Abstract. – OBJECTIVE: To investigate the relationship between lesion patterns of single small infarct (SSI) in perforating territory of the vertebral-basilar artery and early neurological deterioration (END)/short-term functional outcome.

PATIENTS AND METHODS: 126 patients with acute SSI in the perforating territory of the vertebral-basilar artery, admitted within 24 h after symptom onset, were recruited between August 2010 and May 2013. The patients were divided into proximal SSI and distal SSI according to the relationship between their lesion location and their parent artery. Early neurological deterioration (END) was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) ≥ 2 within 3 days after admission. Functional outcome at 30 days after onset was assessed using the modified Rankin Score (mRS) and dichotomized as good (0-2), and poor (≥ 3).

RESULTS: Out of 126 patients, proximal SSI was found in 70 (55.56%) patients and distal SSI in 56 (44.44%) patients. After standard treatment, 36 (28.57%) patients experienced END within 3 days after admission, and 19 (15.70%) patients had a poor outcome at 30 days. Univariate analysis revealed that lesion size, baseline NIHSS score, parent artery disease, diabetes mellitus, and asymptomatic cerebral arterial atherosclerosis were significantly associated with END (with either \( p < 0.05 \) or \( p < 0.01 \)), while the short-term outcome was just as significantly associated with proximal SSI, the baseline NIHSS score and END (with either \( p < 0.05 \) or \( p < 0.01 \)). Results from multiple logistic regression analysis revealed that proximal SSI was an independent predictor of END (odd ratio [OR] 3.222, 95% CI 1.170-8.874, \( p=0.024 \)) and that the END independently predicted a poor outcome (OR 4.126, 95% CI: 1.241-13.713, \( p=0.021 \)) at 30 days after onset.

CONCLUSIONS: Proximal SSI in the perforating territory of the vertebral-basilar artery was closely related to the presence of END, and the END independently predicted the subsequent poor outcome at 30 days after onset.

Key Words
Vertebral-basilar artery, Perforating artery, Infarct, Early neurological deterioration, Outcome.

Introduction
Traditionally, single small infarctions (SSI) in the perforating territory of the middle cerebral artery, the basilar artery, and the vertebral artery, are considered as a result of hyaline degeneration of the vertebral artery lipids1,2. However, more and more studies3,4 showed that perforating SSI could also have resulted from the parental artery disease (PAD) or tiny atherosclerosis plaque in the proximal area of the perforating branch. Nah et al5 divided SSI into proximal SSI and distal SSI according to the relationship between the location of the infarction and the arterial trunk. Studies have found that SSI in the proximal area of the perforating branch is often characterized by atherosclerosis, while distal SSI is typically characterized by small vessel disease. These findings indicated that the perforating branch SSI was divided on the basis of the relationship between the location of the infarction and the arterial trunk and that each might have a different pathogenesis. Compared with large area infarction, SSI was usually defined as a favorable prognosis. Nevertheless, there were still a large number of SSI patients deteriorating in the acute period of the disease, especially their motor symptoms, which can result in serious disability and may seriously affect the patients’ prognosis6-9. Currently, most of the researches on progressive strokes in the perforating branch are mainly focused on middle cerebral artery territory. Nevertheless, the risk factors of progressive strokes in the perforating branch of the posterior circulation and its relationship with lesion mode and the PAD are still unclear. In our work, we have studied patients with acute SSI in the perforating territory of the vertebral-basilar artery and analyzed their vascular risk factors, clinical performance, and imaging data, to determine the clinical predictive factors related to their progress. Meanwhile, we also analyzed the functional prognosis of these patients 30 days after onset.
Patients and Methods

Patients
A total of 126 patients, consisting of 83 males and 43 females, with an average of 63.8±12.1 years old, were recruited in this study between August 2010 and May 2013. These patients had acute SSI in the perforating territory of the vertebral-basilar artery, and were admitted within 24 h after symptom onset. They were divided into two groups according to neurological scoring: the early neurological deterioration (END) group, consisting of 36 patients, and the non-END group, consisting of 90 patients. Successful follow-up was achieved in 121 patients, who were then assigned according to the modified ranking score (mRS) into the favorable prognosis group (mRS 0-2 points), consisting of 102 patients, and the poor prognosis group (mRS ≥ 3 points), consisting of 19 cases. Diagnosis of SSI was confirmed in all recruited patients via a cerebral MRI examination within 24 h after admission, when the diameter of their lesions was ≥ 20 mm. Diagnosis and treatment of all cases conformed to Guidelines of Diagnosis and Treatment of Acute Ischemic Stroke in China (2010 version)10. Exclusion criteria consists of (1) patients with complications of other kinds of infarctions except for infarctions in the perforating territory of the vertebrobasilar artery; (2) patients with complications of intracranial hemorrhage, infection, and serious heart, lung, and kidney diseases; (3) patients with potential cardiogenic embolism (such as atrial fibrillation, recent myocardial infarction, rheumatic heart disease, dilated cardiomyopathy or infectious endocarditis, and so forth); (4) patients with a history of stroke; (5) patients under endovascular treatment and thrombolytic therapy; (6) patients with arterial trunk branch stenosis of >50% (patients with pontine infarctions who had vertebral artery stenosis of >50% and patients with medullary infarction who had extracranial vertebral artery stenosis of >50% were also excluded). Our study was approved by the Ethical Committee of our Hospital, and informed consent was obtained from patients’ family members.

Methods
Baseline Status
The baseline status of patients was collected, and relevant risk factors were evaluated at the time of admission. General information on patient status included age, gender, blood pressure, history of hypertension, diabetes mellitus, coronary heart disease, etc. On the second day after admission, venous blood was drawn from the patients, and conventional hematological examinations were completed.

Imaging Examination
Within 24 h after admission, a 1.5 T supracondution magnetic resonance imaging scanner (General Electric Company) was used to conduct a complete cerebral MRI examination on all of the patients. It included conventional resonance angiography such as T1 weighted imaging, T2 weighted imaging, diffusion weighted imaging (DWI), and magnetic resonance angiography (MRA). Following the previous studies, the location of the infarction was determined using axial DWI: (1) cerebral infarction in the perforating territory of the vertebral-basilar artery was limited to the paramedian pontine area; (2) cerebral infarction in the perforating territory of the vertebral artery was limited to the medial medulla. Infarction was divided, according to the relationship between the location of infarction and the arterial trunk1, into proximal infarction (lesion extended to the branch of the stem and involving the pons or the surface of the ventral medulla) and distal infarction (lesion did not extend to the branch of the stem, see Figures 1-2). The judgment of infarction location was determined by two experienced neuroimaging practitioners. During the period of admission, patients were required to undergo a series of angiological examinations including MRA, CT angiography or digital subtraction angiography (DSA). The results of the examinations were used to determine the PAD by the offending artery (intracranial segment of the vertebral artery or the basilar artery) having over 50% stenosis, and to evaluate the concomitant asymptomatic cerebral arterial atherosclerosis (ACAS). The results were defined as intracranial and extracranial cerebral arterial atherosclerosis, which were unrelated to stroke onset.

Patient Classification and Functional Evaluation
The National Institute of Health Stroke Scale (NIHSS) was used to evaluate the degree of neurologic impairment on patients at the time of admission. The NIHSS was re-evaluated at random intervals after admission for 72 h, if the highest mark increased by 2 points compared with the result on admission. Then, it was de-
fined as early neurological deterioration (END). SSI patients were then categorized into either the END group or the non-END group. Furthermore, we have used the mRS to evaluate the functional prognosis of stroke patients 30 days after onset. Among the 126 cases enrolled, 5 cases could not be followed up, and the 121 cases that were successfully followed up were divided into the favorable prognosis group (mRS 0-2 points) and the poor prognosis group (mRS ≥ 3 points).

**Statistical Analysis**
SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA) was applied to perform data analysis. Numerical data were presented as $x \pm s$. Independent sample $t$-test was used to make comparisons between groups. For data presented as a percentage, the $\chi^2$-test, or the Fisher exact test, was used to make comparisons between groups. Binary logistic regression analysis was adopted to detect independent correlation factors.
Relationship between lesion patterns of single small infarct

Results

Baseline Conditions
Among the 126 patients with acute SSI were 91 cases with basal artery perforator infarctions and 35 cases with vertebral artery perforator infarctions. The infarction lesions were located in the proximal area of 70 cases and in the distal area of 56 cases. The associated cerebrovascular disease risk factors included 82 cases of hypertension (65.1%), 26 cases of diabetes mellitus (20.6%), 45 cases of hyperlipidemia (35.7%), 38 cases of smoking (30.2%), and 19 cases of drinking (15.1%). 46 cases were complicated by PAD (36.6%) and 42 cases had asymptomatic intracranial atherosclerosis (33.3%).

Comparison Between the END Group and the non-END Group
Compared with the non-END patients, the occurrence of diabetes, baseline NIHSS scoring, lesion diameter, PAD and ACAS, the ratio of the proximal SSI END patients were significantly higher, and the differences were statistically significant (p<0.005 or p=0.01, see Table I). Logistic regression analysis indicated that proximal SSI was independently related with END (OR = 3.222, 95% CI: 1.170-8.874, p=0.024, see Table II).

Functional Outcome 30 Days After the Onset of a Stroke
Compared to the poor prognosis group, the baseline NIHSS, the proportion of proximal SSI, and END of the favorable prognosis group were lower, and the differences were statistically significant (Table III). Logistic regression analysis indicated that baseline NIHSS scoring and END were in-

Table I. Comparison of the general clinical characteristics in the END group and the non-END group.

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>END group (N=36)</th>
<th>non-END group (N=90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>63.3±10.56</td>
<td>63.9±12.68</td>
<td>0.809</td>
</tr>
<tr>
<td>Male [case (%)]</td>
<td>22 (61.1)</td>
<td>61 (67.8)</td>
<td>0.476</td>
</tr>
<tr>
<td>Hypertension [case (%)]</td>
<td>25 (69.4)</td>
<td>57 (63.3)</td>
<td>0.516</td>
</tr>
<tr>
<td>Diabetes [case (%)]</td>
<td>12 (33.3)</td>
<td>14 (15.6)</td>
<td>0.026</td>
</tr>
<tr>
<td>Hyperlipidemia [case (%)]</td>
<td>15 (41.7)</td>
<td>30 (33.3)</td>
<td>0.378</td>
</tr>
<tr>
<td>Smoking [case (%)]</td>
<td>10 (27.8)</td>
<td>28 (31.1)</td>
<td>0.713</td>
</tr>
<tr>
<td>Drinking [case (%)]</td>
<td>4 (11.1)</td>
<td>15 (16.7)</td>
<td>0.431</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>146.4±17.48</td>
<td>143.6±15.14</td>
<td>0.371</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>87.7±8.87</td>
<td>85.2±10.98</td>
<td>0.224</td>
</tr>
<tr>
<td>Baseline NIHSS scoring (points)</td>
<td>6.08±2.56</td>
<td>4.98±2.86</td>
<td>0.046</td>
</tr>
<tr>
<td>Diameter of lesion (mm)</td>
<td>12.29±4.29</td>
<td>10.41±4.04</td>
<td>0.022</td>
</tr>
<tr>
<td>PAD [cases (%)]</td>
<td>21 (58.3)</td>
<td>25 (27.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACAS [case (%)]</td>
<td>18 (50.0)</td>
<td>24 (26.7)</td>
<td>0.012</td>
</tr>
<tr>
<td>Proximal SSI [case (%)]</td>
<td>28 (77.8)</td>
<td>42 (46.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ACAS: asymptomatic carotid artery stenosis; PAD: peripheral artery disease; SSI: single small infarct.

Table II. Logistic regression analysis of END.

<table>
<thead>
<tr>
<th>Project</th>
<th>OR value</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0.568</td>
<td>0.203-1.588</td>
<td>0.281</td>
</tr>
<tr>
<td>Baseline NIHSS scoring (points)</td>
<td>1.139</td>
<td>0.971-1.337</td>
<td>0.109</td>
</tr>
<tr>
<td>Diameter of lesion (mm)</td>
<td>1.111</td>
<td>0.996-1.239</td>
<td>0.060</td>
</tr>
<tr>
<td>PAD</td>
<td>2.304</td>
<td>0.889-5.972</td>
<td>0.086</td>
</tr>
<tr>
<td>ACAS</td>
<td>1.894</td>
<td>0.725-4.950</td>
<td>0.193</td>
</tr>
<tr>
<td>Proximal SSI</td>
<td>3.222</td>
<td>1.170-8.874</td>
<td>0.024</td>
</tr>
</tbody>
</table>
dependently correlated with the poor outcome 30 days after onset (OR = 4.126, 95% CI: 1.241-13.713, p = 0.021; OR = 1.275, 95% CI: 1.016-1.601, p = 0.036, see Table IV).

**Discussion**

A previous research has demonstrated that END was quite different from late neurologic deterioration, which resulted from systemic complications such as infection. At present, the pathogenesis of END remains unclear, and the diagnostic criteria of END are dissimilar. In clinical practice, treatment options that can effectively prevent or stop the development of acute stroke are still lacking. Therefore, it is quite important to determine the clinical predictive factors relevant to the progression of this disease.

Our study showed that among the 126 patients with acute SSI, 36 cases (28.6%) had END, consistent with previous reports. We evaluated the pathogenetic conditions of patients within 72 h on admission. It was a relatively strict time window as it was less affected by subjective views of the evaluators themselves. We found that SSI patients whose lesions had extended to the perforating territory of the vertebral-basilar artery were quite unstable during their clinical course and were quite vulnerable to END during their hospitalization. It was reported that proximal SSI in the perforating territory of the vertebral-basilar artery was closely related to the atherosclerotic plaque on the arterial trunk where perforating branches are numerous, the perforating territories among the perforating branches are lacking in a collateral circulation link and are greatly affected by the fluctuation of hemodynamics. When patients were involved in vigorous activities, agitated, or when their blood pressure was unstable, the cerebral tissues next to the lesion had lower blood perfusion, based on their original stenosis, and then new ischemic symptoms appeared. Moreover, inflammatory reactions, during the acute period, edema and excitatory poisoning were also considered as the possible pathogenesis of END. However, this theory is still in need of verification through further investigations.

For proximal SSI, the appearance of atherosclerotic pathological changes on the arterial trunks or in the proximal perforating territory, the overlay of focal thrombus in acute period (which gradually blocks blood vessels) or unstable plaque begin to migrate from proximal territory to distal territory, and thus result in the enlargement of the original lesion, or the occurrence of new lesions, which lead to further clinical deterioration. On the other hand, when a proximal SSI lesion is close to the arterial trunk where perforating branches are numerous, the perforating territories among the perforating branches are lacking in a collateral circulation link and are greatly affected by the fluctuation of hemodynamics. When patients were involved in vigorous activities, agitated, or when their blood pressure was unstable, the cerebral tissues next to the lesion had lower blood perfusion, based on their original stenosis, and then new ischemic symptoms appeared. Moreover, inflammatory reactions, during the acute period, edema and excitatory poisoning were also considered as the possible pathogenesis of END. However, this theory is still in need of verification through further investigations.
studies. Some scholars believed that PAD was an important cause of perforating branch infarction and it was closely related to clinical deterioration or fluctuation. However, our study did not confirm this supposition. Numerous recent reports have shown that the presence of tiny atheromatous plaque on the arterial trunk was a significant cause of SSI. Nevertheless, in this work, our attention was focused on the relationship between moderate and severe PAD and END, and not on the PAD having a very slight lesion. Therefore, according to the methods and results of our study, we cannot make any claims concerning the predictive effect of PAD on END. Additionally, we analyzed the short-term functional prognosis on patients 30 days after the onset of a stroke. We found that the prognosis of patients was independently related to the severity of their illness and their history of END. Our paper further confirmed that patients with progressive strokes had a poor short-term prognosis, but their long-term prognosis remained unclear, which may be the subject of our future study. Our study has a great clinical significance. SSI patients whose lesions were located near to the opening of the perforating branch had a higher tendency to develop END. Conventional antplatelet therapy should be given to these patients. Additionally, strengthened management during their hospitalization, combined with intensive drug treatment should also be applied. As for distal SSI patients, active depressurization is the most appropriate therapeutic regimen. The present paper had some limitations. Firstly, this was a single institutional study, and the number of enrolled patients (N=126) was still limited. Secondly, due to the limit of blood vessel inspection technology, we could not pay close attention to the PAD with a minor lesion. Instead, we focused on examining the relationship between moderate and severe PAD and END. Moreover, we did not perform a follow-up imaging examination on patients under progressive conditions to confirm their neurological deterioration. Nevertheless, future investigations will recruit more patients and provide additional evidence to verify our findings.

Conclusions

We showed that the occurrence of patients’ fluctuating condition was closely related to their lesion location. Proximal SSI in perforating territory of the vertebral-basilar artery should be monitored closely for the possible complication of PAD, and be treated actively.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References


