestyle interventions are efficacious in lowering blood pressure, evidence that they have a beneficial effect on target organs has been lacking.

Objective: To assess the effects of regular aerobic exercise or exercise plus weight management counseling on left ventricular mass and geometry in overweight, sedentary men and women with high-normal or mildly elevated blood pressure.

Methods: Eighty-two participants in a randomized, controlled trial were assigned to supervised aerobic exercise only, a behavioral weight management program that included exercise, or a waiting-list control group for 6 months. Blood pressure and echocardiographic measures of left ventricular structure were measured at baseline and at the conclusion of the treatment phase.

Results: The 45 women and 37 men had a mean±SD age of 47±9 years and had a mean±SD blood pressure of 140±10/93±5 mm Hg. Blood pressure fell by 7/6 mm Hg in the weight management group and by 3/4 mm Hg in the aerobic exercise group. In association with these decreases in blood pressure, participants in the intervention groups exhibited significant decreases in left ventricular relative wall thickness ($P = .003$), posterior wall thickness ($P = .05$), and septal thickness ($P = .004$) and a trend toward a decrease in indexed left ventricular mass ($P = .08$) relative to the control group.

Conclusions: In a cohort of overweight, sedentary men and women, exercise and weight loss reduced blood pressure and induced favorable changes in left ventricular structure.

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Hypertrophy and concentric remodeling of the left ventricle are important manifestations of hypertension that are associated with an enhanced risk for morbidity and mortality. In the general population and in cohorts with hypertension or coronary artery disease, increased left ventricular mass is a predictor of cardiovascular events independent of blood pressure or other traditional risk factors. The geometric pattern of hypertrophy is also of prognostic importance. Patients with concentric remodeling, ie, an increase in the ratio of wall thickness to chamber dimension but normal left ventricular mass, have a cardiovascular risk intermediate between those with normal left ventricular structure and those with concentric hypertrophy. Regression of hypertrophy is associated with a reduction in cardiovascular risk.

A number of studies have demonstrated that lowering blood pressure with medication results in regression of left ventricular hypertrophy. Although lifestyle modifications such as regular aerobic exercise are viewed as important elements of antihypertensive therapy in patients with high-normal or mildly elevated blood pressure, the effects of nonpharmacologic measures on left ventricular mass and structure have not been extensively evaluated. Published reports have not consistently demonstrated a beneficial effect of weight loss or of weight loss combined with exercise on left ventricular structure.
SUBJECTS AND METHODS

SUBJECTS

Participants were aged at least 29 years and were generally healthy, with no history of cardiac disease, renal insufficiency, or diabetes mellitus and no evidence of secondary hypertension. None had been treated with antihypertensives for at least 6 weeks. Inclusion criterion consisted of a casual systolic blood pressure of 130 to 180 mm Hg and/or diastolic blood pressure of 85 to 110 mm Hg, determined by averaging blood pressure measurements from 4 separate visits during a 3-week period. All subjects were overweight or obese (body mass index [BMI], 25-37) and sedentary (not performing regular aerobic exercise). None were treated with medications that have hemodynamic effects, and none had a history of abuse of alcohol or other drugs.

PROTOCOL

Details of the study protocol have been described previously. The protocol was approved by the institutional review board at Duke University Medical Center, Durham, NC, and informed consent was obtained from each subject before participation.

Subject eligibility for the study was established during a series of screening visits that included a history and physical examination, measurement of height and weight, determination of baseline casual blood pressure, and assessment of dietary content. Exercise capacity was determined by treadmill exercising testing, and left ventricular geometry and mass were measured by echocardiography. Participants were then randomized in a 2:2:1 ratio, by sex, to 1 of the following 6-month treatment conditions: (1) exercise, (2) exercise plus a behavioral weight loss program, or (3) waiting-list control. In addition, 5 subjects who met all eligibility criteria but were unable to commit to regular participation in the supervised exercise sessions were included in the control group. At the conclusion of treatment, measurements of weight, blood pressure, dietary content, exercise capacity, and left ventricular structure were repeated.

Echocardiograms of high technical quality were obtained before and after treatment in 82 subjects. Of the 144 subjects originally enrolled, 4 (3%) did not have baseline echocardiograms; 16 (11%) did not return for a follow-up study; and 42 (29%) had studies in which left ventricular dimensions or wall thicknesses could not be quantified with confidence. The subjects with interpretable ultrasound studies tended to weigh less (91.7±16.8 vs 97.6±13.9 kg; P=.03) and have a lower BMI (31.4±4.1 vs 34.2±3.9; P<.001) than those with unsatisfactory images; no differences were seen in age, sex, race, or baseline clinic blood pressure. The results described in this manuscript refer to the 82 subjects for whom complete echocardiographic data were available.

Characteristics of the study population and subjects in each intervention group are noted in Table 1. The 3 groups were comparable in all baseline clinical and demographic characteristics except that the control group had more nonwhite subjects than the active treatment groups (P=.03).

Echocardiographic characteristics of subjects in the 3 groups are shown in Table 2. For the study group as a whole, 25 participants (30%) had left ventricular hypertrophy, defined as a left ventricular mass index exceeding the 95th percentile for a lean, normotensive ref-

RESULTS

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MEASUREMENTS

Blood Pressure

Blood pressure was measured by a trained technician using a random-zero sphygmomanometer. On each visit, blood pressure was measured 4 times at 2-minute intervals after an initial 5-minute rest. The last 3 measurements were averaged to represent the blood pressure value for that visit, and the values for each of 4 visits during a 3-week period were averaged to determine the casual blood pressure. Blood pressure determinations were made in this standardized manner at baseline and after the 6-month intervention.

Body Weight

Weight was measured in kilograms using a standard balance scale, and height was measured in meters. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Exercise Capacity

Exercise capacity was assessed by measuring maximum oxygen consumption using the Duke–Wake Forest Protocol. This protocol begins at 3.2 km/h (2.0 mph) and 0% grade, and the workload is increased at a rate of 1 metabolic equivalent per minute. Expired gases were collected for the determination of peak oxygen consumption using a metabolic cart.

Dietary Content

Subjects recorded all food intake for 4 consecutive days in a diet diary that was analyzed for energy and nutritional content.

Echocardiography

Echocardiography was performed with the use of an imaging system (Hewlett-Packard, Palo Alto, Calif) equipped with a 2.5-MHz phased-array transducer. Images were
INTERVENTIONS

Exercise

Subjects in this group participated in supervised exercise sessions 3 to 4 times per week for 6 months. The exercise protocol consisted of 10 minutes of warm-up exercise; 35 minutes of bicycle ergometry, walking, or jogging on a track to achieve a heart rate between 75% and 85% of the maximal heart rate reserve; and 10 minutes of cool-down exercise. All training sessions were supervised by an exercise physiologist, who monitored the heart rates of each participant several times per session. Subjects in this treatment group were instructed to maintain their usual diets.

Weight Management

Subjects randomized to this intervention exercised 3 to 4 times weekly as described in the previous paragraph. In addition, they participated in a behavioral modification program designed to facilitate weight loss. This program consisted of 26 weekly group sessions. Sessions were based on the LEARN program, which focuses on the following 5 elements: lifestyle, exercise, attitudes, relationships, and nutrition. Topics of discussion included distinguishing cravings from hunger, planning healthy meals, shopping for food, dealing with pressure to eat, eating away from home, and coping with relapse. The primary goal of the intervention was a weight loss of 0.5 to 1.0 kg/wk achieved by decreasing energy and fat intake through permanent lifestyle changes. Initial dietary goals consisted of an energy intake of approximately 1200 calories for women and 1500 calories for men, with 15% to 20% of this energy from fat.

Waiting-List Control

Subjects in the waiting-list control group were contacted monthly and encouraged to maintain their usual dietary and exercise habits until the second evaluation after 6 months of observation. They were then offered the opportunity to participate in either of the active treatment groups.

ANALYSIS OF DATA

Descriptive statistics of the study cohort and the participants in each intervention were expressed as mean±SD. We assessed baseline differences among treatment groups using 1-way analysis of variance for continuous variables and χ² tests for categorical variables. We evaluated the treatment effects on weight, exercise duration, blood pressure, and left ventricular dimensions using a general linear model, with the posttreatment value for the measurement of interest serving as the dependent variable and treatment group and baseline values for the measurement of interest serving as independent variables. Because controlling for baseline values of the outcome variables of interest has the effect of producing residualized change scores, the present analyses can be interpreted as testing treatment group differences on the change in outcome variables. Orthogonal contrasts were estimated by comparing the weight management group with the exercise group and the combined treatment groups with the control group. Tests for homogeneity of slopes (treatment group×sex and treatment group×race) were conducted to exclude an influence of sex or race on the treatment effects on measures of left ventricular structure.

Figure 1 illustrates posttreatment values for weight, BMI, peak oxygen consumption, and blood pressure, corrected for baseline values, for subjects in each of the 3 groups. Significant group differences were seen in postintervention weight and BMI (P<.001 for the exercise group vs the weight management group; P<.001 for both active treatment groups vs the control group). Participants in the weight management group exhibited an average weight loss of 7.4 kg, compared with a loss of 2.3 kg in the exercise group and a gain of 0.2 kg in the control group. Both interventions also resulted in improved exercise capacity, as demonstrated by increases in peak oxygen consumption (P<.001 for the active treatment groups vs the control group). Adjusted posttreatment diastolic blood pressure was significantly lower (P<.001), and posttreatment systolic blood pressure was margin-
ally lower \((P = .09)\) in the active treatment groups relative to the control group. The average reductions in blood pressure were 6.8/5.9 mm Hg and 3.2/4.4 mm Hg in the weight management and exercise groups, respectively, compared with an increase of 0.1/0.8 mm Hg in the control group.

The effects of the interventions on echocardiographic variables are shown in Figure 2. Relative to the control group, subjects in the active intervention groups had significantly smaller adjusted posttreatment posterior wall \((P = .05)\) and septal \((P = .004)\) thicknesses and a nonsignificant trend toward a greater end-

**Table 1. Baseline Characteristics of the Study Population by Intervention Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight Management ((n = 36))</th>
<th>Exercise Only ((n = 27))</th>
<th>Control ((n = 19))</th>
<th>Entire Cohort ((N = 82))</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 ± 10</td>
<td>46 ± 8</td>
<td>47 ± 8</td>
<td>47 ± 9</td>
<td>.35</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>61</td>
<td>52</td>
<td>47</td>
<td>55</td>
<td>.58</td>
</tr>
<tr>
<td>Ethnicity, % nonwhite</td>
<td>14</td>
<td>26</td>
<td>47</td>
<td>26</td>
<td>.03</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>90.1 ± 16.9</td>
<td>93.7 ± 16.6</td>
<td>92.1 ± 7.8</td>
<td>91.7 ± 16.9</td>
<td>.70</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.1 ± 4.0</td>
<td>31.6 ± 3.5</td>
<td>31.8 ± 5.0</td>
<td>31.4 ± 4.1</td>
<td>.81</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>142 ± 11</td>
<td>137 ± 7</td>
<td>143 ± 11</td>
<td>140 ± 10</td>
<td>.06</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>93 ± 5</td>
<td>94 ± 4</td>
<td>94 ± 5</td>
<td>93 ± 5</td>
<td>.42</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL·kg(^{-1}·)min(^{-1})</td>
<td>25.9 ± 6.4</td>
<td>28.6 ± 7.0</td>
<td>28.1 ± 7.4</td>
<td>27.2 ± 6.8</td>
<td>.34</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise noted. BMI indicates body mass index; BP, blood pressure.
†\(P\) values indicate significance of differences between groups in baseline characteristics.

**Table 2. Baseline Echocardiographic Characteristics of the Study Population by Intervention Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight Management</th>
<th>Exercise Only</th>
<th>Control</th>
<th>Entire Cohort</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²(^{2/7})</td>
<td>47.8 ± 9.6</td>
<td>50.1 ± 11.0</td>
<td>50.9 ± 13.7</td>
<td>49.3 ± 11.1</td>
<td>.56</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.43 ± 0.09</td>
<td>0.46 ± 0.08</td>
<td>0.44 ± 0.08</td>
<td>0.44 ± 0.08</td>
<td>.47</td>
</tr>
<tr>
<td>End diastolic dimension, mm</td>
<td>47.0 ± 5.0</td>
<td>47.6 ± 5.2</td>
<td>47.3 ± 5.3</td>
<td>47.0 ± 5.1</td>
<td>.96</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>10.1 ± 1.2</td>
<td>10.7 ± 1.8</td>
<td>10.2 ± 1.8</td>
<td>10.3 ± 1.6</td>
<td>.36</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>9.9 ± 1.6</td>
<td>10.6 ± 1.7</td>
<td>10.6 ± 2.1</td>
<td>10.3 ± 1.8</td>
<td>.26</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. LV indicates left ventricular.
†\(P\) values indicate significance of differences between groups in baseline echocardiographic characteristics.
Subjects in the weight management group exhibited 5% decreases in posterior wall and septal thicknesses and a 3% increase in end-diastolic diameter. Those in the exercise group had similar changes, with a 3% decrease in posterior wall thickness, a 5% decrease in septal thickness, and a 2% increase in left ventricular chamber dimension. No significant changes in these dimensions were noted in the control group. In part due to the increase in chamber size associated with exercise training, the adjusted decrease in left ventricular mass index in the intervention groups was modest and not statistically significant ($P=0.08$). However, subjects in the active treatment groups had a significantly smaller adjusted posttreatment relative wall thickness compared with those in the control group ($P=0.003$). During the intervention, relative wall thickness decreased by 7% in the weight management group and by 6% in the exercise group. This decrease in relative wall thickness in the intervention groups remained significant when analyses controlled for baseline differences in race ($P=0.01$) and when the 5 nonrandomized controls were excluded ($P=0.04$). No significant interactions were noted between treatment group and race or sex for any of the measures of left ventricular structure.

**COMMENT**

In our study of overweight, sedentary subjects with high-normal or mildly elevated blood pressure, lifestyle interventions consisting of regular aerobic exercise and weight management counseling resulted in improved exercise capacity, weight loss, and decreases in blood pressure that were associated with ventricular remodeling. Regular aerobic exercise with or without weight loss led to decreases in posterior wall and septal thicknesses, a decrease in relative wall thickness, and a trend toward a decrease in indexed left ventricular mass, independent of sex or race.

**LEFT VENTRICULAR ADAPTATIONS TO EXERCISE AND WEIGHT LOSS**

Aerobic conditioning in normotensive individuals is associated with an increase in the end-diastolic dimension of the left ventricle and a proportionate increase in wall thickness.$^{29}$ These adaptations to exercise develop rapidly, with significant changes in left ventricular architecture detectable by echocardiography within weeks of the initiation of training.$^{30}$ Cross-sectional studies document that obesity is associated with eccentric hypertrophy, an increase in left ventricular chamber size and wall thickness, at all levels of blood pressure.$^{31-33}$ Most weight reduction intervention trials that have used echocardiography have found that weight loss leads to a decrease in left ventricular wall thickness but has little effect on chamber size.$^{19,20}$

**EXERCISE AND WEIGHT LOSS INTERVENTIONS IN HYPERTENSION**

Few studies have evaluated the effects of lifestyle modifications on left ventricular structure in patients with hypertension. Kokkinos et al$^{14}$ described the changes in left ventricular mass and architecture observed in severely hypertensive, medically treated African American men who completed a 12-week program of moderately intensive exercise. Subjects participating in the exercise intervention exhibited a decrease in diastolic blood pressure from 89 to 84 mm Hg, accompanied by decreases in left ventricular mass and wall thickness but no sig-
nificant change in end-diastolic diameter. Previous studies in patients with mild hypertension have examined smaller numbers of patients and have generally not included randomized control groups. Reid et al\textsuperscript{15} described the effects of 12 weeks of exercise, weight loss, or both in 23 obese individuals with a mean baseline blood pressure of 131/84 mm Hg. Exercise and weight loss resulted in significant blood pressure reduction, and the effects of these interventions were additive. No significant changes were noted in left ventricular mass or dimensions, however. Baglivo et al\textsuperscript{17} demonstrated a decrease in blood pressure in 25 middle-aged hypertensive subjects after endurance exercise training, with a marginally significant decrease in left ventricular mass. Eleven older adults with mild to moderate hypertension were studied by Turner et al.\textsuperscript{18} After 7 months of regular aerobic exercise, resting systolic blood pressure, left ventricular wall thickness, and the wall thickness-radius ratio were significantly decreased. Finally, Zanettini et al\textsuperscript{16} described reductions in left ventricular mass and wall thickness, with no significant change in chamber diameter, in an uncontrolled trial of aerobic exercise in 14 patients with mildly elevated diastolic blood pressure.

In our study, significant blood pressure reductions were observed in both active intervention groups, but the amount of weight loss and the magnitude of blood pressure lowering were greater in those who received weight management counseling in addition to exercise training. Subjects in the 2 groups exhibited similar changes in left ventricular structure, however. This observation suggests that, in a relatively short 6-month intervention, exercise has a greater influence on left ventricular architecture than does weight loss. Additional research will be required to determine whether weight loss sustained over a longer period results in incremental changes in left ventricular wall thickness and mass.

**CLINICAL SIGNIFICANCE OF THE FINDINGS**

Previous observational studies using echocardiography have demonstrated that left ventricular hypertrophy and remodeling are predictors of cardiovascular morbidity and mortality, independent of blood pressure and other traditional risk factors.\textsuperscript{1,6} More recent data suggest that favorable changes in left ventricular structure are associated with a reduction in risk.\textsuperscript{7,9} Lifestyle interventions such as regular aerobic exercise and weight loss are recommended as initial therapy in overweight patients with high-normal or mildly elevated blood pressure. Although a number of studies have suggested that these interventions are efficacious in reducing blood pressure, evidence that they minimize end-organ damage or prevent cardiovascular events has been lacking. Our study demonstrates that these nonpharmacologic measures not only reduce blood pressure but also induce favorable changes in left ventricular structure. These findings support a strategy of lifestyle modification as an initial approach in the management of overweight, sedentary patients with high-normal or mildly elevated blood pressure.


