Reflux of Anterior Spinal Artery Predicts Recurrent Posterior Circulation Stroke in Bilateral Vertebral Artery Disease

Hitoshi Fukuda, MD; Kosuke Hayashi, MD; Akira Handa, MD; Yoshitaka Kurosaki, MD; Benjamin Lo, MD; Sen Yamagata, MD

**Backgrounds and Purpose**—Predictive value of reflux of anterior spinal artery for recurrent posterior circulation ischemia in bilateral vertebral arteries steno-occlusive disease was evaluated.

**Methods**—We retrospectively reviewed 55 patients with symptomatic bilateral posterior circulation stroke caused by bilateral stenotic (>70%) lesions of the vertebral artery. We investigated any correlation of clinical and angiographic characteristics including collateral flow patterns, with recurrent stroke. Risk factors for poor 3-month functional outcome were also evaluated.

**Results**—Recurrent posterior circulation stroke was observed in 15 (27.3%) patients. Multivariable analysis using Cox proportional hazards model showed anterior spinal artery reflux as a significant risk factor for stroke recurrence (adjusted hazard ratio, 19.3 [95% confidence interval, 5.35–69.9]; *P*<0.001). Anterior spinal artery reflux was also correlated with poor functional outcome (modified Rankin Scale score, 3–6; adjusted odds ratio, 7.41 [95% confidence interval, 1.24–44.4]; *P*=0.028).

**Conclusions**—In patients with symptomatic bilateral vertebral artery occlusive disease, anterior spinal artery reflux predicted recurrent posterior circulation stroke and poor functional outcome. (*Stroke*. 2015;46:3263-3265. DOI: 10.1161/STROKEAHA.115.011246.)

**Key Words:** atherosclerosis • ischemia • risk factors • stroke • vertebral artery

Symptomatic bilateral occlusion or severe stenosis of vertebral artery (VA) is associated with recurrent ischemic strokes because bilateral disease is hemodynamically less stable than unilateral disease. It is important to predict which subgroup of bilateral VA disease is refractory to best medical treatment and at risk for stroke recurrence.

Bilateral VA diseases are often compensated by collateral flow via various anastomotic channels. Among them, reflux of anterior spinal artery (ASA) is minute in volume and may suggest critical hypoperfusion of the posterior circulation. The purpose of this study is to clarify whether ASA reflux predicts recurrence of posterior circulation stroke in patients with bilateral VA atherosclerotic disease.

**Methods**

Our institutional stroke database was searched for patients who were admitted for posterior circulation stroke between January 2005 and December 2014. Catheter cerebral angiography was performed when the stroke was atherosclerotic and was attributable to bilateral VA severe stenosis or occlusion on magnetic resonance or computed tomographic angiography. Patients were included when (1) catheter angiography was performed before the onset of recurrence, (2) at least unilateral intracranial VA is occluded or severely stenosed (>70%), and (3) contralateral VA represented occlusion or severe stenosis (>70%) at any segment. Fifty-five consecutive patients with symptomatic bilateral VA steno-occlusive disease met inclusion criteria for review.

In diagnostic angiography, possible collateral channels supplying VA or basilar artery were investigated and categorized into ASA, posterior communicating artery, thyrocervical trunk, and occipital artery (Figure 1). In particular, collateral through ASA was defined as ascending contrast flow in the ASA, visualized in serial angiographic images every 0.25 s, with contrast reaching the VA union no later than the corresponding anterograde flow through the ipsilateral VA. Dual antiplatelet therapy was primarily administered after the first stroke, and statin was used according to history of hyperlipidemia and high total cholesterol level during hospitalization. When posterior circulation stroke recurred despite medical therapy, endovascular or surgical intervention was proposed.

Patients’ baseline characteristics, clinical presentation, and angiographic findings were analyzed to identify risk factors for stroke recurrence of the posterior circulation. Functional outcome at 3 months after the initial onset was determined with modified Rankin Scale, and dichotomized into good (modified Rankin Scale score, 0–2) and poor (modified Rankin Scale score, 3–6). Relationship between pattern of collateral circulation and functional outcome was analyzed.

Commercially available software (SPSS version 22, IBM Corp, Armonk, NY) was used for statistical analysis. Chi-square test was performed to evaluate covariates for binary categorical dependent

Received August 19, 2015; final revision received August 19, 2015; accepted August 31, 2015.

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*Stroke* is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.011246

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variables. Risk factors of stroke recurrence were analyzed by log-rank test and Cox proportional hazards model. Decision tree analysis was performed to properly stratify the risk of recurrence by combination of multiple predictors, using the Classification And Regression Trees method. The probability of freedom from stroke recurrence was estimated using the Kaplan–Meier method; comparisons of survival curves by the stratified risk groups were performed using the log-rank test. Univariate and multivariable logistic regression analyses were performed to determine risk factors for poor functional outcomes (modified Rankin Scale score, 3–6). The odds ratio and 95% confidence interval were determined in logistic regression analyses.

Results

Recurrent posterior circulation stroke was observed in 15 (27.3%) patients. Clinical and angiographic characteristics of 55 patients with (n=15) and without (n=40) recurrence are shown in Table. The median length of follow-up was 485 days (interquartile range, 158–1365 days).

The log-rank test revealed that ASA reflux as a collateral was significantly correlated (P<0.001) with stroke recurrence. In multivariable analysis using Cox proportional hazards model, ASA collateral (P<0.001) and hyperlipidemia (P=0.009) were significantly correlated with stroke recurrence. According to decision tree analysis, risk of recurrence was stratified into 3 groups: low-risk group (neither ASA collateral nor hyperlipidemia, n=30), medium-risk group (no ASA collateral but with hyperlipidemia, n=13), and high-risk group (ASA collateral, n=12; Figure 2A). There was a significant difference for freedom from stroke recurrence among these stratified groups (Figure 2B).

Surgical or endovascular intervention was performed in 9 (16.4%) patients. Five patients were lost to clinical outcome follow-up at 3 months. Univariate regression analyses demonstrated that ASA reflux was significantly associated with poor functional outcome (odds ratio, 6.07 [95% confidence interval, 1.29–28.5]; P=0.022). After adjustment for potential confounders including increasing age, initial National Institutes of Health Stroke Scale, and recurrent stroke, ASA collateral remained an independent predictor of poor functional outcome (odds ratio, 7.41 [95% confidence interval, 1.24–44.4]; P=0.028).

Discussion

Occlusive disease of the intracranial VA is associated with high stroke recurrence rates. In particular, bilateral VA disease is often associated with hemodynamic compromise of the posterior circulation, more frequently leading to recurrent strokes. Previous studies have proposed dual antiplatelet therapy and use of statin as aggressive medical treatment for symptomatic intracranial atherosclerotic disease. As second

Table. Univariate Analyses to Examine Factors for Stroke Recurrence From Bilateral Vertebral Artery Disease

<table>
<thead>
<tr>
<th>Characteristic (n=55)</th>
<th>Stroke Recurrence</th>
<th>Unadjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[+] (n=15)</td>
<td>[-] (n=40)</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>8 (53.3)</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>Female sex</td>
<td>2 (13.3)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (80.0)</td>
<td>22 (55.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (40.0)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (46.7)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Initial NIHSS &gt;3</td>
<td>8 (53.3)</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>Bilateral intracranial lesion</td>
<td>12 (80.0)</td>
<td>21 (52.5)</td>
</tr>
</tbody>
</table>

Collateral flow

Anterior spinal artery | 10 (66.7) | 2 (5.0) | <0.001* |
Posterior communicating artery | 3 (20.0) | 14 (35.0) | 0.31 |
Thyrocervical trunk | 2 (13.3) | 9 (22.5) | 0.46 |
Occipital artery | 1 (6.7) | 3 (7.5) | 0.95 |

Data are presented as the number of patients (%). NIHSS indicates National Institutes of Health Stroke Scale.
*Variables marginally or significantly associated with the recurrence by log-rank test (P<0.10).
strokes often lead to irreversible neurological deficit, it is important to identify patient subgroups who have unstable hemodynamics and, therefore, may benefit from therapeutic revascularization before recurrent stroke.

Bilateral VA diseases are often compensated by collateral flow via various anastomotic channels. We assumed that hypoperfusion as one of the major causes of recurrent strokes can be assessed by the pattern of collateral flow. Among possible collateral channels, the mean diameter of ASA is 0.7 mm and smaller than the others including posterior communicating artery and occipital artery (1.4–1.9 mm; Figure 1).2,3,5,6 With its small diameter, ASA reflux may be recruited only when anterograde VA or other larger collateral flow becomes critically insufficient at the terminal stage of posterior circulation ischemia. However, because of its small diameter, collateral flow through ASA may be unable to compensate for critical hypoperfusion. This increases likelihood of recurrent strokes with associated poor functional outcome. In our study, hyperlipidemia was independently correlated with stroke recurrence risk in patients without ASA collateral. This suggests potential distal embolic phenomenon from vulnerable plaque associated with hyperlipidemia.

Selection bias exists in this study. Patients who presented rapid stroke recurrence before diagnostic angiography were not captured. This subgroup may have distinct features other than ASA reflux on angiography. Further investigation would be warranted to address causative mechanisms involved in stroke recurrence in bilateral VA disease, along with optimal treatment options for posterior circulation ischemia with ASA reflux.

Conclusions
Reflux of ASA in bilateral VA atherosclerotic disease predicted recurrence of posterior circulation strokes, and was associated with poor functional outcome.

Disclosures
None.

References

Figure 2. A, Decision tree analysis to stratify the risk of recurrence by combination of multiple predictors. Those with neither ASA collateral nor hyperlipidemia, those without ASA collateral but with hyperlipidemia, and those with ASA collateral are categorized into low-risk (group A), medium-risk (group B), and high-risk (group C) groups, respectively. B, Kaplan–Meier plot of cumulative freedom from stroke recurrence for 300 days by the groups (A–C) stratified by the decision tree analysis. ASA indicates anterior spinal artery; NSR, no stroke recurrence; and SR, stroke recurrence.
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Stroke. 2015;46:3263-3265; originally published online September 29, 2015; doi: 10.1161/STROKEAHA.115.011246
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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