Greater Impact of Coexistence of Hypertension and Diabetes on Silent Cerebral Infarcts

Kazuo Eguchi, MD; Kazuomi Kario, MD; Kazuyuki Shimada, MD

Background and Purpose—Silent cerebral infarcts (SCIs), often found in the elderly and hypertensives, have been proposed as an indicator of poorer cerebrovascular prognosis. The aim of this study was to evaluate the prevalence and determinants of SCI in hypertensives with or without diabetes mellitus (DM).

Methods—We studied 360 asymptomatic hypertensive subjects with or without DM (mean age, 67.4 years; range, 41 to 88 years). We performed 24-hour ambulatory blood pressure (BP) monitoring and brain MRI. The subjects were classified into a diabetic hypertension group with DM (DHT, n=159) or a non-DM hypertension group (non-DHT, n=201).

Results—SCIs (presence of ≥1) were found in 82% of the DHT and 58% of the non-DHT (P<0.001) group; multiple SCIs (the presence of ≥3) were found in 62% of the DHT and 35% of the non-DHT group (P<0.001); and 24-hour ambulatory BP levels were comparable between groups. DM was a powerful determinant of both SCIs (odds ratio [OR], 2.95; P<0.01) and multiple SCIs (OR, 3.05; P<0.001) independently of age and 24-hour systolic BP, whereas only multiple SCIs were associated with 24-hour systolic BP. When patients were subclassified by ambulatory BP and the presence of DM (sustained hypertension [SHT]+DM, white-coat hypertension [WCHT]+DM, SHT, and WCHT groups), the prevalence of SCI and multiple SCIs was higher in the SHT+DM than in the SHT group, and only multiple SCIs were higher in the WCHT+DM than the WCHT group.

Conclusions—Diabetes was the major determinant of SCIs in both SHT and WCHT. (Stroke. 2003;34:2471-2474.)

Key Words: blood pressure monitoring, ambulatory □ diabetes mellitus □ hypertension □ infarcts, silent

Diabetes mellitus (DM), which is rapidly increasing in Japan and other developed countries, is a major risk factor for stroke.1 About 40% to 60% of DM patients are complicated with hypertension,2 which is the strongest risk factor for stroke. When DM and hypertension coexist, the risk of a stroke further increases. Asymptomatic or “silent” cerebral infarct (SCI) is sometimes detected incidentally by MRI or other imaging modalities in patients who demonstrate no localized neurological symptoms of stroke.3 4 A SCI, which is now classified as a type III cerebrovascular disorder by the National Institute of Neurological Disorders and Stroke, is a specific marker of target organ damage in the brain and a powerful predictor of clinical stroke.5-8 Ambulatory blood pressure (ABP) is superior to casual BP in predicting SCT9 and cardiovascular events.7 10 However, in diabetic patients, few reports use ABP to assess the relationship between abnormal circadian BP rhythm and cardiovascular prognosis.11 Thus, we studied the impact of DM and ABP on SCIs in 360 asymptomatic hypertensive patients with or without DM.

Methods

Patients
We studied 360 older asymptomatic hypertensive patients (mean age, 67.4 years; range, 41 to 88 years; 134 men, 226 women): 159 with essential hypertension coexisting with diabetes (DHT group) and 201 essential hypertensives without diabetes (non-DHT group). We enrolled subjects in our study from 3 participating institutes (1 clinic, 2 hospitals). Hypertensive patients were consecutively selected according to the following criteria: (1) essential hypertension with average clinical systolic BP (SBP) >140 mm Hg and/or average clinical diastolic BP (DBP) >90 mm Hg (average for each patient on ≥2 occasions)12 and (2) hypertensive patients >40 years old. Clinical BP was measured after resting for at least 5 minutes in patients in the sitting position. No patient had taken any antihypertensive medication for at least 1 week before the ABP monitoring study. We excluded patients with renal failure, hepatic damage, secondary or malignant hypertension, ischemic heart disease or other cardiac disease, congestive heart failure, arrhythmias (including atrial fibrillation and other arrhythmias), stroke (including transient ischemic attacks), or other severe concomitant disease. The duration of hypertension was based mainly on information from self-report and medical records, with hypertension diagnosed by a physician with or without treatment according to the patient’s information. One-time hypertension was not included in the history.

We defined DM according to the criteria of the American Diabetes Association.13 Body mass index (BMI) was calculated as weight (kg) divided by height (m²). Left ventricular mass index (LVMI) detected by echocardiography (SSD 2200, Aloka) was calculated by the method introduced by Devereux et al.14 This study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School (Japan). All subjects studied were ambulatory and gave informed consent for the study.

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ABP Monitoring (24 Hour)
Noninvasive ABP monitoring was carried out on a weekday with an automatic system using electric cuff inflation (TM2421, A&D), which recorded both BP (by the oscillometric method) and pulse rate every 30 minutes for 24 hours. The accuracy of this device was previously validated.15 Sleep BP was defined as the average BP measurements from the time when the patient went to bed until the time he or she awoke; awake BP was the average of the BP measurements recorded during the rest of the day. Sustained hypertension (SHT) was defined as clinical SBP >140/90 mm Hg (either) and 24-hour SBP ≥135/80 mm Hg (either); white-coat hypertension (WCHT) was defined as clinical SBP >140/90 mm Hg (either) and 24-hour SBP <135/80 mm Hg (both). The patients were subclassified into 4 groups according to ABP levels and presence of DM: 117 SHT+DM, 42 WCHT + DM, 140 SHT (without DM), and 61 WCHT (without DM).

Brain MRI
Brain MRI was carried out in all 360 patients with a superconducting magnet with a main strength of 0.5 T (Toshiba MRT50GP) within 3 months of their ABP monitoring. The brain was imaged in the axial plane at a 7-mm slice thickness. T1-weighted images were obtained with a short spin-echo pulse sequence with a repetition time of 470 milliseconds and an echo time of 15 milliseconds. T2-weighted images were obtained with a long spin-echo pulse sequence with a repetition time of 4000 milliseconds and an echo time of 120 milliseconds. The matrix size was 256×256 pixels. An SCI was defined exclusively as a low-signal-intensity area (≥3 mm, but all were <15 mm in size) depicted on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images as described previously.8,16 The MRI images of the subjects were randomly stored and interpreted by reviewers blinded to subject names and characteristics. The interreader and intrareader interclass (non-SCI, 0; 1 or 2 SCIs, 1; multiple SCIs, 2) k statistics were 0.70 and 0.80, respectively, in our laboratory.

Statistical Analysis
All statistical analyses were carried out with SPSS for Windows, version 11.0J (SPSS Inc). The χ2 test was used to calculate proportions. One-way analysis of variance was performed to detect differences among groups in mean values, and unpaired t tests were used for comparison of variables between the DHT and non-DHT groups. Tukey’s honestly significant difference test was used for multiple comparisons of the mean BPs between 2 of the 4 subgroups (SHT+DM, WCHT + DM, SHT, and WCHT groups). These data are expressed as the mean (SD) or prevalence. Odds ratios with 95% confidence intervals for no or some SCIs (0 present) were calculated by logistic regression analysis using selected covariates for cardiovascular risk such as age, sex (0=female, 1=male), BMI, smoking (0=absent, 1=present), duration of hypertension, presence of DM (0=absent, 1=present), 24-hour SBP, and total cholesterol. A value of P<0.05 was considered significant.

Results
Baseline Characteristics of the Patients
The mean clinical SBP and DBP of the overall study group were 159±17 and 86±12 mm Hg, respectively, and the 24-hour SBP and DBP were 144±15 and 81±9 mm Hg. The prevalence of SCI (the presence of ≥1) was 68.6% and that of multiple SCIs (the presence of ≥3) was 46.9% in the overall study group.

Table 1 shows the characteristics of the 360 patients separated into 2 groups: hypertension with DM (DHT group; n=159) and hypertension without DM (non-DHT group; n=201). Age, BMI, prevalence of current smokers, LVMI, serum cholesterol, hematocrit, and serum creatinine were comparable between the 2 groups, but the prevalence of male sex, duration of hypertension, and serum triglycerides were significantly higher in the DHT group than in the non-DHT group. The clinic SBP, 24-hour BP, awake BP, and sleep BP were also comparable between the 2 groups; only clinic DBP was lower in the DHT group than in the non-DHT group.

Silent Cerebral Infarcts
As shown in Table 1, the number of SCIs and prevalence of SCI and multiple SCIs were significantly higher in the DHT group than in the non-DHT group. To clarify the determinants of SCI and multiple SCIs, we performed logistic regression analysis (Table 2). The results show that female sex, presence of DM, and duration of hypertension. On the other hand, the determinants of multiple SCIs were age, male sex, presence of DM, duration of hypertension, and 24-hour SBP.

WCHT Versus SHT
To clarify the impact of high ABP and DM status for SCI, we further analyzed the prevalence of SCI among the 4 subgroups classified by DM status and 24-hour BP. The number±SD of SCIs (per person) was 5.2±4.2 in the SHT+DM group, 2.8±3.5 in the WCHT+DM group, 2.3±2.6 in the SHT group, and 1.4±1.8 in the WCHT group. As shown in the Figure, the prevalence of SCI and multiple

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tr>
<td>Measures</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Male sex, %</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Duration of hypertension, y</td>
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<tr>
<td>Duration of diabetes, y</td>
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<tr>
<td>Current smokers, %</td>
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<tr>
<td>LVMI, g/m²</td>
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<tr>
<td>Hematocrit, %</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
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<tr>
<td>Triglyceride, mmol/L</td>
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<tr>
<td>Creatinine, μmol/L</td>
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<tr>
<td>Clinic SBP, mm Hg</td>
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<tr>
<td>Clinic DBP, mm Hg</td>
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<td>24-hour SBP, mm Hg</td>
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<td>24-hour DBP, mm Hg</td>
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<tr>
<td>Awake SBP, mm Hg</td>
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<tr>
<td>Awake DBP, mm Hg</td>
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<tr>
<td>Sleep SBP, mm Hg</td>
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<tr>
<td>Sleep DBP, mm Hg</td>
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<tr>
<td>SCI, n/person</td>
</tr>
</tbody>
</table>

Data are shown as mean±SD when appropriate. Overall probability values are for 2-group comparison of means (unpaired t test) or percentages (χ2 test).

*P<0.05 †P<0.001 vs non-DHT group.
SCIs was the highest in the SHT+DM group, followed by the WCHT+DM, SHT, and WCHT groups. The 24-hour SBP levels were not significantly different between the SHT+DM (151/82 mm Hg) and SHT (151/84 mm Hg) groups or between the WCHT+DM (126/74 mm Hg) and WCHT (128/76 mm Hg) groups; the prevalence of SCI and multiple SCIs was significantly higher in the SHT+DM group than in the SHT group; and the prevalence of multiple SCIs was significantly higher in the WCHT+DM group than in the WCHT group.

Discussion

SCIs assessed by brain MRI are a clinically important pathological condition relating to the incidence of future stroke events5-8 and cerebrovascular dementia.17 In this study, we found that the presence of DM coexisting with hypertension was the most powerful independent determinant of SCI (especially for multiple SCIs). This is the first report to use ABP monitoring to assess the impact and relationship of ABP and the presence of DM on SCIs.

Prevalence of SCIs

In this study, the prevalence of SCI and multiple SCIs were 68.6% and 46.9%, respectively, in all patients. The prevalence of SCI in this study was higher than in previous reports: 47% in 73 patients with essential hypertension by Shimada et al.3 40.2% in 219 elderly patients at an outpatient clinic by Uehara et al.16 and 65% for total SCI and 39% for multiple SCIs in essential hypertension by Kario et al.7 The higher prevalence of SCI in this study may be due to the higher prevalence of DM (44%) in our patients.

Impact of DM

As is widely known, patients with glucose intolerance are 2 to 5 times more susceptible to stroke compared with normal patients.19 In a prospective study of Hawaiian Japanese,20 there was twice the risk of thromboembolic stroke in DM patients compared with non-DM patients.

As shown in Table 2, the prevalence of SCI and multiple SCIs increased 3-fold in hypertensive patients with DM independently of age and ABP. This is in accordance with previous reports that DM contributes to a 2- to 4-times-greater incidence of symptomatic stroke.20-22

Although BP was significantly higher in the SHT group than in the WCHT+DM group, the risks for any SCI and multiple SCIs were similar among the groups (the Figure). These risks were comparably higher in the SHT and WCHT+DM groups than in the WCHT group. Therefore, DM is a powerful and independent determinant of SCI in both SHT and WCHT.

Multiple SCIs in DM

The prevalence of multiple SCIs was higher in the WCHT+DM group than in the WCHT group (the Figure). In our previous report, multiple SCIs were also significantly associated with hyperinsulinemia in hypertensive patients.16 Although the present patients were not associated with the previous reports, the presence of DM and accompanying hyperinsulinemia may accelerate the formation of multiple SCIs, not only when 24-hour BP is higher but also at lower 24-hour BP levels. Therefore, hypertensive target organ damage is more advanced in DM patients, even at relatively lower ABP levels (WCHT).

Impact of ABP

The strongest risk factors for stroke are hypertension and age, according to recent epidemiological report in Japan.21 Hypertension is also the strongest risk factor for SCI.5,6 In hypertensive patients, ABP can preferably predict the prevalence of SCI and incidence of stroke.6 In DM subjects, Nakao et al11

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**TABLE 2. Determinants of SCI**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prevalence of SCI (n=360)</th>
<th>Multiple SCIs (n=360)</th>
</tr>
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<tbody>
<tr>
<td>Age (10-y groups)</td>
<td>2.80 (1.95–4.05)‡</td>
<td>2.51 (1.81–3.52)‡</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.74 (0.87–3.50)</td>
<td>2.07 (1.15–3.73)‡</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.97 (0.89–1.05)</td>
<td>0.94 (0.87–1.01)</td>
</tr>
<tr>
<td>Duration of hypertension (10 y)</td>
<td>1.79 (1.06–2.97)‡</td>
<td>1.88 (1.32–2.71)†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.95 (1.56–5.75)‡</td>
<td>3.05 (1.84–5.06)‡</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.71 (0.44–1.15)</td>
<td>0.76 (0.45–1.29)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>1.01 (1.00–1.01)</td>
<td>1.01 (1.00–1.02)</td>
</tr>
<tr>
<td>24-hour SBP (10 mm Hg)</td>
<td>1.17 (0.96–1.45)</td>
<td>1.31 (1.10–1.54)†</td>
</tr>
</tbody>
</table>

The odds ratios (ORs) and (95% confidence intervals (CIs) for SCI or for silent multiple SCIs were calculated by multiple logistic regression analysis. We used the following conventional risk factors as covariates: age, sex, BMI, smoking status, total cholesterol, duration of hypertension, 24-hour SBP, and presence of DM.

**TABLE 3. Probability Values for Comparisons of 4 Groups in the Figure**

<table>
<thead>
<tr>
<th>WCHT vs SHT</th>
<th>0.122</th>
<th>0.010</th>
</tr>
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<tbody>
<tr>
<td>WCHT vs WCHT+DM</td>
<td>0.160</td>
<td>0.047</td>
</tr>
<tr>
<td>WCHT vs SHT+DM</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SHT vs WCHT+DM</td>
<td>0.856</td>
<td>1.000</td>
</tr>
<tr>
<td>SHT vs SHT+DM</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WCHT+DM vs SHT+DM</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Probability values for SCI (multiple SCIs) were calculated by χ² test.
investigated the stroke incidence of DM patients using ABP. The incidence of stroke was much higher in reverse-pattern patients whose sleep BP was higher than their waking BP. In this study, the prevalence of SCI was significantly higher in high ABP groups (SHT+DM and SHT groups). Therefore, we confirmed that ABP was useful for predicting hypertensive target organ damage not only in essential hypertension patients but also in hypertensives with DM.

Impact of Coexisting DM and Hypertension

In our study, patients with SHT and DM had the highest prevalence of SCI, particularly for multiple SCIs. The clinical impact of DM coexisting with hypertension on cardiovascular disease was recently reviewed; this status can worsen the cardiovascular prognosis. The risk factors for stroke previously reported were diabetic history, SBP, and insulin resistance. In a report on poststroke patients, hypertension and DM were closely related to multiple SCIs. We recently reported that insulin resistance–related hemostatic abnormality is associated with multiple SCIs in hypertensive patients. Those subjects were not associated with the present study. Although the precise mechanism is unknown, there may be a synergistic effect between hypertension and DM for the risk of SCI involving other risk factors such as hemostatic factors.

Conclusions

These results suggest that the presence of DM is the most powerful determinant of SCI in hypertensive patients. Even in WCHT, DM is a powerful risk factor for multiple SCIs.

References

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