Independent Association of Plasma Leptin Levels and Left Ventricular Isovolumic Relaxation in Uncomplicated Hypertension

Maurizio Galderisi, Maria Rosaria Tagliamonte, Arcangelo D’Errico, Carlo Carella, Gina Varricchio, Sergio Mondillo, Oreste de Divitiis, and Giuseppe Paolisso

**Background:** On the basis of evidence of plasma leptin (LE) effects on cardiovascular system, we assessed possible association of LE and Doppler-derived left ventricular (LV) diastolic function in arterial hypertension.

**Methods:** Doppler echocardiography, blood sample for fasting plasma LE levels, and euglycemic hyperinsulinemic glucose clamp were performed on 15 healthy insulin-sensitive men and 40 newly diagnosed hypertensive men, who were divided into two groups according to insulin sensitivity degree: 15 insulin sensitive (IS) and 25 insulin resistant (IR) individuals (whole body glucose disposal $>$33.3 and $<$33.3 μmol/kg, respectively).

**Results:** The IR hypertensives had significantly higher body mass index (BMI), waist/hip ratio, LE and LV mass index than the other two groups. IR hypertensives had lower LE (even after adjusting for BMI and waist/hip ratio) and among LV diastolic indexes, lower E peak velocity ($P < .05$) and longer isovolumic relaxation time (IVRT) ($P < .001$) in comparison to IR hypertensives. IR hypertensives had the lowest E/A ratio (0.88 ± 0.2) compared to IS patients (1.03 ± 0.1 $P < .05$) and controls (1.31 ± 10.2 $P < .001$). By multiple linear regression analyses performed both in the overall population and hypertensives, LV mass index and LE were independently associated to IVRT ($R^2 = 0.41$ in overall population, $R^2 = 0.42$ in hypertensives, both $P < .0001$), whereas age, heart rate, diastolic and systolic blood pressure (BP), BMI, waist/hip ratio, and insulin action were not significant.

**Conclusions:** Our study underscores an independent association of increased plasma LE and lengthening of isovolumic relaxation in uncomplicated hypertension. Further studies will need to understand the conditions underlying both these phenomena. Am J Hypertens 2001;14:1019–1024 © 2001 American Journal of Hypertension, Ltd.

**Key Words:** Leptin, insulin resistance, arterial hypertension, diastole, Doppler echocardiography.

Leptin (LE), the product of the ob gene, is a peptide hormone produced by adipose tissue and involved in body weight control, has been shown to increase in insulin-resistant conditions such as obesity and arterial hypertension. On the basis of evidence reporting heart rate (HR) and blood pressure (BP) increase after LE infusion, mainly due to stimulation of cardiac sympathetic nervous system, LE might also exert an influence on left ventricular (LV) structure and function. Our recent article has already reported an association between LE concentration and increased LV wall thickness in arterial hypertension, independent of insulin sensitivity and BP levels.

Left ventricular diastolic dysfunction is a frequent complication of arterial hypertension. It may precede but also determine alone (ie, without changes of LV systolic indexes) symptoms of heart failure. Because of its association with elevated BP values as well as with overweight, it is reasonable to suppose that LE might exert some effect on LV diastolic relaxation and filling, which are influenced by both afterload and preload changes.

In the present study, we investigated the hypothesis that plasma LE could be associated with LV diastolic dysfunction in arterial hypertension. Thus, we evaluated possible relationships between plasma LE levels and Doppler diastolic measurements in patients affected by uncomplicated arterial hypertension, with reference to BP levels and insulin sensitivity.

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Methods

Patients Selection

Forty consecutive male patients with newly diagnosed essential arterial hypertension and 15 healthy male subjects were considered eligible to participate in the study, after their informed consent and approval of the institutional ethics committee were obtained. Patients were considered hypertensive according to clinic BP (diastolic BP >90 mm Hg and systolic BP >140 mm Hg as mean of three different measurements in at least three different visits at 1-week intervals). Exclusion criteria from the study were the use of cardiac medications and drugs interfering with glucose metabolism, coronary artery disease, congestive heart failure and valvular heart disease, glucose intolerance, diabetes mellitus, family history of diabetes, and obesity. Patients with impaired glucose tolerance and diabetes mellitus were detected by an oral glucose tolerance test (75 g of glucose).11

On different days, patients underwent euglycemic hyperinsulinemic glucose clamp and Doppler echocardiography. According to the degree of insulin sensitivity, as determined by the euglycemic clamp, hypertensives were divided into two groups: 15 insulin sensitive, with a whole body glucose disposal (WBGD) >33.3 μmol/kg/min, and 25 insulin resistant, with a WBGD <33.3 μmol/kg. As previously described,12 cut-off point for lower WBGD was obtained from a reference group of 45 controls having a normal glucose tolerance test. These subjects had been categorized into WBGD quartiles derived from a glucose clamp measurement in which steady-state plasma glucose and insulin concentrations were comparable to those of the present study. The mean WBGD value for the lowest quartile (x = 33.3 μmol/kg/min) was chosen as the cut-off point for insulin resistance, this value being supported by previous reports.13

Procedures

Anthropometric Determinations

Body weight and height were measured and body mass index (BMI) was derived as weight/height squared (kg/m²). Body fat and fat free mass (FFM) were measured using a four terminal bioimpedance analyzer (RJL Spectrum Bioelectrical Impedance, BIA 101/SC Akern, RJL-System, Florence, Italy).14 Waist circumference was measured at midpoint between the lower rib margin and the iliac crest (normally umbilical level) and hip circumference at the trochanter level. Both circumferences were measured at the nearest 0.5 cm with plastic tape and the ratio between them provided the waist/hip ratio (WHR).

Metabolic Determinations

Euglycemic hyperinsulinemic glucose clamp15 was carried out. In this test a fixed insulin infusion rate (7.1 pmol/kg/min) for 120 min and a variable amount of glucose (as 20% solution) were delivered. The WBGD was calculated during the final 60 min of the clamp according to the formula:

\[ \text{WBGD} = \text{glucose infusion rate} + \text{pool correction}, \]

where the pool correction takes into account change in the whole body glucose pool, as estimated from plasma glucose concentration change.16 This correction was always <5% of the glucose infusion rate during the glucose clamp. This calculation is valid when no entry of glucose in plasma from the liver occurs. In nondiabetic17 and hypertensive patients,18 hepatic glucose output has been found fully suppressed during a glucose clamp at this insulin infusion rate. Furthermore, in preliminary clamps an insulin infusion rate of 7.1 pmol/kg/min fully suppressed (but without negative numbers) hepatic glucose output.

Analytical Methods

Plasma glucose was determined by the plasma glucose method (Beckman, Autoanalyzer, Fullerton, CA). Blood samples for insulin measurements were collected in heparinized tubes. After centrifugation serum insulin was determined by commercially available RIA kit (Sorin, Biomedical, Milan, Italy; c.v. = 3.2 ± 0.3%). At baseline and at the end of the glucose clamp blood samples for plasma LE were drawn and LE concentration determined by radioimmunooassay (Linco Research, St. Louis, MO; c.v. = 4.3 ± 0.5%).

Doppler Echocardiographic Determinations

The examinations were performed according to the standard methods by a Sector Imager 5000 (OTE-Biomedica, Florence, Italy) equipped with a 2.5-MHz transducer and recorded on super VHS videotapes and strip-chart paper (velocity of 50 to 100 mm/sec). The HR and cuff BP (mean of three measurements by a mercury sphygmomanometer) were estimated at the end of the study by a physician blinded with respect to metabolic and echocardiographic determinations. Consecutively coded, Doppler echocardiographic tracings were examined by two readers, unaware of BP values, using the average of at least three cardiac cycles. M-mode analysis was performed according to the American Society of Echocardiography.19 The LV mass was calculated by the Penn convention20 and indexed for body height21 (LV mass index = LVMI). Relative diastolic wall thickness was determined by the sum of posterior and septal wall thicknesses divided by LV internal diastolic dimension, fractional shortening calculated as percentage of change in LV internal dimension between systole and diastole. Our methods and reproducibility of Doppler diastolic indexes was previously reported.12 E and A peak velocities (m/sec) and E/A ratio, atrial filling fraction (= time velocity integral of A wave/time velocity integral of total diastole × 100), and E wave deceleration time (DT) (msec) were measured as indexes of LV filling, and isovolumic relaxation time (IVRT) (msec) (between the end of systolic output flow and transmitral E wave onset, by placing sample volume between outflow and inflow tracts) as an index of LV active diastolic relaxation.
Table 1. Clinical and metabolic characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Control Group (n = 15)</th>
<th>Insulin-Sensitive Hypertensives (n = 15)</th>
<th>Insulin-Resistant Hypertensives (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>43 ± 10.4</td>
<td>45.7 ± 7.7</td>
<td>46.1 ± 7.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.8 ± 8.6</td>
<td>71.9 ± 9.9</td>
<td>71.0 ± 9.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129 ± 5</td>
<td>135.4 ± 15.8†</td>
<td>129.3 ± 10.2¶</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78 ± 5</td>
<td>99.4 ± 4.0**</td>
<td>102.4 ± 7.6§</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 1.2</td>
<td>25.9 ± 2.3</td>
<td>28.0 ± 3.0</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 ± 0.04</td>
<td>0.90 ± 0.03</td>
<td>0.92 ± 0.04</td>
</tr>
<tr>
<td>2h plasma glucose (mmol/L)</td>
<td>4.8 ± 0.16</td>
<td>4.6 ± 0.56</td>
<td>4.8 ± 0.4</td>
</tr>
<tr>
<td>FP glucose (mmol/L)</td>
<td>72.1 ± 2.3</td>
<td>75.6 ± 5.9</td>
<td>76.5 ± 4.3‡</td>
</tr>
<tr>
<td>FP insulin (pmol/L)</td>
<td>5.6 ± 0.4</td>
<td>6.7 ± 0.5</td>
<td>6.8 ± 0.5</td>
</tr>
<tr>
<td>WBGD (µmol/kg FFM × min)</td>
<td>38.5 ± 2.5</td>
<td>33.7 ± 6.3††</td>
<td>26.6 ± 6.2‡‖</td>
</tr>
<tr>
<td>FP total cholesterol (mmol/L)</td>
<td>5.0 ± 0.6</td>
<td>5.2 ± 0.9</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>FP tryglycerides (mmol/L)</td>
<td>1.01 ± 0.03</td>
<td>1.02 ± 0.05</td>
<td>1.08 ± 0.04‡#</td>
</tr>
<tr>
<td>FP leptin (ng/mL)</td>
<td>4.6 ± 1.5</td>
<td>4.6 ± 2.3</td>
<td>7.4 ± 2.9*§</td>
</tr>
</tbody>
</table>

BP = blood pressure; BMI = body mass index; WHR = waist/hip ratio; FP = fasting plasma; WBGD = whole body glucose disposal; FFM = fat free mass.

All results are mean ± SD.

* P < .001, † P < .01, and †† P < .05 insulin-resistant v insulin-sensitive hypertensives.

§ P < .0001, ¶ P < .001, and # P < .05 insulin-resistant hypertensives v control group.

** P < .0001, ‡‡ P < .001 insulin-sensitive hypertensives v control group.

Statistical Analysis

All analyses were performed by SPSS/PC for Windows release 6.0 statistical package (Chicago, IL). To approximate a normal distribution, plasma insulin and tryglycerides were log-transformed in all calculation and then back-transformed for results presentation. Analyses of variance (ANOVA) by Scheffe post-hoc test for multiple comparisons were performed to estimate intergroup differences. Linear regression analyses and partial correlation test using Pearson’s method were used to assess univariate relations. Multiple regression analyses were used to weight independent contribution of each covariate to IVRT change. A P value < .05 was considered statistically significant.

Results

Characteristics of the Study Population

Clinical and metabolic characteristics are reported in Table 1. The three groups were comparable for age and HR, with a prevalent central body fat distribution. Insulin-resistant hypertensives had significantly higher BMI and WHR, as well as higher fasting plasma tryglycerides and LE levels in comparison with both controls and insulin-sensitive hypertensives. The LE was higher in insulin-resistant than in insulin-sensitive hypertensives, even after adjusting for BMI and WHR (3.76 ± 1.97 ng/mL v 6.39 ± 2.5 ng/mL, P < .001).

Doppler Echocardiographic Analysis

M-mode and Doppler analyses are reported in Table 2. The LVMI was higher in insulin-resistant than in insulin-sensitive hypertensives (P < .01). Among Doppler-derived diastolic indexes, both E peak velocity and E/A ratio were lower (P < .05), and IVRT longer (P < .001) in insulin-resistant hypertensives than in hypertensives with normal insulin sensitivity.

Relationships of IVRT With Demographic, Echocardiographic, and Metabolic Variables

Univariate correlations between IVRT and demographic, metabolic, and echocardiographic variables in the overall population and, separately, in controls and hypertensive patients are summarized in Table 3. The IVRT had positive correlations with BMI, WHR, LVMI, and LE, whereas inverse relations were found with WBGD and HR. The relation of LE and IVRT, after adjusting for BMI and WHR, is shown in Fig. 1.

Two multiple linear regression analyses were performed separately in the overall population as in hypertensives to weigh the independent effect of variables having univariate relations with IVRT. In the first models including age, HR, diastolic and systolic BP, BMI, WHR, WBGD, and LVMI as potential determinants, LVMI (β coefficient = 0.45, P < .001 in the overall population, β = 0.48, P < .0005 in hypertensives), WBGD (β = −0.30, P < .01 and β = −0.37, P < .005, respectively) and, only in the overall population, HR (β = −0.21, P < .05) were independently associated to IVRT (cumulative R² = 0.41 SE = 8.3 msec, P < .0001 in the overall population, cumulative R² = 0.41, SE = 8.7 msec, P < .00001 in hypertensives). In the second models, including also LE, LVMI (β = 0.42, P < .001 in the overall population, β = 0.40, P < .005 in hypertensives) and LE (β = 0.35 and β = 0.39, respectively, both P < .005) were independently associated to IVRT (cumulative R² = 0.41, SE = 8.4
LV end-diastolic diameter (mm) 50.5
LV end-systolic diameter (mm) 34.5
Fractional shortening (%) 31.7
Relative diastolic wall thickness 0.34
E peak velocity (m/sec) 0.63
A peak velocity (m/sec) 0.48
Peak velocity E/A ratio 1.31
Deceleration time (msec) 145.6
Atrial filling fraction (%) 25.0
IVRT (msec) 71.5
Posterior wall thickness (mm) 7.9
Septal wall thickness (mm) 9.4
LVMI

LVMI – left ventricular mass index; NS – not significant; other abbreviations as in Tables 1 and 2.

Table 2. Doppler echocardiographic analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Control Group</th>
<th>Insulin-Sensitive Hypertensives</th>
<th>Insulin-Resistant Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal wall thickness (mm)</td>
<td>9.4 ± 1.1</td>
<td>10.2 ± 1.0</td>
<td>11.7 ± 1.4†§</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>7.9 ± 1.1</td>
<td>9.4 ± 1.4††</td>
<td>10.5 ± 1.5†§</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>50.5 ± 2.2</td>
<td>49.5 ± 5.1</td>
<td>50.3 ± 4.5</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>34.5 ± 1.8</td>
<td>34.5 ± 4.2</td>
<td>35.0 ± 3.9</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>31.7 ± 3.0</td>
<td>30.2 ± 2.9</td>
<td>30.4 ± 4.1</td>
</tr>
<tr>
<td>Relative diastolic wall thickness</td>
<td>0.34 ± 0.04</td>
<td>0.40 ± 0.07§§</td>
<td>0.45 ± 0.08§§</td>
</tr>
<tr>
<td>LV mass index (kg/m)</td>
<td>99.7 ± 14.3</td>
<td>108.0 ± 22.6</td>
<td>135.8 ± 24.8*§</td>
</tr>
<tr>
<td>E peak velocity (m/sec)</td>
<td>0.63 ± 0.12</td>
<td>0.60 ± 0.09</td>
<td>0.52 ± 0.12*¶</td>
</tr>
<tr>
<td>A peak velocity (m/sec)</td>
<td>0.48 ± 0.05</td>
<td>0.58 ± 0.07††</td>
<td>0.59 ± 0.10</td>
</tr>
<tr>
<td>Peak velocity E/A ratio</td>
<td>1.31 ± 0.2</td>
<td>1.03 ± 0.1**</td>
<td>0.88 ± 0.2§§</td>
</tr>
<tr>
<td>Atrial filling fraction (%)</td>
<td>25.0 ± 5.8</td>
<td>32.3 ± 6.3††</td>
<td>34.7 ± 4.9§</td>
</tr>
<tr>
<td>Deceleration time (msec)</td>
<td>145.6 ± 15.6</td>
<td>149.3 ± 25.1</td>
<td>161.6 ± 25.2#</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>71.5 ± 8.7</td>
<td>71.7 ± 8.6</td>
<td>82.7 ± 10.5*</td>
</tr>
</tbody>
</table>

LV = left ventricular; IVRT = isovolumic relaxation time.
All results are mean ± SD.
* P < .001, † P < .01, and ‡ P < .05 insulin-resistant v insulin-sensitive hypertensives.
§ P < .0001, || P < .001, †† P < .01, and # P < .05 insulin-resistant hypertensives v control group.
** P < .0001, ††† P < .001, ‡‡ P < .01, and §§ P < .05 insulin-sensitive hypertensives v control group.

msec, P < .0001 in the overall population, R² = 0.42, SE = 8.8 msec, P < .00001 in hypertensives). After controlling for the effect of LVMI and LE, partial relation coefficients of HR, diastolic and systolic BP, BMI, WHR, and WBGD were not significant.

Discussion

The most significant findings of the present study are that in arterial hypertension 1) both increased fasting plasma LE concentrations and impaired isovolumic diastolic relaxation are evident in the presence of insulin resistance, and 2) LE is an independent predictor of the relation between insulin resistance and isovolumic relaxation.

Insulin Resistance, LE Levels and IVRT Delay

Left ventricular diastolic dysfunction is often evident in conditions with insulin resistance conditions, as well as arterial hypertension and obesity. We have recently observed an association between WBGD and IVRT in hypertensives, independent of BP and LV mass levels. In the present study, insulin-resistant hypertensives presented

Table 3. Univariate correlations of IVRT with main demographic, metabolic, and echocardiographic variables in the study population

<table>
<thead>
<tr>
<th>Correlate</th>
<th>All (n = 55)</th>
<th>Controls (n = 15)</th>
<th>Hypertensives (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>r = 0.16</td>
<td>r = 0.26</td>
<td>r = 0.13</td>
</tr>
<tr>
<td>Heart rate</td>
<td>r = -0.40</td>
<td>r = -0.81</td>
<td>r = -0.28</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>r = 0.19</td>
<td>r = 0.17</td>
<td>r = 0.20</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>r = 0.42</td>
<td>r = 0.22</td>
<td>r = 0.43</td>
</tr>
<tr>
<td>BMI</td>
<td>r = 0.43</td>
<td>r = 0.54</td>
<td>r = 0.36</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>r = 0.47</td>
<td>r = 0.11</td>
<td>r = 0.44</td>
</tr>
<tr>
<td>LVMI</td>
<td>r = 0.58</td>
<td>r = 0.53</td>
<td>r = 0.53</td>
</tr>
<tr>
<td>WBGD</td>
<td>r = -0.56</td>
<td>r = -0.43</td>
<td>r = -0.52</td>
</tr>
<tr>
<td>Fasting plasma leptin</td>
<td>r = 0.54</td>
<td>r = 0.21</td>
<td>r = 0.51</td>
</tr>
</tbody>
</table>

LVMI = left ventricular mass index; NS = not significant; other abbreviations as in Tables 1 and 2.
mild changes in LV diastolic filling, as both E peak velocity and E/A ratio were marginally lower in comparison with the other two groups. Isovolumic relaxation time, however, was markedly longer in comparison with both insulin-sensitive hypertensives and controls. Isovolumic relaxation time is a reliable marker of isovolumic relaxation; that is, the active diastolic phase preceding LV filling and developing at a constant LV volume when both aortic and mitral valve are closed. Of note, insulin-resistant hypertensives had also higher LE than controls. Although this result is not surprising as our insulin-resistant patients also had higher BMI and WHR than the other two groups and obesity is a recognized determinant of increased LE. The levels of LE in the present study remained significantly higher in insulin-resistant hypertensives, even after adjusting for BMI and WHR. Nevertheless, one should point out that the correlation between IVRT and LE was quite weak and has some gray zone, thus indicating that some other factors may be responsible for such a relationship.

**Association of Insulin Action and LE Levels With IVRT**

Univariate relation of IVRT with clinic, echocardiographic, and metabolic variables were tested in an overall study population and, separately, in controls and hypertensives. The lack of relation with age has to be considered in view of the narrow age range of our population, whereas the association of IVRT with BP, BMI, and with HR might be expected. All of these associations were positive, except for HR, which was negative. Shortening of IVRT is usually appreciated in patients with high LV end-diastolic pressure, but in this case, it depends mainly on the cardiac cycle shortening occurring parallel to increasing HR. Among metabolic parameters, IVRT was related positively to WBGD as well as to LE; this last association being significant even after adjusting for BMI and WHR.

Multivariate models provided additional information. According to our report, the first model underscored the independent association of both insulin resistance and LVMI with IVRT in the overall population as well as in hypertensives. The second model, however, evidenced the independent association between fasting LE and IVRT, whereas the effect of WBGD disappeared, thus pointing out how the association between insulin resistance and isovolumic relaxation might be mediated by plasma LE levels. To the best of our knowledge, this is the first study to give evidence about a relationship between plasma LE and LV diastolic relaxation in arterial hypertension. Leptin increases sympathetic nervous activity in animal models and a direct relation between muscle sympathetic nerve activity and plasma LE has been reported. Although controversy exists about this issue, sympathetic overdrive may be a determinant of LV diastolic dysfunction, including impairment of isovolumic relaxation. Alternatively, LE could affect directly isovolumic relaxation, which is a calcium ion energy-dependent phenomenon. The impairment of isovolumic relaxation is due to calcium reuptake abnormalities by sarcoplasmic reticulum when diastolic dysfunction is associated to LV hypertrophy and LE effects on intracellular calcium concentrations have been shown. Finally, because the independent co-variate of IVRT other than LE was LVMI and we have...
already shown an important association between LE levels and increased myocardial wall thickness (ie, an index of myocardial hypertrophy). LE levels increase and changes of both LV structure and diastolic function may be an expression of the underlying insulin resistance condition. An association between the degree of insulin sensitivity and IVRT length has been reported in arterial hypertension.

In conclusion, our study underscores how increased fasting plasma LE levels are associated with prolongation of isovolumic relaxation in arterial hypertension, independent of the influence exerted by obesity, LV hypertrophy, and insulin sensitivity. Whatever the interpretation of these findings, they confirm the important link existing between metabolic changes and cardiac abnormalities occurring in arterial hypertension.

References