Circulating Insulin and Insulin Growth Factor-1 Are Independent Determinants of Left Ventricular Mass and Geometry in Essential Hypertension

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Background—It is unclear whether insulin and insulin-like growth factor-1 (IGF-1) are independent determinants of left ventricular (LV) mass in essential hypertension.

Methods and Results—We studied 101 never-treated nondiabetic subjects with essential hypertension. All had 24-hour noninvasive ambulatory blood pressure (ABP) monitoring and a 75-g oral glucose tolerance test. We determined fasting glucose, insulin, and IGF-1 and postload glucose and insulin 2 hours after glucose. Insulin resistance was estimated by the homeostasis model assessment (HOMA) formula. LV mass showed an association with body mass index (BMI) ($r=0.47$; $P<0.01$), postload insulin ($r=0.54$; $P<0.01$), HOMA ($r=0.39$; $P<0.01$), and IGF-1 ($r=0.43$; $P<0.01$) and a weaker association with average 24-hour systolic and diastolic ABPs ($r=0.29$ and $r=0.26$; $P<0.05$) and basal insulin ($r=0.31$; $P<0.05$). Relative wall thickness was positively related to IGF-1 ($r=0.39$; $P<0.01$) but not to fasting or 2-hour postload insulin, HOMA, and glucose. In a multiple regression analysis, the final LV mass model ($R^2=0.64$) included IGF-1, postload insulin, average 24-hour systolic ABP, sex, and BMI. IGF-1 and postload insulin accounted for >40% of variability of LV mass. The final model ($R^2=0.36$) for relative wall thickness included IGF-1 (16% total explained variability), average 24-hour systolic ABP, sex, BMI, and age but not insulin and HOMA.

Conclusions—These data indicate that insulin and IGF-1 are powerful independent determinants of LV mass and geometry in untreated subjects with essential hypertension and normal glucose tolerance. (Circulation. 1999;100:1802-1807.)

Key Words: hypertension ■ hypertrophy ■ echocardiography ■ insulin ■ growth substances

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eft ventricular (LV) mass determined at echocardiography in 1 single session is a potent independent predictor of cardiovascular morbidity and mortality in essential hypertension,1-3 and its reduction during treatment has a favorable prognostic impact.4,5 However, despite its growing use in clinical practice for cardiovascular risk stratification, the pathophysiological mechanisms underlying the LV structural abnormalities in essential hypertension are still incompletely known.6

Blood pressure (BP) overload explains only in part the changes in LV structure in subjects with hypertension, because the proportion of LV mass variability accounted for in these subjects by BP, either clinic or ambulatory, is small.6

Insulin could be involved in the pathogenesis of essential hypertension.7 An inverse association has been noted between insulin sensitivity, measured by the glucose clamp technique, and LV wall thickness in subjects with essential hypertension.8 Insulin may exert a direct growth-promoting effect on cardiomyocytes.9 Insulin growth factor-1 (IGF-1) may induce cardiac hypertrophy,10 and insulin could stimulate muscle cell growth by binding to the IGF-1 receptors because of the structural similarity between the 2 molecules.11 Also, in subjects with essential hypertension, IGF-1 may be increased and associated with LV mass.12

The above considerations prompted us to plan a study to ascertain the role of insulin and IGF-1 as possible independent determinants of LV mass in uncomplicated, never-treated, and nondiabetic subjects with essential hypertension.

Methods

Study Subjects

The present study was conducted in 115 subjects who consecutively entered the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) registry and fulfilled the following admission criteria:
(1) never-treated essential hypertension with sitting BP ≥140 mm Hg systolic or 90 mm Hg diastolic in ≥3 visits in the previous 3 weeks, (2) no diabetes mellitus, (3) good-quality echocardiographic tracings, (4) ≥1 valid ambulatory BP reading per hour, (5) absence of heart failure or valvular defects, and (6) normal liver and kidney function. Details of the PIUMA protocol have been reported previously. For this project, a 75-g oral glucose tolerance test was performed in all subjects. The study was conducted in accordance with the declarations of Helsinki and Tokyo, and all subjects gave informed consent.

**BP Measurement**

Clinic BP was measured by a physician in the outpatient hospital clinic with a mercury sphygmomanometer, with the subject sitting for ~10 minutes. The average of 3 measurements was considered for the analysis. Ambulatory BP was recorded with an oscillometric device (models 90202 and 90207, SpaceLabs) set to take a reading every 15 minutes throughout the 24 hours. Normal daily activities were allowed and encouraged, and patients were told to keep their nondominant arm still and relaxed to the side during measurements. Reading, editing, and analysis of data were done as previously described. The spontaneous day-to-day variability of ambulatory BP was assessed in some of these patients. Daytime and nighttime periods were defined according to the so-called “narrow fixed clock intervals” (day, from 10 AM to 8 PM; night, from midnight to 6 AM) to mirror the actual patients’ waking-sleeping rhythms.

**Echocardiography**

The echocardiographic study was performed with commercially available machines according to standard laboratory procedures. The M-mode echocardiographic study of the LV was performed under 2-dimensional control according to the American Society of Echocardiography recommendations. Only frames with optimal visualization of interfaces and simultaneously showing septum, LV ID, and posterior wall were used for readings. Tracings were read by 2 observers who were unaware of patients’ clinical data, and the mean value from at least 5 measurements per observer was computed. The intraobserver and intratracing variability in our laboratory has been reported elsewhere. LV mass was calculated according to Devereux et al and normalized by both body surface area and by height to correct for the effect of overweight. Relative wall thickness was calculated as (posterior wall thickness)/LV internal radius, and concentric remodeling or concentric LV hypertrophy was defined by a relative wall thickness >0.45.

**Hormone and Metabolic Investigations**

All participants were instructed to follow a weight-maintaining diet of ≥300 g of carbohydrates per day for the 3 days before the study. On the morning of the study, patients were admitted to the outpatient clinic at 7:30 AM after an overnight fast. A plastic catheter was inserted into a forearm vein for blood sampling and kept patent by a slow saline drip. At 8 AM, a standard oral glucose load (75 g glucose monohydrate) in 300 mL water was given to all subjects. Neither food nor water was allowed during the test. Blood samples were taken immediately before and 2 hours after load for glucose and insulin determinations. IGF-1 levels were determined only in basal samples.

Plasma glucose was immediately determined by the glucose oxidase method (Glucose Analyzer, Beckman; intra-assay coefficient of variation [CV] 2.2%; interassay CV 3.8%). Plasma insulin was determined in duplicate by a highly specific (cross-reactivity: intact proinsulin <0.2%; Des-31,32-HPI <0.2%; Des-64,65-HPI <0.2%; IGF-1 undetectable) and sensitive (2 μU/mL) radioimmunoassay (Linco Research; intra-assay CV 3.3%, interassay CV 4.2%; internal reference values in healthy subjects: 11.6±3.4 [mean±SD] μU/mL). Circulating IGF-1 was determined in duplicate by 2-site specific (cross-reactivity: human insulin undetectable; intact proinsulin undetectable) and sensitive (2.06 ng/mL) immunoradiometric assay (Diagnostic System Laboratories; intra-assay CV 4.4%, inter-

**Homeostasis Model Assessment of Insulin Resistance**

In each subject, the degree of insulin resistance was estimated by the homeostasis model assessment (HOMAIR) as described by Matthews et al and validated by Bonora. Briefly, HOMAIR was calculated by taking into account fasting insulin and blood glucose levels according to the equation HOMAIR = fasting insulin (μU/mL)/[22.5×e 5glucose [mmol/L]]. Low HOMAIR values denote normal insulin sensitivity, whereas high values denote insulin resistance. In our laboratory, the mean value for age-matched, white, normotolerant, normotensive subjects (n=42) was 2.83±0.7 (95th percentile 3.99).

**Statistical Analysis**

Results are given as mean±SD unless otherwise specifically stated. Statistical analyses were performed by use of SAS/STAT (SAS Institute) release 6.12 and JMP (SAS Institute) release 3.2. Two-tailed unpaired t test was used to compare study response variables between subject categories. Correlation coefficients were calculated according to Pearson’s method. Stepwise multivariate linear regression analysis was used to determine the significant independent predictors of LV mass or relative wall thickness. Office and ambulatory BP, plasma insulin, HOMAIR, IGF-1, and the echocardiographic parameters were analyzed as continuous variables, body mass index (BMI) was considered as presence versus absence of overweight or obesity (≥25 versus <25 kg/m²), and sex was considered as male versus female. Stepwise logistic regression analysis was used to determine the independent predictors of LV hypertrophy (LV mass index ≥125 versus <125 g/m²). Office and ambulatory BP, insulin, HOMAIR, IGF-1, and BMI were analyzed as continuous variables, and sex was considered as male versus female. The Spearman test (rS) was used for the correlation of LV mass to the night/day BP ratio in either sex to obviate for possible imbalances in the gaussian distribution in the smaller samples. Probability values <0.05 were considered statistically significant in all analyses.

**Results**

**Patients**

Of 113 subjects examined initially, 8 were excluded for impaired glucose tolerance (2-hour postload plasma glucose >140 and <200 mg/dL) and 4 for diabetes (2-hour postload plasma glucose ≥200 mg/dL). The remaining 101 subjects entered the study.

The main demographic and clinical characteristics of these subjects are reported in Tables 1 and 2. As expected, fasting and postload insulin, HOMAIR, triglycerides, uric acid, and LV mass were increased in the subset with BMI ≥25 kg/m² (all P<0.05), and the increase in LV mass in these subjects was accounted for by an increase in both wall thicknesses and internal diameter (all P<0.05). IGF-1 and office and ambulatory BP did not differ between the 2 groups. HOMAIR exceeded 3.99 in 51% of subjects, in agreement with the prevalence rate reported by Bonora.

**Determinants of LV Mass and Geometry**

As reported in Table 3, LV mass showed a significant association with ambulatory BP (r=0.30 for systolic, 0.27 for diastolic) but not with office BP. There was also a direct association between LV mass and the night/day ratio of systolic BP in the overall population (r=0.25), which held in the female (r=0.32; P=0.04) but not in the male (r=0.20; P=0.14) sex. LV mass also showed a direct association with

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TABLE 1. Main Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects</th>
<th>BMI&lt;25 kg/m²</th>
<th>BMI≥25 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>101</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Sex distribution, F/M</td>
<td>43/58</td>
<td>26/25</td>
<td>17/33</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.5±11</td>
<td>45.7±13</td>
<td>51.3±9*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.7±13</td>
<td>64.8±10</td>
<td>80.9±10*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.2±9</td>
<td>166.6±9</td>
<td>169.8±9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5±3.5</td>
<td>23.04±1.7</td>
<td>28.1±3.08*</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.82±0.2</td>
<td>1.72±0.2</td>
<td>1.92±0.2*</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>96.7±10</td>
<td>95.6±11</td>
<td>97.9±10</td>
</tr>
<tr>
<td>2-hour plasma glucose, mg/dL</td>
<td>98.3±20</td>
<td>95.1±20</td>
<td>100.8±21</td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/mL</td>
<td>17.6±3</td>
<td>16.1±3</td>
<td>19.1±3*</td>
</tr>
<tr>
<td>2-hour plasma insulin, µU/mL</td>
<td>56.6±25</td>
<td>45.9±17</td>
<td>67.2±28*</td>
</tr>
<tr>
<td>HOMAᵢᵢᵢ</td>
<td>4.2±0.9</td>
<td>3.8±0.9</td>
<td>4.6±0.8*</td>
</tr>
<tr>
<td>IGF-1, ng/mL</td>
<td>207.3±76</td>
<td>207.8±70</td>
<td>206.8±81</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>205.1±35</td>
<td>201.8±32</td>
<td>208.5±37</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>110.7±57</td>
<td>97.4±45</td>
<td>124.8±65*</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>4.4±1.4</td>
<td>4.08±1.5</td>
<td>4.7±1.2*</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.94±0.2</td>
<td>0.92±0.2</td>
<td>0.95±0.2</td>
</tr>
</tbody>
</table>

Data are mean±SD. *P<0.05 (BMI<25 vs ≥25 kg/m²).

fasting (r=0.31) and postload (r=0.55) insulin, HOMAᵢᵢᵢ (r=0.39), and IGF-1 (r=0.42). Relative wall thickness showed a significant association with office systolic BP (r=0.21), ambulatory systolic (r=0.42) and diastolic (r=0.29) BP, and IGF-1 (r=0.39) but not with fasting insulin, postload insulin, and HOMAᵢᵢᵢ.

In a stepwise multivariate linear regression analysis (Table 4), the independent determinants of LV mass were postload insulin, sex, IGF-1, BMI, and average 24-hour ambulatory systolic BP. Office BP, BP load, the night/day ratio of systolic BP, and HOMAᵢᵢᵢ did not achieve significance to enter the model. Postload insulin accounted for 30% of total variability of LV mass; a further 12% was accounted for by

TABLE 2. Office and Ambulatory BP and Heart Rate and Echocardiographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects</th>
<th>BMI&lt;25 kg/m²</th>
<th>BMI≥25 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>152.1±14</td>
<td>150.7±15</td>
<td>153.3±13</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>99.2±9</td>
<td>100.4±9</td>
<td>98±9</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>74.7±11</td>
<td>77.2±11</td>
<td>72.2±9*</td>
</tr>
<tr>
<td>Average 24-hour systolic BP, mm Hg</td>
<td>135.6±12</td>
<td>134.5±11</td>
<td>136.7±12</td>
</tr>
<tr>
<td>Average 24-hour diastolic BP, mm Hg</td>
<td>87.7±9</td>
<td>87.3±9</td>
<td>88.1±10</td>
</tr>
<tr>
<td>Average 24-hour heart rate, bpm</td>
<td>75.3±9</td>
<td>76.7±9</td>
<td>73.9±8</td>
</tr>
<tr>
<td>Interventricular septum thickness, cm</td>
<td>1.2±0.2</td>
<td>1.1±0.2</td>
<td>1.3±0.2*</td>
</tr>
<tr>
<td>LV ID, cm</td>
<td>4.8±0.4</td>
<td>4.6±0.3</td>
<td>4.9±0.4*</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>1.07±0.15</td>
<td>1.04±0.15</td>
<td>1.1±0.15</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>204.5±48.4</td>
<td>179.6±35.1</td>
<td>229.6±47.3*</td>
</tr>
<tr>
<td>LVMI (mass/BSA), g/m²</td>
<td>111.8±20.5</td>
<td>104.3±18.6</td>
<td>119.3±19.7*</td>
</tr>
<tr>
<td>LVMI/height²/m², g/m²</td>
<td>50.2±10.3</td>
<td>45.3±8.7</td>
<td>55.1±9.4*</td>
</tr>
<tr>
<td>Relative wall thickness, %</td>
<td>45.3±8.13</td>
<td>45.8±8.4</td>
<td>44.8±7.8</td>
</tr>
</tbody>
</table>

LVMI indicates LV mass index; BSA, body surface area. Data are mean±SD. *P<0.05 (BMI<25 vs ≥25 kg/m²).

sex, 9% by IGF-1, 9% by BMI, and finally, 5% by average 24-hour ambulatory systolic BP. The multiple r was 0.81, which indicates that the whole model accounted for 65% of total variability of LV mass. Figure 1 shows that the association between LV mass and postload insulin held in the normal-weight (r=0.32, P<0.05) as well in the overweight (r=0.48, P<0.001) subjects. Figure 2 shows that the closeness of the association between LV mass and IGF-1 did not differ in the normal-weight (r=0.49, P<0.01) compared with overweight (r=0.49, P<0.01) subjects.

Figure 3 shows the values of fasting insulin, 2-hour postload insulin, HOMAᵢᵢᵢ, and IGF-1 in the presence and absence of echocardiographic LV hypertrophy. In a stepwise logistic regression analysis, the independent predictors of LV hypertrophy were IGF-1 (P<0.01), postload insulin.
average 24-hour systolic BP (P<0.01), and BMI (P<0.05). The adjusted odds ratio of LV hypertrophy was 1.68 (95% CI 1.21 to 2.33) for every 10-μU/mL increase in postload insulin, 1.27 (95% CI 1.12 to 1.44) for every 10-ng/mL increase in IGF-1, 1.64 (95% CI 1.16 to 2.30) for every 5–mm Hg increase in average 24-hour systolic BP, and 1.91 (95% CI 1.02 to 3.56) for each 3-kg/m² increase in BMI. Office BP, BP load, the night/day ratio of systolic BP, and HOMA IR did not enter the model.

The independent determinants of relative wall thickness are reported in Table 5. Relative wall thickness was accounted for by average 24-hour ambulatory systolic BP, IGF-1, age, BMI, and sex. Average 24-hour ambulatory systolic BP accounted for 17% of total variability of relative wall thickness; a further 11% was accounted for by IGF-1, 3% by age, 3% by BMI, and 2% by sex. The whole model accounted for ≈36% of total variability of LV mass (multiple r=0.60). As shown in Figure 4, the univariate association between LV mass and IGF-1 was comparable in the normal-weight (r=0.35, P<0.05) and overweight (r=0.45, P<0.01) subjects.

When subjects were subdivided by LV geometry (Figure 5), postload plasma insulin did not differ between the subset with normal LV geometry and that with concentric remodeling, whereas it was increased in the group with eccentric hypertrophy compared with that with concentric hypertrophy (P<0.001). In contrast, IGF-1 did not differ between the group with eccentric and that with concentric hypertrophy, whereas it was increased in the subjects with concentric LV remodeling compared with those with normal LV geometry (P<0.05).

**Discussion**

Insulin and IGF-1 were powerful independent determinants of LV mass in never-treated subjects with essential hypertension and normal glucose tolerance. Together, these 2 hormones accounted for 39% of variability of LV mass, and a further 26% of variability was explained by overweight, sex, and average 24-hour ambulatory systolic BP, leading to 65% of LV variability being explained by these factors. Moreover, IGF-1, but not insulin, independently accounted for 11% of variability of relative wall thickness, with a further 25% of variability explained by 24-hour ambulatory systolic BP, age, sex, and overweight. These findings have been obtained in a population of nondiabetic subjects with normal glucose tolerance, thus removing the potential objection that hyperinsulinemia might have been an obvious relevant confounder.

It is well established that peripheral hyperinsulinemia in subjects with essential hypertension is a marker of insulin resistance. The HOMA IR was calculated to obtain a better quantitative estimate of insulin resistance. Although this index was increased in subjects with LV hypertrophy, it was not an independent predictor of LV mass after control for postload insulin, IGF-1, sex, overweight, and ambulatory BP.
Because HOMA IR reflects fasting insulin levels, our data suggest that postload insulin is more important than fasting insulin as a potential determinant of LV mass.

Previous studies have examined the relation of insulin or IGF-1 with LV mass in subjects with essential hypertension, but none of these studies assessed the independent association of these 2 hormones with LV mass in the same population.

The present study not only disclosed an independent relationship of insulin and IGF-1 to LV mass but also lent support to the view that such an association may be mediated by different mechanisms of action by these hormones on the concentric and eccentric components of LV geometry. In this setting, the potential clinical importance of the different patterns of LV geometry has been increasingly appreciated in the past few years, on the basis of longitudinal studies that examined the possibility that the different LV geometric patterns could provide prognostic information beyond the overwhelming contribution of LV mass in subjects with essential hypertension.

**Effects of Insulin and IGF-1 on LV Geometry**

Experimental and clinical data suggest that insulin might interfere with both the concentric and eccentric patterns of LV mass growth. Stimulation of myocardial cell growth and activation of the sympathetic nervous system might preferentially lead to concentric LV hypertrophy through a direct trophic effect and pressure overload, whereas sodium and water retention could lead to eccentric LV hypertrophy through volume overload. The direct effect of insulin on myocardial cell growth could be mediated, at least in part, by the IGF-1 receptors. Unfortunately, we did not assess sympathetic nervous system activity or plasma volume; hence, we were unable to quantify the impact of these mechanisms in our population. Other potential nonhemodynamic determinants of LV mass, including angiotensin, aldosterone, atrial natriuretic peptide, and ACE genotype, could not be assessed. Our findings are partially in keeping with those of Paolisso et al, who found an impaired whole-body glucose disposal, determined with euglycemic hyperinsulinemic clamp, in hypertensive subjects with concentric LV remodeling or frank LV hypertrophy compared with a group of subjects with normal LV geometry. In a study carried out in nonobese and nondiabetic hypertensive subjects, Phillips et al found an independent relationship of mean 24-hour ambulatory BP and insulin sensitivity index (frequently sampled intravenous glucose tolerance test) to LV mass determined at echocardiography.

As far as IGF-1 is concerned, some studies suggest that this 70-amino-acid peptide, synthesized primarily in the liver under the influence of growth hormone, could contribute to increasing LV mass in subjects with hypertension. IGF-1 directly stimulates the growth of cardiac myocytes through induction of cardiac protein synthesis. Unfortunately, we could not determine IGF-1 binding proteins in our study. More than 90% of total IGF-1 circulates bound to proteins, and the distribution of these binding proteins seems to be shifted from the high-molecular-mass forms toward the low-molecular-mass forms in hypertensive subjects with LV hypertrophy. This may have important implications because the low-molecular-mass forms may cross the capillary barrier, thus shuttling IGF-1 to myocardial and other target cells. However, a complex equilibrium seems to exists between insulin and IGF-1. In fact, the distribution of the IGF-1 binding proteins is also affected by insulin, because the low-molecular-mass forms, and hence the tissue availability of IGF-1, tend to decrease with increasing insulin resistance.

**Conclusions**

There is growing evidence of a link between insulin and cardiovascular risk, although the independent role of insulin is still undetermined. This study suggests that insulin and IGF-1 are important determinants of LV mass and geometry in subjects with essential hypertension and normal glucose tolerance and
that this relation is independent of sex, overweight, and office and ambulatory BP. Insulin and IGF-1 could lead to increased LV mass through different basic effects on LV geometry.

Acknowledgments

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