Arterial Pulsatility as an Index of Cerebral Microangiopathy in Diabetes

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Background and Purpose—This study was designed to evaluate cerebral hemodynamic changes related to diabetes mellitus (DM) with transcranial Doppler ultrasonography (TCD).

Methods—We measured the flow velocities and the Gosling pulsatility index (PI) of the middle cerebral artery (MCA), extracranial internal carotid artery (ICA), and basilar artery (BA) in 56 stroke-free, normotensive patients with type 2 DM and 70 age- and gender-matched healthy volunteers. Patients were divided into 2 groups according to the presence of microvascular complications such as retinopathy, nephropathy, and neuropathy.

Results—Patients showed slightly lower hematocrit and higher serum fibrinogen levels than control subjects, but other clinical profiles, including stroke risk factors except for diabetes, were comparable between patients and controls. The flow velocity of the ICA but not the MCA and BA in patients regardless of the complication was significantly higher than that in controls. The PIs of the MCA and ICA were significantly higher in patients with complication than those without complication, as well as in controls. The PI of the BA was also significantly higher, even in patients without complication, than in controls. The PIs of the MCA and ICA but not the BA were closely correlated with the duration of DM ($r^2=0.46$ and $0.34$, respectively).

Conclusions—This study defines TCD findings of diabetes-related cerebral hemodynamic changes and suggests that the PI reflects microangiopathic changes of cerebral vessels. (Stroke. 2000;31:1111-1115.)

Key Words: cerebral blood flow ■ cerebrovascular disorders ■ diabetes mellitus ■ ultrasonography, Doppler, transcranial

Diabetes mellitus (DM) is a major risk factor for ischemic stroke. The major vascular changes related to DM are macroangiopathy and microangiopathy occurring in the cerebral as well as systemic blood vessels. Compared with healthy people, patients with DM show more extensive atherosclerosis of extracranial and intracranial vessels, a higher prevalence of carotid artery stenosis, and increased carotid artery intima-media wall thickness. In addition, microvascular damage is also one of the major complications of DM. In diabetic humans as well as experimental animals, morphological abnormalities, including arterial endothelial cell necrosis and thickened capillary basement membranes, have been observed in small cerebral vessels. Besides these morphological changes, diabetic patients have also shown impaired cerebrovascular reactivity to hypercapnia, acetazolamide, and blood pressure changes. These vascular changes may alter cerebral blood flow (CBF) and eventually produce a stroke.

The main purpose of DM control is to prevent its complications. Thus, regular and systematic screening for diabetic complications, including blood glucose concentrations, glycosylated hemoglobin level, renal function, blood pressure, retinopathy, and signs of diabetic foot has been recommend-
related atherosclerotic change was more frequently noted in these vessels than the MCA. Thus, we performed TCD measurements of the MCA, ICA, and BA in stroke-free, normotensive patients with type 2 DM.

**Subjects and Methods**

The study population consisted of 56 patients with type 2 DM (mean±SD age, 59±9 years; 23 men and 33 women; median duration of DM, 12 years), and 70 age- and gender-matched healthy volunteers (age, 57±6 years; 27 men and 43 women). The volunteers were selected from subjects visiting Yonsei University Medical Center for a health screening program who agreed to participate in this study after a full explanation of its purposes, risks, and potential benefits. All of the diabetic patients were referred from the Diabetes Clinic in our hospital, where the diagnosis of type 2 DM had been made according to the established criteria, and they were followed up at regular intervals. At the Diabetes Clinic, diabetes-related complications such as retinopathy, nephropathy, and peripheral neuropathy were evaluated as a baseline check-up program. Most of the patients received oral hypoglycemic agents or subcutaneous insulin or both. Subjects who had any previous history suggesting stroke or had lesions compatible with stroke as found in brain CT or MRI were excluded. We also excluded subjects who had either hypertension or other medico-surgical illnesses that influence CBF, such as anemia (hematocrit <30%), polycythemia (hematocrit >48%), or known heart diseases that can alter cardiac output. Patients who had either retinopathy, nephropathy, or peripheral neuropathy were defined as “complicated patients”; the term “non-complicated patients” was applied to patients without those complications.

All TCD studies were performed with a 3-dimensional mapping instrument (Trans-scan, EME) and examination techniques similar to those previously described. Doppler signals from the main stem of the MCA were obtained with a 2-MHz probe attached to a stereotactic headpiece through a transtemporal window at a depth of 56 to 60 mm. Those from the ICA were obtained with a 4-MHz hand-held probe below the mandible at a depth of 25 to 35 mm, and those from the BA were obtained with a 2-MHz hand-held probe below the occiput at a depth of 80 to 90 mm. For each artery, the mean, systolic, and diastolic velocities were measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity–diastolic velocity)/mean velocity. At least 3 measurements were performed at a similar depth for each artery, and the median value was selected and used in this study. All other major intracranial and extracranial cerebral arteries were also examined by TCD to exclude the possibility of major vascular lesion involvement in those vessels. The systolic and diastolic blood pressures; hematocrit; serum fibrinogen, cholesterol, and triglyceride concentrations; and the height and weight of the subjects were checked on the same day that the TCD was performed. In patients, fasting and postprandial blood glucose, glycosylated hemoglobin, and c-peptide levels were also checked.

Data were expressed as mean±SD. Statistical analyses were performed with a computerized program, Statview II. An unpaired Student t test was used to assess the significance of differences between 2 subject groups, and ANOVA was used to assess the significance of differences among 3 subject groups. The χ² test was performed to compare the distribution of nonparametric data, such as gender distribution and frequency of smoking, among subject groups. Correlation analysis was used to assess the significance of the relationship between the duration of DM and TCD measurements in patients, and Spearman rank correlation was also used if the correlation was nonlinear. Stepwise regression analysis was used to exclude the possible confounding effect of other variables on the result of each correlation analysis. Values of P<0.05 were regarded as significant.

**Results**

Among the subject groups, there was no significant difference in gender distribution, body mass index, systolic and diastolic blood pressures, serum cholesterol and triglyceride levels, and the percentage of smokers as well as the amount of their

**TABLE 1. Clinical Profiles of Subjects**

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Noncomplicated</th>
<th>Complicated</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±10</td>
<td>60±8*</td>
<td>57±6</td>
</tr>
<tr>
<td>Gender, men/women</td>
<td>11/12</td>
<td>12/21</td>
<td>27/43</td>
</tr>
<tr>
<td>Median duration of DM, y</td>
<td>6</td>
<td>15</td>
<td>ND</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.3±3.2</td>
<td>23.2±3.2</td>
<td>24.2±2.8</td>
</tr>
<tr>
<td>Smoking (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>27.8</td>
<td>33.3</td>
<td>22.2</td>
</tr>
<tr>
<td>Pack-years (in smokers)</td>
<td>29±30</td>
<td>31±22</td>
<td>34±9</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>129±12</td>
<td>134±16</td>
<td>127±16</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82±10</td>
<td>84±9</td>
<td>81±11</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.86±0.97</td>
<td>5.32±1.49</td>
<td>5.31±0.78</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.74±1.11</td>
<td>2.17±1.86</td>
<td>2.15±1.24</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.5±5.4*</td>
<td>36.5±2.9*</td>
<td>40.9±3.5</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.89±1.09*</td>
<td>4.08±0.98*</td>
<td>3.48±0.63</td>
</tr>
<tr>
<td>Blood sugar, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>9.75±3.50*</td>
<td>11.23±3.21*</td>
<td>4.99±0.46</td>
</tr>
<tr>
<td>Postprandial</td>
<td>13.05±4.98</td>
<td>15.19±4.21</td>
<td>ND</td>
</tr>
</tbody>
</table>

Values are mean±SD. ND indicates not done.

*P<0.05 vs controls.
smoking. Patients showed lower hematocrit but higher fasting blood sugar and serum fibrinogen concentrations than volunteers. Complicated patients were slightly older than noncomplicated patients and control subjects. Complicated patients had a significantly longer duration of diabetes and higher fasting blood sugar levels than noncomplicated patients, but postprandial sugar levels were comparable between the 2 patient groups (Table 1).

The velocity measurements and the PI of the tested arteries in the subject groups are shown in Table 2. The velocity measurements of the MCA and BA were comparable among the subject groups, but noncomplicated as well as complicated patients showed significantly higher mean and systolic flow velocities of the ICA than volunteers. The PI of the BA was significantly increased in noncomplicated as well as complicated patients, but the PI of the MCA and ICA was increased only in complicated patients (Table 2). Although a large overlap of PI values was observed between patient groups (Figure), most noncomplicated patients (87%) showed a PI of ≤0.8 for the MCA, whereas more than half of complicated patients (54%) showed a PI higher than that for the MCA (P<0.005). All but one ICA measurements in noncomplicated patients showed a PI of ≤1.0, whereas 24% of ICA measurements in complicated patients, particularly those in whom the duration of DM was >10 years, showed a PI higher than that (P<0.05).

Correlation analysis of the data obtained from patients revealed that the duration of DM was most significantly correlated to the PI of the MCA ($r^2=0.46$, $P<0.001$; Figure, panel A), followed by the PI of the ICA ($r^2=0.34$, $P<0.001$; panel B). The equations of these correlations were as follows: PI of the MCA = 0.001(DM duration)$^2-0.011$(DM duration)$+0.745$, and PI of the ICA = 0.001(DM duration)$^2-0.012$(DM duration)$+0.816$. To exclude the confounding effect of hematocrit, fibrinogens and amount of smoking on these correlations, we performed stepwise regression analysis which demonstrated DM duration as the only significant variable influencing the PI of tested arteries. Among velocity measurements, only diastolic velocity of the MCA and ICA was significantly and negatively but weakly correlated to the duration of DM ($r^2=0.14$, $P<0.005$ and $r^2=0.04$, $P<0.05$, respectively). Velocity measurements and the PI of tested arteries did not correlate to the fasting or postprandial blood glucose level, glycosylated hemoglobin level, or serum c-peptide level of the patients.

**Discussion**

This study demonstrated that the flow velocity of the ICA and the PIs of all tested arteries increased in diabetic patients.
Increased flow velocity of the ICA may result from either luminal narrowing of the ICA or reduced resistance of the distal vessels. However, unaltered MCA flow velocity in this study and previous reports showing reduced cerebrovascular reactivity in DM\textsuperscript{10–12,21} eliminated the possibility of reduced cerebrovascular resistance. Occlusive lesions in the ICA were observed in up to 20% of adult diabetic patients.\textsuperscript{28} In addition, the intima/media wall thickness of the ICA increased up to 0.8 mm in diabetic patients, even in newly diagnosed patients, compared with age-matched healthy people.\textsuperscript{5,6} According to Poiseuille’s law for steady laminar flow in long cylindrical tubes, the flow velocity is inversely correlated to the (radius)\textsuperscript{4} if the flow volume is fixed.\textsuperscript{29} Since the mean diameter of the ICA is about 5 to 8 mm,\textsuperscript{30} an increase of about 0.8 mm in wall thickness could produce significant elevation of ICA flow velocity. On the other hand, no difference in mean flow velocity was observed between patients and controls for either the MCA or the BA, which may imply that there is no significant difference in the intracranial vessel diameter between patients and controls.

The Gosling PI was originally designed to measure vascular resistance\textsuperscript{26} and this relationship was proved in the brachial artery of normal humans.\textsuperscript{31} Thus, the increased PI observed in this study presumably represents enhanced cerebrovascular resistance in the cerebral circulation. The PI of the MCA and ICA was increased only in complicated patients, whereas the PI in uncomplicated patients was comparable to that in control subjects. These results were quite consistent with those of Lippera et al.\textsuperscript{20} They demonstrated significantly increased pulsatility of the MCA in diabetic patients with retinopathy compared with those without retinopathy. However, most of their patients were hypertensive, and long-standing hypertension could also increase the pulsatility of the MCA and ICA,\textsuperscript{32,33} as well as reduce cerebrovascular reactivity.\textsuperscript{33,34} Thus, their study could not exclude the effect of hypertension. Since our patients and controls were normotensive and had similar stroke risk factor profiles, including smoking and serum cholesterol levels, the pulsatility change in this study must be related to diabetes. Blood viscosity, one of the major factors influencing pulsatility as well as the flow velocity of cerebral vessels, is mainly determined by hematocrit and serum fibrinogen concentrations.\textsuperscript{35–37} Diabetic patients in this study showed lower hematocrit and higher serum fibrinogen concentration than controls. Reduced hematocrit may increase the flow velocity, but decrease the pulsatility, while increased serum fibrinogen may exert the opposite influence on CBF. However, the differences in hematocrit and serum fibrinogen between patients and controls appeared too small to influence the results of this study. Aging has been reported to reduce the flow velocity and increase the pulsatility of cerebral vessels.\textsuperscript{38,39} Our patients with microvascular complication were slightly older than patients without complication, as well as controls. However, this difference in mean age does not appear to affect the present results.

Considering the concomitant occurrence of microangiopathy in other organs such as the retina, kidney and peripheral nerve, increased pulsatility appears to mainly represent microangiopathic damage to cerebral arterioles. In contrast to the MCA and ICA, the PI of the BA was significantly increased even in noncomplicated patients compared with controls. This finding suggests that pulsatility changes occur earlier in the posterior circulation than in the anterior circulation. The cerebral vessels have rich adrenergic innervation which regulates vascular tone in response to various stimulations.\textsuperscript{40} In diabetic humans as well as experimental animals, cerebral vasodilatory responses are impaired, presumably related to beta-adrenergic or sympathetic neuronal dysfunction.\textsuperscript{41,42} In diabetic rats, the number of beta-adrenergic receptors is reduced in cerebral microvessels,\textsuperscript{43} which can be attributed to the impaired beta-adrenergic receptor-mediated vasodilatory response in DM, resulting in enhanced pulsatility. Vessels in the posterior cerebral circulation, since they have fewer adrenergic neurons than in the anterior cerebral circulation,\textsuperscript{40} may have a restricted vasodilatory response and enhance the susceptibility of DM-related neuronal dysregulation of cerebral vessels. This can be attributed to the mechanism of earlier pulsatility changes that occurred in the BA, rather than in the MCA and ICA.

In this study, the pulsatility of the MCA and ICA was closely correlated to the duration of diabetes. These results suggest that those vascular changes become more pronounced as the diabetic duration is extended. In the scattergrams in the Figure, the pulsatility of those arteries appeared stable during the first 10 years of DM but increased quickly thereafter. Because the PI is derived from (systolic velocity–diastolic velocity)/mean velocity,\textsuperscript{27} it may be more variable than either of the 3 velocity measurements. The diastolic velocity of the MCA and ICA was also significantly and inversely correlated to the duration of DM, but its significance was much weaker than that of PI. This result suggests that the PI change observed in our patients was determined not only by a reduction in diastolic velocity, but also by a reduced mean velocity as well as an increased systolic velocity, although their changes were not statistically significant. The PI change, considering the fact that it represented a combined effect of each velocity change, appears to reflect changes in cerebrovascular resistance rather than simply being influenced by certain velocity measurements.

This study defines TCD findings of diabetes-related cerebral hemodynamic changes and suggests that the PI reflects microangiopathic changes of cerebral vessels. Although a large overlap of PI values between patient groups was observed, only a few uncomplicated patients showed PI values of \textasciitilde0.8 for MCA and \textasciitilde1.0 for ICA, whereas a significant proportion of complicated patients showed a PI higher than these values. These results are not sufficient to set the cutoff values for distinguishing complicated patients but suggest that high PI values in these arteries beyond a certain range raise the possibility of concomitant microvascular complications. This study has some limitations, including a possible bias related to patient selection and a relatively small number of subjects. Despite these, our data suggest that TCD may have utility in the evaluation of interventions designated to prevent vascular complications of diabetes.

References

35. Lee et al. Cerebral Pulsatility Changes in Diabetes. 1115
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