Executive Dysfunction in Patients With Cerebral Hypoperfusion After Cerebral Angiostenosis/Occlusion

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Abstract

Impairment of executive functions (EFs) was investigated in patients with cerebral hypoperfusion after cerebral angiostenosis/occlusion and healthy subjects. Several EFs were measured in patients with cerebral angiostenosis/occlusion and control group. The vascular conditions, regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), mean transit time (MTT), time to peak (TTP), and delay time were assessed. The scores of the vascular stenosis/occlusion group were significantly lower than those of the control group. rCBV and rCBF were negatively correlated with the error response times in the Stroop test, and the persistent error responses in the Wisconsin Card Sorting Test (WCST) were positively correlated with the Montreal Cognitive Assessment (MoCA) scores. TTP was positively correlated with the reaction and error reaction times, and the persistent error response in WCST was negatively correlated with the times of sorting in WCST and MoCA scores. MTT was positively correlated with the persistent error response in WCST. In the Stroop test, delay time was positively correlated with response time, and negatively correlated with error response times, and the persistent error response in WCST and MoCA scores. Patients with cerebral hypoperfusion after cerebral angiostenosis/occlusion had executive dysfunctions in working memory, sustained attention, response inhibition, cognitive flexibility, thought organization, planning, and implementation. Moreover, their executive dysfunctions were related with the decline in rCBF and rCBV. The prolonged TTP, MTT, and delay time suggested a slow blood flow and the poor compensation of collateral circulation, resulting in impairment of the EFs.

Key words: cerebral hypoperfusion, cerebrovascular stenosis, cerebrovascular occlusion, executive function, computed tomography perfusion imaging

Introduction

Vascular cognitive impairment seriously affects the quality of life of the elderly, including their mental and physical health. Many researchers have increasingly focused on the risk factors for cognitive decline and early warning signals because of the current poor treatment of vascular cognitive impairment. Cerebrovascular stenosis/occlusion may not lead to stroke, but this condition can cause focal cerebral hypoperfusion, also known as chronic cerebral ischemia.7) The main symptoms of focal cerebral hypoperfusion include executive function (EF) impairments in the acute period, which can eventually lead to lasting or progressive cognitive and neurological dysfunctions. EFs are cognitive neuro-mechanisms that coordinate various cognitive processes to operate in active and optimized ways when a person accomplishes a specific objective.5) EFs are considered early sensitive indicators that reflect cognitive impairments because the EFs may decline prior to the deterioration of daily activities. Thus, the EFs may or may not be impaired in the early stage of cerebrovascular stenosis/occlusion, and can serve as criteria for the occurrence of vascular dementia in the later stages.

The present study evaluated the findings of computed tomography (CT) perfusion imaging in 25 patients who presented with vascular stenosis/occlusion, and in 23 normal healthy people, and compared their EFs using neuropsychological tests.
Materials and Methods

The patient group consisted of 25 patients with vascular stenosis/occlusion who were selected from outpatients and inpatients seen at our hospital from June 2009 to December 2011. Among these 25 patients, 2 patients had stenosis and 1 had occlusion of the carotid siphon, 6 patients had stenosis and 1 had occlusion of the anterior cerebral artery, and 13 patients had stenosis and 2 had occlusion of the middle cerebral artery. The inclusion criteria were as follows: age 45 to 75 years old, either sex, and any level of education; transient ischemic attacks, but without head CT evidence of cerebral lesions; brain magnetic resonance angiography or transcranial Doppler sonography confirmation of intracranial artery stenosis or occlusion; unimpaired daily activities; and mini-mental state examination (MMSE) scores according to education level of illiterate \( > 17 \), primary \( > 20 \), and secondary or higher \( > 24 \). The exclusion criteria of the study group were as follows: heart or lung failure and other serious physical illnesses; long history of alcohol abuse; cerebral infarction; focal neurological deficits; anxiety, depression, and other mental disorders within the past week; thyroid dysfunctions; and brain imaging evidence of moderate to severe brain atrophy or confluent white matter density of osteoporosis. The control group consisted of 23 healthy volunteers from the community of retired officers and staff with the following characteristics: age 40 to 76 years old, either sex, and any level of education; and no history of serious physical illnesses; no anxiety, depression, or other mental disorders; and able to undergo neuropsychological examination. The differences in sex, age, and years of education between the groups were not significant \((p > 0.05)\), as shown in Table 1. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The First Affiliated Hospital of Xinxiang Medical University. Written informed consent was obtained from all participants.

Neuropsychological examination of all subjects used unified and standardized survey questionnaire terminology in a quiet environment without interferences, and all neuropsychological tests with one subject were completed on the same day.

The Montreal Cognitive Assessment (MoCA) test\(^1\) included the implementation of visual spatial ability, naming, memory, attention, verbal fluency, abstract thinking, delayed memory, and orientation for a total of 30 points. The MoCA test was conducted to rectify the educational level of the bias correction, and subjects with education of less than 12 years were given an additional 1 point on their test scores. A higher score indicates better cognitive function, and subjects with score \( \geq 26 \) were considered normal.

The revised version of the Stroop test\(^2\), divided into color stimulation (Form C) and color-word stimulation (Form CW), was used. Form C listed the Chinese characters for red, blue, brown, and green arranged as 112 random words, and each character was randomly colored red, blue, brown, or green. The Stroop-C test required subjects to read the Chinese characters for these colors as quickly and accurately as possible to determine whether the subject could distinguish between more than four colors and read the character. The Stroop-CW test required the subjects to read the color of the different characters quickly and accurately. The error response times and response time of the Stroop-CW test were recorded.

The revised edition of the Wisconsin Card Sorting Test (WCST)\(^3\) was used, and the test included four stimulation cards and 128 response cards. Each 8 cm \( \times \) 8 cm card contained 1 to 4 figures, such as triangle, star, square, and circle, which were colored red, green, yellow, and blue, respectively. The subjects were only told “correct” or “mistake” when they sorted the cards without knowing the principle of classification, and the principle would be changed when they had eight consecutive corrects. The order of principle was color–shape–number–color and so on. The test was complete after all of the 128 cards were sorted. We recorded the times of sorting, incorrect responses, and persistent incorrect responses.

All CT studies were performed on a 320-slice CT scanner (Toshiba Medical Systems, Otawara, Tochigi, Japan).

Table 1 Comparison of sex, age, education, and mini-mental state examination (MMSE) of the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Sex (male:female)</th>
<th>Age (yrs)†</th>
<th>Education (yrs)†</th>
<th>MMSE score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>25</td>
<td>13:12</td>
<td>59.81 ± 9.65</td>
<td>9.35 ± 5.41</td>
<td>24.98 ± 5.71</td>
</tr>
<tr>
<td>Control group</td>
<td>23</td>
<td>12:11</td>
<td>61.04 ± 9.54</td>
<td>9.85 ± 4.23</td>
<td>25.06 ± 6.30</td>
</tr>
</tbody>
</table>

†Values are \( x \pm s \).
CT perfusion used 40 ml of nonionic iodinated contrast medium (Omnipaque, 300 mg/ml of iodine; Amersham Heath, Princeton, New Jersey, USA) injected intravenously at 4 ml/sec. Nineteen volumes covering the whole brain were acquired, and each volume consisted of 320 images (0.5 mm thick) covering a total of 16-cm depth of the head in the z-direction. The first volume was acquired with an acquisition delay of 7 seconds after the injection of contrast medium. The time delay allowed the acquisition of baseline images without contrast enhancement, which were used as masks for bone subtraction for the subsequent CT angiography. The acquisition parameters for the first volume were 80 kVp and 300 mA. Then, 13 volumes of the brain were acquired starting at 11 seconds after the injection of contrast medium at a sampling interval of one volume every 2 seconds. These volumes were acquired during the arterial and capillary phases. Then, five volumes were acquired at a sampling interval of one volume every 5 seconds. The acquisition parameters for all volumes after the first volume were 80 kVp and 100 mA. The total duration of the acquisition was 60 seconds.

CT angiography detected intracranial artery stenosis or occlusion in the 25 patients, including artery occlusion in 4 patients, 70% or more stenosis in 4 patients, 50–70% stenosis in 12 patients, and 50% or less stenosis in 5 patients, and no abnormal findings in the 23 subjects.

Post-processing was performed on a Vitrea fx, version 1.0 workstation (Vital Images Inc., Minnetonka, Minnesota, USA) using the delay-insensitive singular-value decomposition and the nonparametric deconvolution method. The supraclinoid segment of the internal cerebral artery was chosen for measuring the reference arterial input function to avoid any volume averaging. The posterior portion of the superior sagittal sinus was selected for the same reason and to evaluate the venous output function.

Color maps of the hemodynamic parameters, such as regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), mean transit time (MTT), time to peak (TTP), and delay time, were calculated using the singular-value decomposition and deconvolution method. The specific hemodynamic information of the diseased portion of the brain was obtained by drawing various regions of interest (ROIs) in the affected area and then comparison with ROIs of the normal brain.

In most cases, the referring physicians requested CT perfusion imaging for clinical indications. In other cases, CT perfusion imaging data were acquired from the time-resolved CT angiograms of the brain performed for other clinical indications.

SPSS 11.5 was used for statistical processing. Neuropsychological scores in each group were signed with $\bar{x} \pm s$, and the $t$-test was used in the significance tests of mean. The Pearson correlation analysis was performed between the results of the neuropsychological and brain perfusion imaging tests, which were all two-sided, and $p < 0.05$ was considered statistically significant.

**Results**

Significant differences were observed in the results of the MoCA test between the two groups in six subscales, trail making, copy cube, clock drawing, attention, abstract thinking, and delayed memory (Table 2). Significant differences were also observed in the reaction time and error response times of the Stroop test as well as in the persistent error response and times of sorting in the WCST (Table 3).

CT perfusion imaging found abnormal perfusion in 21 patients at the basal ganglia level: the anterior cerebral artery area (zone 1) in 6 cases, the cortex branch of the middle cerebral artery (zone 2) in 9 cases, the deep perforating branch of the middle cerebral artery (zone 3) in 6 cases, and both zones 2 and 3 in 5 cases, as shown in Fig. 1. Four patients with cerebral stenosis had normal perfusion in the corresponding areas, as shown in Fig. 2.

Figure 1 illustrates a case of severe stenosis of the right middle cerebral artery, in which TTP and delay time were prolonged compared to the contralateral area in the cortex and deep perforating branch of the middle cerebral artery, whereas the rCBV, rCBF, and MTT showed no significant changes compared with the contralateral area. We considered that the collateral circulation had formed already, but perfusion in the affected area was insufficient.

Figure 2 demonstrates a case of severe stenosis of the right anterior cerebral artery area, but the indicators of bilateral vascular perfusion were symmetrical, suggesting that effective collateral circulation had been established in the areas of the stenosis vessels, and the signs of low perfusion had disappeared.

rCBV and rCBF were negatively correlated with the error response times in the Stroop test, and the perseverative errors in the WCST, rCBV, and rCBF were positively correlated with the total scores of MoCA. TTP was positively correlated with the reaction time and error response times in the Stroop test. The perseverative errors in the WCST and TTP were negatively correlated with the times of sorting in the WCST and total scores of MoCA. MTT was positively correlated with the perseverative errors in the WCST, and delay time was positively correlated...
<table>
<thead>
<tr>
<th>Group</th>
<th>Visual space and execution</th>
<th>Copy cube</th>
<th>Clock drawing</th>
<th>Total score</th>
<th>Orientation</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient group</td>
<td>0.33 ± 0.24</td>
<td>0.47 ± 0.19</td>
<td>2.32 ± 1.03</td>
<td>2.49 ± 0.57</td>
<td>0.34</td>
<td>-0.40**</td>
</tr>
<tr>
<td>Control group</td>
<td>0.79 ± 0.15</td>
<td>0.76 ± 0.14</td>
<td>2.01 ± 1.03</td>
<td>6.34 ± 1.24</td>
<td>0.79</td>
<td>-0.79**</td>
</tr>
<tr>
<td>Probability</td>
<td></td>
<td></td>
<td></td>
<td>-0.34</td>
<td>-0.40**</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. Significant difference (*p < 0.05, **p < 0.01) by t-test.

Table 2: Comparison of the executive functions in the Montreal Cognitive Assessment test of the two groups

with reaction time in the Stroop test. The perseverative errors in the WCST and total scores of MoCA, as well as delay time, were negatively correlated with the error response times in the Stroop test (Table 4).

Discussion

Previous animal studies using a cerebral hypoperfusion animal model based on ligation of the bilateral carotid arteries or ligation of the bilateral carotid and left subclavian arteries found that chronic cerebral hypoperfusion could cause brain regional abnormal protein synthesis, energy metabolism, decreased glucose utilization, absence of cholinergic receptors, further loss of neurons, and impairment of functions. Memory impairment emerges when the cholinergic neurons are damaged. The brain is unable to maintain its normal cell function, and cascade reaction would occur if perfusion pressure drops to a certain extent. This condition leads to posterior brain metabolism descent, cognitive function impairment, and pathological nerve changes. Dementia would appear eventually. In the present study, the patients with cerebrovascular stenosis/occlusion had worse scores in the Stroop test and WCST, suggesting obvious executive dysfunctions in attention inhibition, working memory, cognitive flexibility, planning, and diversion.

The MoCA was used to measure separately eight cognitive domains from the visual spatial EFs (alternate trail making, copy cube, and clock drawing), language functions (naming, sentence repetition, and verbal fluency), attention (attention, concentration, and alertness), calculation, abstract thinking, memory (delayed memory), and orientation. Compared with the commonly used MMSE, MoCA offers more sensitivity and specificity. In the present study, patients with cerebrovascular stenosis/occlusion had worse scores in the Stroop test and WCST, suggesting obvious executive dysfunctions in attention inhibition, working memory, cognitive flexibility, planning, and diversion.
Table 3  Comparison of the executive functions in the Stroop test and Wisconsin Card Sorting Test (WCST) of the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Stroop test</th>
<th>WCST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response time (sec)</td>
<td>Error response times (numbers)</td>
</tr>
<tr>
<td>Patient group</td>
<td>219.46 ± 53.13</td>
<td>12.37 ± 9.47</td>
</tr>
<tr>
<td>Control group</td>
<td>139.86 ± 39.24</td>
<td>4.39 ± 1.20</td>
</tr>
<tr>
<td>Probability</td>
<td>89.39*</td>
<td>7.54**</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. Significant difference (*p < 0.05, **p < 0.01) by t-test.

Fig. 1  Representative case of severe stenosis of the right middle cerebral artery, in which time to peak and delay time were prolonged in the cortex and deep perforating branch of the middle cerebral artery compared to the contralateral area, whereas the regional cerebral blood volume, regional cerebral blood flow, and mean transit time showed no significant changes.

The WCST is currently used for measuring the EFs of the frontal lobe. This test primarily evaluates the course of problem-solving by experience, which not only needs strategy generation, sorting recapitulation, cognitive shift, task handling, and monitoring, but also working memory to ensure the accomplishment of the task. Persistent incorrect response may have better sensitivity and specificity in the WCST. The pathological inertia and adhesiveness of the subjects during task execution worsened with more persistent incorrect responses, and so they could not make use of the feedback message correctly to perform the cognitive shift and adjust the task strategy. Furthermore, they had difficulties in revising the incorrect strategy, indicating the decline in their cognitive flexibility. Patients with cerebrovascular stenosis/occlusion showed this characteristic in the neuropsychological tests. The patients had increased persistent error response in the WCST, which may be concerned with sorting recapitulation impairment, and the decline in working memory capacity plays an important role. These results are in agreement with the results of the animal experiments. The Stroop task could evaluate the behavior control functions using the conflict between perception and speech. This test not only evaluates word fluency, sustained attention, and speed of information processing, but also the selective inhibition to...
Fig. 2  Representative case of severe stenosis of the right anterior cerebral artery, but the indicators of the bilateral vascular perfusion were symmetrical, suggesting that effective collateral circulation had been established in the areas of stenosis vessels, and the signs of low perfusion had disappeared.

Table 4  Correlation analysis of the executive functions and perfusion imaging findings in patients with cerebral artery stenosis/occlusion

<table>
<thead>
<tr>
<th>Executive functions</th>
<th>Perfusion imaging findings†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rCBV (4.83 ± 1.71 ml/100 g)</td>
</tr>
<tr>
<td>Total scores of MoCA test</td>
<td>0.395**</td>
</tr>
<tr>
<td>Stroop test</td>
<td></td>
</tr>
<tr>
<td>response time</td>
<td>−0.041</td>
</tr>
<tr>
<td>error response times</td>
<td>−0.402**</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
</tr>
<tr>
<td>persistent error response times</td>
<td>−0.429**</td>
</tr>
<tr>
<td>times of sorting</td>
<td>0.251*</td>
</tr>
</tbody>
</table>

†Values are means ± standard deviation. Significant difference (*p < 0.05, **p < 0.01) by two-sided Pearson correlation analysis.  MoCA: Montreal Cognitive Assessment, MTT: mean transit time, rCBF: regional cerebral blood flow, rCBV: regional cerebral blood volume, TTP: time to peak, WCST: Wisconsin Card Sorting Test.

indifferent stimulus and impulse control ability. Patients with cerebrovascular stenosis/occlusion showed decline in attention inhibition in the Stroop task, which caused the patients to fail to inhibit in the face of response conflict.

Cerebral vascular stenosis/occlusion is the primary cause of ischemic cerebrovascular diseases. Sudden interruption in the rCBF may lead to stroke, but persistent moderate decline in CBF may affect memory function, which can then lead to vascular cognitive impairment. In the present study, patients with cerebrovascular stenosis/occlusion had executive dysfunctions in attention inhibition, working memory, cognitive flexibility, visual spatial ability analysis, and synthesis compared with the subjects in the control group. Our previous studies found that executive dysfunction is not related to the volume and quantity of infarction focus. CT perfusion imaging represented the CBF mainly through the following parameters: rCBF reflects regional blood flow within the brain organization; rCBV is the vascular volume in the ROI, including capillaries and large blood vessels; MTT mainly refers to the time when the contrast agent passes the capillaries; TTP is the time from when the contrast agent was injected in the brain to the point when the contrast agent reached the maximum peak enhancement time within the tissue. The ischemic region can be de-
fined, and the collateral circulation can be evaluated by analyzing the rCBV, rCBF, and MTT using the CT angiography and CT perfusion images. Functional magnetic resonance imaging of patients with mild cognitive impairment discovered that low brain perfusion in different brain regions, mainly in the middle and upper frontal areas, posterior cingulate, and precuneus, was associated with cognitive impairment. Another study in China had similar results. In the present study, we found that six patients had normal perfusion with cerebral angiostenosis, suggesting that effective collateral circulation was already established. Moreover, the EFs, such as the working memory, attention inhibition, and cognitive flexibility, of these six patients were not significantly impaired. This phenomenon suggests that executive dysfunctions could be avoided if the available collateral circulation is promptly established, and the CBF reserve is adequate.

In summary, cerebrovascular stenosis/occlusion in patients can lead to low perfusion, and then to executive dysfunctions in working memory, sustained attention and response inhibition, cognitive flexibility, thought organization, planning, and Einstellung shift. Executive dysfunctions are correlated with decreases in rCBF and rCBV. Prolonged TTP, MTT, and delay time indicate slow blood flow and poor collateral circulation, indicating that the EFs prone to impairment. Thus, CT perfusion imaging can be applied to determine cerebrovascular stenosis/occlusion, assess collateral circulation, and provide effective interventions. The impairment of the EFs can thus be prevented, and onset of dementia could be averted.

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Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article.

References


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