Effects of Antihypertensive Therapy on Glucose and Insulin Metabolism and on Left Ventricular Mass

A Randomized, Double-Blind, Controlled Study of 21 Obese Hypertensives

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Background—Glucose and insulin levels are associated with left ventricular mass (LVM) in insulin-resistant individuals. Antihypertensive drugs have different effects on glucose and insulin metabolism (GIM) and on LVM. To evaluate whether the effects of antihypertensive therapy on LVM are associated with its effects on GIM, we compared the effects of atenolol and perindopril on these parameters in a group of insulin-resistant, obese hypertensives.

Methods and Results—A total of 21 obese, nondiabetic hypertensives who were aged 55 ± 12 years, had a body mass index of 32.8 ± 5.0 kg/m², were free of coronary or valvular heart disease, and had normal LV function were randomized to treatment with atenolol (n = 11) or perindopril (n = 10). Echocardiographic LVM corrected for height (LVM/height) and GIM (3-hour intravenous glucose tolerance test) were measured after 4 to 6 weeks of washout and 6 months of treatment. Baseline characteristics were similar in both groups. Atenolol and perindopril effectively reduced blood pressure (from 149 ± 13/98 ± 4 to 127 ± 8/82 ± 6 mm Hg and from 148 ± 9/98 ± 4 to 129 ± 9/82 ± 6 mm Hg, respectively, for the atenolol and perindopril groups; P = 0.002). Atenolol significantly worsened GIM parameters, fasting glucose levels (5.3 ± 0.9 to 6.0 ± 1.5 mmol/L; P = 0.003), fasting insulin levels (121 ± 121 to 189 ± 228 pmol/L; P = 0.03), and most other relevant metabolic measures (P < 0.05 for all). Perindopril did not affect GIM. Atenolol did not affect LVM/height (119 ± 12 to 120 ± 17 g/m²; P = 0.8), whereas perindopril significantly reduced LVM/height (120 ± 13 to 111 ± 19 g/m²; P = 0.04).

Conclusions—In obese, hypertensive individuals, adequate and similar blood pressure control was achieved with perindopril and atenolol. However, perindopril but not atenolol was associated with a more favorable GIM profile and led to a significant regression of LVM. (Circulation. 2000;102:1802-1806.)

Key Words: obesity • hypertension • insulin

The pathophysiology underlying the regression of left ventricular hypertrophy (LVH) in hypertension is multifactorial and only partly related to the hemodynamic effects of blood pressure (BP) lowering. Different antihypertensive strategies, including weight loss, lifestyle modification, and pharmacological therapy, have had variable effects on the regression of left ventricular mass (LVM). A recent meta-analysis of drug therapy demonstrated that despite a similar BP reduction across the different therapeutic classes, superior LVM regression was achieved with angiotensin-converting enzyme (ACE) inhibitors. This effect is likely related to the effects of ACE inhibitors on nonhemodynamic factors, including the renin-angiotensin system, the adrenergic nervous system, and growth and metabolic factors, including insulin. The effect of antihypertensive therapy on insulin levels varies from class to class, with ACE inhibitors having a neutral or positive effect and β-blockers a deleterious effect on insulin sensitivity.

An association between hyperinsulinemia and LVH was previously described, but little has been written about the association between changes in insulin sensitivity and changes in LVM with antihypertensive therapy. In this study, we hypothesized that the effects of antihypertensive therapy on glucose and insulin metabolism (GIM) are associated with their effects on LVM regression. We tested this hypothesis in a group of insulin-resistant, obese hypertensives by using agents with similar BP-lowering effects but known discrepant effects on insulin sensitivity.

Methods

Study Population
Obese, nondiabetic, hypertensive patients were recruited from primary care practices in metropolitan Toronto. All patients maintained a stable weight over the preceding year, and none were involved in a regular exercise program. Inclusion criteria were as follows: sitting systolic BP >160 mm Hg and/or a diastolic BP between 96 and 114 mm Hg that was untreated or that resulted from a 4- to 6-week period of withdrawal from antihypertensive therapy; a body mass index (BMI) between 27 and 45 kg/m²; a fasting glucose level <7.8 mmol/L; normal sinus rhythm; normal global and regional LV function, with no structural abnormalities on a screening echocardiogram; and a LV mass index >75 g/m² for women and >100 g/m² for men.
Patients with a BP outside this range, secondary hypertension, or a history or clinical evidence of ischemic heart disease, congestive heart failure, valvular disease, chronic lung disease, or diabetes were excluded.

Patients were randomized to treatment with atenolol 50 to 100 mg daily or perindopril 4 to 8 mg daily for a period of 6 months. Because atenolol and perindopril cannot be formulated in identical tablets, each patient received 2 tablets per day, active perindopril and placebo atenolol or active atenolol and placebo perindopril. We did not use a placebo and placebo arm. We anticipated that 60% to 80% of patients would achieve adequate BP control on monotherapy. For the more resistant cases, combination therapy with an agent of known neutral effect on insulin resistance was allowed. The first add-on, when needed, was indapamide (1.25 to 2.5 mg/d); the second was amlodipine (5 to 10 mg/d).

After randomization and 4 to 6 weeks of placebo washout, the patients underwent a detailed echocardiographic examination and an intravenous glucose tolerance test (IVGTT); these tests were repeated after 6 months of treatment.

Patients were seen every 4 weeks for BP measurements and adjustment of the antihypertensive therapy regimen. The study protocol was approved by the ethics committee on Human Research at the University of Toronto, and each patient gave informed consent.

Baseline Measurements
Weight (kilograms) and height (meters) were measured at the first visit. BMI (kilograms per square meter) was calculated and used as an index of obesity. BP was measured in both of the patient’s arms using the first and fifth phase of the Korotkoff sounds by column mercury sphygmomanometer after 10 minutes of rest in the sitting position. A 20-cm-wide cuff was used in patients with an arm circumference >35 cm. The average of 3 consecutive blood pressure measurements, taken after consecutive 10-minute resting periods, was used for analysis.

Echocardiographic Methods
Echocardiographic studies were performed at rest with the patient at a steady state in the left lateral position, using commercially available Hewlett Packard 1000 or newer systems with 2.5 MHz transducers. Two-dimensional, guided, M-mode measurements of LV end-diastolic dimension, interventricular septal thickness, and posterior wall thickness were made at the LV minor axis at the level of the chordae tendineae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography (ASE). Every effort was made to obtain optimal echocardiographic images, with the M-mode cursor perpendicular to the LV long axis. LVM was calculated using measurements of LV end-diastolic dimension, interventricular septal thickness, and posterior wall thickness, which were made according to the standard ASE leading edge to leading edge methodology at the onset of the QRS complex on a simultaneously acquired ECG. Measurements were made off-line by 2 experienced echographists who were blinded to the clinical and metabolic data. Interrater variability at our laboratory was previously described. The average of 3 cardiac cycles was used for data analysis. LVM was calculated using the corrected ASE formula described by Devereux et al, as follows:

\[ LVM (g) = 0.80 \times (1.04 \times (LVDD + IVS + PWT) - 1.0) \times 1.06 \]

where LVDD indicates LV end-diastolic dimension; IVS, interventricular septal thickness; and PWT, posterior wall thickness. LVM was corrected for height by dividing it by height (LVM/height), as previously reported; this measurement was expressed in grams per meter.

Metabolic Investigations
Insulin and glucose responses to IVGTT were evaluated as previously described. Each participant was instructed to adhere to a diet rich in carbohydrates (at least 250 g/d) and to refrain from either strenuous physical exercise or inactivity for ≥3 days before the investigation.

Patients were admitted to the hospital on the morning of the study after an overnight fast (10 to 12 hours). Samples for baseline insulin and glucose levels were drawn at 15, 20, 25, and 30 minutes after the intravenous catheter insertion. IVGTT was then performed with a standardized bolus injection of 300 mg of glucose per kilogram of body weight (in a 50% solution given over 1 minute). Plasma glucose and insulin levels were drawn after 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes.

Plasma glucose levels (millimoles per liter) were measured by the glucose oxidase method using a Beckmann analyzer (Beckmann Instruments). Plasma insulin levels (picomoles per liter) were measured by radioimmunoassay using a Pharmacia insulin kit. All glucose and insulin assays and the above calculations were performed at the Banting and Best Diabetes Center Core Research Laboratory, University of Toronto.

Fasting insulin and glucose levels were defined as the average of levels drawn before glucose infusion. On the basis of our previous findings, the following metabolic indices were used to quantitate GIM: fasting insulin level, peak insulin level after infusion, insulin level after 90 minutes, insulin integration over 180 minutes of IVGTT (total insulin integration area), fasting glucose level, peak glucose level, glucose levels after 90 minutes, and glucose integration over 180 minutes of IVGTT (total glucose integration area).

Statistical Analysis
Summary data are expressed as mean±1SD and range (minimum to maximum; when appropriate). Due to the relatively small sample size, nonparametric tests were used. Wilcoxon rank tests were used to compare the characteristics of both groups at baseline. Signed rank tests were used to detect a change from baseline to 6 months for each of the antihypertensive therapies.

Results
The study population consisted of 22 obese, hypertensive, nondiabetic subjects. One patient was lost to follow-up, and the results on the remaining 21 patients (9 men and 12 women) are reported. Mean age was 55±12 years, BMI was 32.8±5.0 kg/m², systolic BP was 148.5±10.8 mm Hg, and diastolic BP was 97.6±3.7 mm Hg.

Eleven patients were treated with atenolol and 10 with perindopril. Seven patients (33.3%), 4 in the atenolol group and 3 in the perindopril group, required additional treatment with indapamide or amlodipine. Only peak insulin levels were significantly different between the groups at baseline. This was an isolated finding that was considered of no clinical significance given the high variability in peak insulin measurements, especially in insulin-resistant individuals.

As shown in Table 1, perindopril and atenolol led to a significant and similar reduction in both systolic BP (from 148 to 129 mm Hg and from 149 to 127 mm Hg for perindopril and atenolol, respectively; P<0.002) and diastolic BP (from 97 to 81 mm Hg and from 98 to 82 mm Hg, respectively; P<0.002). Perindopril-treated patients showed no significant changes in any of the metabolic parameters, but they did have a significant reduction in LVM/height (from 120 to 111 g/m; P=0.04). Atenolol-treated patients showed a significant deterioration in most of the metabolic parameters, including fasting glucose levels (P<0.003), fasting insulin levels (P<0.03), glucose after 90 minutes (P=0.002), insulin after 90 minutes (P=0.04), peak glucose (P=0.005), total glucose integration area (P=0.02), and total insulin integration area (P=0.006). No significant changes in LVM/height (from 119 to 120 g/m; P=0.19) occurred in the atenolol group.

We further analyzed the data to calculate the predictive values of directional changes in GIM on LVM/height using total insulin integration area as the marker for GIM. Changes in GIM had a
positive predictive value of 80% and a negative predictive value of 68.7% on changes in LVM/height (Table 2).

**Discussion**

LVH regression with antihypertensive therapy is only partially related to the hemodynamic effects of BP lowering.\(^4\) ACE inhibitors seem to promote LVH regression more effectively than other antihypertensive agents due to their beneficial effects on nonhemodynamic factors, such as the renin-angiotensin system,\(^5\) the adrenergic nervous system,\(^6\) and growth and metabolic factors, including insulin.\(^7\) In this study, we assessed the effects of treatment with the ACE inhibitor perindopril and the β-blocker atenolol on LVM and GIM in a group of insulin-resistant, obese, hypertensive subjects. We found a similar reduction in BP but different effects on LVM and GIM.

Perindopril had a neutral effect on insulin sensitivity and caused a significant reduction in LVM, whereas atenolol had a negative or deleterious effect on GIM and caused no reduction in LVM. These findings support the hypothesis that the effects of antihypertensive therapy on GIM parallel the effects of the therapy on LVM in obese, hypertensive, insulin-resistant individuals.

Insulin resistance is characterized by a blunted response of peripheral tissues to circulating insulin, with a consequent reduction in glucose uptake and compensatory hyperinsulinemia.\(^17\) The reason for this reduction in glucose uptake is not completely understood, but it has been related to the presence of at least 2 defects in the skeletal muscle of obese subjects: a defect in insulin-stimulated cellular glucose extraction and a defect in endothelium-derived vasodilation.\(^18\) This reduction in glucose uptake in insulin-resistant individuals seems to be selective, as demonstrated by Nuutila et al\(^19\) and Utriainen et al\(^20\) with reduced glucose uptake in skeletal muscle but normal and well-preserved uptake in the cardiac muscle, which maintains normal insulin sensitivity.

This long-term increase in insulin burden would magnify the direct and indirect effects of insulin on the heart, leading to an increase in LVM.

**Insulin and LVM**

Since the description of the association between increased LVM and insulin resistance in rare genetic disorders,\(^21,22\) several studies have confirmed this association in the obese and hypertensive populations.\(^9,10,13,23,24\) Sasson et al\(^13\) reported the relationship between LVM and insulin levels after an IVGTT in 40 healthy, normotensive, obese individuals. LVM was strongly correlated with circulating insulin levels; indices of glucose and insulin metabolism were the only independent predictors of LVM in this population. Vetta et al\(^23\) studied 49 normotensive elderly patients, 29 obese

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**TABLE 1. Hemodynamic and Metabolic Effects of Perindopril and Atenolol in Obese Hypertensives**

<table>
<thead>
<tr>
<th></th>
<th>Perindopril (n=10)</th>
<th>Atenolol (n=11)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>148±9</td>
<td>129±10</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>97±3</td>
<td>81±5</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate</td>
<td>78.5±15.4</td>
<td>74.2±13.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Double product</td>
<td>11 159±2273</td>
<td>9583±1821</td>
<td>0.01</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.06±0.18</td>
<td>2.05±0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34.4±4.5</td>
<td>34.5±4.5</td>
<td>0.21</td>
</tr>
<tr>
<td>LVM, g</td>
<td>201±26</td>
<td>188±38</td>
<td>0.04</td>
</tr>
<tr>
<td>LVM/height, g/m²</td>
<td>98±9</td>
<td>91±14</td>
<td>0.04</td>
</tr>
<tr>
<td>TIIA, pmol/L per min</td>
<td>26 207±12 870</td>
<td>27 302±5454</td>
<td>0.30</td>
</tr>
<tr>
<td>TIGA, mmol/L per min</td>
<td>1308±144</td>
<td>1326±204</td>
<td>0.38</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>72±34</td>
<td>101±100</td>
<td>0.38</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.6±0.7</td>
<td>5.6±0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Peak insulin, pmol/L</td>
<td>399±346</td>
<td>401±325</td>
<td>0.26</td>
</tr>
<tr>
<td>PEAK glucose, mmol/L</td>
<td>18.0±3.6</td>
<td>17.2±2.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Insulin T90, pmol/L</td>
<td>133±41</td>
<td>126±40</td>
<td>0.20</td>
</tr>
<tr>
<td>Glucose T90, mmol/L</td>
<td>6.0±1.0</td>
<td>5.9±1.3</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**TABLE 2. Predictive Value of Directional Changes in Total Insulin Integration Area on LVM/Height**

<table>
<thead>
<tr>
<th>All patients (n=21)</th>
<th>Total Insulin Integration Area</th>
<th>Improved</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM/height</td>
<td>Improved, n</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Worsened, n</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

Positive predictive value was 80%; negative predictive value was 68.7%.
subjects, and 20 age-matched lean individuals. In the obese but not lean subjects, LVM correlated with the insulin levels observed after an oral glucose tolerance test. Phillips et al\(^24\) studied 29 nonobese hypertensives who were free of diabetes or glucose intolerance; they found a significant relation between the insulin sensitivity index and LVM.

Insulin may lead to myocardial hypertrophy and an increase in LVM through a variety of pathways; an important part of this increase seems to be an antiproteolytic effect in the heart. This effect of insulin was described in an animal study by Young et al\(^25\) who analyzed myocardial protein turnover during hyperinsulinemic euglycemic clamp and demonstrated a 50% reduction in heart protein degradation during hyperinsulinemia. MacNulty et al\(^26\) studied the effects of insulin on myocardial protein synthesis, degradation, and net balance in 11 individuals and observed a significant antiproteolytic effect of insulin on the heart. This reduction in protein degradation occurred without any change in cardiac work.

Insulin, when given in supraphysiological amounts, stimulates heart protein synthesis in vitro\(^27\), but more recent studies have failed to demonstrate such an effect in vivo in adult animals.\(^28\) Insulin may also affect LVM by increasing blood volume through its effect on sodium absorption in the kidney\(^29,30\) and through the stimulation of the sympathetic nervous system.\(^31\)

**β-Blockers and Insulin Sensitivity**

The mechanisms by which β-blockers modify insulin sensitivity are not fully understood. Long-term treatment with β-blockers alters the first phase of insulin secretion, which plays an important role in controlling postload glycemia, so that more insulin is needed in the second phase.\(^32\) β-blockers also seem to attenuate insulin clearance in insulin-resistant patients,\(^32,33\) leading to >10% higher steady-state plasma insulin levels\(^34–38\); the resulting hyperinsulinemia could downregulate the insulin receptors and, consequently, lower insulin sensitivity. In addition, β-blockers tend to increase total peripheral resistance, leading to a reduction in skeletal muscle blood flow and glucose uptake, which increases insulin resistance. This theory is reinforced by the findings that the new generation of vasodilating β-blockers, such as divedalol,\(^37\) celiprolol,\(^39\) and carvedilol,\(^38\) induce an improvement in peripheral vascular resistance and a slight improvement in insulin sensitivity in nonobese individuals. Finally, β-blocker treatment is often associated with a significant weight gain,\(^40\) as was seen in this study. This weight gain may lead to a further reduction in insulin sensitivity. However, this mechanism does not seem to play a major role: as in previous studies, a reduction in insulin sensitivity was also observed in those who had no change in body weight.\(^34–38\)

**ACE Inhibitors and Insulin Sensitivity**

Several clinical studies have shown that the administration of ACE inhibitors results in increased insulin-stimulated glucose disposal in diabetics or hypertensive individuals.\(^41\) The mechanisms of this action were initially thought to be exclusively related to an improvement in capillary blood flow. ACE inhibitors increase bradykinin levels through the inhibition of kininase II, which causes vasodilation and augmented capillary blood flow\(^42\) and thereby increases the delivery of insulin and glucose to skeletal muscle.\(^43,44\)

Anderson et al\(^45\) randomized 50 nonobese (mean BMI, 26 kg/m\(^2\)), hypertensive patients for treatment with fosinopril or atenolol and correlated the effects of these drugs on skeletal muscle blood flow during a hyperinsulinemic euglycemic clamp with their effects on LV wall thickness. Despite a more pronounced reduction in BP with atenolol, patients treated with fosinopril had a significantly greater reduction in LV wall thickness, which correlated with enhanced skeletal muscle blood flow, suggesting that in nonobese hypertensive individuals, impaired peripheral blood flow and consequent increased afterload may mediate the association between insulin resistance and LVH. This may be less important in the obese population. Laine et al\(^46\) infused bradykinin into the femoral artery of 1 leg of 8 obese and 7 nonobese patients under hyperinsulinenic euglycemic conditions and demonstrated that obese patients required twice as much bradykinin to induce vasodilation. Despite a 75% increase in blood flow after the infusion, glucose uptake was not augmented, indicating that blood flow alone does not mediate insulin resistance. This prompted the need for new studies to clarify the effects of ACE inhibition on GIM in this population.

**Limitations**

First, insulin resistance was assessed indirectly with IVGTT-derived metabolic indices that used insulin and glucose levels at baseline and after standardized intravenous glucose challenge. This method provides an accurate and reliable method of insulin resistance in subjects with normal or high basal insulin levels and an intact insulin response to glucose challenge. It becomes inaccurate in patients with inadequate insulin secretion, in whom a more direct mode of measurement of insulin resistance, such as the clamp method\(^46\) or the minimal model, may be required.\(^47\) However, because our patients were not diabetic, according to both previous criteria\(^48\) and the current, more stringent guidelines,\(^49\) and because our population had higher than normal insulin secretion rates, we are confident that insulin resistance was adequately demonstrated by the method used. This is further supported by the strong correlation we found among obesity/hypertension and the levels of IVGTT-derived metabolic parameters, which is in accordance with the well-established association among obesity, hypertension, and hyperinsulinemia.\(^46,50\)

Second, although the validity of this study may be limited by the small study sample and by the fact that only 55% of our patients had LVH at baseline, as defined as LVM/height >102 g/m for women and >143 g/m for men,\(^15\) the results are consistent with the currently available literature, which demonstrates the differential effects of β-blockers and ACE inhibitors on insulin resistance and LVM.\(^8\)

We concluded that in obese, hypertensive individuals, the ACE inhibitor perindopril and the β-blocker atenolol led to a similar reduction in BP. However, perindopril was associated with a more favorable metabolic profile and a significant LVM reduction and, therefore, may be a preferable agent in this population.

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References


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