Insulin Resistance Is Related to Silent Cerebral Infarction in Patients With Essential Hypertension

Kei Kamide, Hiromi Rakugi, Nobuaki Nakano, Mitsuru Ohishi, Yukiko Nakata, Seiju Takami, Tomohiro Katsuya, Jitsuo Higaki, and Toshio Ogihara

Recently, hyperinsulinemia or insulin resistance has been suggested to be a risk factor for cardiovascular diseases. We evaluated the role of insulin resistance in the occurrence of silent cerebral infarction in 28 patients with essential hypertension (40 to 75 years, \(157 \pm 48/92 \pm 2\) mm Hg). Patients with diabetes mellitus or obesity (BMI > 30) were excluded. Insulin resistance was evaluated by means of constant glucose infusion rate (M value) during euglycemic-hyperinsulinemic glucose clamp test. Infarction was defined as a focal area with prolonged T1 and T2 relaxation times that was > 5 mm in diameter on brain magnetic resonance imaging. The severity of periventricular hyperlucency was evaluated by the distribution of the high intensity area. The number of silent infarctions significantly correlated only with the M value (F = 7.58, \(R^2 = 0.23, P = .01\)) in multiple regression analysis using all variables: age, blood pressure, smoking history, lipid profile, levels of plasma glucose and insulin on fasting, and total amounts during 75-g OGTT. However, the severity of periventricular hyperlucency did not show a correlation with any factors. The occurrence of cerebral infarction was significantly correlated with thickening of the intima-media complex (IMC) of the common carotid artery on B-mode ultrasonography (F = 8.43, \(R^2 = 0.25, P < .01\)). In conclusion, insulin resistance and thickening of IMC show a close relationship with the occurrence of silent cerebral infarction. Therefore, it may be important to improve insulin resistance for prevention of cerebral infarction in essential hypertensives.

Insulin resistance, compensatory hyperinsulinemia, hypertension, and dyslipidemia are reported to sometimes coexist and lead to an increased cardiovascular risk.1-4 Cerebrovascular disease is also a very serious complication induced by hypertension. With the development of computed tomography (CT) and magnetic resonance imaging (MRI), the accuracy of diagnosis of cerebrovascular disease has greatly increased, and small cerebral infarction without symptoms, so-called silent cerebral infarction (SCI), is able to be detected. It was reported that SCI showed significant relations with hypertension,5 aging,6 and carotid wall thickening on B-mode ultrasonography.7 As SCI is generally considered an important predictor of symptomatic cerebral infarction, to detect SCI and to clarify its cause are very important for the prevention of symptomatic or lethal cerebrovascular attacks.
Recent reports showed that cerebral infarction has an association with hyperinsulinemia.\(^8,9\) Zunker et al\(^9\) demonstrated that hyperinsulinemia was significantly related to the presence of cerebral small-vessel disease such as lacunar infarction. Shinozaki et al\(^8\) showed, using the steady-state plasma glucose (SSPG) method, a relationship between insulin resistance in association with compensatory hyperinsulinemia and the presence of atherothrombotic cerebral infarction, but not with lacunar infarction and cardioembolic infarction. To our knowledge, there is no report on the relationship between insulin resistance and SCI. In this study, we evaluated the role of insulin sensitivity estimated by euglycemic glucose clamp method in the occurrence of SCI in patients with essential hypertension.

**METHODS**

**Subjects** The study subjects, 28 patients (12 men, 16 women; mean ± SE of age: 60 ± 1 years) with essential hypertension, were chosen from consecutive patients who were admitted to our university hospital from January to December 1995. Essential hypertension was defined as blood pressure of 140/90 mm Hg or higher measured with patients in the supine position on three separate occasions several days after admission.\(^10\) Patients with secondary hypertension as defined by clinical and laboratory findings, and patients treated with antihypertensive medications were excluded. We also excluded from this study patients aged <40 and >75 years, and those with severe obesity (body mass index >30 kg/m\(^2\)), diabetes mellitus (DM) diagnosed by 75-g oral glucose tolerance test (OGTT) (WHO criteria, 1985), valvular disease, myocardial infarction, or atrial fibrillation. These exclusion criteria were used for the following reasons. Aging affects insulin resistance independently of hypertension. Severe obesity (four patients) causes difficulty in performing venipuncture for continuous blood sampling. Insulin sensitivity of DM patients cannot be measured with the euglycemic clamp method. Valvular disease, myocardial infarction, and atrial fibrillation are diseases associated with a high risk for embolic cerebral infarction. Patients with less than optimal B-mode ultrasonographic recordings of the common carotid artery were also excluded. Informed consent was obtained from each patient before the study.

**Euglycemic Glucose Clamp Test** To evaluate insulin sensitivity, euglycemic hyperinsulinemic glucose clamp was performed according to the method of DeFronzo et al\(^11\) with slight modification.\(^4\) We used STG-22 (Nikkiso Co. Ltd., Tokyo, Japan), an artificial pancreas system. The infusion rate of insulin was set at 40 mU/m\(^2\)/min. The M value (mg/kg/min), the mean glucose disposal rate during the time (90 to 120 min) of glucose clamp, was used as the measure of insulin sensitivity.

**Assessment of Silent Cerebral Infarction by Magnetic Resonance Imaging** MRI was performed using a field stretch of 0.1 T (SIGNA advantage 1.5T, General Electronics, Milwaukee, WI) in the orbitomeatal plane with 10 mm thickness, using an inversion recovery technique with a repetition time (TR) of 2.1 sec, an inversion time of 0.4 sec, and an echo time (TE) of 0.018 sec to achieve T1-weighted images, and a spin echo technique (TR, 2.2 sec; TE, 0.1 sec) to achieve T2-weighted images. We defined SCI on MRI according to the criteria of Hougaku et al.\(^5\) SCI was defined as a focal area with prolonged T1 and T2 relaxation times >5 mm in diameter. In this study, lesions <5 mm detected on both T1- and T2-weighted images were not counted, to exclude interpreting an enlarged perivascular space as a sign of ischemic disease.

We defined severity of periventricular hyperintensities on MRI in the subjects according to the criteria of Shimada et al.\(^6\) Grade I was defined as no abnormality or minimal periventricular signal hyperintensities in the form of caps only in the anterior horns or rims lining the ventricle. Grade II was defined as caps in both anterior and posterior horns of the lateral ventricles or periventricular unifocal patches. Multifocal periventricular hyperintense punctuate lesions and their early confluent stages were classified as grade III. Multiple high signal intensity areas that reached confluence in the periventricular region were defined as grade IV.

**Assessment of Intima-Media Complex of Carotid Artery** Atherosclerotic lesions of the common carotid artery were assessed by the method previously described.\(^4\) B-mode ultrasonography was performed with an ultrasound imager (SONOLAYER-SSA260A, Toshiba Medical Co. Ltd., Tokyo, Japan) with a 7.5 MHz linear transducer. Patients were examined in the dorsal decubitus position in a quiet room after 15 min of relaxation. The thickness of the intima-media complex (IMC) was measured as the distance between the lumen-intima interface and the media-adventitia interface on B-mode image.\(^12\) IMC of the far wall of the common carotid artery was measured from the enddiastolic image using electrocardiographic R-triggering. Measurements were bilaterally performed in three different directions (anterior-oblique, lateral, and posterior-oblique planes). The thickest point of IMC was chosen in the portion from 1 to 2 cm distal to the carotid bulb in each patient, then the thickness of that point was measured in three directions, and the mean of three values was calculated. In this study, we defined IMC as the larger value of either the left or right common carotid artery.

Ultrasonographic measurement was performed by...
TABLE 1. CHARACTERISTICS OF TOTAL STUDY POPULATION

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 0.6</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>157 ± 3/89 ± 2</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.61 ± 0.13</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.24 ± 0.08</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>3.90 ± 0.33</td>
</tr>
<tr>
<td>Fasting PG (mmol/L)</td>
<td>5.33 ± 0.17</td>
</tr>
<tr>
<td>Fasting IRI (pmol/L)</td>
<td>40.8 ± 4.8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>57</td>
</tr>
<tr>
<td>Number of SCI lesions</td>
<td>128</td>
</tr>
<tr>
<td>Age of SCI lesions</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 0.6</td>
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<tr>
<td>Smoking (%)</td>
<td>57</td>
</tr>
</tbody>
</table>

Results are given as mean ± SEM; BMI, body mass index; HDL, high density lipoprotein; PG, plasma glucose; IRI, immunoreactive insulin.

the same observer blinded to the subjects’ background. The intraobserver variability of IMC thickness was 4.4%.

Statistical Analysis All statistical analyses were conducted using Abacus Concepts, StatView 4.02 (Abacus Concepts, Inc., Berkeley, CA). Summary data are expressed as mean ± SEM. Correlation tests were performed to assess the correlation between M value as insulin sensitivity and the number of SCI, severity of PVH on MRI, and thickness of carotid wall on ultrasonography. Stepwise regression analysis was performed to assess the effects of insulin sensitivity and several risk factors for cerebrovascular disease on number of SCI on MRI. P values < .05 were considered significant.

RESULTS

Table 1 shows the characteristics of the total study population. In the study population, plasma renin activity, aldosterone, adrenaline and noradrenaline were 0.09 ± 0.02 ng/L/sec, 413.3 ± 25.0 pmol/L, 163.3 ± 30.0 pmol/L and 1.89 ± 0.24 pmol/L, respectively. Total plasma glucose (ΣPG), and immunoreactive insulin (ΣIRI) at 0, 30, 60, 120 min during 75-g OGTT and M value were 32.0 ± 1.4 mmol/L, 960 ± 108 pmol/L and 4.15 ± 0.26 mg/kg/min, respectively.

The results of simple regression analysis between M value and indexes of blood pressure, lipid profile, and glucose metabolism showed that body mass index (F = 10.61, P = .003, R² = 0.28), triglyceride (F = 5.79, P = .02, R² = 0.18), fasting IRI (F = 6.08, P = .02, R² = 0.18), and SIRI (F = 5.35, P = .03, R² = 0.17) were associated with M value, but every value of R² was low.

SCI lesions were found in 24 of 28 study subjects (86%), with a total of 128 lesions. All of the SCI lesions were localized in the subcortical white matter or in the basal ganglia. The distribution of SCI lesions was not significantly different between left and right hemispheres. All lesions were smaller than 2 cm in diameter; 111 lesions (87%) were smaller than 1 cm. There was no difference in lesion size between left and right hemispheres.

Number of SCI was significantly correlated with M value (F = 7.68, P = .01, R² = 0.23) (Figure 1), HDL-cholesterol (F = 7.53, P = .01, R² = 0.23), and triglyceride (F = 5.60, P = .03, R² = 0.18). There was no correlation between SCI and age. To identify independent risk factors that directly affect SCI, we performed stepwise multiple regression analysis using indexes of glucose metabolism (FPG, fasting-IRI, ΣPG, ΣIRI, M-value) and other risk factors for silent cerebral infarction (age, BMI, blood pressure, and lipid profile). It revealed that only M value is a predictor for SCI (df = 1, intercept 9.40, coefficient −1.13, standard error 0.41, R² = 0.23, F = 7.58, P = .01). There was no significant correlation between M value and severity of PVH.

IMC on B-mode ultrasonography was significantly correlated with M value (P < .01, R² = 0.25) (Figure 2). IMC also showed a significant correlation with number of lacunar infarctions (P < .05, R² = 0.23) (Figure 2). However, there was no significant correlation between IMC and severity of PVH.

DISCUSSION

The present study demonstrated that the severity of insulin resistance is the most important predictor for SCI including lacunar infarction in patients with essential hypertension. We cannot exclude the possibility that the correlation between insulin resistance and SCI is due to the fact that both pathophysiological changes are induced in accordance with the develop-

![Number of infarctions (>5 mm)](image)

FIGURE 1. Correlation between M value and number of silent cerebral infarctions.
ment of hypertension. Our investigation, however, strongly supports the concept that insulin resistance is a fundamental and important cause of risk factors for atherosclerotic cardiovascular diseases such as hypertension and dyslipidemia, via hyperinsulinemia. There is much supportive evidence that insulin resistance induces atherogenic changes, independent of hypertension.

First, insulin resistance-induced dyslipidemia may cause atherosclerosis. In fact, low HDL-cholesterol and high TG levels significantly correlated with the number of SCI, and M value correlated with triglyceride level in the present study. Second, insulin resistance is an important factor in hyperinsulinemia. Our results showed a correlation between M value and SIRI. Insulin itself is known to induce the growth of cardiac myocytes, fibroblasts, and vascular smooth muscle cells via insulin receptors or insulin-like growth factor-I (IGF-I) receptors. In the present study, however, insulin levels on fasting and during OGTT showed no relation with SCI. It was recently reported that IGF-I increased with insulin level in essential hypertensive patients, and that IGF-I was significantly related to the progression of atherosclerosis. Another possibility regarding the correlation between insulin resistance and SCI is that both are just observed phenomena in generalized cardiovascular-metabolic disease. It is known that the altered intracellular ionic milieu, resulting in excess steady state levels of [Ca]_v, reciprocal depletion of [Mg]_v, and lowered pH, is one of mechanisms for insulin resistance. These cellular ionic abnormalities also induce proliferation of the vascular wall cells and decrease endothelial protective effects on vascular cell proliferation. Insulin resistance may induce SCI in association with these cellular ionic abnormalities in cerebral microvessels. Further studies are required to clarify the precise mechanisms of the involvement of insulin resistance in the presence of SCI.

In a previous report, the number of SCI and severity of PVH were significantly correlated with age. However, such relations were not recognized in the present study. This discrepancy may have been caused by the following: 1) the small sample size of our study, and 2) our study population comprised only hypertensives who already had a risk of cerebrovascular disease.

Severity of PVH also showed no correlation with any indexes of insulin sensitivity. Pathologically, PVH is considered to represent demyelination of central nerves, hydrocephalus, or subcortical arteriosclerotic encephalopathy. In the progression of PVH, atherosclerosis related to insulin resistance might be less important than pathological changes such as demyelination and hydrocephalus. Another possible reason for the lack of correlation was that we did not observe a significant correlation in a few subjects classified as grade III or IV in the present study.

SCI is a warning for serious complications in patients with essential hypertension, although it is not accompanied by any neurological symptoms. The occurrence of SCI was closely correlated with the severity of atherosclerosis of the carotid artery evaluated by B-mode ultrasonography, so that SCI is considered to reflect the progression of atherosclerosis in the brain. In the present study also, SCI was related to the severity of thickening of the carotid artery. The risks for SCI, however, would not be the same with those for carotid atherosclerosis. Most cases of SCI were diagnosed as small lacunar infarction. It is well reported that the pathogenesis of these lacunar infarctions is based on lipohyalinosis of deep, small, penetrating arteries, and they are rather different from atherothrombotic infarctions related to atherosclerosis of extracranial large arteries such as the carotid artery. Therefore, we think that the present study is signifi-

![FIGURE 2](https://example.com/figure2.png)
cant in demonstrating that insulin resistance may be related to atherosclerosis in both small intracranial and large extracranial arteries.

In summary, our results suggest that insulin resistance in essential hypertension is associated with the progression of SCI as the strongest risk factor of any other risk factors including glucose metabolism indexes, lipid profile, blood pressure, and age. It may be important to improve insulin sensitivity by weight control, adequate exercise, and controlled calorie diet for preventing symptomatic or serious cerebrovascular disease. It is concluded that vascular changes in the increased cerebrovascular morbidity and mortality associated with insulin resistance.

REFERENCES