Insulin Resistance and Hyperinsulinemia
No Independent Relation to Left Ventricular Mass in Humans

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Background—Hyperinsulinemia and insulin resistance may contribute to the development of cardiac hypertrophy. In humans, however, the evidence is inconclusive.

Methods and Results—We studied 50 nondiabetic subjects covering a wide range of age (20 to 65 years), body mass index (BMI, 19 to 40 kg·m⁻²), and mean blood pressure (72 to 132 mm Hg). Plasma insulin concentrations and secretory rates were measured at baseline and during an oral glucose tolerance test; insulin sensitivity was measured by the insulin clamp technique. Left ventricular mass (LVM) (by 2D M-mode echocardiography) was distributed normally and was higher in obese (BMI ≥27 kg·m⁻², n=16) or hypertensive patients (blood pressure >140/90 mm Hg, n=21) (50±8 and 55±10 g·m⁻², respectively) than in 13 nonobese, normotensive subjects (40±8 g·m⁻², P=0.0004). In a multivariate model adjusting for sex, age, BMI, and blood pressure, neither insulin concentrations (fasting or postglucose) nor insulin sensitivity or secretory rates were significant correlates of LVM. Systolic blood pressure (P=0.003) and BMI (P=0.01) were the only independent correlates of LVM. From the regression, the impact of hypertension (as a systolic pressure of 180 versus 140 mm Hg=+20%) was twice as large as that of obesity (as a BMI of 35 versus 25 kg·m⁻²=+11%), the two factors being additive.

Conclusions—When adequate account is taken of body mass and blood pressure, insulin, as concentration, secretion, or action, is not an independent determinant of LVM in nondiabetic subjects. (Circulation. 2000;102:2233-2238.)

Key Words: hypotrophy ■ ventricles ■ insulin ■ obesity ■ hypertension

Myocyte hypertrophy leading to cardiac growth has been identified as a major cardiovascular risk factor in humans. Characteristically, cardiac hypertrophy is secondary to hypertension, but some degree of cardiac hypertrophy can also be found in normotensive obese subjects, in patients with ischemic heart disease, and in diabetic patients. Cardiac hypertrophy may precede the development of essential hypertension.

Hemodynamic as well as nonhemodynamic factors influence the development of left ventricular hypertrophy (reviewed in Reference 8). A role for insulin resistance with the attendant hyperinsulinemia and/or hyperglycemia in the genesis of cardiac hypertrophy has been suggested on the basis of several observations. First, an enlarged left ventricular mass (LVM) has been described not only in obesity but in endocrine diseases such as acromegaly and hypothyroidism and rare genetic syndromes such as leprechaunism, which are characterized by insulin resistance, hyperinsulinemia, and various degrees of glucose intolerance. Second, in vitro hyperinsulinemia can induce cardiac cell growth through the stimulation of insulin-like growth factor-1 receptors. Third, patients with essential hypertension or ischemic heart disease, in whom cardiac hypertrophy is prevalent, are often insulin resistant. Finally, in humans, acute insulin administration suppresses myocardial protein degradation by 80%, a physiological effect implying that chronic hyperinsulinemia has the potential to contribute to myocardial hypertrophy.

There is evidence to indicate that plasma glucose per se could make a contribution to the left ventricular growth process. Thus, hypertensive individuals with diabetes have been found to have higher LVM than nondiabetic hypertensive patients with similar blood pressure (BP) levels. In Arizona Indians, impaired glucose tolerance has been related to left ventricular wall thickness. In vitro, glucose itself can stimulate vascular smooth muscle cell growth. The in vivo studies that have sought an association between insulin and LVM have yielded conflicting results (Table 1). The present study was therefore undertaken to assess the differential impact of insulin (concentrations, secretory rates, and sensitivity) and glucose tolerance status on myocardial mass in a large group of nondiabetic subjects enriched with obese and hypertensive individuals.

Methods

Study Subjects
Fifty subjects (18 women, 32 men) were recruited. Inclusion criteria were age 20 to 65 years, normal oral glucose tolerance, and normal serum lipid concentrations (ie, serum LDL cholesterol concentration

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<7 mmol/L and serum triglycerides <3.5 mmol/L). All subjects were free from current acute or chronic illness (as judged by clinical and laboratory workup), were currently nonsmokers, and were on a weight-maintaining diet. By defining obesity as a body mass index (BMI) ≥27 kg · m⁻², 17 subjects were obese (BMI 27.1 to 40.2 kg · m⁻²). By conventional criteria, 21 subjects were hypertensive: on the basis of the clinical workup, the diagnosis was essential hypertension for each of them, and antihypertensive medication was discontinued at least 2 weeks before enrollment. Of the other study subjects, 13 were nonobese and normotensive. All obese subjects were normotensive; 5 hypertensive subjects had a BMI ≥27 kg · m⁻².

The protocol was approved by the Institutional Review Board. The purpose, nature, and risks involved in the study were explained to all the patients before obtaining their consent to participate.

**Echocardiography**

Echocardiography was performed with an HP Sonos 1000 system with a 2.5-MHz transducer. Echocardiograms were obtained with the subject resting in the left lateral position. Two-dimensional, guided M-mode measurements of left ventricular (LV) end-diastolic dimension, interventricular septum thickness, and posterior wall thickness were obtained along the LV short axis at the level of the chordae tendineae just beyond the mitral leaflet tips, as recommended. Every effort was made to obtain optimal echocardiographic images, with the M-mode cursor perpendicular to the LV long axis. LV mass (LVM) was calculated at the onset of the QRS complex (on a simultaneously recorded ECG with a continuous DII derivation) according to the Penn convention. An average of 2 cardiac cycles was used for data analysis. LVM was calculated according to Devereux et al. LVM was corrected for height to the 2.7 power (g · m⁻²), according to De Simone et al. Echocardiographic parameters were measured by consensus of 2 experienced cardiologists who were blinded to the metabolic data. Interobserver and intraobserver variation coefficients were 6% and 4%, respectively.

**Oral Glucose Tolerance Test**

After at least 3 days of a 250-g carbohydrate diet and after an overnight (10 to 12 hours) fast, glucose tolerance was assessed by a 2-hour, 75-g oral glucose tolerance test (OGTT). At baseline and at 30-minute intervals during the OGTT, blood samples were obtained for glucose and insulin determination.

**Insulin Sensitivity**

Insulin action was measured by the euglycemic clamp technique with an insulin infusion rate of 40 mU · min⁻¹ · m⁻² (280 pmol · min⁻¹ · m⁻²). Briefly, polyethylene cannulas were inserted into an antecubital vein (for the infusion of glucose and insulin), and, retrogradely, into a wrist vein heated at 60°C in a hot box (for intermittent sampling of arterialized venous blood). At time zero, a primed-constant infusion of regular insulin was begun and continued for 120 minutes. Four minutes into the insulin infusion, an exogenous glucose infusion was started and adjusted every 5 to 10 minutes to maintain plasma glucose within ±10% of its baseline value. Blood samples were obtained at timed intervals in the fasting state and during the clamp for the measurement of plasma glucose and insulin levels.

**Analytical Procedures**

Blood samples were kept in an ice bath, then centrifuged at 4°C. The plasma was aliquoted and stored at −20°C until assay. Plasma glucose concentration was immediately assayed by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments). Plasma insulin was measured by radioimmunoassay (INS-KIT, Sorin). Serum cholesterol, triglycerides, HDL cholesterol, and its subfractions were determined as described elsewhere.

**Data Analysis**

Insulin action was expressed as the whole-body glucose disposal during steady-state euglycemic hyperinsulinemia. With the insulin dose used in the current study, endogenous glucose output has been previously shown to be fully suppressed in old as well as young subjects. Therefore, glucose disposal (M value) was calculated from the exogenous glucose infusion rate during the last 60 minutes of the clamp after correction for changes in glucose concentration in a total distribution volume of 250 mL · kg⁻¹. Whole-body glucose disposal was normalized per kilogram of lean body mass (LBM), as
calculated by Hume’s formula in its sex-specific version. Fat mass was obtained as the difference between body weight and LBM.

The rate at which endogenous insulin is delivered to the systemic circulation after transhepatic passage (termed posthepatic insulin delivery rate) was obtained as the product of fasting systemic plasma insulin concentration and posthepatic insulin clearance rate. The latter was measured from the clamp experiment as the ratio of the exogenous insulin infusion rate to the plasma insulin concentration attained during the final 40 minutes of the clamp. The rationale for this measurement is that because of the fast metabolic clearance rate of insulin, a primed-constant infusion of exogenous hormone lasting for 120 minutes results in steady-state plasma insulin levels. Under these conditions, the ratio of infusion rate to steady-state plasma concentration equals the metabolic clearance rate of systemically administered insulin.

Statistical Analysis

For statistical analysis, insulin concentration, clearance rate, and posthepatic delivery rate values were log-transformed to normalize their distribution (normality was tested by the Shapiro-Wilk W test). Data are given as mean ± SD. Power analysis was carried out to compare independent dichotomous outcomes as well as to test slopes of simple linear regression lines. Group comparisons were carried out by Kruskall-Wallis test for continuous variables and by x2 test for proportions. Simple and multiple regression analyses were carried out by standard techniques.

### Results

Age, degree of obesity, and BP levels covered a wide range (Table 2). Likewise, metabolic parameters varied severalfold among study subjects: fasting (9-fold) and postglucose (6-fold) plasma insulin concentrations, insulin clearance (5-fold) and delivery rates (6- to 7-fold), and insulin sensitivity (4-fold) (Table 3). Power calculations indicated that at a level of α = 0.05, the present sample size (n = 50) had 90% power to detect a minimal difference in population means of 8 μmol · min⁻¹ · kg LBM⁻¹ in M value, that is, an 18% deviation from the mean value and one fifth the range of the whole study group. The corresponding minimal detectable difference for fasting plasma insulin concentration was 20 pmol/L.

In univariate analysis, insulin sensitivity was inversely related to indexes of body adiposity (BMI, fat mass, and percent fat mass; r = 0.25 to 0.35, P = 0.05 to 0.01) and to plasma insulin concentrations and delivery rates (r = 0.41 to 0.53, probability values all < 0.001), as expected.

LVM was normally distributed (W = 0.97, P = NS) (Table 4 and Figure 1) and was higher in obese and hypertensive individuals (50 ± 8 and 55 ± 10 g · m⁻², respectively) than in control subjects (40 ± 8 g · m⁻², P = 0.0004) (Figure 2). In univariate analysis, a larger LVM was significantly associated with older age (r = 0.41, P < 0.005), a larger glucose area-under-the-curve (r = 0.31, P = 0.03), and a higher systolic (r = 0.49, P < 0.001), diastolic (r = 0.30, P = 0.03), mean (r = 0.40, P = 0.004), and pulse BP (r = 0.50, P = 0.0002). LVM was only weakly related to BMI (r = 0.23, P = 0.1).

In contrast, LVM was not related to any insulin parameter, namely, insulin concentrations (fasting, any time point during

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**TABLE 3. Metabolic Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.2 ± 0.5</td>
<td>3.8–6.1</td>
<td>9</td>
</tr>
<tr>
<td>Fasting plasma insulin, pmol/L</td>
<td>63 ± 31</td>
<td>18–165</td>
<td>49</td>
</tr>
<tr>
<td>Glucose area, mol · L⁻¹ · 2 h</td>
<td>0.83 ± 0.15</td>
<td>0.54–1.11</td>
<td>19</td>
</tr>
<tr>
<td>Insulin area, mol · L⁻¹ · 2 h</td>
<td>36 ± 15</td>
<td>14–83</td>
<td>40</td>
</tr>
<tr>
<td>Steady-state plasma insulin, pmol/L</td>
<td>488 ± 160</td>
<td>198–938</td>
<td>33</td>
</tr>
<tr>
<td>Posthepatic insulin clearance, L · min⁻¹</td>
<td>1.06 ± 0.39</td>
<td>0.46–2.51</td>
<td>37</td>
</tr>
<tr>
<td>M value, μmol · min⁻¹ · kg LBM⁻¹</td>
<td>44 ± 13</td>
<td>17–68</td>
<td>30</td>
</tr>
<tr>
<td>Fasting insulin delivery, pmol/min</td>
<td>61 ± 25</td>
<td>24–142</td>
<td>41</td>
</tr>
<tr>
<td>Post-OGTT insulin delivery, pmol · 2 h</td>
<td>38 ± 21</td>
<td>17–122</td>
<td>50</td>
</tr>
</tbody>
</table>

%CV indicates percent coefficient of variation.
the OGTT, area under the OGTT curve), insulin clearance and delivery rates (fasting or postglucose), or insulin sensitivity (Figure 3). The latter result was unchanged when LVM was normalized by height or LBM or was used as the absolute value. This pattern of correlations was essentially unchanged when LVM was replaced by the interventricular septum or posterior wall thickness. Power analysis indicated that at a level of $\alpha = 0.05$, the present sample size ($n = 50$) had 70% power to detect an association between $M$ and LVM with a slope of $0.25$, or between fasting plasma insulin and LVM with a slope of $0.15$.

In a multiple regression model adjusting for age and sex, systolic BP ($P = 0.003$) and BMI ($P = 0.01$) were the only independent correlates of LVM, together explaining 33% of its observed variability. No statistically significant interaction between the independent variables tested was found. From the regression equation and by using the mean population data, the estimated effect of a BMI of 35 versus 25 kg · m$^{-2}$ and that of a systolic BP of 180 versus 140 mm Hg were calculated (Figure 4). With these values, hypertension had twice the impact of obesity on LVM, the two effects being additive.

**Discussion**

For the present study, we included nondiabetic subjects in whom the 2 main known risk factors for cardiac hypertrophy (obesity and hypertension) were segregated into distinct groups. In the whole group, LVM spanned an almost 3-fold range. The metabolic parameters, on the other hand, covered an even wider range despite the fact that by selection, all study subjects had normal glucose tolerance. Thus, in addition to comparing predefined groups, the data set was suitable for exploring associations between LVM and metabolic variables over a continuum, thereby avoiding potential biases caused by definitions.

Our results demonstrate that when accounting for body size and BP, insulin, as plasma level, secretion rate, or action, is not related to LVM (within the probability boundaries set by our sample size). The associations between age or the glucose area and LVM, emerging from univariate analysis, were lost...
in the multivariate analysis, suggesting that they were driven by each other or confounded by the main factors. Of the latter, BP (particularly, the systolic value) was a stronger correlate than obesity, both statistically and in terms of size of effect. In fact, we calculated that in a middle-aged subject with a BMI of 35 kg m\(^{-2}\) (=27 kg heavier than the norm), LVM is expected to be increased by 11% if BP is 140 mm Hg. In a middle-aged subject with a systolic BP of 180 mm Hg, (ie, 40 mm Hg higher than the norm), LVM is expected to be increased by 20% if body size is unchanged (BMI=25 kg \(\cdot\) m\(^{-2}\)). The effect of a combined increase in BMI and BP is additive (no statistically significant interaction) (Figure 4). Clearly, these estimates neglect associated circumstances, such as the duration of obesity and hypertension, which must play role of their own in increasing cardiac muscle work load. Nevertheless, they do establish that hypertension alone has a stronger impact on heart mass than obesity per se. By applying the definition of LV hypertrophy (LVH) suggested by De Simone et al \(^3\) (LVM \(>47\) g \(\cdot\) m\(^{-2}\) in women and \(>50\) g \(\cdot\) m\(^{-2}\) in men), LVH was present in 1 of 12 (8%) control subjects, 7 of 17 (41%) obese subjects, and 14 of 21 (67%) hypertensive subjects \((\chi^2=10.6, P=0.005)\). Our series, therefore, reproduced the high prevalence of LVH in obesity and the still higher prevalence in hypertension reported by others.\(^3\),\(^4\),\(^7\),\(^8\) Nevertheless, the \(M\) value averaged 41 \(\mu\)mol \(\cdot\) min\(^{-1}\) \(\cdot\) kg LBM\(^{-1}\) in subjects with LVH (mean LVM=60 g \(\cdot\) m\(^{-2}\)) and 45 \(\mu\)mol \(\cdot\) min\(^{-1}\) \(\cdot\) kg LBM\(^{-1}\) in subjects without LVH (mean LVM=42 g \(\cdot\) m\(^{-2}\)). Among the unmeasured nonhemodynamic factors are the presence of microalbuminuria (which in hypertensive patients clusters with LVH \(^9\)), the distribution, visceral versus peripheral, of excess body fat\(^2\),\(^3\),\(^\text{20,2}\),\(^\text{25,50}\) the activity of the renin-angiotensin-aldosterone and the adrenergic nervous systems,\(^8\) and genetic predisposition.\(^5\)

A number of studies have examined the relation between insulin and LVM with conflicting results (Table 1). Number and kind of patients studied (healthy, obese, hypertensive, diabetic, and combinations thereof), index measurement (fasting plasma insulin, plasma insulin at various times after a glucose load, intravenous glucose tolerance test, insulin clamp), and adjustment for confounders have been quite variable, probably contributing to the discrepant outcome. For example, in the report by Sasson et al\(^1\) only obese subjects were studied, and only insulin at time 90 minutes after intravenous glucose was found to correlate with LVM independent of BMI. The lack of a control group of lean individuals may have caused an underestimation of the influence of body size on LVM. By contrast, in a group of obese women also investigated with by intravenous glucose, Avignon et al\(^1\) found no relation of plasma insulin (or insulin sensitivity) to LVM independent of BMI, but arterial BP also failed to associate with LVM. Here, the lack of a control group of hypertensive individuals may have downplayed the impact of BP on LVM. In a recent study in hypertensive individuals,\(^3\) plasma insulin levels measured 2 hours after a glucose load but not fasting plasma insulin levels or indexes of insulin resistance were positively related to LVM but not to relative wall thickness. In the 3 previous studies\(^1\),\(^9\),\(^2\),\(^7\),\(^3\) that have used the insulin clamp technique to measure insulin sensitivity, only hypertensive patients were included. The relatively high prevalence of insulin resistance and the attendant hyperinsulinemia among obese, hypertensive, and diabetic patients\(^2\) makes it difficult to dissect their separate roles in cardiac hypertrophy compared with the effect of body size, BP, and hyperglycemia. Furthermore, even in otherwise healthy individuals, insulin resistance/hyperinsulinemia tend to aggregate with small, subclinical changes in BMI, BP, and glucose level.\(^3\) Because of this clustering, we adopted the conservative approach of examining associations multidimensionally, over wide ranges, and in a sufficiently large series of subjects. Moreover, we tested all possible insulin variables as well as interactions among them. Our results, while confirming expected associations (eg, insulin resistance and obesity), rule out a major effect of insulin per se on LVM. In a recent study by Takala et al\(^3\) LVM was measured in 8 endurance-trained (long-distance runners) and 8 resistance-trained (weight lifters) athletes, in whom insulin sensitivity was measured by the clamp technique. The results showed that cardiac hypertrophy was similar in the 2 groups (as compared with sedentary control subjects) despite the fact that whole-body insulin sensitivity was twice as high in endurance as in resistance-trained athletes or sedentary control subjects. The dissociation observed in these subjects is in full agreement with our results that hemodynamic factors dominate in the genesis of cardiac hypertrophy.

It should be emphasized that a biological effect of chronic hyperinsulinemia and/or insulin resistance on cardiac muscle growth and remodeling is fully plausible and may mediate, at least in part, the effect of body size and BP on LVM. Our analysis only shows that a separate influence of insulin beyond the measurable effects of obesity and hypertension does not emerge from in vivo data.

That the impact of insulin may be different in hyperglycemic individuals deserves further attention. Hyperglycemia per se can induce proliferation and hypertrophy of vascular smooth muscle cells, possibly through the activation of the phospholipase D and protein kinase C pathways,\(^3\) and a potential interference of insulin in these pathways remains possible.

References

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