The relation between the renin-angiotensin-aldosterone (RAA) system and carbohydrate metabolism and insulin sensitivity in essential hypertension has not been investigated systematically. Twenty non-diabetic patients (age, 49 ± 1 years; body mass index (BMI), 26.1 ± 0.4 kg/m²) with essential hypertension (blood pressure, 155 ± 3/105 ± 1 mm Hg) received an oral glucose tolerance test (OGTT) at the end of a 1-month placebo period and again monthly during 3 months of angiotensin converting enzyme (ACE) inhibition (cilazapril, 5 mg/day). Furthermore, a two-step euglycemic insulin clamp was performed after placebo and again at the end of treatment. Blood pressure fell by 7 ± 4/10 ± 5 mm Hg (p < 0.001), while BMI remained stable. On the euglycemic clamp, insulin-mediated (plasma insulin, 470 pM) whole body glucose use averaged 42.5 ± 1.6 µmol/min kg⁻¹ before and 43.6 ± 1.9 after ACE inhibition (p = NS). Substrate concentrations and oxidative rates and energy expenditure (as estimated by indirect calorimetry) were not altered by ACE inhibition, either in the fasting state or in response to insulin. In contrast, oral glucose tolerance was significantly (p < 0.05) improved after treatment (area under OGTT curve (AUC), 240 ± 24 versus 282 ± 23 mmol²/hr⁻¹). The latter change was associated with enhanced (+16%, p < 0.05) insulin responsiveness to glucose (estimated as the insulin AUC divided by the glucose AUC) throughout the 3 months of ACE inhibition. At baseline, both the OGTT and the clamp had a marked hypokalemic effect (mean decrements in plasma potassium of 0.75 ± 0.05 and 0.92 ± 0.05 mmol/l, respectively) in association with plasma aldosterone reductions of 30% and 50%. Chronic ACE inhibition caused a further 20% (p < 0.03) lowering of plasma aldosterone concentrations but attenuated insulin-induced hypokalemia. Plasma sodium, which was unaltered by the pretreatment tests, fell during the posttreatment tests (by 3 mmol/l, p < 0.001). In the urine, the ratio of the fractional excretion of potassium to that of sodium was decreased by both oral glucose (-22%, p < 0.01) and ACE inhibition (-21%, p < 0.001). Higher plasma potassium levels before treatment predicted a better blood pressure response to ACE inhibition (r = 0.60, p < 0.005). In conclusion, in essential hypertension 1) chronic ACE inhibition does not interfere with insulin's effect on glucose uptake, substrate oxidation, or thermogenesis, but causes resistance to the potassium-lowering action of insulin; 2) this electrolyte change is associated with heightened insulin secretory response to glucose stimulation and improved oral glucose tolerance; and 3) higher plasma potassium levels predict a better blood pressure response to ACE inhibition.

KEY WORDS • essential hypertension • glucose • insulin resistance • angiotensin converting enzyme inhibitors • blood pressure

A wealth of epidemiological evidence supports a strong association between essential hypertension and impaired glucose tolerance.¹ The link between the two conditions can be independent of obesity² and is marked by hyperinsulinemia.³ Resistance to the blood glucose-lowering action of insulin has been detected in lean patients with untreated essential hypertension⁴ and is reputed to be the origin of the hyperinsulinemia. The salient features of the insulin resistance of essential hypertension are that it involves mostly the peripheral tissues (i.e., skeletal muscle)⁵ and that it is apparently pathway-specific (lipid and protein metabolism being unaffected⁶). Its origin remains, however, obscure.

The renin-angiotensin-aldosterone (RAA) system is involved in blood pressure homeostasis at multiple levels. Apart from the glucose intolerance of hyperaldosteronism,⁷ the interrelations between the RAA system and glucose tolerance and insulin sensitivity in essential hypertension have not been explored systematically. A recent study⁸ has raised the interesting possibility that inhibition of the angiotensin converting enzyme (ACE) may improve the insulin resistance of
Study Design

The study was designed as an open trial in which 12 weeks of active therapy were preceded by 4 weeks of a single-blind, placebo-controlled period. For the patients previously on antihypertensive treatment, all drugs were withdrawn for at least 2 weeks. During this washout period, patients were requested to have their blood pressure measured and recorded at least three times a week. At the end of this period, only the patients whose mean diastolic blood pressure was less than 115 mm Hg were included in the run-in period (week -4 to week 0). At week -4, a complete physical and clinical examination was performed, including laboratory measurements and electrocardiogram recording. Blood pressure was measured twice with a mercury sphygmomanometer, with the patient in the sitting position after resting quietly for 5 minutes, and then two more times after the patient had been standing for 1 minute. Systolic and diastolic blood pressure values were defined as Korotkoff Phase I and V, respectively. Heart rate was measured after each blood pressure measurement. Compliance to drug treatment was assessed by capsule counting at each visit and was expressed as percent of capsules consumed times days of therapy. If this percentage was below 80%, the patient was excluded from the study. At week -1, subjects received an oral glucose tolerance test (OGTT); at week 0, after the final assessment of inclusion criteria (mean sitting diastolic blood pressure below 100 and 115 mm Hg, compliance 80% or greater, and normal glucose tolerance), insulin sensitivity was assessed with the use of the euglycemic insulin clamp technique. Patients were asked to take the active drug (cilazapril, 2.5 mg) once a day in the morning before breakfast for the first week. At the end of week 1, patients were again checked for compliance and adverse events and, if mean sitting diastolic blood pressure was not reduced to less than 75 mm Hg, were started on the full dosage (5 mg/day). All patients had the dose increased. The OGTT was repeated at the end of the fourth, eighth, and twelfth week of active treatment. On all these occasions, blood pressure and heart rate values were recorded, and compliance was reassessed. At week 12, the euglycemic insulin clamp was repeated.

The nature of the investigation and the potential risks associated with it were fully explained to all subjects, who gave their consent before participating in the study. The research protocol was approved by the Institutional Review Board of the C.N.R. Institute of Clinical Physiology.

Methods

The study group consisted of 20 ambulatory patients (two women and 18 men) with moderate, established essential hypertension. The clinical characteristics are given in Table 1. All patients had mean sitting diastolic blood pressure values between 100 and 115 mm Hg on at least three measurements by the same physician. A complete medical workup was carried out to exclude secondary forms of hypertension. Renal, liver, and endocrine function was normal; no patient had experienced recent changes in body weight or dietary habits, or intercurrent illness. Additional criteria for inclusion in the study were normal body weight (less than 25% above or below desirable body weight, according to life insurance tables) and normal tolerance to oral glucose (according to the criteria set by the National Diabetes Data Group). Known duration of hypertension was 3.4 ± 0.8 years. Four patients had never received any therapy at the time of enrollment in the study. In the other patients, previous treatment of hypertension in the 3 months before entry into the study had consisted of monotherapy with ACE inhibitors (n = 2), β-blockers (n = 1), diuretics (n = 1), α-adrenergic receptor blockers (n = 1), calcium channel blockers (n = 3), or combination therapy (ACE inhibitors plus hydrochlorothiazide in four patients, calcium channel blockers plus β-blockers in two, calcium channel blockers plus ACE inhibitors in two). Only five patients were smokers (with a mean consumption of 20 cigarettes per day).

Subjects

The study group consisted of 20 ambulatory patients (two women and 18 men) with moderate, established essential hypertension. The clinical characteristics are given in Table 1. All patients had mean sitting diastolic blood pressure values between 100 and 115 mm Hg on at least three measurements by the same physician. A complete medical workup was carried out to exclude secondary forms of hypertension. Renal, liver, and endocrine function was normal; no patient had experienced recent changes in body weight or dietary habits, or intercurrent illness. Additional criteria for inclusion in the study were normal body weight (less than 25% above or below desirable body weight, according to life insurance tables) and normal tolerance to oral glucose (according to the criteria set by the National Diabetes Data Group). Known duration of hypertension was 3.4 ± 0.8 years. Four patients had never received any therapy at the time of enrollment in the study. In the other patients, previous treatment of hypertension in the 3 months before entry into the study had consisted of monotherapy with ACE inhibitors (n = 2), β-blockers (n = 1), diuretics (n = 1), α-adrenergic receptor blockers (n = 1), calcium channel blockers (n = 3), or combination therapy (ACE inhibitors plus hydrochlorothiazide in four patients, calcium channel blockers plus β-blockers in two, calcium channel blockers plus ACE inhibitors in two). Only five patients were smokers (with a mean consumption of 20 cigarettes per day).
**Analytical Procedures**

Plasma glucose was assayed by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, Calif.). Plasma insulin and aldosterone were measured by radioimmunoassay. For substrate determination, blood was drawn into chilled tubes containing 1 N perchloric acid (1:1, wt/wt) and immediately centrifuged. The deproteinized supernatants were stored at −20°C until analysis, which was always carried out within a few days. Glucose, lactate, pyruvate, glycerol, β-hydroxybutyrate, and alanine were all assayed by enzymatic methods by continuous-flow fluorimetry. FFA were measured on the plasma samples by an enzymatic method (Wako Chemical GmbH, Neuss, FRG). Serum triglycerides, total cholesterol, creatinine, and urea were assayed by standard enzymatic methods. Plasma and urine sodium and potassium were assayed in duplicate by an ion selective electrode method (KNA 2 Sodium Potassium Analyzer, Radiometer, Copenhagen), and nonprotein urinary nitrogen by the Kjeldhal method.

**Data Analysis**

Steady-state plasma glucose and insulin concentrations were calculated as the mean of the values obtained during the last hour of the hyperinsulinemic clamp. The amount of exogenous glucose required to maintain euglycemia (glucose infusion rate) was averaged every 20 minutes. Whole body glucose disposal (M) was calculated from the glucose infusion rate after correction for changes in glucose levels in a distribution volume of 250 ml·kg⁻¹·h⁻¹. Such calculation assumes that endogenous glucose production is completely suppressed. In the present protocol, the first hyperinsulinemic step maintained for 2 hours was used as a means for ensuring complete, tight inhibition of liver glucose output while avoiding the use of radioactive glucose tracers. The metabolic clearance rate of glucose was calculated by dividing M by the glucose concentration averaged over corresponding time intervals. Finally, an insulin sensitivity index (CR/I, the volume of plasma cleared of glucose every minute per unit of plasma insulin concentration) was calculated by dividing metabolic clearance rate by the mean insulin concentration during the same period of time. Since insulin-stimulated glucose use is linearly related to the logarithm of circulating insulin levels over the physiological range, CR/I was calculated by using the natural logarithm of plasma insulin concentrations. Glucose and insulin areas under the OGTT curve were computed by trapezoidal integration. Both total and incremental areas were calculated. Protein oxidation was estimated from the urinary nonprotein nitrogen excretion rate, after correcting for changes in the body urea pool. Whole body net rates of carbohydrate and lipid oxidation and energy expenditure were estimated from gaseous exchange measurements (and protein oxidation rates) according to standard calorimetric equations, as described elsewhere. Since the resting rate of energy expenditure is a faithful reflection of the entire body mass of metabolically active cells, rates of substrate oxidation were normalized by the resting energy expenditure.

**Results**

**Blood Pressure**

As shown in Table 1, in the patients as a group both systolic and diastolic blood pressure had fallen significantly from baseline at the end of ACE inhibition. The mean decrement was 7 ± 4 mm Hg for the systolic, and 10 ± 3 mm Hg for the diastolic pressure. A significant decrease of diastolic blood pressure was achieved already after the first month of therapy (Figure 1), and this change was sustained for the following 8 weeks. Five of 20 patients (25%) did not respond to the antihypertensive treatment: their blood pressure increased slightly over the 3-month follow-up period. In the remaining 15 subjects, blood pressure lowering was 13 ± 3 mm Hg for systolic and 17 ± 2 mm Hg for diastolic pressure. Only two patients experienced transient headache during the first month of therapy. No other adverse events were recorded. The mean change in body weight over 3 months of treatment was −0.16 ± 0.28 kg (p = NS versus zero), with a range of −3.0 to +1.6 kg.
TABLE 2. Net Whole Body Rates of Carbohydrate, Lipid, and Protein Oxidation, and of Energy Expenditure During the Oral Glucose Load at Baseline and After Three Months of Therapy

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate oxidation (mmol/kg REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>129±14</td>
<td>182±18</td>
<td>246±19</td>
<td>257±18</td>
</tr>
<tr>
<td>3 months</td>
<td>135±13</td>
<td>179±22</td>
<td>233±20</td>
<td>223±20</td>
</tr>
<tr>
<td>Lipid oxidation (mmol/kg REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44±4</td>
<td>45±4</td>
<td>29±4</td>
<td>25±4</td>
</tr>
<tr>
<td>3 months</td>
<td>41±3</td>
<td>58±5</td>
<td>44±5</td>
<td>25±5</td>
</tr>
<tr>
<td>Protein oxidation (mmol/kg REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87±9</td>
<td>49±9</td>
<td></td>
<td></td>
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<tr>
<td>3 months</td>
<td>100±10</td>
<td>49±10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy expenditure (kJ/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.9±0.2</td>
<td>5.2±0.2</td>
<td>5.4±0.2</td>
<td>5.2±0.2</td>
</tr>
<tr>
<td>3 months</td>
<td>4.8±0.2</td>
<td>5.2±0.2</td>
<td>5.3±0.2</td>
<td>5.4±0.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. REE, resting energy expenditure.

Basal rates of substrate oxidation were similar at baseline and at the end of 12 weeks of treatment (Table 2). At baseline, glucose ingestion induced a marked increase in carbohydrate oxidation (averaging +80% over the 3 hours of the test), a consistent 60% decrease in lipid oxidation, and a 50% decline in protein oxidation. These metabolic responses to oral glucose were all similar at 12 weeks. Energy expenditure was significantly stimulated (+9% on the average over 3 hours) by oral glucose (diet-induced thermogenesis) in a parallel fashion on the two occasions (Table 2).

Insulin Sensitivity

During the baseline clamp study, plasma insulin was maintained at plateaus of 254±7 and 473±36 pmol/l by the lower (3.6 pmol • min⁻¹ • kg⁻¹) and higher (7.2 pmol • min⁻¹ • kg⁻¹) insulin infusion rate, respectively. Virtually identical plasma insulin levels (255±14 and 477±21 pmol/l) were achieved after 12 weeks of treatment (Figure 2). Plasma glucose levels were maintained stable throughout the 4 hours of the clamp on both occasions. The amounts of exogenous glucose required to hold plasma glucose levels constant were similar at all time points before and after treatment (Figure 2). The mean M value (i.e., the rate of whole body glucose metabolism during the last 60 minutes of the clamp) was 42.5±1.6 mmol • min⁻¹ • kg⁻¹ before and 43.6±1.9 after therapy (p=NS). Expressing the data as mean insulin-stimulated glucose clearance rate (i.e., the M value divided by the prevailing plasma glucose level and normalized by the concurrent plasma insulin concentration) did not change this result (1.39±0.001 versus 1.43±0.001 ml • min⁻¹ • kg⁻¹ per picomole per liter plasma insulin, before versus after treatment, p=NS).

As in the case of the OGTT, basal rates of substrate oxidation on the day of the clamp study were similar before and after therapy (Table 3). Euglycemic hyper-insulinemia induced a 120% stimulation of net carbohydrate oxidation during the last hour of the clamp,

Oral Glucose Tolerance

Fasting plasma glucose and insulin levels were not significantly changed throughout the study. The time-integrated increments in plasma glucose and insulin concentrations above their respective basal values in response to oral glucose (area under curve) on all four OGTTs that each patient received at monthly intervals are shown in Figure 1. The incremental glucose area was significantly (p<0.05) reduced in comparison to baseline only on the final test (240±24 versus 282±23 mmol 2 hr⁻¹), whereas the changes in the insulin area did not reach statistical significance. The ratio of insulin area to glucose area, on the other hand, was significantly higher at all test times during ACE inhibition as compared with baseline.
Santoro et al Insulin Resistance and ACE Inhibition

All these responses were reproduced very closely on the occasion of the repeat clamp study after 12 weeks of ACE inhibition (Table 3). Blood lactate concentrations increased by 13% during the final hour of the clamp, whereas the circulating concentrations of pyruvate, FFA, glycerol, and β-hydroxybutyrate fell during euglycemic hyperinsulinemia (Table 4). All of these metabolic responses to insulin were similar after treatment.

Sodium and Potassium

The time course of the changes in plasma sodium and potassium levels during oral glucose loading as well as during the clamp are depicted in Figure 3. As can be seen, plasma potassium fell during both tests, but less at week 12 than at baseline. Plasma sodium showed smaller changes during either test and generally remained higher before than after treatment. The statistical analysis of these data is reported in Table 5 for the electrolyte concentrations averaged over the baseline period (mean of three determinations) and over the entire test (mean of six and 12 determinations, for the OGTT and the clamp, respectively). A three-way ANOVA design was used to test for the independent effects of the test itself (OGTT or clamp), of antihypertensive treatment (by comparing week — 1 to week 12), and of the type of test applied (by comparing the OGTT with the clamp). Both tests induced a significant fall in plasma potassium levels (p<0.001); the clamp was significantly more potent than the OGTT (p<0.03). Antihypertensive treatment per se, on the other hand, was associated with a blunted fall in plasma potassium (p=0.08). Neither test induced significant changes in plasma sodium concentrations; in contrast, ACE inhibition caused a decrease in plasma sodium during testing (OGTT as well as clamp, p<0.001). Consequently, the ratio of plasma sodium to plasma potassium concentrations (Na/K ratio) rose in association with both oral glucose and insulin clamping (p<0.001), but significantly (p<0.001) less so after than before ACE inhibition. Table 5 also reports the plasma aldosterone concentrat-

Table 3. Net Whole Body Rates of Carbohydrate, Lipid, and Protein Oxidation, and of Energy Expenditure During the Clamp Study at Baseline and After Three Months of Therapy

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>40</th>
<th>80</th>
<th>120</th>
<th>160</th>
<th>200</th>
<th>240</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate oxidation (µmol/kJ REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>125±12</td>
<td>147±11</td>
<td>182±12</td>
<td>205±11</td>
<td>234±14</td>
<td>263±15</td>
<td>292±14</td>
</tr>
<tr>
<td>3 months</td>
<td>117±17</td>
<td>153±19</td>
<td>171±18</td>
<td>194±20</td>
<td>223±18</td>
<td>256±20</td>
<td>296±19</td>
</tr>
<tr>
<td>Lipid oxidation (µmol/kJ REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>43±3</td>
<td>47±4</td>
<td>38±4</td>
<td>31±3</td>
<td>29±4</td>
<td>22±4</td>
<td>14±4</td>
</tr>
<tr>
<td>3 months</td>
<td>43±5</td>
<td>47±4</td>
<td>41±4</td>
<td>36±4</td>
<td>30±5</td>
<td>22±6</td>
<td>11±5</td>
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<tr>
<td>Protein oxidation (µmol/kJ REE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>96±10</td>
<td>.</td>
<td>.</td>
<td>58±10</td>
<td>.</td>
<td>.</td>
<td>38±9</td>
</tr>
<tr>
<td>3 months</td>
<td>116±12</td>
<td>.</td>
<td>.</td>
<td>60±10</td>
<td>.</td>
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<td>58±6</td>
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<tr>
<td>Energy expenditure (kJ·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.11±0.14</td>
<td>5.16±0.14</td>
<td>5.25±0.15</td>
<td>5.28±0.16</td>
<td>5.33±0.15</td>
<td>5.43±0.16</td>
<td>5.47±0.17</td>
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<tr>
<td>3 months</td>
<td>4.95±0.16</td>
<td>5.05±0.14</td>
<td>4.99±0.13</td>
<td>5.05±0.12</td>
<td>5.18±0.14</td>
<td>5.27±0.16</td>
<td>5.35±0.17</td>
</tr>
</tbody>
</table>

Values are mean±SEM. REE, resting energy expenditure.
TABLE 4. Blood Substrate Concentrations, Plasma Free Fatty Acid, and Glycerol Levels at Baseline and After Three Months of Treatment

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Basal</th>
<th>40</th>
<th>80</th>
<th>120</th>
<th>160</th>
<th>200</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>0.910±0.097</td>
<td>0.977±0.074</td>
<td>0.939±0.056</td>
<td>0.828±0.047</td>
<td>0.914±0.057</td>
<td>0.958±0.058</td>
<td>1.097±0.066</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>1.004±0.092</td>
<td>1.012±0.059</td>
<td>0.996±0.042</td>
<td>0.934±0.042</td>
<td>0.947±0.042</td>
<td>1.034±0.049</td>
<td>1.140±0.0254</td>
</tr>
<tr>
<td>FFA</td>
<td>101±11</td>
<td>104±8</td>
<td>95±7</td>
<td>76±5</td>
<td>85±6</td>
<td>74±6</td>
<td>71±7</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.461±0.032</td>
<td>0.195±0.022</td>
<td>0.134±0.018</td>
<td>0.117±0.014</td>
<td>0.094±0.009</td>
<td>0.097±0.011</td>
<td>0.092±0.010</td>
</tr>
<tr>
<td>Butyrate</td>
<td>53±3</td>
<td>22±2</td>
<td>18±2</td>
<td>17±2</td>
<td>13±2</td>
<td>12±1</td>
<td>12±1</td>
</tr>
<tr>
<td>Basal</td>
<td>184±39</td>
<td>81±15</td>
<td>50±6</td>
<td>36±4</td>
<td>34±4</td>
<td>28±3</td>
<td>28±2</td>
</tr>
<tr>
<td>3 months</td>
<td>148±26</td>
<td>75±8</td>
<td>45±5</td>
<td>41±4</td>
<td>36±3</td>
<td>33±3</td>
<td>34±3</td>
</tr>
</tbody>
</table>

FFA, free fatty acids. Values are mean±SEM in millimoles per liter.

Measurements of urinary sodium and potassium excretion were obtained basally and after oral glucose loading, at week —1 and again at week 12 (Table 6). Urine flow rate averaged ~1 ml·min⁻¹ during the basal period (141±27 and 119±8 minutes of urine collection, at week —1 and 12, respectively), and increased by 50% on average during the OGTT (236±12 and 224±8 minutes of urine collection). Plasma creatinine clearance was not affected by either glucose loading or ACE inhibition. Urinary sodium excretion increased (by ~20%) during the OGTT and tended to be higher after than before treatment (by 18%, p=0.09), whereas urinary potassium excretion was not modified by either manipulation. At baseline, the fractional excretion of potassium and sodium averaged 12.0% and 0.64%, respectively. Although neither glucose loading nor ACE inhibition induced large enough changes in these excre-

Figure 3. Line graphs show plasma sodium (top panel) and potassium (bottom panel) concentrations during the oral glucose tolerance test (OGTT) (left panel) and the euglycemic clamp (right panel) in hypertensive patients at baseline and after 3 months of angiotensin converting enzyme inhibition.
Correlation Analysis

At baseline, insulin sensitivity (i.e., the M value during the last hour of the clamp study) was inversely related to body mass index and the incremental insulin area (Figure 4). With regard to electrolytes, the fractional excretion of potassium was directly related to that of sodium both basally (r = 0.78, p < 0.001) and during the OGTT (r = 0.55, p < 0.001) and inversely related to the mean plasma potassium concentration during the OGTT (r = 0.47, p < 0.05). Thus, the urinary excretions of the two electrolytes were coupled to one another, and a greater fractional urinary loss of potassium was associated with lower kalemia during insulin stimulation.

When the changes induced by 3 months of treatment were examined, it was found that the observed fall in mean arterial blood pressure was significantly related (r = 0.53, p < 0.02) to the changes in body mass in a direct fashion (even within the very narrow range of body weight changes observed).

When the treatment-induced changes in blood pressure were related to the baseline measurements, it was found that the extent of blood pressure decrease was predicted by higher plasma potassium concentrations, both during fasting and during the OGTT, and by lower fractional urinary potassium excretion, basally as well as during the OGTT (Figure 5).

Discussion

The patients studied here were moderately hypertensive after at least 6 weeks of pharmacological wash-out; were within 25% of their ideal body weight; had normal glucose tolerance and normal plasma lipid, electrolyte, and aldosterone concentrations. At baseline, the patients whose insulin sensitivity was relatively lower were also relatively heavier, and their insulin response to oral glucose was correspondingly greater (Figure 4). Within the group, there was a weak inverse relation between insulin sensitivity and blood pressure. Thus, in subjects with essential hypertension we observed the same relations that are found in normotensive, healthy individuals: in vivo insulin sensitivity is adversely affected by relative overweight and, to a lesser extent, by higher blood pressure, whereas hyperinsulinemia in response to glucose compensates for reduced insulin action.

The rise in plasma insulin concentrations induced by oral glucose or intravenous insulin caused marked hy-

<table>
<thead>
<tr>
<th>Measurements</th>
<th>OGGT</th>
<th>Clamp</th>
<th>Test</th>
<th>Week</th>
<th>OGTT vs. clamp</th>
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<tr>
<td><strong>Parameters</strong></td>
<td><strong>Week 0</strong></td>
<td><strong>Week 12</strong></td>
<td><strong>Week 0</strong></td>
<td><strong>Week 12</strong></td>
<td><strong>Week</strong></td>
</tr>
<tr>
<td>UFR (ml/min)</td>
<td>0.9±0.1</td>
<td>1.1±0.2</td>
<td>1.6±0.2</td>
<td>1.4±0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PCC (ml/min)</td>
<td>119±11</td>
<td>125±12</td>
<td>152±24</td>
<td>160±25</td>
<td>NS</td>
</tr>
<tr>
<td>UNaV (mEq/min)</td>
<td>93±10</td>
<td>120±18</td>
<td>135±19</td>
<td>148±12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UKV (mEq/min)</td>
<td>58±7</td>
<td>59±8</td>
<td>52±6</td>
<td>52±3</td>
<td>NS</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>12.0±1.4</td>
<td>11.7±1.5</td>
<td>10.9±1.0</td>
<td>10.0±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>FEna (%)</td>
<td>0.64±0.07</td>
<td>0.77±0.07</td>
<td>0.76±0.10</td>
<td>0.80±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>FEK/FEna</td>
<td>20.2±1.4</td>
<td>16.0±1.2</td>
<td>15.8±1.2</td>
<td>12.6±0.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Value of p for the effects of insulin (test) and treatment (week), and type of test (OGTT vs. clamp) by three-way analysis of variance with repeated measures over treatment.

UFR, urine flow rate; PCC, plasma creatinine clearance; UNaV, sodium excretion; UKV, potassium excretion; FEK, fractional excretion of potassium; FEna, fractional excretion of sodium; FEK/FEna, ratio of fractional excretion of sodium to fractional excretion of potassium.
meal (oral glucose plus salt), and under these conditions of marked extracellular volume expansion; this maneuver may have masked any insulin-induced antinatriuresis and causes hypokalemia; the latter in turn reduces aldosterone output and kaliuresis. Of these responses, the first three would raise blood pressure, but a reduced aldosterone would lower it. Since aldosterone and natriuresis do not contribute to rapid changes in blood pressure, the net effect of adrenergic activation and hypokalemia after glucose ingestion should be a rise in blood pressure. However, a consistent increase in blood pressure has not been found either during an OGTT or during an insulin clamp in humans. In fact, we have observed a transient decline in blood pressure in hypertensive patients after glucose ingestion whether or not insulin-induced hypokalemia was prevented (Natali et al, unpublished observations). Thus, it is clear that the hemodynamic response to glucose must involve sufficient peripheral vasodilation (or redistribution of cardiac output) to counteract the pressor signals generated by feeding.

Three months of ACE inhibition reduced blood pressure (especially diastolic blood pressure, Figure 1) in three fourths of the patients but failed to change their insulin sensitivity significantly (Figure 2). This result stands in contrast to that reported by Pollare et al with the use of captopril. In the latter study, the improvement in insulin sensitivity associated with ACE inhibition was small but statistically different from a decrease in insulin sensitivity induced by high doses of hydrochlorothiazide in a crossover design. In evaluating this discrepancy, the following points should be considered in addition to possible differences between individual drugs of the same class (captopril versus cilazapril).

First, ACE inhibiting drugs acutely vasodilate forearm blood vessels, although they do not usually change forearm blood flow because of the concurrent reduction in blood pressure. Vasodilation of muscle tissue during insulin administration would in fact enhance glucose uptake by recruiting previously unperfused areas. Such a mechanism for enhancing insulin sensitivity should be common to any vasodilating agent and independent of any interference with the RAA system. In the present study, the morning dose of cilazapril was withheld on the test days specifically to avoid any acute, blood flow–related effects. Second, changes in body weight influence in vivo insulin sensitivity strongly. In the current studies, consistent dietary monitoring resulted in maintenance of body weight in the patients as a group (Table 1). Nevertheless, the observed, very small changes in body mass index correlated inversely with changes in insulin sensitivity (r=0.36, p=0.11) and directly with changes in blood pressure. A sizeable proportion (25%) of the overall variability of blood pressure changes over 3 months was statistically explained by the changes in body mass index (data not shown). In previous studies, the confounding influence of body weight changes on the relation between insulin sensitivity and response to antihypertensive treatment has not been accounted for. Third, in normotensive, insulin-dependent diabetic patients, in whom any drug-related effect on insulin secretion can be excluded, insulin-mediated glucose disposal was not altered by 3 weeks of enalapril treatment. Finally, in
hypertensive patients with non-insulin-dependent diabetes, 3 months of treatment with captopril did not alter insulin sensitivity (Seghieri et al, unpublished results). Thus, the weight of evidence indicates that chronic interference with the RAA axis at the converting enzyme level does not per se modify insulin sensitivity.

Chronic ACE inhibition resulted in an improved tolerance to oral glucose at the end of the third month of treatment (Figure 1). This change was associated with a heightened insulin response to oral glucose. That such higher response resulted from enhanced insulin secretion rather than decreased plasma insulin clearance is documented by the clamp studies (Figure 2), in which the exogenous insulin infusion gave rise to virtually identical hyperinsulineemic plateaus before and after treatment. Performing OGTTs at monthly intervals made it possible to follow the sequence of these metabolic events. The insulin secretory response to glucose (expressed as area under the curve) rose at 1 and 2 months of treatment, then fell to pretreatment values at the third month, i.e., at the time when the glucose area under the curve was significantly below pretreatment values (Figure 1). Thus, it is the sensitivity of insulin release to glucose stimulation (expressed as the insulin/glucose area, Figure 1) that was specifically enhanced by ACE inhibition, and caused a better glucose tolerance.

This finding may explain previous anecdotal reports of hypoglycemia in non-insulin-dependent diabetic patients after initiation of captopril treatment.36-38

Chronic ACE inhibition was associated with distinct changes in electrolyte metabolism. In the plasma, potassium levels were higher and sodium levels lower after rather than before treatment. In the urine, sodium excretion during the OGTT was slightly greater after rather than before ACE inhibition, and the K/Na ratio was significantly lower (Table 6). These findings can all be explained by the lower aldosterone levels (Table 5): enhanced urinary excretion of the acute sodium load during the posttreatment test increases distal sodium delivery, thereby maintaining the absolute rate of potassium excretion unchanged. However, relative to sodium and prevailing plasma levels (K/Na ratio), less potassium than sodium is excreted, and more potassium than sodium is found in the plasma (Figure 3). Thus, in descriptive terms chronic ACE inhibition results in resistance to the potassium-lowering action of insulin. On a long-term basis, this would result in an expansion of whole body potassium stores, which would further oppose plasma potassium decrements during insulin stimulation. Whether and how these electrolyte changes were causally related to the blood pressure response to ACE inhibition cannot be established firmly. Extracellular potassium level is reputed to be a prime regulator of membrane potential and tension in smooth muscle cells: within the physiological range of potassium concentrations, increasing potassium induces hyperpolarization and reduced tension of cell membranes, thereby causing vasodilation.39 Of note is that the treatment-induced changes in plasma potassium and sodium were minimal in the fasting state but emerged clearly during insulin stimulation (OGGT or clamp, Figure 3). This implies that such potassium-sparing effect, however small, is extended to every meal, resulting in a higher average extracellular potassium concentration around the clock (in humans, the fed state lasts twice as long as the fasting state). Such persistent, relative hyperkalemia might contribute to keeping blood pressure at a lower level.

One important consequence of these electrolyte changes is the improvement in the insulin response to

![Figure 5](https://hyper.ahajournals.org/)

**Figure 5.** Scatterplots show relation between the changes in diastolic (DBP) or systolic (SBP) blood pressure induced by 3 months of angiotensin converting enzyme inhibition and the mean plasma potassium concentrations in the fasting state or during the oral glucose tolerance test (OGTT) measured at baseline (i.e., before treatment). The right side of the figure shows similar correlations for the fractional urinary potassium excretion in the fasting state and during the OGTT, both measured at baseline.
glucose that resulted from ACE inhibition. Larger increases in the insulin/glucose ratio over 3 months of treatment were significantly associated with greater decrements in plasma Na/K ratio during the tests. Thus, at least one factor responsible for the augmented sensitivity of insulin secretory response to glucose stimulation could be identified with some degree of certainty. Hypokalemia is believed to be responsible for the glucose intolerance of primary or secondary hyperaldosteronism,40 Barter’s syndrome,41 and diuretic administration.42 Short-term (1 week) experimental potassium depletion blunts the plasma insulin response to sustained hyperglycemia in normal men.43 The present study adds to the available information by suggesting that in individuals with essential hypertension, even a small improvement in the K/Na status is associated with a detectable augmentation of insulin response to glucose and glucose tolerance.

An intriguing observation was that higher plasma potassium concentrations or lower fractional potassium losses (Figure 5) at baseline (i.e., before treatment) both predicted a better blood pressure response to ACE inhibition. A high urinary K/Na ratio has been found to be associated with higher blood pressure in several surveys.44,45 Furthermore, potassium depletion raises blood pressure in normotensive men, and potassium supplementation reduces blood pressure in hypertensive patients.46 Precisely how the initial potassium status should be indicative of subsequent blood pressure response to ACE inhibition is, however, not clear. If relative hyperkaliuresis and hypokalemia were signs of excessive aldosterone activity, then interrupting the RAA axis should produce the most dramatic decrements in blood pressure, such as happens in secondary hyperaldosteronism.47 The reverse, however, was true in our patients. If, on the other hand, a high salt diet (resulting in hyperkaliuresis) or selective renal potassium leakage were the origin of the relative hypokalemia, then aldosterone secretion would be less stimulated, and ACE inhibition would be less effective in lowering blood pressure via aldosterone. The present data cannot differentiate the origin (dietary or renal) of the plasma potassium differences among our hypertensive patients because balance conditions were not attempted. We can, however, exclude that changes in dietary salt intake over the period of treatment may have contributed to the observed blood pressure response, because urinary sodium excretion (which was measured at weeks −1, 0, 4, 8, 11, and 12 in each patient) remained stable (data not shown).

Acknowledgments

The excellent technical assistance of Giuseppe Buzzigoli, Claudio Boni, Demetrio Ciociaro, Neda Pecori, and Giovanna Sanna is gratefully acknowledged. We thank Dr. Timothy Goggin from Roche Department of Clinical Research (Basel) for his contribution and support and Prof. Antonio Salvetti for critically reading the manuscript.

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Hypertension. 1992;20:181-191
doi: 10.1161/01.HYP.20.2.181

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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