

Neurocognitive Improvement After Carotid Artery Stenting in Patients With Chronic Internal Carotid Artery Occlusion and Cerebral Ischemia

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Background and Purpose—Chronic cerebral hypoperfusion may lead to impairment in neurocognitive performance in patients with chronic internal carotid artery occlusion, and the effects of carotid artery stenting on neurocognitive function have been unclear.

Methods—We prospectively enrolled 20 chronic internal carotid artery occlusion patients with objective ipsilateral hemisphere ischemia, in whom carotid artery stenting was attempted. Functional assessments, including the National Institutes of Health Stroke Scale, Barthel Index, and a battery of neuropsychological tests, including the Mini-Mental State Examination, Alzheimer Disease Assessment Scale–Cognitive Subtest, verbal fluency, and Color Trail Making A and B, were administered before and 3 months after intervention.

Results—Successful recanalization was achieved in 12 of 20 patients (60%). There was no procedural or new cerebral ischemic event, except for 1 intracranial hemorrhage, which occurred during the procedure and had neurologic sequelae; this case was excluded from analysis. The demographics and baseline cognitive performance were similar between the group with a successful outcome (group 1, $n=12$) and patients who did not (group 2, $n=7$). Ten of 12 patients in group 1 had improvement in ipsilateral brain perfusion after the procedure, but none in group 2 had improvement. Significant improvement in the scores on the Alzheimer Disease Assessment Scale–Cognitive Subtest (before, 7.7 ± 8.9 versus after, 5.7 ± 7.1 ; $P=0.024$), Mini-Mental State Examination (before, 25.8 ± 3.8 versus after, 27.7 ± 2.7 ; $P=0.015$), and Color Trail Making A (before, 123.2 ± 68.6 versus after, 99.3 ± 51.5 ; $P=0.017$) were found in group 1 but not in group 2.

Conclusions—Successful carotid artery stenting improves global cognitive function as well as attention and psychomotor processing speed in patients with chronic internal carotid artery occlusion. (*Stroke*. 2011;42:2850-2854.)

Key Words: carotid occlusion ■ carotid stenting ■ brain perfusion ■ neurocognitive function

Patients with chronic internal carotid artery occlusion (ICAO) are at risk of future transient or permanent neurologic deficits. Instead of embolism, a compromised cerebral perfusion may be the most important etiology of ipsilateral ischemic events in a sizable proportion of patients.^{1,2} The detrimental effect of cerebral infarction on cognitive function is well known,^{3,4} and cognitive deficits in asymptomatic ICAO patients have also been documented.⁵ In the latter, cerebral hypoperfusion may be an important cause.^{6–8}

Treatment for carotid artery stenosis includes carotid artery stenting and carotid endarterectomy. In trials with postproce-

dural stroke, myocardial infarction, and mortality as primary end points, both stenting and endarterectomy have been proven to prevent future stroke. However, the effects of carotid revascularization on cognitive outcome are controversial.^{9,10} Several factors may contribute to the diversity in cognitive responses seen clinically, including differences in baseline cerebral perfusion status, detrimental effects of procedural emboli, temporary flow interruption, and the beneficial effect of improved cerebral hemodynamics.

The feasibility and safety of endovascular recanalization for chronic ICAO have been recently demonstrated.^{11,12} We

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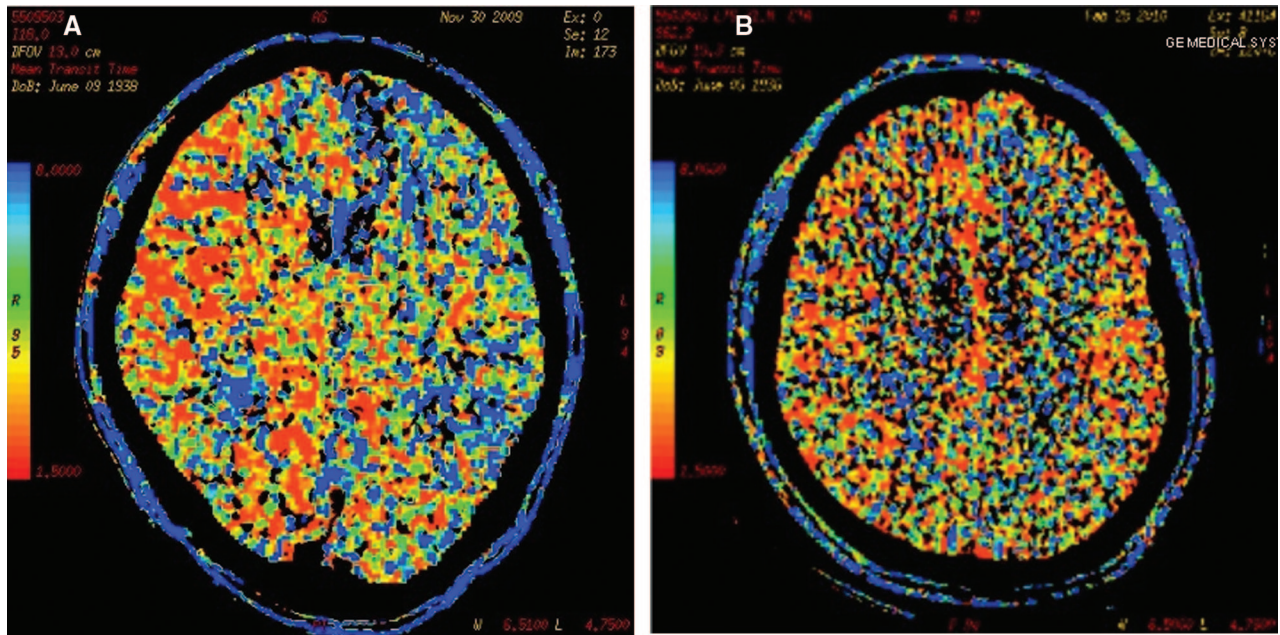


Figure. Improvement in ipsilateral hemisphere perfusion after successful recanalization for chronic internal carotid artery occlusion. A, Brain perfusion computed tomography before recanalization, showing delayed transit time in the left hemisphere. B, Three months after the procedure, repeated computed tomography imaging shows symmetrical transit time in both hemispheres.

report for the first time the results of short-term effects of carotid artery stenting on neurocognitive function in patients with chronic ICAO and objective cerebral ischemia.

Patients and Methods

Patients

All patients were 18 years of age or older. ICAO was documented by neck duplex ultrasound, computed tomography (CT) angiography, or magnetic resonance angiography. Objective ipsilateral hemisphere ischemia was documented by perfusion CT with Diamox stress. All patients were followed up clinically for at least 2 months before revascularization. We excluded patients with ischemic stroke within 2 weeks, vascular disease precluding catheter-based techniques, intracranial aneurysm or arteriovenous malformation, any history of a bleeding disorder, any surgery planned within 30 days, life expectancy <1 year, education level below elementary school, aphasia, right-sided hemiparesis, marked depression, or moderate or worse dementia. From January 2008 to August 2009, endovascular intervention was attempted in 20 ICAO patients (17 men; mean \pm SD age, 65.8 ± 11.5 years; range, 47 to 86 years) with objective ipsilateral hemisphere ischemia. Mean duration from the time of documentation of occlusion to the procedure was 416 ± 741 days (range, 57 to 3112 days). Nine patients (45%) had prior ipsilateral ischemic events, and 3 had their last event within 6 months (North American Symptomatic Carotid Endarterectomy Trial symptomatic). Two patients (10%) had a history of neck radiotherapy for nasopharyngeal cancer. Eleven of the 20 patients did not have a prior ischemic event and were thus “asymptomatic.” The reasons why these patients were screened were variable and included conditions such as clinical complaints of dizziness or incidental findings during routine health check-ups. Six patients (30%) had contralateral ICA stenosis >50%, and 5 of these underwent carotid artery stenting according to the established indications before the index procedure.¹³

Neurocognitive Function Evaluation

A battery of neuropsychological tests was applied within 7 days before and 3 months after carotid intervention. Cognitive function evaluation was performed by an independent clinical psychologist, who was blinded to the outcome of the intervention. Cognitive

assessment used global measures that included the Mini-Mental State Examination^{14,15} and Alzheimer Disease Assessment Scale–Cognitive Subscale, a widely used rating instrument that assesses memory, orientation, language, and ideational and constructional praxis; the scores range from 0 to 70, with a higher score indicating lower performance.^{16,17} Additional tests of neuropsychological function such as executive function, working memory, and attention, which tend more often to be affected in vascular cognitive impairment than in Alzheimer disease,^{18,19} were included. Relevant tasks included verbal fluency (category naming: fruits, vegetables, and fishes) and Trail Making A and B.^{18,20} The Color Trail Making assessments were used to replace the more education-dependent conventional Trail Making assessments.

Interventional Procedures and Clinical Follow-Up

Diagnostic cerebral angiography was performed via the femoral route. The definition of ICAO, premedication before the procedure, and details of the interventional technique have been described previously.^{11,12} Technical success was defined as implantation of stents after recanalization of the occlusion, with a final residual diameter stenosis $\leq 20\%$ and Thrombolysis in Myocardial Infarction grade 3 antegrade flow. All patients were sent to the intensive care unit for overnight hemodynamic and neurologic monitoring, where systolic blood pressure was carefully maintained between 100 and 140 mm Hg. Aspirin and clopidogrel were continued for ≥ 3 months after successful intervention. Complete neurologic examinations, including assessment with the National Institutes of Health Stroke Scale and Barthel Index, were performed by an independent neurologist before, 1 week after, and 3 months after the interventional procedure. Neurologic sequelae, intracranial hemorrhages, and deaths were recorded. Follow-up clinical and ultrasound examinations were scheduled at 3 months after the intervention.

CT Follow-Up and Analysis

Follow-up brain CT perfusion and CT angiography by a multidetector CT scanner were scheduled 3 months after the procedure. Assessment of cerebral perfusion (before and after the procedure) was performed by 2 independent investigators who were blinded to clinical and angiographic outcomes. CT perfusion data were analyzed separately off-line at a workstation by using CT software (CT Perfusion 3, Advantage 4.2; GE Healthcare). Cerebral blood volume,

cerebral blood flow, time to peak, and mean transit time were calculated. The topographic pattern was categorized into 3 groups: absence of asymmetry, watershed zones, and vascular territory hypoperfusion. A grading system for qualitative assessment of brain perfusion of the region of interest was proposed as follows: 0=complete perfusion; 1=hypoperfusion with preserved cerebral blood volume (lower cerebral blood flow, delayed time to peak, increased mean transit time, decreased flow, and normal or elevated cerebral blood volume); and 2=hypoperfusion without adequate blood volume (that is, decreased cerebral blood volume). Improvement in brain perfusion after the procedure was defined as at least a 1 categorical number decrease in the region of interest according to the grading system. The Figure is an image of a patient who had significant improvement in ipsilateral brain perfusion after left carotid stenting.

Statistical Analysis

Continuous data are presented as mean \pm SD. Discrete data are given as counts and percentages. The χ^2 or Fisher exact test (when the group number was ≤ 5) was used to compare groups of categorical data. The Wilcoxon-Mann-Whitney *U* test was applied to compare groups of continuous unpaired data. Paired continuous data were compared by the Wilcoxon signed rank sum test. Pearson's correlation coefficients were used to assess the correlation between the change in brain perfusion and the changes in the results of 5 neuropsychological tests. A 2-sided probability value <0.05 was considered statistically significant. STATA/SE 11.0 for Windows (Stata Corp LP, College Station, TX) was used for statistical analyses.

Results

Technical success was achieved in 12 patients (12 of 20, 60%), with another 7 cases of guidewire crossing failure. There was no periprocedural neurologic or vascular complication noted in these 19 patients. One patient (1 of 20, 5%) with left ICAO experienced a small, nonfatal ipsilateral intracranial hemorrhage 5 hours after successful recanalization and stenting, possibly owing to hyperperfusion. The patient's neurologic condition was stabilized by medical treatment only, and the patient was discharged 1 week later. This patient was excluded from further neurocognitive function evaluation owing to the complication of right-sided hemiparesis.

Table 1 summarizes the baseline clinical characteristics and neurocognitive status of the patients with a good outcome successful ($n=12$) and those without ($n=7$). There were no significant differences between the 2 groups. The average duration from ICAO documentation to the procedure was longer, though statistically insignificant, in the failed cases. The preprocedural scores from the National Institutes of Health Stroke Scale and Barthel Index and the results of neuropsychological tests results were similar between the unsuccessful and unsuccessful groups.

Ten of 12 patients in the successful group had improvements in ipsilateral brain perfusion 3 months after the procedure, but none was found in the unsuccessful group. Table 2 shows neurocognitive and neurologic functions at baseline and 3 months after the procedure in successful and unsuccessful groups. Significant improvements in the Alzheimer Disease Assessment Scale (before, 7.7 ± 8.9 versus after, 5.7 ± 7.1 ; $P=0.024$), Mini-Mental State Examination (before, 25.8 ± 3.8 versus after, 27.7 ± 2.7 ; $P=0.015$), and Color Trail Making A (before, 123.2 ± 68.6 versus after, 99.3 ± 51.5 ; $P=0.017$) and a trend toward improvement in Color Trail

Table 1. Baseline Characteristics and Neurocognitive Function

	Successful Group ($n=12$)	Unsuccessful Group ($n=7$)	<i>P</i>
Male sex	10 (83%)	6 (86%)	1.00
Age, mean \pm SD, y	66.0 ± 10.7	64.7 ± 14.2	0.79
Hypertension	10 (83%)	7 (100%)	0.51
Diabetes mellitus	3 (25%)	1 (14%)	1.00
Hyperlipidemia	8 (67%)	5 (71%)	1.00
Smoking	6 (50%)	3 (43%)	1.00
Coronary artery disease	7 (58%)	5 (71%)	0.66
Prior myocardial infarction	1 (8%)	1 (14%)	1.00
Prior neck radiotherapy	1 (8%)	1 (14%)	1.00
Prior ipsilateral ischemic event	6 (50%)	3 (43%)	1.00
NASCET symptomatic at procedure	3 (25%)	0 (0%)	0.26
Occlusion in left ICA	8 (67%)	5 (71%)	1.00
Contralateral ICA stenosis $>50\%$	5 (42%)	1 (14%)	0.33
Duration from ICAO documentation to procedure, mean \pm SD, days	259.1 ± 406.2 (range, 61 to 1331)	685.1 ± 1101.9 (range, 61 to 3112)	0.33
NIHSS score, mean \pm SD	0.6 ± 0.9	0.6 ± 0.8	0.81
Barthel Index, mean \pm SD	97.5 ± 8.7	95.7 ± 7.3	0.12
ADAS score, mean \pm SD, before	7.7 ± 8.9	7.9 ± 9.1	0.97
MMSE score, mean \pm SD, before	25.8 ± 3.8	25.3 ± 5.4	0.97
Color Trail Making A, mean \pm SD, before, seconds	123.2 ± 68.6	129.7 ± 97.1	0.93
Color Trail Making B, mean \pm SD, before, seconds	196.2 ± 99.3	167.3 ± 79.1	0.61
Verbal fluency, mean \pm SD, before	26.3 ± 14.0	28.6 ± 9.0	0.45

NASCET indicates North American Symptomatic Carotid Endarterectomy Trial; ICA, internal carotid artery; ICAO, ICA occlusion; NIHSS, National Institutes of Health Stroke Scale; ADAS, Alzheimer Disease Assessment Scale; MMSE, Mini-Mental State Examination; SD, standard deviation.

Making B (before, 196.2 ± 99.3 versus after, 175.1 ± 85.5 ; $P=0.169$), were observed in the successful group. In comparison, there was no significant change in all test parameters at follow-up in the unsuccessful group. National Institutes of Health Stroke Scale and Barthel Index values were similar in both groups at the 3-month follow-up compared with baseline.

There were moderate correlations between the change in perfusion and the change in Mini-Mental State Examination score ($r=-0.46$), the change in Color Trail Making A ($r=0.27$), and the change in Color Trail Making B ($r=0.38$).

Table 2. Neurocognitive and Neurologic Function at Baseline and 3 Months After the Procedure

	Successful Group (n=12)			Unsuccessful Group (n=7)		
	Baseline	3 mo After Procedure	P Value	Baseline	3 mo After Procedure	P Value
ADAS score	7.7±8.9	5.7±7.1	0.024	8.7±9.7	9.7±11.1	0.268
MMSE score	25.8±3.8	27.7±2.7	0.015	24.7±5.6	25.7±4.9	0.422
Color Trail Making A, seconds	123.2±68.6	99.3±51.5	0.017	141.3±101.0	138.3±103.7	0.799
Color Trial Making B, seconds	196.2±99.3	175.1±85.5	0.169	176.8±82.1	182.0±92.3	0.397
Verbal fluency	26.3±14.0	27.3±10.2	0.937	27.5±9.4	25.3±6.5	1.0
NIHSS score	0.6±0.9	0.4±0.7	0.157	0.6±0.8	0.6±0.8	
Barthel Index	97.5±8.7	98.8±4.3	0.317	95.7±7.3	97.1±3.9	0.317

Values are mean±SD.

ADAS indicates Alzheimer Disease Assessment Scale; MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

Correlations between the change in perfusion and changes in the Alzheimer Disease Assessment Scale ($r=0.05$) and verbal fluency ($r=0.12$) were weak.

Discussion

In patients with symptomatic or asymptomatic ICAO, chronic cerebral hypoperfusion has been established as an important causal factor leading to ischemic events^{1,2} and cognitive impairment.⁵ In patients without clinical or imaging evidence of ischemic events, high-grade carotid stenosis²¹ or occlusion⁶ can still lead to cognitive decline. These observations suggest that restoration of cerebral circulation may lead to cognitive improvement in certain patient subsets.

Chronic carotid “occlusion” was thought to be a contraindication for carotid endarterectomy, ascribable either to technical difficulty or a lack of clinical benefit in stroke prevention.²² External-internal carotid bypass surgery is an intuitive approach in restoring cerebral perfusion. The reversibility of cognitive function impairment after surgery, however, is controversial. Despite case reports demonstrating cognitive function improvement after bypass,^{23–26} a prospective, randomized trial failed to show any benefit in patients with ICAO.²⁷ Several confounding factors may influence the net result of carotid revascularization on cognitive outcome. Restored cerebral perfusion after intervention may lead to improvement in patients with viable but ischemic brain tissue, whereas procedure-related embolism may result in worsened performance. Clamping or arterial manipulation during carotid endarterectomy or external-internal carotid bypass may also reduce critical perfusion, causing permanent neuron damage and worsened cognitive function. In the clinical setting, patient heterogeneity, variable severity of carotid stenosis, lack of a control group, and a possible “learning effect” on neurocognitive tests are all potential issues to be considered in evaluating the results of carotid revascularization on neurocognitive function.

Endovascular recanalization was shown to be feasible and safe in patients with chronic ICAO.^{11,12} To the best of our knowledge, the present series is the first report demonstrating cognitive function improvement after stenting in chronic ICAO patients with objective hemisphere ischemia. In addition, some of the confounding factors associated with cognitive outcome after surgical revascularization may have been

clarified in our series. First, none of the 19 patients had a new ischemic event after the procedure, according to independent neurologic examination. Carotid stenting does carry the risk of subclinical microembolism, which may negatively affect cognitive performance.^{28–31} The unsuccessful cases in our series were all due to guidewire crossing failure. Therefore, antegrade flow was never established during the procedure in these 7 patients, and in theory, it was less likely for them to have a microembolism. Hence, our results may actually underestimate the effects of successful revascularization on cognitive function improvement. Second, the unsuccessful cases served as the control group in the present study. The baseline characteristics were similar in both groups, and the failed attempt may be regarded as a sham procedure. In addition, the static neurocognitive test results in the unsuccessful group excluded the possibility of a learning effect that has been observed in previous studies.^{9,32} In our study, increased cerebral perfusion was reflected in improved global cognitive function as represented by scores on the Mini-Mental State Examination and Alzheimer Disease Assessment Scale–Cognitive Subscale, as well as attention, visual scanning, and psychomotor processing speed as represented by the time needed to complete the Color Trail Making A test. Therefore, the improvement in cognitive function in the successful group can only be explained by restoration of cerebral perfusion and correction of hemisphere ischemia.

The current study has several limitations. Despite the significant overall improvement in the successful group, there were still variations in individual patients and individual tests. Small patient numbers may be the reason, but more specific neuropsychological tests localizing specific cortical functional zones will be necessary in future studies. The generalizability of our result is also limited owing to the exclusion of patients with hemiparesis, aphasia, depression, and limited education. Apparently, the duration of occlusion was different in successful and unsuccessful groups, although the difference was statistically insignificant. In fact, it is extremely difficult to define the timing of occlusion, especially in asymptomatic patients. Hence, the “duration” we actually measured was the time between “documentation” and the “procedure.” A longer duration of occlusion may potentially affect the reversibility of cognitive function, but it is very difficult to define its impact clearly in such a small popula-

tion. Metabolic imaging, such as ^{18}F -fluorodeoxyglucose positron emission scanning, may also help to correlate anatomic reperfusion and recovery of specific cortical functions after ICAO recanalization. The follow-up interval in the present study was relatively short, and a longer observation period is needed to demonstrate persistent improvement in cognitive function.

Conclusions

We conclude that in patients with objective hemisphere ischemia, revascularization of chronic ICAO by carotid stenting leads to neurocognitive improvement by 3 months after the procedure. Higher patient enrollment and longer follow-up duration accompanied by functional evaluation are mandatory to evaluate the clinical value of cognitive improvement after carotid revascularization.

Disclosures

None.

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