Insulin and Diastolic Dysfunction in Lean and Obese Hypertensives

Genetic Influence

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Abstract—We investigated the influence of genetic predisposition to hypertension by studying the relation between insulin sensitivity and left ventricular (LV) mass and function in untreated lean and obese hypertensives. We selected 50 lean hypertensives with normotensive parents (negative family history of hypertension [F−]), 64 lean hypertensives with 1 or both parents hypertensive (positive family history of hypertension [F+]), 40 obese F− hypertensives, and 43 obese F+ hypertensives. The 4 groups were comparable regarding age, gender, 24-hour blood pressure profile, and known duration of hypertension. We measured glucose, insulin, and C-peptide during fasting and during an oral glucose tolerance test; LV morphology and function were assessed by digitized M-mode echocardiography. Glucose (fasting and test) levels were normal in all and similar among the 4 groups. Insulin and C-peptide (fasting and stimulated) levels were higher in obese hypertensives than in lean hypertensives; at similar body mass index, insulin and C-peptide levels were higher in F+ than in F− groups. Compared with lean hypertensives, obese hypertensives had greater LV mass index; LV systolic function was normal in all and similar among the groups. The indices of LV diastolic function were significantly lower in F+ than in F− groups. LV mass index did not correlate with metabolic parameters; the indices of LV diastolic function were inversely correlated with insulin area during test in only the 2 F+ groups. In conclusion, genetic predisposition to hypertension is associated with a reduced insulin sensitivity and affects the response of the myocardium to increased insulin levels, inducing a greater impairment of diastolic function. Insulin sensitivity and genetic predisposition to hypertension seem to have no influence on LV mass. (Hypertension. 1999;34:1208-1214.)

Key Words: insulin • diastole • hypertension, essential • obesity • hypertrophy

Essential hypertension and obesity are often associated, and each one, per se, can induce myocardial hypertrophy and left ventricular (LV) diastolic dysfunction. Insulin resistance and hyperinsulinemia have been described in both hypertension and obesity. In experimental studies, insulin has been demonstrated to exert a growth-stimulating effect on cardiomyocytes and to increase collagen production in fibroblasts; therefore, clinical studies have evaluated the possible contribution of insulin resistance and hyperinsulinemia to the development of myocardial hypertrophy and diastolic dysfunction in hypertension and in obesity and have obtained conflicting results. Recently, it has been suggested that genetic factors play an important role in the link between insulin resistance, hypertension, and obesity. In fact, a reduced insulin sensitivity has been demonstrated in lean and obese normotensives and hypertensives with hypertensive parents (positive family history of hypertension [F+]) compared with offspring of normotensive parents (negative family history of hypertension [F−]). Moreover, genetic predisposition to hypertension seems to influence the modulation of blood pressure (BP) in response to insulin. Therefore, we considered it of interest to evaluate whether genetic predisposition to hypertension can also influence the relation between insulin sensitivity and LV mass and function. We studied lean and obese untreated hypertensives in F+ and F− groups; we evaluated 24-hour BP profile, insulin sensitivity (by means of glucose, insulin, and C-peptide response to an oral glucose load), and LV mass and function (by digitized M-mode echocardiography).

Methods

Patients

We selected hypertensive patients between 35 and 45 years of age, lean (body mass index [BMI] ≤25 kg/m²) or obese (BMI ≥30 kg/m²), with upper body obesity: waist/hip ratio >0.92 [men] and >0.82 [women], with fasting plasma glucose <5.6 mmol/L and without family history of diabetes mellitus. Arterial BP was evaluated on the basis of at least 3 measurements by sphygmomanometer, taken on different days. We selected subjects with BP >160 (systolic) and/or >95 (diastolic) mm Hg. Subsequently, each patient underwent a 24-hour noninvasive ambulatory BP monitoring, and patients with
mean 24-hour BP $>$ 140 (systolic) and/or $>$ 90 (diastolic) mm Hg were enrolled for the study. A basic criterion of selection was the opportunity to directly assess family history of hypertension on the basis of parents' histories and BPs. F− was established when both parents were living and had BP $<$ 140/90 mm Hg; F+ was established when at least 1 parent was living and had BP $>$ 160/95 mm Hg or 1 or both parents had a history of chronic antihypertensive treatment. Parental BP was measured by sphygmomanometer 3 times in different days by one of the investigators. Other criteria of selection were as follows: LV M-mode echocardiogram of good quality; no clinical, ECG, or echocardiographic evidence of heart failure, myocardial infarction, angina pectoris, or congenital or valvular heart diseases; no previous regular antihypertensive treatment or withdrawal from therapy at least 6 weeks before the study; and no systemic diseases, such as connective tissue disorders, which, per se, could induce changes in LV structure and function. Following these criteria, we selected 197 hypertensive patients and grouped them as follows: LHF−, 50 lean hypertensives (31 men) with both parents normotensive; LHF+, 64 lean hypertensives (39 men) with 1 (42 patients) or both (22 patients) parents hypertensive; OHF−, 40 obese hypertensives (25 men) with both parents normotensive; and OHF+, 43 obese hypertensives (26 men) with 1 (28 patients) or both (15 patients) parents hypertensive.

Of the 197 patients, 138 had been already included, with respect to 24-hour BP profile and metabolic parameters, in 2 previous studies.44-46 Involvement of the influence of genetic predisposition to hypertension on insulin sensitivity in hypertensive subjects. The patients were judged to have essential hypertension on the basis of history, physical examination, and laboratory findings. Among the patients selected, 30 LHF− (60%), 38 LHF+ (59%), 25 OHF− (62%), and 27 OHF+ (63%) had never been regularly treated with antihypertensive drugs; 11 LHF− (22%), 15 LHF+ (23%), 10 OHF− (25%), and 9 OHF+ (21%) had been on regular medication with angiotensin-converting enzyme inhibitors; 7 LHF− (14%), 8 LHF+ (12.5%), 5 OHF− (12.5%), and 5 OHF+ (11.6%) had been treated with calcium antagonists; and 2 LHF− (4%), 3 LHF+ (4.7%), and 2 OHF+ (4.6%) had been treated with β-blockers. Mean duration of therapy was 8 ± 3 months, and drugs failed to control BP in 46 patients; we do not have reliable information regarding BP control during therapy in the remaining 31 patients. Antihypertensive treatment was discontinued at least 6 weeks before the study in all the 77 patients; mean duration of drug withdrawal before the study was 11 ± 5 weeks. Of the 197 patients, 112 were nonsmokers, and 85 smoked < 10 cigarettes per day; alcohol intake overall was < 30 g per day. No subject was involved in regular and sustained physical activity, and no subject had had changes in body weight or dietary habits for at least 4 months before the study. The study was approved by the Ethical Committee of the Department of Clinical and Biological Sciences, and all the subjects gave their informed consent.

### Oral Glucose Tolerance Test

Two or 3 days after the 24-hour ambulatory BP monitoring, each subject underwent, at 8:00 AM after an overnight fast, a 75 g oral glucose tolerance test (OGTT). Plasma glucose (G), serum insulin (I), and C-peptide were determined before and 30, 60, 90, and 120 minutes after the glucose load. The values obtained during OGTT have been expressed as area under the curve (AUC), measured by the trapezoidal rule. Using insulin and glucose values at the glucose peak (subscript p), we calculated an index of peripheral insulin activity (Ia) based on the following formula: $Ia = \frac{10^4 / g}{1 / L_c}$.28 We also evaluated the fasting insulin/C-peptide ratio as an index of hepatic insulin clearance. Serum insulin was measured by an antibody method with a solid-phase $^{125}$ I radioimmunoassay (Coat-A-Count Insulin, Diagnostic Products Corp), as was the C-peptide (Biodata). The method for insulin measurement has a sensitivity of 6.6 pmol/L and a coefficient of variation of 7.1% at insulin values of 6 to 240 pmol/L. For C-peptide determination, the method has a sensitivity of 0.03 nmol/L and a coefficient of variation of 3.5% at C-peptide values of 0.16 to 1.76 nmol/L.

### Echocardiographic Examination

Immediately after the 24-hour BP monitoring, each subject underwent an echocardiographic examination that was performed by use of a Hewlett-Packard Sonos 1500 with a 2.0/2.5-MHz transducer. LV M-mode echocardiograms were recorded under 2-dimensional control, at a paper speed of 100 mm/s, with a simultaneous ECG. The M-mode tracings were blindly evaluated by a single operator who digitized 4 consecutive cardiac cycles of each echocardiogram, as originally described by Upton and Gibson,26 by use of a Numosonic 2205 graphic tablet. An IBM personal computer processed digitized data, averaging the 4 cardiac cycles. We evaluated LV end-diastolic diameter, end-diastolic thickness of interventricular septum and posterior wall, LV mass,26 peak shortening rate and peak lengthening rate of LV diameter, and peak thinning rate of LV posterior wall. LV mass was normalized for height to the 2.7 power, and LV diastolic diameter was normalized for height to the first power, because we wanted to take into account the influence of obesity on cardiac anatomy, an influence that is partly overlooked when indexing for body surface area.31

The normal limits of the parameters in our laboratory have been derived from the evaluation of 200 normal adults. The reproducibility of the echocardiographic measurements has been tested on 20 normal subjects (each examined 3 times by the same ultrasonic technique); the same operator digitized 4 consecutive cardiac cycles of each echocardiogram. The coefficients of variation were as follows: LV end-diastolic diameter 0.4%, septal thickness 3.2%, posterior wall thickness 3.4%, peak shortening rate 1.1%, peak lengthening rate 4.7%, and peak thinning rate 7.3%.

Mitrail inflow velocities were evaluated by pulsed-wave Doppler, with the sample volume placed at the tips of mitral leaflets, from the apical 4-chamber view. Using the average of 5 beats for the analysis, we measured the ratio between peak early transmural flow velocity and peak late transmural flow velocity (E/A ratio) and the deceleration time of early transmural flow velocity (time from peak early transmural flow velocity to the time when E-wave descent interrupted the zero line).

### 24-Hour Ambulatory BP Monitoring

Noninvasive ambulatory BP monitoring was performed with a portable automated Takeda TM 2421, and a simultaneous 24-hour heart rate monitoring was obtained. The unit was set to take readings every 15 minutes throughout the 24 hours. The following parameters have been evaluated: mean 24-hour daytime (from 7 AM to 10 PM) and nighttime (from 10 PM to 7 AM) systolic and diastolic BP, and heart rate, along with the percent overnight drop in systolic and diastolic BP.

### Statistical Analysis

Data are expressed as mean ± SD. Comparisons of lean and obese hypertensives and of offspring of hypertensive parents and offspring of normotensive parents were made by means of 2-factor ANOVA followed by Scheffé tests. The Pearson linear correlation coefficient was used to evaluate linear correlations between variables. Multiple regression analyses were performed to identify independent predictors of LV mass and LV diastolic function by a stepwise procedure, with, as dependent variables, respectively, LV mass index and peak lengthening rate of LV diameter; we used the following as independent variables: BMI, age, 24-hour systolic and diastolic BP, 24-hour heart rate, fasting glucose, fasting insulin, G-AUC, I-AUC, Ia, and predisposition to hypertension (as a dummy variable by assigning 1 to F+ and 2 to F−); LV mass index was added as independent variable in the analysis for diastolic function. All the variables were normally distributed, and the variances were homogeneous across the groups. A value of $P < 0.05$ was considered statistically significant.

### Results

**Metabolic Parameters**

Descriptive statistics for the subject groups are provided in Table 1. The 4 groups were not significantly different (Table
1) regarding age, gender, heart rate, 24-hour BP profile, and known duration of hypertension (LHF− 2.4±1.6 years, LHF+ 2.3±1.9 years, OHF− 2.5±1.7 years, and OHF+ 2.4±1.7 years); BMI was not different between LHF− and LHF+ or between OHF− and OHF+. The waist/hip ratio was similar between OHF− (0.94±0.06) and OHF+ (0.93±0.04). There were also no differences in smoking habits (there were 23 LHF−, 27 LHF+, 16 OHF−, and 19 OHF+ smokers) or alcohol consumption. Glucose (fasting and during OGTT) was normal in all the subjects and not significantly different among the 4 groups, as was the fasting insulin/C-peptide ratio (Table 2). From 2-factor ANOVA (Table 2), main effects were observed for obesity status and for genetic predisposition to hypertension on insulin and C-peptide (both fasting and stimulated) and on Ia: insulin and C-peptide (fasting and stimulated) were higher and Ia was lower in obese individuals than in lean subjects and in F+ groups than in F− groups.

### LV Anatomy and Function

LV anatomy and function are shown in Table 3. LV end-diastolic diameter was normal (<56 mm) in all the patients; LV hypertrophy (LV mass index >50 g/m² in men and >47 g/m² in women), which was due to increased (>11 mm) septal and posterior wall thickness, was found in 14 LHF− (28%), 19 LHF+ (29.7%), 15 OHF− (37.5%), and 18 OHF+ (42%). A significant effect was observed for obesity on LV end-diastolic diameter and LV mass index; both were greater in obese than in lean subjects, whereas no interaction was found between genetic predisposition to hypertension and LV anatomy. For LV function, the peak shortening rate of LV diameter, an index of systolic function, was normal (>1.9 s⁻¹) in all patients and not significantly different among the 4 groups. LV diastolic function was impaired (peak lengthening rate of LV diameter <3.6 s⁻¹ and/or peak wall thinning rate of LV posterior wall <8.4 cm/s) in 17 LHF− (34%), 23 LHF+ (36%), 16 OHF− (40%), and 22 OHF+ (51%).

### Table 1. Values of BMI, Age, SBP, DBP, and HR in LHF−, LHF+, OHF−, and OHF−

<table>
<thead>
<tr>
<th>Baseline Data</th>
<th>LHF−</th>
<th>LHF+</th>
<th>OHF−</th>
<th>OHF+</th>
<th>L/O</th>
<th>F−/F+</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>23.5±1.3</td>
<td>23.6±1.1</td>
<td>32.3±1.8</td>
<td>32.5±1.9</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>41±2</td>
<td>40±3</td>
<td>42±2</td>
<td>41±3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (24-h), mm Hg</td>
<td>146±14</td>
<td>148±17</td>
<td>145±16</td>
<td>149±14</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (24-h), mm Hg</td>
<td>92±6</td>
<td>94±7</td>
<td>92±7</td>
<td>93±8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (day), mm Hg</td>
<td>154±15</td>
<td>153±14</td>
<td>151±16</td>
<td>154±15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (day), mm Hg</td>
<td>95±9</td>
<td>96±7</td>
<td>95±8</td>
<td>97±9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (night), mm Hg</td>
<td>135±14</td>
<td>136±17</td>
<td>133±16</td>
<td>134±14</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (night), mm Hg</td>
<td>82±9</td>
<td>81±11</td>
<td>83±8</td>
<td>83±10</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, % fall</td>
<td>12.2±7.8</td>
<td>11.4±8.5</td>
<td>11.7±8.4</td>
<td>12.4±7.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, % fall</td>
<td>13.4±6.8</td>
<td>12.3±7.9</td>
<td>12.4±9.1</td>
<td>13.8±8.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HR (24-h), bpm</td>
<td>73±12</td>
<td>76±15</td>
<td>72±13</td>
<td>71±15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HR (day), bpm</td>
<td>78±16</td>
<td>82±18</td>
<td>80±15</td>
<td>83±13</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HR (night, bpm)</td>
<td>67±7</td>
<td>65±9</td>
<td>68±9</td>
<td>65±10</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. L/O indicates lean vs obese; F−/F+, F− vs F+; SBP and DBP, systolic and diastolic BP, respectively; HR, heart rate; and NS, not significant.

### Table 2. Values of Glucose, Insulin, and C-Peptide During Fasting and During OGTT and of Ia and I/Cp in LHF−, LHF+, OHF−, and OHF−

<table>
<thead>
<tr>
<th>Metabolic Data</th>
<th>LHF−</th>
<th>LHF+</th>
<th>OHF−</th>
<th>OHF+</th>
<th>L/O</th>
<th>F−/F+</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-f, mmol/L</td>
<td>4.5±0.7</td>
<td>4.7±0.6</td>
<td>4.6±0.7</td>
<td>4.8±0.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>G-AUC</td>
<td>27.3±5.4</td>
<td>28.7±5.3</td>
<td>26.8±5.7</td>
<td>27.9±5.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>I-f, pmol/L</td>
<td>44.4±25.2</td>
<td>63.3±24.9</td>
<td>81±35.4</td>
<td>157.2±40.8†</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>I-AUC</td>
<td>912±360</td>
<td>1170±510*</td>
<td>1462±420†</td>
<td>1830±456‡</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cp-f, mmol/L</td>
<td>0.51±0.26</td>
<td>0.71±0.33*</td>
<td>0.94±0.47†</td>
<td>1.51±0.61‡</td>
<td>0.0005</td>
<td>0.0008</td>
</tr>
<tr>
<td>Cp-AUC</td>
<td>6.82±1.68</td>
<td>8.78±1.89*</td>
<td>9.97±1.65†</td>
<td>11.65±2.02‡</td>
<td>0.0007</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ia</td>
<td>5.3±1.2</td>
<td>4.2±1.3*</td>
<td>3.3±1.5†</td>
<td>2.7±1.1‡</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>I/Cp</td>
<td>89.3±28.5</td>
<td>85.4±24.3</td>
<td>84.8±36.5</td>
<td>92.3±31.7</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. G indicates glucose; I, insulin; Cp, C-peptide; and f, fasting data. *0.01<P<0.001 LHF+ vs LHF−; †0.01<P<0.001 OHF− vs LHF−, and ‡P<0.001 OHF+ vs OHF− by Scheffé test.
Table 3. Values of Echocardiographic Parameters in LHF−, LHF+, OHF−, and OHF+

<table>
<thead>
<tr>
<th>Echocardiographic Data</th>
<th>LHF−</th>
<th>LHF+</th>
<th>OHF−</th>
<th>OHF+</th>
<th>L/O</th>
<th>F−/F+</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDD, mm</td>
<td>47±6</td>
<td>46±8</td>
<td>49±7</td>
<td>48±5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVDDi, mm/m</td>
<td>27.7±2.3</td>
<td>27.4±2.9</td>
<td>28.9±2.6*</td>
<td>28.6±2.4*</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>LVM, g</td>
<td>193±49</td>
<td>185±55</td>
<td>226±68*</td>
<td>232±65*</td>
<td>0.0009</td>
<td>NS</td>
</tr>
<tr>
<td>LVMi, g/m²−7</td>
<td>45.9±11.3</td>
<td>45.2±12.1</td>
<td>54.3±15.2*</td>
<td>55.2±14.8*</td>
<td>0.0006</td>
<td>NS</td>
</tr>
<tr>
<td>−dD/dt, s⁻¹</td>
<td>3.5±1.2</td>
<td>3.7±1.4</td>
<td>3.6±1.1</td>
<td>3.4±1.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>+dD/dt, s⁻¹</td>
<td>5.9±1.8</td>
<td>4.9±1.8‡</td>
<td>5±1.5</td>
<td>4.1±1.3‡</td>
<td>0.002</td>
<td>0.0002</td>
</tr>
<tr>
<td>dW/dt, cm/s</td>
<td>13.1±4.2</td>
<td>10.7±4.5†</td>
<td>10.9±3.4</td>
<td>8.5±2.9†</td>
<td>0.001</td>
<td>0.0003</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.24±0.37</td>
<td>1.15±0.33</td>
<td>1.18±0.31</td>
<td>1.02±0.35‡</td>
<td>0.045</td>
<td>0.016</td>
</tr>
<tr>
<td>DT, ms</td>
<td>165±44</td>
<td>184±46†</td>
<td>176±43</td>
<td>197±49‡</td>
<td>0.033</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVDD indicates LV end-diastolic diameter; LVDDi, LV end-diastolic diameter index; LVM, LV mass; LVMi, LV mass index; −dD/dt, peak shortening rate of LV diameter; +dD/dt, peak lengthening rate of LV diameter; dW/dt, peak thinning rate of LV posterior wall; E/A ratio, ratio between peak early transmural flow (E) velocity and peak late transmural flow (A) velocity; and DT, deceleration time of E velocity.

*0.05< P<0.001 OH vs LH, †0.05< P<0.001 LHF+ vs LHF−, and ‡0.05< P<0.001 OHF+ vs OHF− by Scheffé test.

Relation Between Metabolic Parameters, LV Mass, and Diastolic Function

When all the 197 patients are taken into consideration, multiple regression analysis (r²=0.49, P<0.0001) showed that the main independent predictors for LV mass index were 24-hour systolic BP (β=0.38, P<0.0001) and BMI (β=0.31, P=0.0005), whereas metabolic parameters and predisposition to hypertension did not enter the equation.

For LV diastolic function, from multiple regression analysis (r²=0.53, P<0.0001) the variables entering the equation as independent predictors of peak lengthening rate of LV diameter were in the following order: LV mass index (β=−0.36, P<0.0001), I-AUC (β=−0.33, P=0.0002), BMI (β=−0.26, P=0.0005), and genetic predisposition to hypertension (β=−0.24, P=0.0008). The relations of I-AUC and LV mass index with LV diastolic function have been also investigated in each of the 4 groups by means of linear correlation coefficients: I-AUC was inversely correlated with peak lengthening rate and peak wall thinning rate in the 2 F+ groups, whereas the parameters did not correlate in LHF− and OHF− groups (Figures 2 and 3, Table 4). In F+ groups, LV diastolic indices were significantly (P<0.01) more closely correlated with I-AUC than with LV mass index. We did not find any significant correlation between Doppler-derived filling parameters and insulin parameters. In addition, the elimination of the 77 patients on medication before the study did not affect the results (data not shown).

Discussion

Because BP response to insulin seems to be influenced by genetic predisposition to hypertension, we tested the hypothesis that family history of hypertension could also influence the relation between insulin levels and LV mass and ...

Figure 1. Prevalence of diastolic dysfunction in lean (L) and obese (O) hypertensives (H) with (F+) and without (F−) family history of hypertension.

Figure 2. Correlation between insulin area during OGTT (I-AUC) and peak lengthening rate of LV diameter (+dD/dt) in lean hypertensives with (LHF+) and without (LHF−) family history of hypertension.
function. In designing the present study, we tried to avoid some potentially confounding factors by selecting never treated hypertensives or patients who stopped the antihypertensive therapy at least 6 weeks before the study, because many drugs have been proved to influence LV anatomy and function and also insulin sensitivity.32–34 Moreover, for the assessment of family history, we did not trust parents’ histories, with the exception of parents on chronic antihypertensive treatment, and we selected patients with living parents, whose BP we measured directly at least 3 times. Obviously, these criteria significantly reduced the number of patients eligible for the study, but they also eliminated some possible bias. Insulin sensitivity was assessed by means of glucose, insulin, and C-peptide response to an oral glucose load. This method does not allow a direct measurement of insulin sensitivity, but insulin area during OGTT and the index of peripheral insulin activity derived from glucose and insulin values at glucose peak have been demonstrated to correlate well with insulin sensitivity measured by the euglycemic clamp.28,35 Although glucose levels (fasting and stimulated) were normal in all the patients and similar among the 4 groups, fasting and stimulated insulin and C-peptide levels were significantly higher and the index of peripheral insulin activity was lower in obese patients than in lean ones; at similar BMI, insulin and C-peptide levels were higher and insulin peripheral activity was lower in F+ groups than in F− groups. The hepatic clearance of insulin was similar among the groups, as demonstrated by the fasting insulin/C-peptide ratio. We point out that the 4 groups were comparable regarding age, gender, and 24-hour BP profile. BMI was similar between the 2 lean groups and between the 2 obese groups; besides, because body fat distribution influences insulin sensitivity,36 we selected only obese subjects with upper body obesity. The waist-hip ratio was similar between the 2 groups. Because the differences in insulin levels and peripheral insulin activity between F+ groups and F− groups are not accounted for by differences in age, gender, BMI, or BP, the reduced insulin sensitivity in F+ groups, as previously demonstrated,22–24 appears to be related to a genetic pattern more than to hypertension or obesity, per se, with obesity and genetic predisposition to hypertension having an additive negative effect on insulin sensitivity.

As regards the LV, obesity was associated with greater LV mass index, whereas family history of hypertension did not influence myocardial mass. Glucose and insulin levels (fasting and during OGTT) and the peripheral insulin activity index did not correlate with LV mass index. This lack of correlation between metabolic parameters and myocardial mass is in keeping with some,14,17,18 but not all, the previous studies; some authors have found a direct correlation between insulin resistance and/or hyperinsulinemia and myocardial hypertrophy in hypertensives and in obese subjects.13,16,19,20 These conflicting results can probably be ascribed to differences in age, gender, BMI, number of subjects studied, enrollment of patients who withdrew from the therapy only a few days before the evaluation, and differences in the method of evaluation of LV mass and insulin sensitivity. From our results, insulin resistance and hyperinsulinemia do not account for the development of myocardial hypertrophy, which appears to be significantly influenced by 24-hour systolic BP and BMI. A possible relation between insulin resistance and LV diastolic dysfunction in hypertension has been evaluated in a few previous studies,14,15,18,19 with partly conflicting results: LV diastolic function appears to be negatively influenced only by increased glucose levels at fast or during load, according to some authors,14,15,18 or by insulin resistance and not by glucose levels, according to others.39 Besides measuring Doppler-derived E/A velocity ratio and the deceleration time of early transmitral flow velocity, we evaluated LV diastolic function also by means of peak lengthening rate of LV diameter and peak thinning rate of posterior wall, both obtained from digitized M-mode echocardiography. These 2 parameters, less popular than Doppler-derived diastolic indices, have been proven more accurate and specific than Doppler parameters in discriminating between normal and abnormal diastole in patients with myocardial hypertrophy.37 In agreement with previous reports,1,32,38 we found an impairment of diastolic function in many lean and obese hypertensives, whereas systolic function was normal in all and similar among the 4 groups. To the best of our knowledge, this is the first study testing the hypothesis that genetic predisposition to hypertension can influence the myocardial response to insu-

**TABLE 4. Correlations of +dD/dt and +dW/dt With Insulin Area During OGTT and With LVMi in LHF−, LHF+, OHF−, and OHF+**

<table>
<thead>
<tr>
<th>Variable</th>
<th>LHF−</th>
<th>LHF+</th>
<th>OHF−</th>
<th>OHF+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+dD/dt</td>
<td>dW/dt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+dD/dt</td>
<td>dW/dt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-AUC</td>
<td>−0.08*</td>
<td>−0.05</td>
<td>−0.39*</td>
<td>−0.41*</td>
</tr>
<tr>
<td>LVMi</td>
<td>−0.53*</td>
<td>−0.41†</td>
<td>−0.30‡</td>
<td>−0.25§</td>
</tr>
</tbody>
</table>

*P<0.001, †P<0.01, ‡P<0.02, and §P<0.05.
lin, and we think that our results support this hypothesis. In fact, LV diastolic function was more impaired in the obese groups than in the lean groups, as previously found, but at a similar BMI, the diastolic dysfunction was significantly greater in F+ groups than in F− groups. It is well known that diastolic function is influenced by several factors, such as age, preload, LV mass, and BP load. However, the difference found between F+ and F− groups cannot be ascribed to differences between groups in terms of age, BMI, or 24-hour BP profile, as underlined above, or to differences in preload or LV hypertrophy, in view of the fact that LV end-diastolic diameter, index of preload, and LV mass index were similar between the 2 lean groups and between the 2 obese groups. From multiple regression analysis, in addition to LV mass index and BMI, stimulated insulinemia and genetic predisposition to hypertension were also significant predictors of LV diastolic dysfunction. However, when the 4 groups were evaluated separately, both diastolic indices were inversely correlated with stimulated insulinemia in only the 2 groups. From multiple regression analysis, in addition to LV mass index and BMI, stimulated insulinemia and genetic predisposition to hypertension were also significant predictors of LV diastolic dysfunction. However, when the 4 groups were evaluated separately, both diastolic indices were inversely correlated with stimulated insulinemia in only the 2 F+ groups, and this correlation was closer than the correlation between diastolic function and LV mass found in all 4 groups. Theoretically, because insulin stimulates collagen synthesis from fibroblasts, chronic hyperinsulinemia can affect LV diastolic function through an increase of myocardial interstitial fibrosis. Our results, however, indicate that high fasting and stimulated insulin levels, per se, do not account for the reduced diastolic function. In fact, if we compare LH+ and OH−, despite obesity and higher insulin levels in this latter group, the indices of LV diastolic function were similar between the 2 groups. Moreover, in OH−, stimulated insulinemia and LV diastolic indices were not correlated, indicating that the correlation is not simply due to higher levels of insulinemia. Therefore, hyperinsulinemia and diastolic dysfunction appear to be related only in the presence of genetic predisposition to hypertension; this result, obtained in a small group of subjects, has to be confirmed by studies involving larger populations.

Obviously, the present study does not explore the pathophysiology of the possible link between genetic predisposition to hypertension, hyperinsulinemia, and diastolic dysfunction. However, taking into account experimental studies demonstrating that LV fibroblasts from spontaneously hypertensive rats differ from fibroblasts isolated from normotensive Wistar-Kyoto rats in many aspects, such as growth rate in culture, expression of angiotensin II receptors, structure, and steroid responsiveness, we could hypothesize that genetic predisposition to hypertension also influences the response of the fibroblasts to the promoting effect of insulin on collagen production, increasing interstitial collagen accumulation in the myocardial wall.

In conclusion, in untreated lean and obese hypertensives, genetic predisposition to hypertension is associated not only with a reduced insulin sensitivity but also with the response of the myocardium to increased insulin levels, inducing a greater impairment of diastolic function. On the other hand, myocardial hypertrophy, which is significantly related to 24-hour systolic BP and BMI, seems to be influenced neither by genetic predisposition to hypertension nor by insulin sensitivity.

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Insulin and Diastolic Dysfunction in Lean and Obese Hypertensives: Genetic Influence
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