Research Report

Central Retinal Artery Doppler Flow Parameters Reflect the Severity of Cerebral Small-Vessel Disease

Masahiko Hiroki, MD, PhD; Kotaro Miyashita, MD, PhD; Hiroshi Yoshida, MD, PhD; Shunsaku Hirai, MD, PhD; Hidenao Fukuyama, MD, PhD

Background and Purpose—We investigated the usefulness of central retinal artery (CRA) Doppler flowmetry in patients with cerebral small-vessel disease (SVD).

Methods—CRA Doppler flowmetry was performed in 103 SVD patients who underwent MRI. Sixty-four adjusted control subjects were also registered. We assessed average CRA flow parameter values for both eyes with the clinical and MRI findings.

Results—Each Doppler flowmetry was performed within 5 minutes. Patients with SVD had significantly lower end-diastolic and mean velocities of the CRA than control subjects; they also had higher pulsatility and resistive indexes. Multivariate analysis showed that the number of small infarcts was an independent predictor of peak systolic and mean velocities. Grade of periventricular hyperintensities was an additional independent predictor of peak systolic and mean velocities, whereas the number of small infarcts was predictive of end-diastolic velocity.

Conclusions—Flow parameters may be useful for the quantitative assessment of SVD severity. (Stroke. 2003;34:e92-e94.)

Key Words: retinal artery ■ small-vessel disease ■ ultrasonography, Doppler

Early and quantitative assessment of small-vessel disease (SVD) is important, but a method has not been established. Recently, we have focused on the central retinal artery (CRA), ~0.15 to 0.20 mm in diameter distally, which corresponds to a small artery. Because CRA Doppler flowmetry causes minimal discomfort, requires little time, and has high reproducibility, it seems useful for the quantitative assessment of SVD. In this study, we investigated the clinical backgrounds of the CRA flow parameter in patients with SVD confirmed by MRI.

Subjects and Methods

CRA Doppler flowmetry followed carotid ultrasonography in 466 consecutive patients at Tokyo Metropolitan Neurological Hospital between February 2000 and November 2001. We excluded 92 patients who had not had MRI within the year and 58 with ophthalmic disease that affected CRA flow velocity, large-vessel disease, and various therapies. Using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, we selected 103 patients with isolated SVD (mean age, 70.9 ± 9.0 years; 66 men). Furthermore, 64 age- and sex-adjusted controls were selected (the Figure). Informed consent was obtained from all subjects.

Hypertension and high blood pressure were defined by World Health Organization criteria. All clinical background factors except blood pressure and age were assessed as present or absent. Doppler flowmetry was performed by Powervision 6000 (Toshiba Inc, Tokyo) with 5.0-MHz color and pulsed Doppler transducer set at 12.0-kHz pulse frequency and 50-Hz low-cut filter. A 1.0-mm sample volume was positioned in the CRA 3.5 mm below the optic disc. The average value of each flow parameter of both eyes and the common carotid arteries (CCAs) was determined. MRI (1.5-T, Signa Horizon Hispeed, GE) was performed with a spin-echo pulse sequence to generate T1-weighted (repetition time/echo time, 300/8.0 ms) and T2-weighted (repetition time/echo time, 4000/90.0 ms) axial brain images with 6.0-mm slice thickness. On these MR images, lacunar and small white-matter medullary infarcts were defined as small infarcts (<1.5 cm in greatest diameter). Periventricular hyperintensities (PVHs) were graded into 3 groups.

Background factors and CRA flow parameters were compared between SVD and control groups with the Mann-Whitney U test or χ² test. In the SVD group, multiple linear regression analysis of each CRA flow parameter was done for variables with a significant difference or correlation univariately by the Mann-Whitney U test, Kruskal-Wallis H test, and Spearman’s rank correlation test.

Results

Compared with the control group, the SVD group had a significantly higher prevalence of hypertension, smoking, left ventricular hypertrophy, and pulsatility and resistive indexes of CCA and a lower prevalence of end-diastolic and mean velocities of the CCA (Table 1). CRA end-diastolic and mean velocities were significantly lower and CRA pulsatility and resistive indexes were higher in the SVD group than the control group (Table 2).
Multiple linear regression analysis showed that the small infarct number was an independent predictor of peak systolic ($B = -0.282$, $P = 0.001$) and mean ($B = 0.164$, $P = 0.001$) velocities, and CCA resistivity index was predictive of end-diastolic velocity ($B = -2.231$, $P = 0.016$) and pulsatility ($B = 1.830$, $P < 0.001$) and resistivity ($B = 0.438$, $P < 0.001$) indexes. PVH was an additional independent predictor of peak systolic and mean velocities; small infarct number, of end-diastolic velocity; and age, of pulsatility and resistivity indexes (Table 3).

**Discussion**

We showed that CRA flow parameters, especially end-diastolic and mean velocities, related to the severity of SVD. It is thought that decreases in these velocities reflect increases in small-artery or arteriolar wall resistance by arteriosclerosis. PVH, lacunar infarct, and small white-matter medullary infarct are pathologically known to be caused by small-artery or arteriolar lesions.6,8,9 Overall, CRA flow parameters can reflect the grade of PVH and the number of small infarcts. It is reported that carotid atherosclerosis affects CRA end-diastolic velocity,10 which was related to the CCA resistivity index in our study. Therefore, to assess SVD by ultrasound, both CRA and carotid examinations are necessary. Patients with vascular risk factors such as hypertension often show a
significant reduction in systolic and diastolic CRA velocities, although we did not find these reductions in our subjects. This might be due to organic changes in the small arteries or medical treatment in our subjects.

In conclusion, CRA flow parameters relate to the severity of SVD independently of aging and may be useful as a quantitative indicator. To confirm its clinical application, follow-up study including normal subjects in the community is necessary.

References

### TABLE 3. Independent Variables of Each CRA Flow Parameter in SVD by Multiple Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (SE)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>PSV*</td>
<td>Intercept 9.708 (0.408)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Small infarct 0.282 (0.084)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>PVH 1.497 (0.692)</td>
<td>0.033</td>
</tr>
<tr>
<td>EDV†</td>
<td>Intercept 5.688 (0.718)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CCA resistivity index 2.231 (0.909)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Small infarct 0.070 (0.020)</td>
<td>0.001</td>
</tr>
<tr>
<td>MV‡</td>
<td>Intercept 5.319 (0.212)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Small infarct 0.164 (0.044)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PVH 0.807 (0.360)</td>
<td>0.027</td>
</tr>
<tr>
<td>PI§</td>
<td>Intercept 0.551 (0.242)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>CCA resistivity index 1.830 (0.305)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age 0.006 (0.002)</td>
<td>0.003</td>
</tr>
<tr>
<td>RI</td>
<td>Intercept 0.252 (0.059)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CCA resistivity index 0.438 (0.074)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.002 (0.001)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PSV indicates peak systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; PI, pulsatility index; and RI, resistivity index.

*Adjusted $R^2 = 0.136$, $F = 11.327$, $P < 0.001$; †adjusted $R^2 = 0.233$, $F = 11.372$, $P < 0.001$; ‡adjusted $R^2 = 0.161$, $F = 10.761$, $P < 0.001$; §adjusted $R^2 = 0.380$, $F = 21.670$, $P < 0.001$; and ¶adjusted $R^2 = 0.380$, $F = 21.630$, $P < 0.001$. 

significant reduction in systolic and diastolic CRA velocities, although we did not find these reductions in our subjects. This might be due to organic changes in the small arteries or medical treatment in our subjects.

In conclusion, CRA flow parameters relate to the severity of SVD independently of aging and may be useful as a quantitative indicator. To confirm its clinical application, follow-up study including normal subjects in the community is necessary.
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