Insulin Sensitivity and Endothelial Function in Hypertension

A Comparison of Temocapril and Candesartan

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**Background:** Recent studies have suggested that angiotensin-converting enzyme inhibitors (ACEi) have a more pronounced effect on endothelial function (END) than angiotensin II receptor blocker (ARB); however, whether this pronounced effect is more beneficial to patients with insulin sensitivity (IS) remains uncertain. The present study compared the effects of ACEi and ARB on END and IS in patients with hypertension.

**Methods:** A total of 23 patients with hypertension were given either ACEi or ARB alternatively in a cross-over manner for 8-week intervals. Both END and IS were examined after each treatment period; END was assessed by the response of forearm blood flow to reactive hyperemia and IS by an insulin tolerance test. The plasma levels of bradykinin (BK), NOx, tumor necrosis factor (TNF-α), and adiponectin (Adi) were also measured after each treatment.

**Results:** We found that END, BK, and NOx were higher after the ACEi treatment than after the ARB treatment. Although the IS and the Adi levels were similar after both treatments, the TNF-α level was lower after the ARB treatment than after the ACEi.

**Conclusions:** We conclude that ACEi and ARB may have similar effects on insulin sensitivity, irrespective of the more pronounced effects of ACEi on endothelial function. The BK–NO pathway might contribute, at least in part, to the pronounced effect of ACEi. On the other hand, the underlying mechanisms affecting insulin sensitivity might differ for both treatments. These results suggest that endothelial function is not a major determinant of insulin sensitivity under physiologic conditions. Am J Hypertens 2005;18:178–182 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Vascular endothelium, insulin resistance, angiotensin-converting enzyme inhibitor, angiotensin II type 1 receptor blocker, bradykinin.

Abnormal glucose metabolism complications in patients with hypertension augment atherosclerotic vascular damage and lead to a poor prognosis. Proper management of these complications is thus crucial to prevent atherosclerotic cardiovascular events. Endothelial dysfunction is an early marker of atherosclerotic vascular damage, and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARB) improve not only abnormal glucose metabolism but also this dysfunction. Some studies have suggested that ACEi have a more pronounced effect on endothelial function. Although several studies have demonstrated the association between endothelial dysfunction and insulin resistance, the concomitant changes in insulin sensitivity with the pronounced effects of ACEi on endothelial function are not clear. The present study was conducted to compare the effects of ACEi and ARB on endothelial function and insulin sensitivity in patients with hypertension. The study was performed in a cross-over manner under conditions resulting in a similar decrease in blood pressure (BP) levels for both treatments.

**Methods**

**Subjects**

A total of 22 patients treated for essential hypertension at Tokyo Medical University Hospital between June 2003 and November 2003 were enrolled in the present study. None of the patients had a history of atherosclerotic cardiovascular diseases. Patients with serious medical prob-
lems requiring specific medical treatment were excluded. All patients had been treated with either an ACEi or an ARB for >6 months before entering this study, and none of the patients were being treated with other drugs apart from the antihypertensive medication. Before entering the study, an ACEi (temocapril, 4 mg, n = 7; or enalapril, 5 mg, n = 3) was prescribed to 10 patients, and an ARB (candesartan, 8 mg, n = 8; or losartan, 50 mg, n = 4) was prescribed to 12 patients. Blood pressure was determined in an office setting using the conventional cuff method. Subjects were seated in a temperature-controlled room for at least 10 min before the measurement. Diastolic BP was determined at Korotoff phase V. Subjects’ BP was controlled at a level of <150/90 mm Hg for at least 6 months before starting the study protocol using the same medication. All women were postmenopausal and none of them had received hormonal replacement therapy. Informed consent was obtained from all participants. The protocol of the present study was approved by the Ethical Committee of Tokyo Medical University.

Medication Protocol

This study was performed in a cross-over manner using a single-blind protocol to avoid biases (that is, no information about the prescribed medication was provided to the examiners who performed the endothelial function test, insulin tolerance test, or data analysis). Patients who had been treated with an ACEi before entering the study were given candesartan (Takeda Co., Osaka, Japan) at a dosage of 8 mg/day instead of the ACEi; 6 weeks later, the candesartan was switched to temocapril (Sankyo Co., Tokyo, Japan) at a dosage of 4 mg/day for the next 6 weeks (without a washout period). Patients who had been given an ARB before entering the study were given temocapril (4 mg/day) for 6 weeks and then candesartan (8 mg/day) for 6 weeks. If patients had been given antihypertensive drugs other than ACEi or ARB before entering the study, such drugs were not changed during this medication protocol period. On the final day of each treatment (the examination day), an endothelial function test, insulin tolerance test, and blood sampling were performed. The medication protocol was organized by one of the investigators (H.T.) without providing any information regarding the medication to the examiners.

Examination Protocol

After a 12-h overnight fast, the patients were asked to remain in a supine position in a temperature-controlled (24°C) room. At 8:00 AM, a plastic needle was placed in the antecubital vein of the left forearm for the blood sampling and insulin tolerance test, and normal saline solution was infused intravenously at a rate of 20 mL/h. Thirty minutes later (8:30 AM), blood was drawn from the left arm, and an endothelial function test was performed in the right arm. Twenty minutes later (8:50 AM), the insulin tolerance test was performed. The examination protocol was performed by three of the investigators (K.M., M.Y., and T.A.), who had no knowledge of the medication protocol.

Endothelial Function Test

Forearm blood flow was measured using strain-gauge plethysmography (model EC5R, DE Hokanson, Inc., Bellevue, WA). A mercury-in-Silastic strain gauge that had been electrically calibrated was placed on the widest part of the right forearm. A wrist cuff was inflated to 50 mm Hg greater than the systolic BP to exclude the hand circulation from the measurements taken 1 min before measuring the forearm blood flow. The upper arm–congesting cuff was inflated to 40 mm Hg. Forearm blood flow was recorded for 7 sec and expressed as milliliters of blood flow per minute per 100 mL of forearm volume. The forearm vasodilatory response to reactive hyperemia was obtained using previously established methods. After obtaining the baseline value of the forearm blood flow using two measurements (the mean of which was used as the baseline value), the upper arm was compressed by inflation of a pneumatic tourniquet at a pressure of 30 mm Hg more than the systolic BP for 4.5 min. After cuff deflation, forearm blood flow was measured until 120 sec after cuff deflation. The reactive hyperemia ratio was calculated as reactive hyperemia divided by the baseline value of the forearm blood flow. Data were analyzed by two investigators (Z.G. and Y.K.) who had no knowledge of the medication protocol and the means of their measurements used. In 22 volunteers, the coefficient of variation for reproducibility was 4.3%.

Insulin Tolerance Test

The insulin tolerance test was performed according to the method of Bonora et al. A bolus of regular insulin (0.1 U/kg) was infused, and blood samples were collected at 3, 6, 9, 12, and 15 min after the infusion. Insulin sensitivity was estimated using the rate constant for plasma glucose disappearance in the insulin tolerance test; the rate constant for plasma glucose disappearance in the insulin tolerance test was calculated using the formula 0.693/t_{1/2}.

Laboratory Measurements

Plasma total cholesterol, high-density lipoprotein cholesterol, triglycerides, and blood sugar were measured by enzymatic methods. The plasma insulin concentration was determined by radioimmunoassay (SRL, Tokyo, Japan), and the Homeostasis Model Assessment (HOMA) was calculated as the fasting plasma glucose (mg/dL) × fasting insulin (μU/mL) / 405. Plasma levels of bradykinin, 8-iso prostaglandin F_{2α}, tumor necrosis factor–α (TNF-α), and adiponectin were determined using commercially available kits. Nitrogen oxide levels were measured in serum using a chemiluminescent technique. The serum level of angiotensin-converting enzyme activity was as-
Table 1. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>15/7</td>
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<tr>
<td>Smoking (no. of subjects)</td>
<td>5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>226 ± 14</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>41 ± 12</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>176 ± 52</td>
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Medication during study period
- No. of subjects taking ACEi alone: 2
- No. of subjects taking ARB alone: 1
- No. of subjects taking other drugs: 11
  - Ca-ant + diuretics: 1
  - Ca-ant + diuretics + β-blocker: 2

ACEi – angiotensin-converting enzyme inhibitor, ARB – angiotensin II type 1 receptor blocker, Ca-ant – calcium channel antagonist, HDL – high-density lipoprotein cholesterol, TC – total cholesterol; TG – triglycerides.

Statistical Analysis

Data were expressed as means ± SD. Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, IL). Differences between treatments were evaluated using the Wilcoxon t test for two paired variables. For parameters showing a significant difference between treatments, the time effect associated with the cross-over design was evaluated using logistic regression analysis. A P value of < .05 was considered to indicate a statistically significant difference.

Results

Table 1 lists clinical characteristics of the study population. Body mass index did not change during the protocol period. Figure 1 shows the changes in the reactive hyperemia ratio and the plasma levels of bradykinin, nitric oxide, and total 8-iso prostaglandin F2α after treatment with either ACEi or ARB. The reactive hyperemia ratio was significantly higher after the ACEi treatment than after the ARB. The plasma levels of bradykinin and nitric oxide were also higher after the ACEi treatment than after the ARB treatment, whereas the plasma level of 8-iso prostaglandin F2α was lower after the ACEi treatment than after the ARB. The plasma level of TNF-α was lower after the ARB treatment than after the ACEi (Fig. 2). All parameters related to glucose metabolism, including the insulin tolerance test results, were similar after both treatment methods (Table 2 and Fig. 2). Logistic regression analysis confirmed that the time effects associated with the cross-over design (that is, which of the two drugs was used first) did not significantly affect any of the previously mentioned variables exhibiting intergroup differences.

Discussion

This is the first study to examine whether the pronounced effects of ACEi on endothelial function are beneficial with regard to insulin sensitivity compared with those of ARB. Although the plasma level of adiponectin and the rate constant for plasma glucose disappearance in the insulin tolerance test were similar after treatment with ACEi or ARB, the plasma levels of bradykinin and TNF-α and the serum level of nitrogen oxides were higher, and the plasma level of 8-iso prostaglandin F2α was lower, after treatment with ACEi, as compared with values after treatment with ARB.

The response of forearm blood flow to reactive hyperemia is regarded as a marker related to endothelial function. Both ACEi and ARB improve the response of forearm blood flow to reactive hyperemia, and some...
studies have reported that improvement of this response is more pronounced after treatment with ACEi.8–10 On the other hand, although ACEi and ARB are beneficial for glucose metabolisms,4–7 only a few clinical studies have compared the effects of both treatments, and the differences have not been fully determined.18 Several lines of evidence suggest the presence of a strong association between insulin resistance and endothelial dysfunction.11–13 Previous studies have demonstrated that the improvement in endothelial function by interventional approaches such as lifestyle modification or oral supplementation with dehydroepiandrosterone are accompanied by an improvement in insulin sensitivity.19,20 However, although the present cross-over study confirmed the pronounced effect of ACEi on endothelial function, insulin sensitivity was similar after both treatments. Thus, insulin sensitivity is not always related to changes in endothelial function. Skeletal muscle blood flow, which is related to insulin sensitivity is not always related to changes in endothelial sensitivity was similar after both treatments. Thus, insulin sensitivity before treatment were not available. A second limitation concerns the definition of equivalent dosages of the two drugs. Although such definitions are difficult to verify, the present finding that both ACEi and ARB treatment lowered BP to a similar level supports dosage equivalency. Furuhashi et al reported that use of telmisartan (4 mg/day) or candesartan (8 mg/day) similarly decreased mean BP.29 The present study suggested some differences in the effects of ACEi and ARB on insulin sensitivity, and the reduction of TNF-α after ARB treatment might have a more pronounced effect on insulin sensitivity than on insulin sensitivity and the reduction of TNF-α after ARB treatment might have a more pronounced effect on insulin sensitivity than on endothelial function. Overall, although ACEi and ARB may have some different effects on possible common factors, they might compensate for each other; this compensation might lead to the similar effects on insulin sensitivity produced by both treatments.

Study Limitations and Future Directions

Although the cross-over design of the present study is a limitation, basal data on endothelial function and insulin sensitivity before treatment were not available. A second limitation concerns the definition of equivalent dosages of the two drugs. Although such definitions are difficult to verify, the present finding that both ACEi and ARB treatments lowered BP to a similar level supports dosage equivalency. Furuhashi et al reported that use of telmisartan (4 mg/day) or candesartan (8 mg/day) similarly decreased mean BP.29 The present study suggested some differences in the effects of ACEi and ARB on insulin sensitivity, and the reduction of TNF-α after ARB treatment might have a more pronounced effect on insulin sensitivity than on insulin sensitivity and the reduction of TNF-α after ARB treatment might have a more pronounced effect on insulin sensitivity than on endothelial function. Overall, although ACEi and ARB may have some different effects on possible common factors, they might compensate for each other; this compensation might lead to the similar effects on insulin sensitivity produced by both treatments.
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References