Hyperinsulinemia, Family History of Hypertension, and Essential Hypertension

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The aim of this study was the evaluation of the relationships among hyperinsulinemia, a family history of hypertension, and essential hypertension. Insulin and C-peptide responses to an oral glucose load were studied in 175 lean normotensives (N) and untreated hypertensives (H) with (F+) and without (F−) a family history of hypertension: 30 NF−, 30 NF+, 45 HF−, and 70 HF+. The groups were comparable for age, sex, body mass index, and blood pressure. The following parameters were evaluated: plasma glucose (G), serum insulin (I), and C-peptide (Cp) before and 30, 60, 90, and 120 min after the glucose load, fasting glucose/insulin ratio (I/SI), fasting insulin/C-peptide ratio (I/Cp), and 24-h ambulatory blood pressure monitoring. Plasma glucose was measured, fasting and during the test, and it and I/Cp were similar in the four groups. Serum insulin and Cp, both fasting and stimulated, were significantly higher and ISI lower in normotensives and hypertensives with hypertensive parents. Grouping the subjects first on the basis of blood pressure and then on the basis of family history, no differences were found between normotensives and hypertensives, whereas I and Cp, fasting and stimulated, were significantly higher and ISI lower in subjects with positive as compared to negative family history. The closest correlations between insulin and ambulatory blood pressure were found in normotensives with hypertensive parents; in hypertensives with hypertensive parents we only found a direct correlation between fasting Cp and nocturnal blood pressure fall; in hypertensives with normotensive parents insulin inversely correlated with nocturnal blood pressure fall. Insulin resistance seems to have a familial basis, independently of the presence of hypertension. Instead of showing a causal relationship between insulin resistance and hypertension, our results indicate that the two are partly independent components of a common familial pattern. Am J Hypertens 1996;9:732–738

KeY words: Hyperinsulinemia, insulin resistance, hypertension, family history of hypertension.

Epidemiological and clinical studies indicate that essential hypertension is frequently associated with insulin resistance or hyperinsulinemia and that this association is independent of obesity, glucose tolerance, and age.¹⁻³ These results have stimulated the hypothesis that insulin resistance and hyperinsulinemia play a role in the pathogenesis of essential hypertension.⁴ However, definitive proof of this causal relationship does not exist and alternative hypotheses are still under evaluation: insulin resistance and hyperinsulinemia could be causally related with hypertension or occur as a secondary change during the development of hypertension.⁵⁻⁶ Recently, it has been suggested that the link between hyperinsulinemia and blood pressure could be on a genetic basis; in fact, an impairment of

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insulin-mediated glucose uptake has been demonstrated in normotensive offspring of hypertensives.\textsuperscript{10-17} It is otherwise known that although a positive family history is an independent predictor of the development of high blood pressure,\textsuperscript{18} only a portion of a hypertensives' offspring will become hypertensive.\textsuperscript{19} Besides, current data suggest that more than half of hypertensives, but not all, have a positive family history of hypertension.\textsuperscript{20} Therefore, in order to gain further information about the relationships among family history of hypertension, hyperinsulinemia, and hypertension, insulin and C-peptide have been evaluated during an oral glucose tolerance test in middle-aged adults, subdivided not only by blood pressure, but also on the basis of positive and negative family history of hypertension.

**METHODS**

**Patients** The subjects selected for the study were lean (body mass index $< 25$ kg/m$^2$), between 35 and 50 years of age, with fasting plasma glucose $< 100$ mg/dL and without family history of diabetes mellitus or obesity. Arterial blood pressure (BP) was evaluated on the basis of at least three measurements by sphygmonanometer, taken on different days. Subjects were defined as normotensive (N) when BP was $< 135/85$ mm Hg and as hypertensive (H) when systolic BP was $> 160$ mm Hg or diastolic BP was $> 95$ mm Hg. Subsequently each patient underwent 24-h noninvasive ambulatory BP monitoring that confirmed normal BP (24-h BP $< 130/80$ mm Hg) in all the subjects previously selected as normotensive. With regard to hypertensives, only the subjects with mean 24-h systolic BP $> 140$ or diastolic BP $> 90$ mm Hg were enrolled.

Family history of hypertension was assessed on the basis of parents' history and BP. Negative family history (F-) was established when both parents were living and had BP $< 140/90$ mm Hg; positive family history (F+) was established when at least one parent was living and had BP $> 160/95$ mm Hg or one or both parents had a history of chronic antihypertensive treatment. Parental BP was measured by sphygmonanometer three times on different days by one of the investigators.

Following these criteria, 175 subjects were selected: NF$: 30$ normotensives (15 men) with both parents normotensive; NF+: 30 normotensives (15 men) with one (18 subjects) or both parents hypertensive; HF$: 45 hypertensives (23 men) with both parents normotensive; HF+: 70 hypertensives (35 men) with one (40 subjects) or both parents hypertensive. Except for essential hypertension, all participating subjects were free of any other disease, as assessed by medical history, physical examination and laboratory findings. Normotensives were taking no drugs.

Among the hypertensives, 32 HF$-$ (71%) and 48 HF$+$ (68%) had never been regularly treated; 6 HF$-$ (13%) and 10 HF$+$ (14%) had been on regular medication with antihypertensives (ACE) inhibitors, 5 HF$-$ (11%) and 7 HF$+$ (10%) with calcium antagonists, and 2 HF$-$ (4%) and 5 HF$+$ (7%) with $\beta$-blockers. Antihypertensive treatment was discontinued 6 to 10 weeks before the study in 29 HF$+$ and 4 weeks in 6 HF$. Out of the 175 subjects, 98 were nonsmokers, 77 smoked $< 10$ cigarettes/day. Alcohol intake overall was $< 30$ g/day. 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 Internal Medicine and all the subjects gave their informed consent.

**Protocol** Two or three days after the 24-h ambulatory BP monitoring, each subject underwent, at 8 AM, after an overnight fast, a 75-g oral glucose tolerance test (OGTT). Plasma glucose (G), serum insulin (I), and C-peptide (Cp) were determined before and 30, 60, 90, and 120 min after the glucose load. Serum insulin was evaluated by an antibody method with a solid-phase radioimmunoassay (Coat-A-Count Insulin, Diagnostic Products Corp., Los Angeles, CA) as was the C-peptide (C-peak, Biodata, Rome, Italy).

The method for insulin measurement has a sensitivity of 1.1 $\mu$U/mL and a coefficient of variation of 6.9% at insulin values of 1–30 $\mu$U/mL. For C-peptide determination, the method has a sensitivity of 0.1 ng/mL and a coefficient of variation of 8.2% at C-peptide values of 0.5–3.5 ng/mL.

The values obtained during OGTT have been expressed as area under the curve (AUC), measured using the trapezoidal rule. We also evaluated the fasting glucose/insulin ratio, as an index of insulin sensitivity (SI), and the fasting insulin/C-peptide ratio (I/Cp), as an index of hepatic insulin clearance.

**24-h Ambulatory BP Monitoring** Noninvasive ambulatory BP monitoring was performed with a portable automated Takeda (Osaka, Japan) TM 2420. Simultaneous 24-h heart rate monitoring was also obtained. The unit was set to take readings every 15 min throughout the 24 h. The following parameters were evaluated: mean 24-h, daytime (from 6:00 AM to 11:59 PM), and nighttime (from 11:00 PM to 6:00 AM) systolic and diastolic BP, percent nocturnal fall of systolic and diastolic BP, and mean 24-h, daytime, and nighttime heart rate.

**Statistical Analysis** The statistical evaluation of the results was carried out by means of one-way analysis of variance (ANOVA), Scheffe test, contrast method, Pearson's linear correlation coefficients, and multiple regression analysis using the computerized SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL) program. For multiple regression analysis, we
TABLE 1. MEAN (±SD) VALUES OF AGE, BODY MASS INDEX (BMI) (kg/m²), SYSTOLIC (SBP) AND DIASTOLIC (DBP) BLOOD PRESSURE (mm Hg), AND HEART RATE (HR) (BEATS/MIN) IN NORMOTENSIVES (N) AND HYPERTENSIVES (H) WITH (F+) AND WITHOUT (F-) FAMILY HISTORY OF HYPERTENSION

<table>
<thead>
<tr>
<th>Variable</th>
<th>NF-</th>
<th>NF+</th>
<th>HF-</th>
<th>HF+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43 ± 6</td>
<td>42 ± 5</td>
<td>44 ± 5</td>
<td>42 ± 7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 0.5</td>
<td>23.6 ± 0.6</td>
<td>24 ± 0.6</td>
<td>23.9 ± 0.6</td>
</tr>
<tr>
<td>SBP 24-h (mm Hg)</td>
<td>120 ± 6</td>
<td>122 ± 7</td>
<td>149 ± 13</td>
<td>150 ± 14</td>
</tr>
<tr>
<td>DBP 24-h (mm Hg)</td>
<td>73 ± 6</td>
<td>72 ± 7</td>
<td>93 ± 9</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>SBP daytime (mm Hg)</td>
<td>127 ± 8</td>
<td>129 ± 7</td>
<td>153 ± 13</td>
<td>155 ± 15</td>
</tr>
<tr>
<td>DBP daytime (mm Hg)</td>
<td>76 ± 5</td>
<td>78 ± 8</td>
<td>96 ± 8</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>SBP nighttime (mm Hg)</td>
<td>107 ± 7</td>
<td>110 ± 10</td>
<td>134 ± 11</td>
<td>132 ± 15</td>
</tr>
<tr>
<td>DBP nighttime (mm Hg)</td>
<td>65 ± 6</td>
<td>68 ± 7</td>
<td>83 ± 9</td>
<td>84 ± 11</td>
</tr>
<tr>
<td>SBP fall (mm Hg)</td>
<td>15.3 ± 5.9</td>
<td>14.8 ± 6.3</td>
<td>12.6 ± 8.5</td>
<td>14.2 ± 8.3</td>
</tr>
<tr>
<td>DBP fall (mm Hg)</td>
<td>14.6 ± 5.2</td>
<td>13.5 ± 6.4</td>
<td>13.1 ± 7.8</td>
<td>12.9 ± 8.6</td>
</tr>
<tr>
<td>HR 24-h (beats/min)</td>
<td>75 ± 6</td>
<td>77 ± 9</td>
<td>75 ± 9</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>HR daytime (beats/min)</td>
<td>77 ± 7</td>
<td>79 ± 8</td>
<td>78 ± 10</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>HR nighttime (beats/min)</td>
<td>63 ± 8</td>
<td>64 ± 7</td>
<td>67 ± 9</td>
<td>56 ± 8</td>
</tr>
</tbody>
</table>

used each metabolic parameter as a dependent variable and all BP parameters as independent variables. A P < .05 was considered statistically significant. All variables were normally distributed and the variances were homogeneous across the groups.

RESULTS

The four groups were comparable (ANOVA, P = NS) with respect to age, sex, body mass index, and heart rate; ambulatory BP was comparable between NF- and NF+ and between HF- and HF+ (Table 1). There were also no differences among the groups in smoking habits (13 NF-, 12 NF+, 21 HF-, and 31 HF+ smoked) or alcohol consumption.

Fasting G and I/Cp ratio were similar in the four groups, whereas fasting I, Cp, and ISI were significantly different among groups, with I and Cp being higher and ISI lower in NF+ and HF+ (Table 2), as demonstrated by the Schefé test. During OGTT, G values were within the normal limits in all the subjects and similar in the four groups at each point of the curve; I and Cp were significantly (P < .001, Scheffé test) higher at each point of the curve in NF+ and HF+ (Figure 1). I and Cp AUC were significantly different among groups, being higher in NF+ and HF+ (Table 2). The contrast method showed that, grouping the subjects on the basis of BP (N = NF- and NF+ vs H = HF- and HF+), all the metabolic parameters were not significantly different between N and H (Table 3). Grouping the subjects on the basis of family history of hypertension (F- = NF- and HF- vs F+ = NF+ and HF+). Plasma glucose, both fasting and AUC, and I/Cp ratio were similar between F- and F+, whereas I and Cp, both fasting and AUC, were significantly higher and ISI was significantly lower in F+ with respect to F- (Figure 2).

Metabolic parameters did not correlate with clinic BP, whereas we found significant correlations with ambulatory BP in NF+, HF-, and HF+. The closest correlations were found in NF+; fasting I (multiple regression analysis r = 0.66, P < .001) was directly

<table>
<thead>
<tr>
<th>Variable</th>
<th>NF-</th>
<th>NF+</th>
<th>HF-</th>
<th>HF+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>G (mg/dL)</td>
<td>79 ± 9</td>
<td>81 ± 10</td>
<td>80 ± 10</td>
<td>81 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>I (μUI/mL)</td>
<td>7.5 ± 3.2</td>
<td>10.5 ± 4.3</td>
<td>7.9 ± 3.1</td>
<td>10.2 ± 4.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cp (ng/mL)</td>
<td>1.5 ± 0.6</td>
<td>2.4 ± 0.9</td>
<td>1.6 ± 0.7</td>
<td>2.3 ± 1.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ISI</td>
<td>14.2 ± 6.8</td>
<td>9.1 ± 3.7</td>
<td>13.9 ± 7.2</td>
<td>9.8 ± 4.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>I/Cp</td>
<td>4.5 ± 1.5</td>
<td>4.4 ± 1.3</td>
<td>4.4 ± 1.8</td>
<td>4.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>G AUC</td>
<td>445 ± 86</td>
<td>458 ± 92</td>
<td>452 ± 96</td>
<td>449 ± 83</td>
<td>NS</td>
</tr>
<tr>
<td>I AUC</td>
<td>145 ± 48</td>
<td>214 ± 63</td>
<td>139 ± 57</td>
<td>198 ± 69</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cp AUC</td>
<td>20.3 ± 5.7</td>
<td>31.5 ± 7.6</td>
<td>22.7 ± 4.8</td>
<td>30.5 ± 7.2</td>
<td>&lt; .001</td>
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related with daytime diastolic BP ($r = 0.25, P < .004$),
daytime systolic BP ($r = 0.23, P < .01$), and nocturnal
systolic BP fall ($r = 0.22, P < .03$); insulin AUC corre-
lated (multiple regression analysis, $r = 0.51, P < .001$)
with nocturnal diastolic BP fall ($r = 0.52, P < .002$); and
ISI (multiple regression analysis, $r = 0.63, P < .001$) with
daytime diastolic BP ($r = -0.23, P < .001$) and day-
time systolic BP ($r = -0.19, P < .005$). In
HF+ no correlations were found, except for a direct
one between fasting Cp and the extent of nocturnal
fall of diastolic BP ($r = 0.36, P < .001$). In HF+- fasting
I (multiple regression analysis, $r = 0.53, P < .001$)
directly correlated with nighttime systolic ($r = 0.35,
$P < .001$) and diastolic BP ($r = 0.26, P < .005$) and
inversely with the extent of nocturnal diastolic BP fall
($r = -0.22, P < .005$). We also found, only in HF−:
a significant correlation between nighttime heart rate
and fasting insulin ($r = 0.44, P < .01$), insulin AUC
($r = 0.47, P < .005$) and insulin sensitivity index ($r
= -0.40, P < .02$).

**TABLE 3. MEAN (±SD) VALUES OF FASTING
GLUCOSE (G), INSULIN (I), C-PEPTIDE (Cp), AREA
UNDER THE OGTT CURVE (AUC) OF G, I AND Cp,
INSULIN SENSITIVITY INDEX (ISI), AND INSULIN/C-
PEPTIDE RATIO (I/Cp) IN NORMOTENSIVES (N)
VERSUS HYPERTENSIVES (H) AND IN NEGATIVE
(F−) VERSUS POSITIVE FAMILY HISTORY OF
HYPERTENSION (F+)**

<table>
<thead>
<tr>
<th></th>
<th>N (NF− and NF+)</th>
<th>H (HF− and HF+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>80 ± 9</td>
<td>81 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>I</td>
<td>8.8 ± 3.5</td>
<td>9.1 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cp</td>
<td>1.9 ± 0.7</td>
<td>2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>ISI</td>
<td>118 ± 4.9</td>
<td>122 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>I/Cp</td>
<td>4.4 ± 1.4</td>
<td>4.5 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>G AUC</td>
<td>452 ± 86</td>
<td>449 ± 89</td>
<td>NS</td>
</tr>
<tr>
<td>I AUC</td>
<td>177 ± 58</td>
<td>172 ± 66</td>
<td>NS</td>
</tr>
<tr>
<td>Cp AUC</td>
<td>25.2 ± 6.5</td>
<td>25.7 ± 6.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>F− (NF− and HF−)</th>
<th>F+ (NF+ and HF+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>80 ± 9</td>
<td>81 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>I</td>
<td>7.4 ± 3.2</td>
<td>10.2 ± 4.3</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Cp</td>
<td>1.6 ± 0.6</td>
<td>2.3 ± 0.5</td>
<td>&lt;.0005</td>
</tr>
<tr>
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<td>9.5 ± 4.1</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>I/Cp</td>
<td>4.4 ± 1.7</td>
<td>4.6 ± 1.5</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>G AUC</td>
<td>450 ± 88</td>
<td>458 ± 85</td>
<td>NS</td>
</tr>
<tr>
<td>I AUC</td>
<td>146 ± 49</td>
<td>210 ± 65</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Cp AUC</td>
<td>21.4 ± 5.3</td>
<td>30.4 ± 7.8</td>
<td>&lt;.0005</td>
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</table>

**FIGURE 1. Mean values of plasma glucose, serum insulin, and
C-peptide at each point of the OGTT curve in normotensives (N) and hy-
pertensives (H) with (F+) and without (F−) family history of hy-
pertension. At each point of the curve, insulin and C-peptide values
were significantly higher (P < .001, Scheffé test) higher in F− and
HF+ with respect to NF− and HF−.**

**DISCUSSION**

The aim of the study was the evaluation of the re-
lationships among hyperinsulinemia, family history of
hypertension, and hypertension. The main problem in
planning this kind of study is related to the selection
criteria employed. First, the validity of a comparison
between subjects with and without a family histo-
y of hypertension depends entirely on a large difference
between BP levels of the parents. Therefore, we
made sure to select offspring of true normotensives
(BP < 140 / 90 mm Hg) and hypertensives (BP > 160 /
95 mm Hg) by measuring parents' BP repeatedly.
Moreover, our subjects were carefully selected in or-
der to exclude the confounding impact of other factors
known to influence insulin sensitivity, namely obe-
sity, drug treatments, and a family history of diabetes
mellitus or obesity. Our results indicate that, in spite of similar fasting
and stimulated plasma glucose concentrations, insu-
lin and C-peptide, both fasting and stimulated, were
significantly higher in... insulin sensitivity index was
The correlation between insulin and BP has been previously investigated in both normotensives and hypertensives with conflicting results, but in the majority of these studies the family history of the subjects was not considered. This is relevant, because from our results it appears that established essential hypertensives with hypertensive parents are, at least for some metabolic aspects, a different population with respect to established essential hypertensives with normotensive parents.

This could account for the observation that a substantial number of hypertensive subjects are not insulin resistant and may also explain the discrepancy between our results and previous studies, which, not evaluating family history of hypertension, found that hypertensives as a group tend to be more insulin resistant or hyperinsulinemic when compared to normotensives. The majority of essential hypertensives have hypertensive parents, therefore recruiting hypertensives without regard to family history makes it highly probable that more than half of the selected population indeed has a positive family history of hypertension, whereas normotensives with hypertensive parents are often excluded in recruiting a control group. Therefore, comparisons between hypertensive groups with prevalence of positive family history and normotensive groups with prevalence of negative family history could explain the discrepancies with our results. Our results are also partly different from those recently published by Neutel and coworkers. These authors found similar values of fasting insulin and insulin sensitivity index in normotensives with hypertensive parents and in hypertensives with and without family history of hypertension; all three groups showed higher values with respect to normotensives with normotensive parents. These different results may possibly be ascribed to the different methods employed to assess the negative or positive family history of the subjects: parents' history in the study of Neutel, as in the studies of Rose and of Ohmori and coworkers versus direct assessment of parents' blood pressure in our study.

In conclusion, insulin resistance seems to be related to a genetic pattern, independently of the presence of hypertension. Moreover, with regard to subjects with positive family history of hypertension, our results indicate that insulin resistance and hypertension are two at least partly independent components of a common familial pattern. This hypothesis is in keeping with that recently suggested by Resnick: insulin resistance, hypertension, obesity, and diabetes mellitus could be different clinical manifestations, determined by differences in genetic or environmental circumstances, of a common underlying pattern of cellular ion alterations.

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