Eccentric Stenosis of the Carotid Artery Associated with Ipsilateral Cerebrovascular Events


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BACKGROUND AND PURPOSE: Eccentric stenosis of the coronary artery is associated with plaque disruption and acute coronary syndrome. The purpose of the present study was to determine whether eccentric stenosis of the carotid artery contributes to cerebrovascular events.

MATERIALS AND METHODS: Of 6859 patients with vascular diseases who underwent duplex carotid ultrasonography, we studied 512 internal carotid arteries in 441 patients who had a maximum area stenosis at or more than 70%, which corresponds with approximately 50% or more by the NASCET method. The maximal (A) and minimal wall thicknesses (B) were measured on cross-sectional sonography images, and an eccentricity index was calculated using the following formula: \( (A - B)/A \). Arteries in the lowest quartile of the eccentricity index (<0.69) were defined as having a concentric stenosis, whereas the others were defined as having eccentric stenosis. The underlying clinical characteristics and plaque morphologies, as well as the occurrence of ipsilateral ischemic stroke or transient ischemic attack in the preceding year, were compared between patients with eccentric and concentric stenosis.

RESULTS: Patient characteristics and plaque morphology were similar between the 2 groups. Cerebrovascular events occurred more frequently ipsilaterally to the artery with eccentric stenosis (13.5%) than to the artery with concentric stenosis (5.5%; \( P = .013 \)); the difference was more evident when cerebrovascular events of presumed carotid arterial origin were assessed (\( P = .005 \)). After adjusting for risk factors and plaque morphology, eccentric stenosis was independently related to the presence of recent cerebrovascular events (odds ratio = 2.76; 95% confidence interval = 1.19–6.40).

CONCLUSIONS: In patients with an area carotid stenosis of 70% or more, eccentric plaque was associated with a significantly increased incidence of ipsilateral cerebrovascular events compared with patients with concentric stenosis.
with severe calcification of which the degree of stenosis could not be measured due to the presence of an acoustic shadow on sonography were excluded from the study.

Sonography examination was performed using a duplex color-coded ultrasonographic device equipped with a linear array 7.5-MHz transducer (mainly Aplio XV; Toshiba, Tokyo, Japan). The most stenotic portion of the ICA was determined by using gray-scale and Doppler sonography, as described previously; the cross-sectional image of the stenotic portion was stored on a computer hard disk together with the other sonography findings. Plaque morphology and the distribution of the stenotic portion were evaluated by investigators who were blinded to the patients’ clinical information. The maximal (A) and minimal (B) thicknesses of the vessel wall were measured on the cross-sectional image by using Scion Image (Scion, Frederick, Md.), and the eccentricity index of the plaque was calculated by using the following formula: \((A - B)/A\) (Fig 1). The 512 ICAs studied were divided into quartiles based on the index; those in the lowest quartile were defined as having concentric stenosis, and those remaining were defined as having eccentric stenosis. The echogenicity of the carotid plaque was categorized as hypoechoic, isoechoic, or hyperechoic. A hypoechoic plaque was defined as having an echogenicity the same as that of the vessel lumen; an isoechoic plaque was defined as having an echogenicity of the soft tissues surrounding the carotid arteries; and a hyperechoic plaque was defined as having a brighter echogenicity than the surrounding soft tissues. A heterogeneous plaque was defined as containing a mixture of hypoechoic, isoechoic, or hyperechoic lesions.

The following clinical characteristics were evaluated: sex, age, hypertension (blood pressure of \(\geq 140/90\) mm Hg or use of antihypertensive medications), diabetes mellitus (fasting blood glucose \(\geq 126\) mg/dL, positive 75-g oral glucose tolerance test result, or use of insulin or oral hypoglycemic agents), hypercholesterolemia (serum total cholesterol \(\geq 220\) mg/dL or use of antihypercholesterolemic medications), ischemic heart disease, peripheral artery disease, aortic aneurysm, current smoking habit, and habitual alcohol consumption (\(\geq 2\) drinks per day).

Recent cerebrovascular events, including ischemic stroke, transient ischemic attack (TIA), and transient monocular blindness (TMB) ipsilateral to the stenotic carotid artery within 1 year preceding the sonography study were reviewed from the medical records. For diagnosis of ischemic stroke, we required identification of culprit infarcts mainly on MR imaging, in addition to the episode of neurologic dysfunction. TIA was defined as a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of acute infarction; an episode caused by retinal ischemia was termed TMB here. As the cerebrovascular events of presumed carotid arterial origin, all of the cerebrovascular events other than those with the small infarct of less than 1.5 cm in diameter in the perforator arterial territory (lacune) and those with the high-risk sources of cardioembolism in Trial of Org 10172 in Acute Stroke Treatment classification were also assessed.

**Statistical Analysis**

Values are expressed as means ± SDs. The clinical variables of the concentric and eccentric plaque groups were compared by using Student t test for continuous variables and the \(\chi^2\) test for categoric variables. To determine the predictors for cerebrovascular events, multivariate logistic regression analysis was performed. To ascertain the reasonableness of our dividing arteries into 2 groups by using the first quartile value of the eccentricity index, we constructed a receiver operating characteristic (ROC) curve and obtained the eccentricity index as the cutoff point for discriminating between patients with recent cerebrovascular events and those without. Statistical test results were considered significant with a \(P\) value <.05. SPSS software (SPSS, Cary, NC) was used for the analyses.

**Results**

The distribution of stenosis geometry of the 512 ICAs by the eccentricity index is shown in Fig 2. The index varied from 0.00 to 0.99; the first quartile, median, and third quartile values were 0.69, 0.87, and 0.95, respectively. Thus, the index

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**Fig 1. A. Eccentricity index = (A - B)/A. B-D. Examples of stenotic internal carotid arteries with eccentricity index values of 0.5, 0.7, and 0.9, respectively.**

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**Fig 2. The eccentricity index histogram of 512 internal carotid arteries.**

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**Fig 3. Distribution of stenosis geometry of the 512 ICAs by the eccentricity index.**
Overall cerebrovascular events 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Concentric Stenosis (n = 128)</th>
<th>Eccentric Stenosis (n = 384)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>73.0 ± 7.5</td>
<td>72.4 ± 7.8</td>
<td>0.476</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>107 (84)</td>
<td>339 (88)</td>
<td>0.171</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>115 (81)</td>
<td>335 (87)</td>
<td>0.306</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>56 (44)</td>
<td>159 (41)</td>
<td>0.642</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>85 (66)</td>
<td>232 (60)</td>
<td>0.227</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>54 (42)</td>
<td>169 (44)</td>
<td>0.711</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>33 (26)</td>
<td>88 (23)</td>
<td>0.509</td>
</tr>
<tr>
<td>Aortic aneurysm, n (%)</td>
<td>13 (10)</td>
<td>50 (14)</td>
<td>0.319</td>
</tr>
<tr>
<td>Current smoking habit, n (%)</td>
<td>32 (25)</td>
<td>79 (21%)</td>
<td>0.292</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>28 (22)</td>
<td>67 (17)</td>
<td>0.264</td>
</tr>
</tbody>
</table>

Plaque morphology

<table>
<thead>
<tr>
<th>Degree of stenosis, mean ± SD, %</th>
<th>83.5 ± 9.0</th>
<th>83.6 ± 8.0</th>
<th>0.909</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%–79%, n (%)</td>
<td>48 (37)</td>
<td>141 (37)</td>
<td>0.489</td>
</tr>
<tr>
<td>80%–99%, n (%)</td>
<td>37 (29)</td>
<td>131 (34)</td>
<td>0.489</td>
</tr>
<tr>
<td>100%, n (%)</td>
<td>43 (34)</td>
<td>112 (29)</td>
<td>0.489</td>
</tr>
<tr>
<td>Hypoechoic, n (%)</td>
<td>48 (38)</td>
<td>135 (35)</td>
<td>0.538</td>
</tr>
<tr>
<td>Heterogeneous, n (%)</td>
<td>91 (72)</td>
<td>247 (64)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Table 2: Comparison of cerebrovascular events between concentric stenosis and eccentric stenosis

<table>
<thead>
<tr>
<th>Cerebrovascular Events</th>
<th>Concentric Stenosis (n = 128)</th>
<th>Eccentric Stenosis (n = 384)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall events</td>
<td>7 (5.5)</td>
<td>52 (13.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5 (3.9)</td>
<td>36 (9.4)</td>
<td>0.048</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0 (0)</td>
<td>9 (2.4)</td>
<td>0.073</td>
</tr>
<tr>
<td>Transient monocular blindness</td>
<td>2 (1.6)</td>
<td>7 (1.8)</td>
<td>0.601</td>
</tr>
<tr>
<td>Events of presumed carotid arterial origin</td>
<td>5 (3.9)</td>
<td>49 (12.8)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 3: Eccentric internal carotid artery stenosis as a predictor of recent cerebrovascular events

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>2.60</td>
<td>1.15–5.90</td>
<td>0.022</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.76</td>
<td>1.20–6.34</td>
<td>0.016</td>
</tr>
<tr>
<td>Model 3</td>
<td>2.76</td>
<td>1.19–6.40</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Note: Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, current smoking habit, and alcohol consumption). Model 3 was adjusted for age, gender, vascular risk factors, and plaque morphologies (degree of stenosis, hypoechoic plaque, and heterogeneous plaque). CI indicates confidence interval.

Discussion

This is the first study to investigate the association between the geometry of carotid artery stenosis and ipsilateral cerebrovascular events using ultrasonography. The major new finding was that, independent of underlying risk factors and other features of plaque morphology, eccentric ICA stenosis was associated with recent cerebrovascular events within the preceding year.

The carotid bifurcation often shows uneven development of atherosclerosis between the inner and outer walls because of different flow streamline patterns and shear stress. The coronary artery may have a similar tendency. A previous study showed that 81% of the coronary arteries examined by intravascular sonography were eccentric, with an eccentricity index at 0.5 or more, and such eccentric plaques were strongly associated with the acute coronary syndrome. Using the same 0.5 index cutoff value in the present study, eccentric carotid artery stenosis was present in 88% of all of the vessels. However, this percentage may be too high to use for appropriate comparisons of clinical features between eccentric and concentric stenosis. Instead, we used the first quartile value of the eccentricity index (0.69) to divide arteries into 2 groups. This value was close to the optimal cutoff value of the eccentricity index by the ROC curve analysis (0.71). Thus, eccentricity defined as an index at 0.69 or more appears to be appropriate.

The association of eccentric coronary artery stenosis with acute coronary syndrome is due to the presence of disruption of the eccentric plaque or superimposed thrombus. Some extent, the same morphologic features may explain the association between eccentric carotid plaques and cerebrovascular events. In addition, hemodynamic changes induced by eccentric stenosis may be an important factor that leads to cerebrovascular events. Relatively low shear stress is reported to play a critical role in the development of atherosclerosis and vulnerable plaques. A computational simulation study using carotid
bifurcation models demonstrated that there were differences be-
tween eccentric and concentric stenosis with respect to the size of
the poststenotic recirculation zone, as well as the severity and
distribution of wall shear stress. Using the models, the deposi-
tion of platelet and monocyte-sized particles on the vessel wall
was more distinct proximal to the eccentric stenosis than proxim-
al to the concentric stenosis. This suggests that eccentric ste-
nosis is more prone to platelet activation and aggregation due to
attenuated platelet deposition and plaque growth, as well as rup-
ture due to attenuated monocyte deposition. Thus, eccentric ste-
nosis may have a high potential for thrombus formation, which
may lead to an increased risk of cerebrovascular events.

Similar plaque morphology can be easily seen by using
multidetector row CT (MDCT) angiography and some types of
MR techniques. In a recent study on MDCT, the relation-
ship between stroke symptoms and plaque morphology was
assessed. In the study, expansive carotid remodeling was
greater in patients with cerebral ischemic symptoms than in
asymptomatic patients, though there was no significant differ-
ence in the plaque eccentricity between symptomatic and
asymptomatic patients. Thus, MDCT and MR techniques, as
well as ultrasonography, seem to be available for evaluation of
the geometry of carotid artery stenosis.

In the present study, hypoechoic plaque and heterogeneous
plaque were not indicative of recent cerebrovascular events,
though they were often reported to be risk factors in the
events. This might be because of the small patient number for
appropriate statistical analysis or because the echogenicity of
the carotid plaque was not evaluated objectively and quantitatively by
using the gray-scale median. Other limitations of the present
study include the following reasons. First, carotid arteries with
advanced calcification were excluded from the study, because the
severe acoustic shadow did not allow the eccentricity index to be
measured on sonography. In our study population, such arteries
might account for 10% of the arteries with maximum area steno-
sis at 70% or more. Although the contribution of carotid calci-
fication to cerebrovascular events is uncertain, the present
results may have been affected by the exclusion of these calcified
arteries from the analysis. Second, although the present retro-
spective analysis demonstrated an association between stenosis
geometry and pre-existent cerebrovascular events, a prospective
trial is required to assess the contribution of eccentric stenosis to
future cerebrovascular events.

In patients with a cross-sectional area carotid stenosis of 70% or
more on sonography, eccentric plaque with an eccentricity
index at 0.69 or more was associated with a significantly increased
incidence of recent ipsilateral cerebrovascular events compared
with a cohort of patients with concentric stenosis. The presence of
eccentric stenosis, as well as the severity of the stenosis, may be
an important indicator for use in the selection of patients for surgical
revascularization of the carotid artery.

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