Impacts of Cigarette Smoking and Basilar Artery Flow on 1-year Recovery in 3-Month survivors of Intracranial Vertebrobasilar Artery Dissection-related Ischemic Stroke

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Abstract-

Objective: Intracranial vertebrobasilar artery dissection (iVBD) is an important etiology for posterior circulation ischemic stroke (PCS); however, its long-term functional outcome has been seldom reported. The present study aimed to elucidate the functional outcomes and the predictors of poor functional recovery at 1-year after iVBD-caused PCS.

Methods: Patients with iVBD-caused PCS who had been recruited in the Stroke Registry of Taipei Veterans General Hospital between January 1, 2012 to February 28, 2014 were included. Multivariate analysis was used to detect predictors for poor 1-year functional recovery [modified Rankin Scale (mRS) ≥ 4].

Results: Sixty patients [age: 66.3±15.1 years; 45(75%) men] were included. At 1-year after stroke, 61.7% of patients had good functional status (mRS 0-1); however, 21.6% of patients were disabled (mRS≥4). Multivariate analyses showed that older age, cigarette-smoking history and low basilar-artery (BA) flow velocity were significantly associated with poor functional recovery independent of stroke severity at admission. The results also revealed a synergistic effect of cigarette-smoking and low BA flow on poor 1-year functional recovery: patients with both, a history of cigarette-smoking and low BA flow (≤24cm/s) had an odds ratio of 276.1 (p=0.007) leading to poor 1-year functional recovery, versus patients with neither cigarette-smoking history nor low BA flow.

Conclusions: Our results suggest that adequate blood flow may be key to functional recovery after iVBD-caused PCS. Methods to improve blood flow and tissue perfusion after iVBD-caused PCS should be considered in the future clinical studies with the purpose to improve functional recovery in these patients.

Key Words: vertebrobasilar artery dissection, posterior circulation, ischemic stroke

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INTRODUCTION

Arterial dissection is an important etiology of posterior circulation ischemic stroke (PCS)\textsuperscript{(1-3)}. In our stroke registry, one quarter of PCS cases were caused by arterial dissection and almost all (98%) of them had
arterial dissection involving intracranial arteries\textsuperscript{(3,4)}. Other studies also showed that compared with the Western population, the Asian population with arterial dissection-caused PCS had more intracranial arteries than cervical arteries\textsuperscript{(5,6)}. However, the clinical course of intracranial vertebrobasilar dissection (iVBD) with PCS is less studied than the extracranial vertebral artery dissection or rupture of an intracranial vertebrobasilar dissecting aneurysm\textsuperscript{(7-11)}. Owing to few clinical pictures, the exact pathophysiology and valid treatment and prevention strategy of iVBD-caused PCS are unclear\textsuperscript{(12)}.

We previously reported the clinical course in patients with arterial dissection-caused PCS during hospitalization and at 3 months’ interval. The results showed that the short-term outcome was not favorable and was comparable to PCS caused by atherosclerotic stenosis of a large artery\textsuperscript{(3,4)}. The present study aimed to evaluate the functional recovery at 1 year and predictors of poor recovery in patients who survived 3 months after iVBD-caused PCS. These results will not only provide information for physicians to use in their clinical practice, but will also help create a management strategy, in order to improve functional recovery in these patients.

METHODS

Study Population

The Stroke Registry from Taipei Veterans General Hospital (TVGHSR) prospectively collects data since Feb 2009, on every patient with acute stroke who is consecutively admitted to emergency room or/and Department of Neurology. We retrieved data from TVGHSR on patients who were consecutively admitted and registered between January 1, 2012 and February 28, 2014. Clinical and imaging details of recruited PCS patients were reviewed and consensus was reached by two neurologists (Dr. Chung and Hu) and one radiologist (Dr. Chang) on the etiology of stroke. The criteria for diagnosing iVBD-caused PCS have been described previously\textsuperscript{(3,4,13,14)}. We have reported previously the short-term (at discharge and 3 months) mortality rates in patients with arterial dissection-caused PCS\textsuperscript{(3,4)}. In this study, we evaluated and analyzed the functional recovery at 1 year in previously analyzed iVBD-caused PCS cases. Patients who were mortality at 3 months’ interval would not be included in the present study. Taipei Veterans General Hospital Institutional Review Board (IRB) has approved this study. The clinical investigation was conducted according to the principles in the Declaration of Helsinki. Patient written consent was waived under IRB approval. Patients’ personal or clinical information were anonymized and could not be identified by authors when they evaluated the available data.

Cerebral Infarcts Patterns

According to their locations, infarcts were categorized as involving proximal, middle, or/and distal posterior circulation territories. Brain lesion involved in more than one category was defined as inclusive lesion; otherwise, it was defined as a single lesion.

Transcranial Color-coded Doppler (TCCD): BA Flow Velocity

BA hemodynamic parameters were assessed by TCCD via the foramen magnum (sub-occipital approach) with a 2-MHz sector transducer (iU22; Philips, New York, NY, USA). All patients received TCCD routinely, within 48 hours of acute stroke. The ultrasound beam was placed approximately 4-cm beneath the occipital protuberance, while the patients were lying in a lateral position with the neck semi-flexed. The examination started at an insonation depth of 10-cm. Color-coded image superimposed on B-mode gray scale image at this site allowed for the typical Y-shaped vertebrobasilar junction to be easily visualized. The axial sample volume of 2.5 mm was kept constant during the measurements. During the course of the examination, color scale and gain settings were chosen individually to provide optimal imaging conditions. Visualization of a color signal at a distal site without a corresponding pulsed Doppler signal was judged to be an artifact. The assessed parameters, systolic and end-diastolic flow velocities (FVs), were measured from the vertebrobasilar junction to the most distant visible segment of the BA. The measurements over the most distant BA were retained for analyses. Mean FV (FVmean) was calculated as $[(2/3 \times \text{end-diastolic FV}) + (1/3 \times \text{systolic FV})]$. 

Statistical Analysis

Statistical analyses were performed with SAS
software, version 9.1 (SAS Institute, Cary, NC, USA). All values were expressed as mean ± SD for continuous variables and number (percentages) for discrete variables. To detect factors associated with poor functional recovery [modified Rankin Scale (mRS) ≥ 4] and good functional recovery (mRS=0-1) at 1 year, we used univariate and multivariate logistic regression analyses. Independent variables for analyses included age, sex, admission NIH stroke scale (NIHSS), infarct location (proximal, middle or distal), lesion pattern (inclusive or single lesions), presence of bilateral VA involvement, presence of BA involvement, BA FVmean, presence of risk factors [hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, and cigarette smoking], and types of managements (antiplatelet therapy, anticoagulants, and vascular intervention). Both, the present and former smokers were defined as positive smoking history in our stroke registry. The χ² test or Fisher’s exact test was performed for categorical variables, as appropriate. The nonparametric Wilcoxon rank sum test was used for continuous numeral variables. Odds ratios (OR) were calculated for associated variables. All statistically significant results were defined by P < 0.05.

To demonstrate the effects of BA flow velocity and cigarette smoking on 1-year recovery, we used the 1st quartile of BA FVmean (24 cm/s) as the cutoff value and we classified the patients into four groups, based on the presence or absence of cigarette-smoking history and BA FVmean ≤ 24 (low flow) or > 24 cm/s.

RESULTS

From Jan-1st-2012 to Feb-28th-2014, TVGHSR prospectively registered 1343 patients with acute ischemic stroke. Among these patients, there were 318 cases with cerebral infarcts in the territory of posterior circulation. Sixty-seven patients were considered as having iVBD-caused PCS. In patients with iVBD-caused PCS, 7 died within 3 months after stroke. Sixty patients who survived 3 months after iVBD-caused PCS [age (mean±SD, range): 66.3±15.1, 21-91 years; gender: 45(75%) men] were included in the present study.

Table 1 shows the characteristics of dissecting-vascular. In our patients with iVBD-caused PCS, dissection most frequently was initiated from the intracranial VA, and the 2nd most frequently, from the BA. Notably, BA was involved in a higher percentage of cases (88.3%).

BA FVmean measured by TCCD is presented in Table 1. The mean insonation depth of BA measured was 88.0 mm (SD = 8.2, range = 75.0–118.0). Since patients with a fetal posterior cerebral artery may present a lower flow volume in the BA, we analyzed the MRA image for every case and the results revealed the absence of this condition in all subjects.

Functional Recovery at 1-year After Discharge

Recovery after iVBD-caused PCS in our population mostly occurred during the first 3-6 months and to a lesser extent, after 6-months (Fig 1). There were no deaths at 6 months and 1 year in patients who survived the acute and subacute stages (3 months) of iVBD-caused PCS. No recurrent stroke was found. At 1-year after stroke, 61.7% of patients were in a good functional status (mRS0-1), however, there were still 21.6% of patients with disability (mRS≥4).

| Table 1. Characteristics of Dissecting Artery and Basilar Artery Flow Velocity |
|----------------------------------|-------------------|
| VA dissection, n (%)            |                   |
| Extracranial, n (%)             | 12(28.6)          |
| Intracranial, n (%)             | 30(71.4)          |
| Extended to BA, n (%)           | 35(83.3)          |
| Bilateral, n (%)                | 12(28.6)          |
| BA dissection, n (%)            | 4( 6.7)           |
| Associated aneurysm, n (%)      | 18(30.0)          |
| BA mean flow velocity, cm/s     |                   |
| mean±SD                         | 34.3±18.8         |
| 1st quartile                    | 24.0              |
| 2nd quartile                    | 29.3              |
| 3rd quartile                    | 39.7              |

PCS=posterior circulation ischemic stroke; VA=vertebral artery; BA=basilar artery; PICA=posterior inferior cerebellar artery; PCA=posterior cerebral artery.
Table 2 shows the results of comparisons between patients with poor functional outcomes (mRS≥4) and the other patients (mRS 0-3). Patients with poor functional recovery at 1 year were older and more frequently, women. After adjusting for age and gender, factors such as a history of cigarette-smoking, more serious stroke (NIHSS) and lower BA FVmean on admission were associated with poor 1-year functional recovery. Other factors, such as locations of cerebral infarct, types of cerebral infarct (single or inclusive lesions), involvement of BA on MRI/MRA, and types of treatments (oral antiplatelet therapy, anticoagulants or/and intervention with stent insertion) were not associated with 1-year functional recovery.

We further performed the multivariate analyses, with variables including age, gender, cigarette smoking, stroke severity (NIHSS at admission) and BA FVmean, in order to determine the predictors of poor functional recovery at 1 year (Table 3). The results revealed that older age, cigarette-smoking history and lower BA FVmean were associated with poor 1-year functional outcome in patients with iVBD-caused PCS. Notably, these predictors were independent of the stroke severity on admission.

**Predictors of Poor 1-year Functional Recovery After iVBD-caused PCS**

Table 2 also shows the results of multivariate analyses for predictors of good 1-year functional recovery (mRS0-1). Similar to predictors for poor functional outcomes, though reversed associated direction, age and cigarette smoking history were associated with good 1-year functional recovery after iVBD-caused PCS. These results were independent of stroke severity on admission, as well.

**Predictors of Good 1-year Functional Recovery After iVBD-caused PCS**

Table 3 also shows the results of multivariate analyses for predictors of good 1-year functional recovery (mRS0-1). Similar to predictors for poor functional outcomes, though reversed associated direction, age and cigarette smoking history were associated with good 1-year functional recovery after iVBD-caused PCS. These results were independent of stroke severity on admission, as well.

**Table 2. Comparisons between Patients with Poor 1-year Functional Recovery (mRS≥4) and Other Patients (mRS 0-3)**

<table>
<thead>
<tr>
<th></th>
<th>mRS0-3 (n=47)</th>
<th>mRS≥4 (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>63.9±15.6</td>
<td>74.9±8.9</td>
<td>0.027</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>38 (80.9)</td>
<td>7 (53.8)</td>
<td>0.070</td>
</tr>
<tr>
<td>Adjusted for age and gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>34 (72.3)</td>
<td>12 (92.3)</td>
<td>0.346</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>23 (48.9)</td>
<td>9 (6.9)</td>
<td>0.316</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>21 (44.7)</td>
<td>3 (23.1)</td>
<td>0.461</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>14 (29.8)</td>
<td>5 (38.5)</td>
<td>0.058</td>
</tr>
<tr>
<td>Admission NIHSS, mean±SD</td>
<td>3.9 (4.3)</td>
<td>11.4 (6.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Bilateral VA involvement, n (%)</td>
<td>9 (19.1)</td>
<td>3 (23.1)</td>
<td>0.638</td>
</tr>
<tr>
<td>BA involvement, n (%)</td>
<td>39 (83.0)</td>
<td>13 (100.0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Mean BA flow velocity, mean±SD</td>
<td>37.7 (19.1)</td>
<td>20.9 (9.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Infarct location, proximal, n (%)</td>
<td>17 (36.2)</td>
<td>3 (23.1)</td>
<td>0.863</td>
</tr>
<tr>
<td>Infarct location, middle, n (%)</td>
<td>28 (59.6)</td>
<td>11 (84.6)</td>
<td>0.257</td>
</tr>
<tr>
<td>Infarct location, distal, n (%)</td>
<td>10 (21.3)</td>
<td>4 (30.8)</td>
<td>0.426</td>
</tr>
<tr>
<td>Antiplatelet after discharge, n (%)</td>
<td>36 (76.6)</td>
<td>9 (69.2)</td>
<td>0.398</td>
</tr>
<tr>
<td>Anticoagulants after discharge</td>
<td>13 (27.7)</td>
<td>2 (15.4)</td>
<td>0.637</td>
</tr>
<tr>
<td>Stent insertion during hospitalization</td>
<td>4 (8.5)</td>
<td>00.999</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS=NIH stroke scale; VA=vertebral artery; BA=basilar artery.
A milder stroke severity at baseline has been also shown to be significantly associated with good functional recovery at 1 year after iVBD-caused PCS.

Cigarette-Smoking and Low BA FV Synergistically Predicted Poor 1-year Functional Recovery After iVBD-caused PCS

We used the 1st quartile of BA FVmean (24 cm/s) as the cutoff value and we classified the patients into four groups, based on the presence or absence of cigarette-smoking history and BA FVmean ≤ 24 (low flow) or > 24 cm/s. After adjusting for age, gender and stroke severity at baseline (NIHSS), patients with both a positive history of cigarette-smoking and low BA FVmean had an odds ratio of 276.1 (95% CI = 4.7-16068.7; \( p = 0.007 \)) leading to poor 1-year functional recovery, which value was much higher than the other two groups, the group with isolated cigarette-smoking history and the group with isolated low BA FVmean (Fig 2). These results suggest a synergistic effect of cigarette-smoking and low BA FVmean at admission, on predicting poor 1-year functional recovery after iVBD-caused PCS.

DISCUSSION

The present study demonstrated the course of functional recovery within 1 year after iVBD-caused PCS. We found that age, stroke severity, cigarette-smoking history and BA FVmean on admission were independent predictors for functional outcomes at 1 year. Furthermore, the cigarette-smoking history and low BA FVmean on admission showed synergistic correlations with poor 1-year functional recovery in these patients.

We previously reported that in our patients with iVBD-caused PCS, 7 (10.4%) died with 3 months after stroke, which were comparable to data reported for the large artery atherosclerotic stenosis-caused PCS\(^3\)\(^4\). This study also showed that there was no mortality after 3 months. Among these survivors at 3 months, 61.7% recovered to an independent status (mRS0-1); however, 21.6% were still severely disabled (mRS≥4) at 1 year. For unruptured iVBD with ischemic symptoms, few data were identified in published studies (most were case studies)\(^\text{15-19}\). There was only one study with a larger study group evaluating the long-term functional outcomes of iVBD-caused ischemic symptoms\(^\text{6}\). Kim analyzed the data of iVBD patients with ischemic symptoms (n=102) and found that 90.2% had a good functional outcome (mRS0-1)\(^\text{6}\). A poorer functional recovery shown in our study

![Table 3. Multivariate Analyses: Predictors of Poor and Good 1-year Functional Recovery](image)
may be due to the difference in the characteristics of the study population. Our patients (1) were older (mean: 66 vs. 48 years), (2) all had infarcts in the territory of posterior circulation, and (3) had a higher percentage of BA involvement (88.3% vs. 15.5%).

Our study reveals the importance of BA in iVBD-caused PCS. Besides a high frequency of BA involvement, a lower BA FVmean on admission was associated with poor 1-year functional outcome. This association was independent of age and stroke severity on admission. Low BA FVmean implies a decreased blood flow and reduced perfusion in the territory of posterior circulation\cite{20,21}, which might impede the recovery of brainstem/cerebellar/hindbrain functions after the stroke. A lower BA FVmean may represent either a severe vascular lumen narrowing or an inadequate endothelial function (e.g., BA itself or the downstream arteriolar vasodilatation) in response to ischemia\cite{22-24}. Increasing BA flow by endovascular intervention (e.g., stenting or angioplasty) and medication that promotes endothelial function might improve functional recovery in iVBD-caused PCS and this deserves further clinical attention.

In the present study, a history of cigarette-smoking was identified as the most significant risk factor for poor 1-year functional recovery after iVBD-caused PCS. Chronic exposure to cigarette-smoking would cause vasoconstriction via activation of the sympathetic system, as well as endothelial dysfunction via oxidative stress and inflammatory mechanisms\cite{25-27}. Moreover, cigarette-smoking elicits a marked activation of leukocyte and platelets which could also lead to vascular damages\cite{26,27}. These mechanisms might impair microvascular functions, e.g., vasodilatation and increase blood flow, in response to tissue ischemia after iVBD-caused PCS and lead to poor functional recovery. Cigarette-smoking added to a low BA flow on admission acts synergistically and increases the risk of poor 1-year functional recovery. These data suggests that impaired vascular function (by cigarette-smoking) in addition to low blood-flow/perfusion at baseline may be involved in the mechanisms of poor functional recovery in iVBD-caused PCS. Meanwhile, a recent study has shown that the functions of endothelial progenitor cell (EPC), which is required for vascular repair after endothelial injury, are impaired in cigarette smokers\cite{28}. Dysfunctional EPCs are unable to heal dissecting vessel structures and this could be the mechanism of the association between cigarette-smoking and poor functional recovery after iVBD-caused PCS. We need future studies to understand how cigarette-smoking affects functional recovery of iVBD-caused PCS.

Our study has few limitations. Since most of our patients had not undergone brain and vascular imaging on follow-up, we could not provide precise information if the extent of vascular healing after iVBD shown on images is associated with (1) functional recovery after PCS or (2) predictors of poor functional recovery found in the present study. Further, our stroke registry had limited information on the duration of positive smoking history, number of cigarettes smoked by patients, and length of time with no smoking before stroke. Therefore, we were unable to assess dose–response for cigarette-smoking on functional recovery at 1 year. There was also lack of information on whether patients ceased cigarette-smoking after stroke and if this factor was associated with 1-year functional recovery. This information may help answer if quitting smoking after iVBD-caused PCS improves 1-year functional recovery. We also lacked the information of the pre-stroke mRS score for our patients. However, all patients had their first stroke and had no dementia, the functional status should not be influenced by the other comorbidities.

**CONCLUSIONS**

Our work expands on studies on the mechanisms of functional recovery after iVBD-caused PCS. Besides the stroke severity at admission, factors that lead to endothelial dysfunction (age and cigarette-smoking)\cite{25-29} and decreased blood flow (low BA FVmean) were associated with poor functional recovery at 1 year. Our results suggest that adequate tissue perfusion in the territory of posterior circulation may be key to functional recovery. Methods to improve blood flow and tissue perfusion after iVBD-caused PCS should be considered in the future clinical studies in order to increase functional recovery in these patients.

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