Elevated Hepatic Insulin Extraction in Essential Hypertension
Alexandra Kautzky-Willer, Giovanni Pacini, Michael Weissel, Maria Capek, Bernhard Ludvik, and Rudolf Prager

Insulin resistance, hyperinsulinemia, and dyslipidemia are common characteristics of patients with untreated hypertension. However, the link between the vascular and metabolic disturbances is still unclear. To provide further insights into the metabolic picture of subjects with hypertension, we evaluated insulin resistance, pancreatic secretion, and hepatic extraction of the hormone in 16 untreated patients with essential hypertension before and after 12–16 weeks of drug treatment in comparison with 16 age-, sex-, and body weight–matched normotensive control subjects. All subjects underwent an oral and a frequently sampled intravenous glucose tolerance test. Metabolic parameters were calculated by the minimal model technique. The hypertensive patients exhibited a highly reduced tissue insulin sensitivity (2.6±0.4 versus 9.6±1.9 10^4 min⁻¹/[microunits/mL]; p<0.001). The basal secretion rate (70±11 versus 35±5 pmol/L per minute) and the total amount of prehepatically secreted insulin (32±4 versus 16±2 nmol/L in 4 hours) were significantly increased in the hypertensive patients compared with the control subjects (p<0.01), whereas the posthepatic insulin delivery rate was not significantly different between the two groups (4.9±0.6 versus 3.5±0.3 nmol/L in 4 hours). Hepatic insulin extraction was found to be significantly elevated in the hypertensive patients compared with control subjects (81±4% versus 69±3%, p<0.04). Increased hepatic insulin extraction partially ameliorated B cell hypersecretion in hypertensive patients. After 12–16 weeks of drug treatment, the blood pressure was normalized, but the metabolic profile of the patients remained unchanged. We conclude that elevated insulin extraction in the liver is a specific characteristic of individuals with essential hypertension and partially compensates pancreatic B cell hypersecretion.

KEY WORDS • hypertension, essential • insulin sensitivity • hepatic insulin extraction

The striking clinical association among hypertension, hyperinsulinemia, and impaired glucose tolerance has attracted considerable attention in recent years, but despite great scientific effort the etiology and pathogenesis of these diseases and the link between high blood pressure and the metabolic aberrations are still unknown. Because these conditions represent predictors for cardiovascular disease and early mortality, it would be of great interest to elucidate the hyperinsulinemia–hypertension link. Moreover, it is still controversial whether drug treatment leads to changes in the metabolic status of patients with essential hypertension and has any effect on coronary artery disease at all.

Although several studies give evidence of high peripheral insulin levels in hypertension, there are only a few investigations on dynamic beta cell function and insulin resistance in this state. To our knowledge, the role of hepatic insulin extraction in the pathogenesis of hyperinsulinemia in essential hypertension has not been elucidated so far. Therefore, this study focused on beta cell insulin secretion, the role of hormone extraction in the liver, and insulin sensitivity in patients with essential hypertension before and 12–16 weeks after treatment with calcium channel blockers, angiotensin converting enzyme inhibitors, or both, drugs that are proposed to lack significant metabolic side effects.

Only invasive methods exist for obtaining direct information on prehepatic insulin release and insulin extraction by the liver, such as catheterization of the portal vein for sampling in situ. The most widely used noninvasive approach has been the C peptide-to-insulin molar ratio; however, the limitations of its use as an indicator of hepatic extraction are extensively discussed by Polonsky and Rubenstein. We exploited a noninvasive method based on two minimal mathematical models: one of C peptide secretion and kinetics and one of insulin delivery and kinetics. This technique, which includes only a few assumptions based on accepted physiological concepts, allows the interpretation of plasma C peptide and peripheral insulin concentration data during a frequently sampled intravenous glucose tolerance (FSIGT) test in humans and provides an estimation of the time courses of the prehepatic insulin secretion rate and the hormone degradation in the liver.

From the Second Medical Department, University of Vienna (Austria), and the Institute of Systems Theory and Biomedical Engineering (LADSEB-CNR), Padua, Italy.

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Address for correspondence: A. Kautzky-Willer, MD, Department of Medicine III, University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.

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was confirmed by repetition of 24-hour blood pressure monitoring, as well as by training electrocardiogram. The blood pressure values are mean values of 24-hour measurements by the same physician on separate days. The blood pressure range, 32-65 years; body mass index [BMI], 26±1 kg/m²; mean systolic blood pressure [SBP], 167±2 mm Hg; mean diastolic blood pressure [DBP], 79±2 mm Hg; <0.0005. Essential hypertension was diagnosed when SBP exceeded 160 mm Hg and DBP exceeded 95 mm Hg on at least three measurements by the same physician on separate days. The blood pressure values are mean values of 24-hour continuous blood pressure monitoring (Reynolds Accutracker II, Medical LTD, Hertford, UK). A complete medical workup was carried out to exclude secondary forms of hypertension. Renal, liver, and endocrine functions were normal. The hypertensive patients were recruited from the outpatient clinic; none had any disease other than hypertension nor any family history of diabetes. The control population was recruited from within the paramedical staff and consisted of 16 healthy subjects matched for sex, age, and body weight (10 men, six women; age range, 27–62 years; BMI, 24±1 kg/m²; SBP, 125±2 mm Hg; DBP, 79±2 mm Hg; see Table 1). After 12–16 weeks of treatment with calcium channel blockers (nifedipine), angiotensin converting enzyme inhibitors (enalapril), or both, the hypertensive patients reached normal blood pressure levels (SBP, 142±6 mm Hg; DBP, 88±3 mm Hg; p<0.01) and were restudied to assess whether changes in their metabolic status occurred. The normalization of blood pressure levels was confirmed by repetition of 24-hour blood pressure monitoring, as well as by training electrocardiogram.

**Oral Glucose Tolerance Test**

All subjects underwent a standard (75 g) oral glucose tolerance test after an overnight fast. Blood was drawn at 0 minutes (before the glucose was drunk) and 30, 60, 90, 120, and 180 minutes after the glucose load for measurement of glucose and insulin levels.

**Frequently Sampled Intravenous Glucose Tolerance Test**

For each subject, tests were started at 8 AM after an overnight fast. A catheter was inserted into an antecubital vein for blood sampling and into a contralateral antecubital vein for glucose injection. Basal samples were drawn at −20, −10, and −1 minutes. At time 0, glucose (300 mg/kg) was injected into the arterial line. Additional samples were collected at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210, and 240 minutes. Blood was rapidly centrifuged and glucose immediately measured by the glucose oxidase method with an automated glucose analyzer (Beckman Instruments Inc., Fullerton, Calif.). The remaining plasma was stored at −20°C for later insulin and C peptide determinations. Insulin (Phar-macia LKB Biotechnology, Uppsala, Sweden) and C peptide (Byk Sangtec, Dietzenbach, FRG) were measured by commercially available radioimmunoassays.

**Data Analysis**

The FSIGT test data were submitted to computer programs that calculate the characteristic metabolic parameters by fitting glucose, insulin, and C peptide data to the minimal models that describe the time courses of glucose and insulin12 and of C peptide10 concentrations. The models assume a first-order linear kinetics for both insulin and C peptide and a glucose-controlled biphasic release from the B cell. The two models have previously been described in detail10–15; here, we briefly present what is useful to the understanding of their application in this study.

**Glucose disappearance minimal model.** The glucose disappearance minimal model12 accounts for the effect of insulin and glucose on glucose disappearance after the exogenous glucose injection. It provides two parameters: S, the insulin sensitivity index (per minute per microunit per milliliter), defined as the ability of insulin to enhance glucose disappearance and to inhibit hepatic glucose production; S, glucose effectiveness (per minute), defined as the ability of glucose per se to enhance its own disappearance and to inhibit glucose production at basal insulin.

**C peptide minimal model.** The C peptide minimal model10 accounts for the effect of glucose on C peptide concentration during an FSIGT test by describing the ability of the beta cells to secrete C peptide in response to the glycemic stimulus and C peptide disappearance after entry into the peripheral circulation. The model provides the time course of C peptide secretion, CPS(t) (picomole per liter per minute), and the value of parameters Φ, which is the C peptide fractional clearance rate (per minute), i.e., the peptide disappearance in unit time per unit volume. C peptide secretion and hepatic extraction. Because insulin and C peptide are secreted in equimolar fashion, the time course of beta cell insulin secretion equals that of C peptide, CPS(t), and basal insulin secretion rate, BSR (picomole per liter per minute), may be computed by multiplying the clearance rate k by the basal C peptide.
concentration. BSR, $\Phi_1$, and $\Phi_2$ give a quantitative description of the individual components (basal and dynamic) of the beta cell secretion.

A previously introduced minimal model to analyze FSIGT insulin data\textsuperscript{11} provides the time course of post-hepatic insulin delivery, IDR(t). Therefore, the time course of the percent hepatic insulin extraction, HE(t), may be computed as the difference between CPS(t) and IDR(t), normalized to CPS(t).\textsuperscript{10}

**Calculations**

The estimation of parameters was carried out with a nonlinear least-squares estimation technique by the computer program MINMOD,\textsuperscript{14} which was modified to account also for C peptide data.\textsuperscript{15} A constant variance structure was assumed for the measurement error: the coefficient of variation assessed in our lab of a single determination was ±1.5% for glucose, ±7% for insulin, and ±12% for C peptide. Accuracy and precision of the estimates were evaluated according to the validation criteria of model identification.\textsuperscript{16}

Parameters and time courses were given by the model analysis per unit volume, rendering correct the comparison between groups with different distribution volumes. The method is also independent of the glucose dose, providing enough glucose was administered to adequately stimulate beta cell insulin release. In our experience, glucose doses greater than 20 g yield sufficiently high dynamic insulin profiles even in low responding subjects.

The initial distribution volume for glucose (V_D, liters) was calculated as the ratio between the injected dose of glucose and the model extrapolation of glycemia to time zero. Parameter S_G, the glucose effectiveness, can be split into two components (both per minute): 1) basal insulin effect (BIE) on glucose disappearance and calculated as basal insulin times S_I and 2) the glucose effectiveness at zero insulin (GEZI), i.e., the contribution to glucose disappearance of non-insulin-dependent glucose uptake, calculated as S_G-BIE.\textsuperscript{17}

The total amounts of insulin secreted by the beta cell (TIS, nanomole per liter in 4 hours) and of insulin delivered into the periphery (TID, nanomole per liter in 4 hours) were computed by the integral, between 0 and 240 minutes, of CPS(t) and IDR(t), respectively.

**Results**

**Metabolic Profile**

Compared with control subjects, the hypertensive patients featured significantly higher triglyceride levels ($p<0.03$) and significantly higher total ($p<0.01$) and low density lipoprotein (LDL) ($p<0.05$) cholesterol levels, whereas the high density lipoprotein (HDL) cholesterol levels did not differ between the two groups (Table 1). Hypertensive patients showed moderate microalbuminuria (98±8 mg/L in 24-hour sampled urine). The levels of uric acid were in the normal range in hypertensive patients (Table 1) but were significantly elevated compared with control subjects ($p<0.04$). Body fat distribution in the hypertensive patients evaluated by measurement of the waist-to-hip-girth ratio ranged from 0.78 to 0.95. The oral glucose tolerance test indicated that no hypertensive patient had overt diabetes (Table 2). According to National Diabetes Data Group criteria,\textsuperscript{18} seven hypertensive patients exhibited impaired glucose tolerance. The remaining nine patients showed normal glucose tolerance. Comparing the two subgroups with normal and impaired glucose tolerance, we found no significant differences in blood pressure, cholesterol, triglycerides, uric acid levels, insulin secretion, and insulin resistance. Neither BMI nor the waist-to-hip-girth ratio correlated with blood pressure, cholesterol levels, or triglyceride levels in hypertensive patients.

After 12–16 weeks of drug treatment with angiotensin converting enzyme inhibitors, calcium channel blockers, or both, there was no significant change in the basal or stimulated insulin and glucose concentration curves (Table 3) as well as in the lipid concentrations (triglycerides, 1.8±0.2 versus 2.2±0.3 mmol/L; total cholesterol, 6.5±0.4 versus 6.05±0.3 mmol/L; HDL cholesterol, 1.17±0.1 versus 1.4±0.1 mmol/L; LDL cholesterol, 3.8±0.3 versus 4.2±0.4 mmol/L; hypertensive patients before versus after

**Table 2. Comparison of Oral Glucose Tolerance Test Results for Normotensive Control Subjects and Hypertensive Patients Before and After Drug Treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (mmol/L)</td>
<td>4.7±0.2</td>
<td>4.7±0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 120 minutes (mmol/L)</td>
<td>5.5±0.3</td>
<td>5.4±0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulated† (mol/L in 3 hours)</td>
<td>2.1±0.3</td>
<td>5.3±0.5</td>
<td></td>
<td>4.6±0.4</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (pmol/L)</td>
<td>60±12</td>
<td>102±12</td>
<td></td>
<td>120±18</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>At 120 minutes (pmol/L)</td>
<td>162±18</td>
<td>654±114</td>
<td>600±84</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stimulated† (nmol/L in 3 hours)</td>
<td>24±3</td>
<td>90±12</td>
<td>78±6</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n=16 for both hypertensive patients and normotensive control subjects.

*Difference between hypertensive patients before treatment and normotensive control subjects.
†Calculated as suprabasal area under the concentration curve.
Insulin Metabolism in Essential Hypertension

Kautzky-Willer et al

Frequently Sampled Intravenous Glucose Tolerance Test for Normotensive Control Subjects and Hypertensive Patients Before and After Treatment

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Normotensive</th>
<th>Hypertensive Before treatment</th>
<th>Hypertensive After treatment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S_0$ (min$^{-1}$/[microunit/mL])</td>
<td>9.6±1.9</td>
<td>2.6±0.4</td>
<td>3.6±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$S_C$ (10$^{-3}$ min$^{-1}$)</td>
<td>32±3</td>
<td>15±2</td>
<td>18±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V_D$ (% body wt)</td>
<td>17.5±0.6</td>
<td>17.2±0.5</td>
<td>17.2±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSR (pmol/L per minute)</td>
<td>35±5</td>
<td>70±11</td>
<td>71±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\Phi_1$ (pmol/L min$^{-1}$/[mg/dL])</td>
<td>175±24</td>
<td>186±30</td>
<td>189±32</td>
<td>NS</td>
</tr>
<tr>
<td>$\Phi_2$ (10$^{-2}$ pmol/L min$^{-1}$/[mg/dL])</td>
<td>48±9</td>
<td>47±5</td>
<td>55±11</td>
<td>NS</td>
</tr>
<tr>
<td>TIS (nmol/L in 4 hours)</td>
<td>16±2</td>
<td>32±4</td>
<td>30±3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hepatic extraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (% secreted insulin)</td>
<td>71±3</td>
<td>83±3</td>
<td>84±2</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>HIE (% secreted insulin)†</td>
<td>69±3</td>
<td>81±4</td>
<td>80±4</td>
<td>&lt;0.04</td>
</tr>
</tbody>
</table>

$t_S$, insulin sensitivity; $S_C$, glucose effectiveness; $V_D$, volume of glucose distribution; BSR, basal insulin secretion rate; $\Phi_1$, first-phase B cell sensitivity to glucose; $\Phi_2$, second-phase B cell sensitivity to glucose; TIS, total insulin secretion; HIE, hepatic insulin extraction. Values are mean±SEM. n = 16 for hypertensive patients and normotensive control subjects.

†Difference between hypertensive patients before treatment and normotensive control subjects.

*Average extraction in 240 minutes.

treatment). Eight of the 16 patients received angiotensin converting enzyme inhibitors, five patients were treated with calcium channel blockers, and three hypertensive patients were on a combination of both antihypertensive drugs. In each subgroup of hypertensive patients, glucose, insulin levels, insulin secretion, and lipid parameters also remained unchanged.

Hb A$\text{lc}$ levels in hypertensive patients were significantly elevated compared with control subjects (5.4±0.2% versus 4.6±0.1%, p<0.01, hypertensive versus control), reflecting the higher blood glucose levels in this patient group. The Hb A$\text{lc}$ levels showed a significant correlation with triglyceride (r=0.03, r=0.6) levels and correlated inversely with HDL cholesterol (p<0.01, r=−0.7).

Neither sex nor the degree of glucose tolerance nor body weight affected blood pressure levels.

Frequently Sampled Intravenous Glucose Tolerance Test and Model Parameters

During the FSIGT test, we observed significantly higher C peptide, insulin, and glucose levels in the hypertensive patients compared with normotensive control subjects (Figure 1). Basal levels were (hypertensive versus control) C peptide, 1.1±0.1 versus 0.55±0.06 nmol/L (p<0.001); insulin, 70±9 versus 42±5 pmol/L (p<0.05); and glucose, 5.3±0.2 versus 4.8±0.1 mmol/L (p<0.05). Integrated insulin concentration was 6.3±0.9 and 3.5±0.6 nmol/L in 240 minutes, p<0.05, in hypertensive patients and controls, respectively.

Concentration curves of hypertensive patients with normal and impaired glucose tolerance were not significantly different.

Insulin sensitivity and glucose effectiveness. The hypertensive group featured a highly significantly reduced insulin sensitivity (Table 2), which correlated inversely with the Hb A$\text{lc}$ levels (r=−0.65, p<0.02). The glucose effectiveness was halved in hypertensive patients and showed a significant relation with HDL cholesterol (r=0.65, p<0.02). Both components of glucose effectiveness were halved in hypertensive patients and controls, respectively.

During the FSIGT test, we observed significantly different C peptide fractional clearance rate between the control and hypertensive groups (0.007±0.007 versus 0.060±0.007 min$^{-1}$, respectively). The calculated time courses of prehepatic insulin secretion are shown in the top panel of Figure 2. The basal C peptide secretion rate, which equals basal insulin prehepatic release, was significantly higher in hypertensive patients than in normotensive control subjects (Table 3). No significant differences were found in the dynamic sensitivities to glucose of the first- and second-phase insulin secretion. The total amount of released C peptide, which equals that of insulin, was twice as much in the hypertensive group as in the control group. Insulin secretion correlated with Hb A$\text{lc}$ (r=0.82, p<0.01).

Hepatic extraction. The time course of estimated hepatic insulin extraction is shown in Figure 3. Basal hepatic extraction was significantly elevated in hypertensive patients as well as its mean value (HIE) during the entire test (Table 3). HIE correlated with both basal peptide secretion rate (r=0.55, p<0.05) and total insulin secretion (r=0.6, p<0.05). The rate of posthepatic delivery of insulin is shown in the bottom panel of Figure 2. The area under this curve (total insulin delivery) represents the amount of insulin in the periphery. Total insulin delivery, although elevated in hypertensive patients, was not statistically significant compared with control subjects (4.9±0.6 versus 3.5±0.3 nmol/L in 4 hours, respectively).

Comparing hypertensive patients with normal and impaired glucose tolerance, we could not find any significant difference in the model parameters.
FIGURE 1. Line graphs show average time courses of measured variables as mean±SEM of normotensive control subjects (○—○; n=16) and hypertensive patients (●—●; n=16) during intravenous glucose tolerance tests. Glucose (0.33 g/kg) was started at 0 minutes and lasted 30 seconds.

The mean BMI of the hypertensive patients was 26±1 kg/m², ranging from 19 to 32 kg/m² (median, 25; Q1, 22.5; Q3, 30.5 kg/m²). The mean BMI did not correlate with any model parameter. We divided the hypertensive group into a leaner (BMI <24 kg/m², n=8) and a more obese (BMI >24 kg/m², n=8) subgroup and compared these two subgroups to further evaluate the influence of BMI on insulin secretion and sensitivity parameters, but again we found no significant difference.

After 12–16 weeks of drug treatment, we found no significant change in any model parameter (Table 3), although insulin sensitivity and glucose effectiveness exhibited a slight tendency to ameliorate. Again, in each subgroup of hypertensive patients with specific drug treatment, we saw no significant change in insulin sensitivity and glucose effectiveness or in any other model parameter.

Discussion

In recent years, interest has been focused on the possible role of glucose intolerance, insulin resistance, and insulin hypersecretion in essential hypertension. Because there is a large overlap in the prevalence of obesity, diabetes, and hypertension in Western civilization, the common finding of insulin resistance and hyperinsulinemia in hypertensive patients is not surprising. However, recent studies have shown that insulin resistance is also a problem of normal-weight nondiabetic hypertensive patients, and the mortality risk has been proposed to be even higher in lean hypertensive patients. Furthermore, it is well known that established drug therapies for hypertension can aggravate the metabolic syndromes of insulin resistance, hyperinsulinemia, and dyslipidemia. Interest focused on the role of hyperinsulinemia per se in the pathogenesis of hypertension. Hyperinsulinemia as a primary cause for or compensatory response to insulin resistance has been suggested to elevate blood pressure through several actions, including activation of the sympathetic nervous system and a direct effect on the kidney, causing sodium retention. Thus it was of great interest to further elucidate insulin metabolism in hypertension.
Impaired glucose metabolism in the hypertensive patients was documented by significantly higher glucose levels during the glucose tolerance tests and by significantly elevated glycosylated hemoglobin, although the Hb A1c levels of the hypertensive patients were still in the normal range. The degree of hyperglycemia, measured by Hb A1c, was significantly correlated with insulin secretion and insulin resistance, as well as the LDL cholesterol and triglyceride levels. In this context, it is of considerable interest that the prevalence of hypertension was found to be clearly increased with the Hb A1c levels among older women in the original cohort of the Framingham Heart Study.

From the analysis of FSIGT data, the hypertensive patients were severely insulin insensitive, featuring insulin sensitivity values reduced by 75% compared with control subjects. The other parameter strictly related to glucose disappearance, i.e., glucose effectiveness, was reduced by 51% in the hypertensive patients. The importance of this parameter in overall glucose metabolism has been recently explored. Because glucose effectiveness measures the ability of glucose per se to increase glucose utilization and to decrease endogenous glucose production, in the absence of changes in plasma insulin, abnormalities in the processes at the level of peripheral tissues as well as in the liver may be accounted for by the impaired glucose effectiveness. A study in experimental animals showed that the relative contribution of glucose per se is at least as important as the insulin-dependent glucose uptake in normalizing the glycaemia after an intravenous glucose load. In addition, the synergistic, independent, and almost comparable effects of insulin sensitivity and glucose effectiveness on glucose disappearance were also demonstrated in obese and cirrhotic humans. It is interesting to notice that the components of insulin sensitivity, i.e., the BIE and the GEZI, were both reduced in hypertensive patients by a similar proportion. The percent ratio of GEZI to insulin sensitivity represents that part of tissue glucose uptake occurring independent of insulin. This ratio was 78% in control subjects and 84% in hypertensive patients, very similar to the 77% found by Kahn and coworkers in normotensive men using a similar approach (glucose clamping technique). The percent ratio of GEZI to insulin sensitivity was only insignificantly higher in the hypertensive patients compared with control subjects. This fact might be ascribed to the increased basal insulin secretion in the hypertensive patients.

Decreased insulin sensitivity and glucose effectiveness resulted in postload hyperglycemia, which produces a larger-than-normal stimulation of the B cells, leading to insulin hypersecretion. Hyperinsulinemia was markedly evident in the hypertensive patients during both the oral and intravenous glucose tolerance tests; for instance, the total area under the FSIGT insulin concentration curve was twice as great as that of normotensive control subjects.

The insulin hypersecretion in the patients with high blood pressure could be factored out in its components by our modeling method. During the dynamic hyperglycemic phases, the B cell of the hypertensive patients reacted as that of control subjects; in fact, both of the components, and , were not different in the two groups. Thus, despite hypertension, the amount of first-phase releasable insulin was maintained intact. Similar values of parameter of the normotensive conclusion that the capacity to synthesize newly releasable hormone was not impaired. What seems to be unequivocal is the elevated basal secretory rate. The increased basal glucose (on average, 0.8 mmol/L) overstimulated the B cell in steady-state conditions (basal secretory rate of hypertensive patients was twice that of control subjects), with a sustained effect probably due to the overt insulin resistance demonstrated in the hypertensive patients.

The clearance of C peptide was not different in the two groups, showing that the kinetic behavior of C peptide was not affected by essential hypertension. The clearance of C peptide in the normotensive subjects was also similar to that found by analyzing the disappearance curve of bolus-injected exogenous biosynthetic human C peptide in normotensive volunteers. This fact made us confident that our findings about insulin through C peptide analysis are not affected by bias due to a different kinetic behavior of C peptide in the two groups.

Although insulin secretion was more than doubled in the hypertensive patients, the posthepatic basal insulin delivery rate did not exhibit a marked difference between the two groups, and the posthepatic total insulin delivery was only insignificantly higher in the hypertensive patients compared with control subjects. This fact brings the focus on the role the liver plays in modulating insulin appearance in the periphery. Hepatic degradation of the hormone was elevated by 15% in hypertensive patients compared with control subjects and significantly correlated with insulin secretion. Higher insulin extraction obviously lowered peripheral hyperinsulinemia in the hypertensive patients. Therefore, the elevated insulin extraction by the liver can be seen as a compensating mechanism to avoid excessive peripheral hyperinsulinemia. As a matter of fact, the compensatory effect between B cell insulin secretion and liver degradation has been suggested in a study on elderly people, in which a reduced secretion and a decreased extraction were considered responsible for maintenance of normal peripheral insulinemia.

Interestingly, the body weight, measured by BMI, was not correlated with glucose tolerance, insulin sensitivity, insulin secretion, and the lipid status in the hypertensive patients investigated in this study. In fact, other investigators also reported severe insulin resistance in lean hypertensive patients and a strong association between...
elevated blood pressure and insulin insensitivity irrespective of the body weight was also documented in nonobese non-insulin-dependent diabetes mellitus patients with hypertension. Thus, insulin resistance and associated insulin hypersecretion as well as dyslipidemia seem to be characteristic features of essential hypertension irrespective of the degree of obesity.

Angiotensin converting enzyme inhibitors, calcium channel blockers, or both were used for drug therapy, because they should not have adverse effects on glucose metabolism. Calcium entry blockers are neutral or slightly positive on glucose insulin, and angiotensin converting enzyme inhibitors were shown to have no effect or to improve insulin sensitivity measured by a clamp technique. Medical treatment and normalization of blood pressure in all hypertensive patients had no significant effect on any of the measured metabolic parameters, and no substantial change in the comprehensive metabolic portrait of the hypertensive patients was observed.

Subtle changes in insulin sensitivity, insulin secretion, and lipid parameters induced by specific drug treatment as seen by others might have been missed in this study because of the small sample size of patients treated with angiotensin converting enzyme inhibitors, calcium channel blockers, or both. On the other hand, a beneficial effect of angiotensin converting enzyme inhibitors on insulin secretion and insulin sensitivity is not consistently reported. Recent studies using the clamp technique showed that treatment with angiotensin converting enzyme inhibitors failed to change insulin sensitivity in hypertensive patients with non-insulin-dependent (type II) diabetes mellitus as well as in non-diabetic patients with essential hypertension despite effective reduction of blood pressure levels. In these studies, however, the patients were restudied 8 weeks or 12 weeks after antihypertensive drug treatment was begun. Thus, the lack of metabolic improvement after pharmacological treatment reported in these studies as well as in this one (12–16 weeks) might be due to the short duration of drug therapy.

It is still controversial whether a direct and independent relation between blood pressure and insulin hypersecretion or insulin resistance really exists. A insulin-and-effect relation between hyperinsulinemia and hypertension has not been proved, and several studies suggest that only a weak correlation exists between plasma insulin concentration and blood pressure in normal humans and that blood pressure does not appear to be very sensitive to changes in blood insulin. Maybe other links between the vascular and metabolic abnormalities exist, which are responsible for the clustering of insulin hypersecretion and hypertension; e.g., hemodynamic alterations and vascular rarefaction in essential hypertension might be a possible cause of insulin resistance.

In conclusion, patients with hypertension are characterized by insulin resistance, insulin hypersecretion, and dyslipidemia irrespective of their body weight. Medical treatment of hypertension at least with angiotensin converting enzyme inhibitors and calcium channel blockers has no effect on these metabolic abnormalities. Hepatic insulin extraction in hypertension is elevated and may serve as a compensatory mechanism to avoid excessive peripheral hyperinsulinemia in these patients.

References

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