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.
HYPERINSULINEMIA AND HYPERTENSION

HYPERINSULINEMIA AND HYPERTENSION

Insulin-mediated glucose uptake has been demonstrated in normotensive offspring of hypertensives.\textsuperscript{10} It is otherwise known that although a positive family history is an independent predictor of the development of high blood pressure,\textsuperscript{19} 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\textsuperscript{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 sphygmomanometer, 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\textsuperscript{-}) was established when at least one parent was living and had BP < 140/90 mm Hg; positive family history (F\textsuperscript{+}) 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 therapy. Parental BP was measured by sphygmomanometer three times on different days by one of the investigators.

Following these criteria, 175 subjects were selected: NF\textsuperscript{-}: 50 normotensives (15 men) with both parents normotensive; NF\textsuperscript{+}: 30 normotensives (15 men) with one (18 subjects) or both parents hypertensive; HF\textsuperscript{-}: 45 hypertensives (23 men) with both parents normotensive; HF\textsuperscript{+}: 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\textsuperscript{-} (71%) and 48 HF\textsuperscript{+} (68%) had never been regularly treated; 6 HF\textsuperscript{-} (13%) and 10 HF\textsuperscript{+} (14%) had been on regular medication with angiotensin converting enzyme (ACE) inhibitors, 5 HF\textsuperscript{-} (11%) and 7 HF\textsuperscript{+} (10%) with calcium antagonists, and 2 HF\textsuperscript{-} (4%) and 5 HF\textsuperscript{+} (7%) with \( \beta \)-blockers. Antihypertensive treatment was discontinued 6 to 10 weeks before the study in 29 HF and 4 weeks in 6 H. 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-peptide, Biodata, Rome, Italy).

The method for insulin measurement has a sensitivity of 1.1 mU/mL and a coefficient of variation of 6.9% at insulin values of 1–30 mU/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 (ISI), 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 11:00 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), Scheffé 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
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 Scheffé 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− (Table 3).

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 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></th>
<th>NF−</th>
<th>NF+</th>
<th>HF−</th>
<th>HF+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</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 ± 6</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>153 ± 5.9</td>
<td>148 ± 6.3</td>
<td>126 ± 8.5</td>
<td>142 ± 8.3</td>
</tr>
<tr>
<td>DBP fall (mm Hg)</td>
<td>146.5 ± 5.2</td>
<td>135 ± 6.4</td>
<td>131 ± 7.8</td>
<td>129.4 ± 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>

### Table 2. 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)

<table>
<thead>
<tr>
<th></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 (µU/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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</tbody>
</table>
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 correlated (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 daytime systolic BP ($r = -0.23, P < .001$). 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 ± 3.4</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>11.8 ± 4.9</td>
<td>12.2 ± 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>NF− and HF−</th>
<th>F+</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>
<td>ISI</td>
<td>14.1 ± 6.7</td>
<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>459 ± 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>29.4 ± 7.8</td>
<td>&lt; .0005</td>
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</table>

**DISCUSSION**

The aim of the study was the evaluation of the relationships 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 history 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 order to exclude the confounding impact of other factors known to influence insulin sensitivity, namely obesity, 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, insulin and C-peptide, both fasting and stimulated, were significantly higher in... insulin sensitivity index was
significantly lower in the two groups of normoten-
atives and hypertensives with a positive family history
of hypertension. The differences in insulinemia were
not related to a different hepatic clearance of insulin,
as demonstrated by comparable values of insulin /C-
peptide ratio in the four groups. Although insu-
linemia is not a direct measurement of insulin resis-
tance, both fasting and postload hyperinsulinemia, in
the presence of normal and equal levels of glycemia,
can be accepted as an index of insulin resistance.24,25

Consequently, taking also into account the values of
insulin sensitivity index, our results indicate that
insulin sensitivity in subjects with hypertensive parents
is reduced. Insulin sensitivity index, fasting and stimu-
lated insulin and C-peptide were comparable in nor-
motensives and established hypertensives with hy-
pertensive parents, whereas established hyperten-
sives with normotensive parents had lower values,
similar to normotensives with negative family history
of hypertension. Moreover, in grouping the patients
on the basis of BP values and subsequently on the
basis of family history, no difference was found be-
tween normotensives and hypertensives, whereas sig-
ificantly higher values of insulin and C-peptide, both
fasting and during OGT, were found in the group
with positive versus negative family history of hy-
pertension. Therefore, insulin resistance seems to be re-
lated to a genetic pattern, independently of the pres-
ence of hypertension. This finding and the lack of hy-
perinsulinemia in hypertensives with normotensive
parents make it unlikely that insulin resistance plays
a significant causal role in the genesis of essential hy-
pertension.

As regards the correlation with BP values, the clos-
est correlations were found in normotensives with hy-
pertensive parents, despite the narrow range of BP
values. In hypertensives with hypertensive parents no
correlations were found, except that fasting C-peptide
and insulinemia was directly related to the extent of nocturnal BP fall. In hypertensives with a negative family history, the higher the fasting insulinemia was, the higher the extent of nocturnal BP fall. Only in this group did we also find a significant positive correlation between insulinemia and nocturnal heart rate. Taking into account that these subjects are not hyperinsulinemic, it can be hypothesized that a slight impairment of insulin sensitivity occurs in patients with higher nocturnal BP and heart rate, as a secondary change due to sympathetic nervous system overactivity.26-38

The correlation between insulin and BP has been
previously investigated in both normotensives and
hypertensives29-29 with conflicting results, but in the
majority of these studies the family history of the sub-
jects 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 sub-
stantial number of hypertensive subjects are not insu-
lin resistant10 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 resis-
 tant or hyperinsulinemic when compared to normo-
tensives.23,22,23,30,41 The majority of essential hyperten-
sives have hypertensive parents,22 therefore recruit-
hypertensives without regard to family history
makes it highly probable that more than half of the
selected population indeed has a positive family his-
tory of hypertension, whereas normotensives with hy-
pertensive parents are often excluded in recruiting a
control group. Therefore, comparisons between hy-
pertensive groups with prevalence of positive family
history and normotensive groups with prevalence of
negative family history could explain the discrep-
ancies with our results. Our results are also partly
different from those recently published by Neutel and
coworkers.43 These authors found similar values of
fasting insulin and insulin sensitivity index in normo-
tensives with hypertensive parents and in hyperten-
sives 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' his-
tory in the study of Neutel, as in the studies of Rose30
and of Ohnori and coworkers42 versus direct assess-
ment 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 com-
mon familial pattern. This hypothesis is in keeping
with that recently suggested by Resnick44: insulin resis-
tance, hypertension, obesity, and diabetes mellitus
could be different clinical manifestations, determined
differences in genetic or environmental circum-
stances, of a common underlying pattern of cellular
ion alterations.

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