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Original Investigation

Cognitive Function After Carotid Endarterectomy: Early Decline and Later Recovery

Hua-Ping ZHANG[1*], Xiao-Dong MA[1*], Li-Feng CHEN[1], Yang YANG[2], Bai-Nan XU[1], Ding-Biao ZHOU[1]

[1]The Chinese PLA General Hospital, Department of Neurosurgery, Haidian District, Beijing, 100853, China
[2]The Chinese PLA General Hospital, Department of Geriatric Neurology, Haidian District, Beijing, 100853, China

*These authors have contributed equally to the manuscript.

ABSTRACT

AIM: To prospectively study neurocognitive performance following carotid endarterectomy (CEA) in various follow-up periods, taking into account the potential confounding factors.

MATERIAL and METHODS: Thirty-six patients with carotid artery stenosis received CEA (group A). Thirty-one patients underwent surgery for femoropopliteal occlusive disease served as controls (group B). Neuropsychological testing and brain magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) was repeated preoperatively, within 3 days and at 3 months after surgery.

RESULTS: No patient had DWI evidence of procedure-related cerebral ischemia. Preoperative baseline scores of groups A and B were not statistically different in mini mental state examination (MMSE) or clock drawing task (CDT) score. MMSE and CDT scores were significantly reduced for patients in group A ($p<0.01$) within 3 days after CEA. Differences of MMSE score ($p=0.48$) and CDT score ($p=0.26$) between baseline and 3 months after surgery in group A were not statistically significant. No statistically significant change of MMSE score and CDT score in group B was observed at 3 days and 3 months after the surgery. Degree of internal carotid artery (ICA) stenosis ($p=0.029$) and duration of ICA clamping ($p=0.031$) were significantly higher in patients with cognitive impairment immediately after CEA than in those without that.

CONCLUSION: Our study demonstrated cognitive decline for the patients with unilateral carotid stenosis at early stage after CEA and a restorative effect at 3 months after CEA. Postoperative early cognitive impairment might be associated with intraoperative temporary hypoperfusion and postoperative hyperperfusion, not the microembolic event.

KEYWORDS: Carotid stenosis, Carotid endarterectomy, Cognitive function, DWI lesion

INTRODUCTION

Change of cognition is one of the threatening diseases. Cerebrovascular disease plays an important role in the development of dementia as reported by the stroke-dementia association (19). Carotid endarterectomy (CEA) provides a significant risk reduction for stroke (7,15), however, the effect of CEA on cognitive function is controversial. Many studies reported different findings including improvement, no change and deterioration of cognitive function following CEA (1,6,8-10,19). Preoperative cognitive impairment, absence or variability of control group, various follow-up periods and influences of anesthesia contributed to obtain inconsistent results in the studies.

We prospectively designed the following study to investigate neurocognitive performance following CEA in various follow-up periods, taking into account the potential factors described above. Our study aimed at investigating the potential role of procedure-related cerebral microembolism during CEA

Corresponding author: Li-Feng CHEN
E-mail: clf301@126.com

embodied by perioperative diffusion-weighted imaging (DWI). The impacts of patient-related factors including demographics, vascular risk profile, surgical features, and preoperative baseline neuropsychological evaluation were examined. In addition, various follow-up periods that potentially influenced cognitive performance were also evaluated.

MATERIAL and METHODS

Patients

The study was reviewed and approved by the Institutional Ethics Committee of the Chinese PLA General Hospital. All the patients gave their informed written consent. Group A included 36 patients with carotid artery stenosis who were diagnosed in our institution according to standardized criteria (15) and received standardized CEA under general anesthesia at our institution from May 2008 to May 2010. To ensure study group homogeneity, the exclusion criteria included patients with preoperative cognitive function deficit; previous strokes resulted in permanent neurological deficit; a contralateral moderate-degree internal carotid artery (ICA) stenosis; and lack of consent to participate in the magnetic resonance imaging (MRI) studies.

The surgical control group (group B) consisted of 31 patients with femoropopliteal occlusive diseases. They received endarterectomy of the superficial femoral artery (FEA) under general anesthesia. The exclusion criteria of group B included patients with preoperative cognitive function deficit, stroke, and moderate-degree ICA stenosis (greater than 50%). All the patients were deemed acceptable surgical candidates after undergoing preoperative evaluation by appropriate medical and general anesthesia services.

The following variables were considered: demographics; years of education; right handedness; heart diseases; conventional cardiovascular risk factors including cigarette smoking, hypertension, diabetes and hypercholesterolemia. Each patient received the best medical therapy to control vascular risk factors before surgery. Aspirin tablet (100 mg/day) was initiated at least 3 days before surgery and aspirin was administered indefinitely.

Surgical Technique

CEA was performed by the senior neurosurgeon (Professor Zhou). All the patients were operated under general anesthesia. Somatosensory evoked potential and electroencephalographic monitoring were routinely prepared. A longitudinal cervical incision was performed (Figure 1A). We began to use the microscope during deep neck dissection. Common carotid artery (CCA), superior thyroid artery (STA), external carotid artery (ECA) and ICA were exposed (Figure 1B). The mean arterial pressure was raised by 10% and 70 IU/kg (5000 IU) intravenous heparin was administered before clamping. Adventitia injection with 1% lidocaine (Figure 1B) was also administered to inhibit carotid sinus baroreceptor activity at carotid bifurcation region before clamping. The temporary clamping of ICA was performed for 5 minutes.

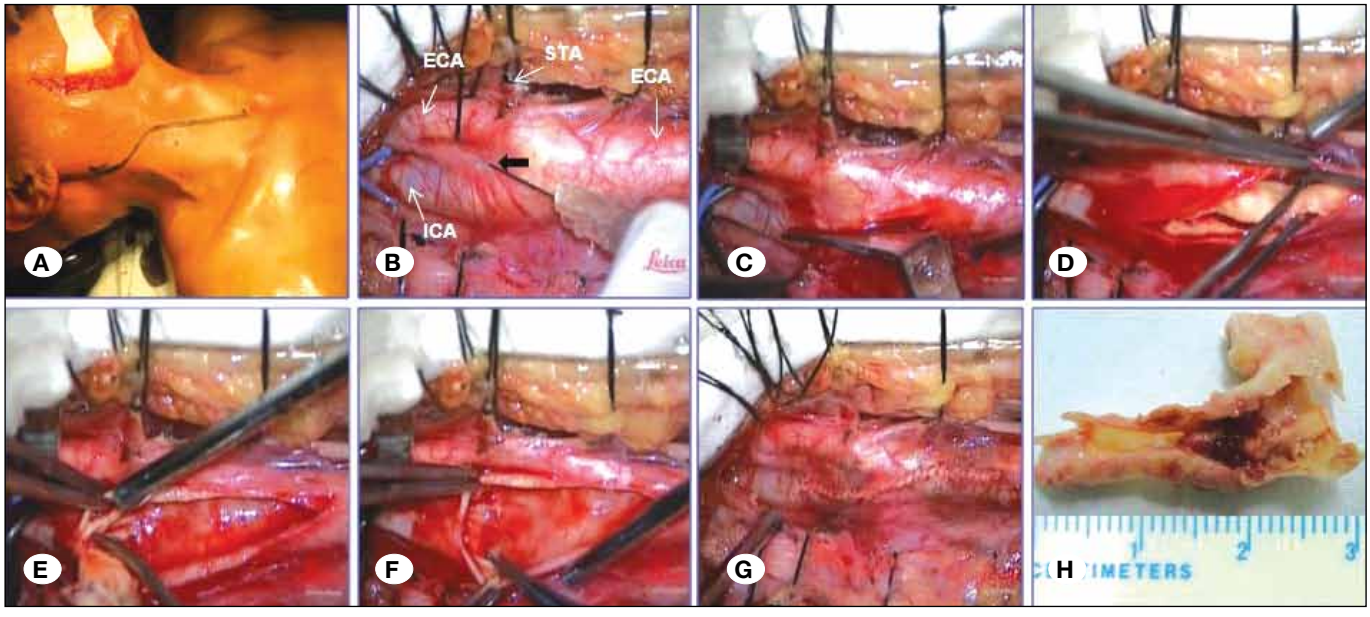

Figure 1: Preferred technique for carotid endarterectomy (CEA). **A)** A longitudinal incision was performed with the patient in the supine position. **B)** The common carotid artery (CCA), carotid bifurcation region, internal carotid artery (ICA) and external carotid artery (ECA), superior thyroid artery (STA) were dissected. Adventitia injection with 1% lidocaine (think arrow) was administered to inhibit carotid sinus baroreceptor activity at carotid bifurcation region before clamping. **C)** The arteriotomy was performed after the STA, ECA CCA, and ICA were sequentially clamped. The atheromatous plaque is dissected circumferentially at the distal CCA **(D)** and extended to the tapering point of the plaque in the ICA **(E)**. **F)** The arterial lumen was inspected carefully under microscopic visualization to identify small residual debris and loose intimal tags. **G)** The vessel was closed with running 6-0 Prolene sutures sewn from ICA end to CCA. **H)** The unstable plaque.

Intraluminal shunting was prepared if somatosensory evoked potential monitoring showed evidence of developing ischemia after temporary clamping of ICA. The STA, ECA CCA, and ICA were sequentially clamped with an angled vascular clamp or temporary aneurysm clips. The CCA was incised (Figure 1C), then, the athermanous plaque was divided circumferentially (Figure 1D) and dissected to the tapering point of the plaque in the ICA (Figure 1E). The arterial lumen was inspected carefully under microscopic visualization with continuous heparin irrigation to identify loose intimal tags or small residual debris (Figure 1F). The vessel was closed by sewing from ICA end to CCA end with a monofilament suture (Proline,6-0) (Figure 1G). Before final closure, back-bleeding of the ICA confirmed the absence of distal occlusion and expelled debris or air through the arteriotomy site. Blood pressure was reduced to normal level. The ECA clip was released, followed by the CCA clip. The ICA clip was released after 30 seconds. The sequence of arterial clamping and releasing described above was used to reduce the potential for debris or air emboli to travel into the cerebral circulation. Carefully hemostasis was ensured, and the wound was closed in routine fashion. The unstable plaque was characterized by the ulcer and bleeding (Figure 1H). Postoperative pharmacological control of blood pressure continued. 35 IU/kg (2500 IU) intravenous heparin was administered once every 6 hours in the first day, and aspirin was administered once a day from the second day postoperatively.

MRI

MRI was performed with a 1.5 T scanner (Siemens Espree, Erlangen, Germany) within 1 to 3 days before surgery and 3 days thereafter (DW, T2 FLAIR-weighted images and DW imaging, respectively). The parameters and details of the scans were the same as reported in our previous publications (21). The technique (TR = 8000, TE = 135, TI = 2500; slice thickness= 3 mm, interslice gap=0) was used to obtain T2 FLAIR-weighted images. Diffusion-weighted imaging was performed with a single-shot echo-planar spin-echo technique. The images were acquired using a single-shot spin echo planar imaging pulse sequence with TR = 3400, TE = 100, b value = 1000, slice thickness = 5 mm, interslice gap = 1 mm. MR imaging analysis was conducted by the neuroradiologist blind to clinical patients' data.

Neuropsychological Evaluation

Cognitive functions of the patients were evaluated with neuropsychological tests within 3 days before, 3 days and 3 months after surgery. The evaluations were conducted and scored by experienced neuropsychological research assistants who were blind to the history of cerebrovascular accidents of the patients. The tests were assessed by the Mini Mental State Examination (MMSE) and the Clock Drawing Task (CDT) (5,22). The MMSE score range was from 0 to 30. Higher scores indicated better cognitive function. The CDT was based on a set of criteria for evaluating clock drawings. The score range of CDT score was from 1 to 10. Higher scores also indicated better performance. Patients with cognitive impairment (MMSE score<25) at baseline were excluded. The differences among the pre-operative, post-operative and follow-up values were analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 software. Age, years of education, and baseline test results were compared with T-test for independent samples after having confirmed parametric distribution. Other characteristics of the groups (right handedness, heart disease, cigarette smoking, hypertension, diabetes and hypercholesterolemia) were compared with chi-square test. The comparisons among preoperative, postoperative and follow-up values for both separate treatment groups were performed with one-Way ANOVA. If there were differences among different periods, post Hoc Multiple Comparisons were performed to determine which periods differed. Differences were considered significant at a level of $p<0.05$.

RESULTS

Patient Demographics and Surgical Results

Sixty-seven consecutive patients were eligible for CEA. Of 31 patients who were excluded, 12 for contralateral high-degree ICA stenosis, 6 for preoperative baseline cognitive impairment, 5 for MRI evidence of cerebral infarction, and 5 patients did not agree to participate in the study. Three patients with CEA were lost because they were very fatigued and it was too difficult to complete the postoperative early neuropsychological test. The patients' demographic and lifestyle characteristics were showed in Table I. There were no significant differences in age, educational level, sex ratio, and heart disease and vascular risk factors (cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus) between 2 groups.

Degree of ICA stenosis in the 36 patients with CEA varied from 55% to 99%. One patient had a minor stroke, and 24 had one or more transient ischemic attacks. 17 patients underwent the left CEA, and 19 underwent the right CEA. The carotid arteries were clamped for approximately 21 to 45 minutes. An intraluminal shunt was used in only 1 patient (3%). No patient received patch angioplasty. One patient (3%) had temporary hypoglossal nerve paresis after CEA, and no other new neurological deficits were observed in group A. 1 patient died because of myocardial infarction at 2 months after CEA. Of the 31 patients with FEA, 3 patients were lost at 3 months after FEA. All the FEA performed without major complications in group B.

Neuropsychological Change

Preoperative baseline scores of groups A and B were not statistically different in MMSE or CDT score (Table I). Table II and Table III showed the MMSE and CDT scores of the different follow-up periods according to the groups. At 3 days after the surgery, MMSE score and CDT score were significantly reduced for patients in group A ($p<0.01$). Differences of MMSE score ($p=0.48$) and CDT score ($p=0.26$) between baseline and 3 months after the surgery in group A were not statistically significant (Table II). No statistically significant change of MMSE score and CDT score in group B was observed at 3 days and 3 months after the surgery

(Table III). Degree of ICA stenosis (p=0.029) and duration of ICA clamping (p=0.031) were significantly higher in patients with cognitive impairment immediately after CEA than in those without cognitive impairment (Table IV). Postoperative cognitive impairment developed in 11 patients (31%) within 3 days after CEA. Permanent cognitive impairment developed in only 1 patient (3%) at 3 months after CEA.

DWI Lesions After CEA

All patients underwent DWI within 1day to 3 days before CEA. Preoperatively, 1 participant was found to have a DWI hyperintensity in the middle cerebral artery territory of the ipsilateral hemisphere. Postoperative DWI was performed in all the 36 patients within 3 days after CEA. We did not find any new DWI lesion after CEA.

■ DISCUSSION

Most of the studies that had inconsistent results about the effect on cognitive function of CEA suffered from poor methodology. First, natural spontaneous brain repair of the patient with preoperative cognitive function impairment had been ignored. Second, there were no control groups in some studies, or the control group consisted of patients with unrelated disease or healthy persons (18). Third, varying follow-up periods after surgery and the effect of anesthesia

Table I: Preoperative Characteristic of Patients with CEA and Control Subjects

Demography and lifestyle	Group A (n=36)	Group B (n=31)	X^2	p
Age, y, mean (SD)	67 (9)	65 (8)		0.075*
Men, n (%)	25 (69)	22 (71)	0.018	0.892#
Years of education, y, mean (SD)	8 (5)	7 (4)		0.192*
Right-handedness, n (%)	34 (94)	28 (90)	0.410	0.522#
Hypertension, n (%)	35 (97)	29 (94)	0.526	0.468#
Hypercholesterolemia, n (%)	34 (94)	30 (97)	0.237	0.626#
Cigarette smoking, n (%)	28 (78)	24 (77)	0.001	0.972#
Diabetes mellitus, n (%)	25 (69)	21 (68)	0.022	0.881#
Atrial fibrillation, n (%)	5 (14)	3 (10)	0.281	0.596#
Coronary heart disease, n (%)	12 (33)	9 (29)	1.781	0.182#
MMSE, mean (SD)	28.0 (1.3)	28.5 (1.2)		0.521*
CDT, mean (SD)	9.2 (0.7)	9.3 (0.5)		0.384*

**T-test for independent samples.*
#chi-square test.

Table II: Cognitive Performances of Patients in Group A (Patients with CEA)

Test	Preoperative (n=36)	Postoperative (n=36)	Follow-up (n=35)	F	P&
MMSE, mean (SD)	28.0 (1.3)	25.6 (2.4)	28.1 (1.2)	4.46	0.03*
CDT, mean (SD)	9.2 (0.7)	7.3 (2.1)	9.1 (0.8)	6.51	0.01#

&One-Way ANOVA.
**Post Hoc Multiple Comparisons: significant within-subject contrast between: pre and postoperative testing (p<0.01); preoperative and follow-up Testing (p=0.48).*
#Post Hoc Multiple Comparisons: significant within-subject contrast between: pre and postoperative testing (p<0.01); preoperative and follow-up Testing (p=0.26).

Table III: Cognitive Performances of Patients in Group B (Patients with FEA)

Test	Preoperative (n=31)	Postoperative (n=31)	Follow-up (n=28)	F	P&
MMSE, mean (SD)	28.5 (1.2)	27.9 (1.8)	29.0 (0.9)	1.76	0.43
CDT, mean (SD)	9.3 (0.5)	9.1 (0.8)	9.2 (0.6)	0.81	0.79

& One-Way ANOVA.

had usually been ignored. To avoid such factors, only patients without cognitive impairment and with a unilateral ICA stenosis were included in our study. The potential impact from preoperative cognitive impairment and the contralateral ICA stenosis or occlusion was avoided. Furthermore, vascular risk factors that are associated with a gradual cognitive function decline should be considered when selecting the appropriate control subjects (13). Elwood et al. (3) reported that the patients with peripheral disease had a significant reduction in cognitive function equivalent to about 4 or 5 years of additional age, so the patients without atherosclerosis are unsuitable as controls. We selected the patients with femoropopliteal occlusive disease as a control group. The demographic and medical characteristics of the control participants were similar with those of the patients with carotid stenosis, so the possible practice effects could be the same for the participants of two groups (1). The FEA is highly comparable with CEA with vascular procedure including general anesthesia, duration of surgery, and expected recovery time. It can be controlled that the positive effect on cognitive function from psychological relief after surgery and the possible negative influence from surgery and anesthesia. In our study, the demographic and medical characteristics of the two groups did not statistically differ. The important influences of surgery or anesthesia were controlled, and baseline cognitive functions of the two groups were normal indicated that they were comparable.

This study showed a significant decline was identified in MMSE and CDS tests at 3 days after CEA, whereas patients in group B did not demonstrate any significant impairment after FEA. Bossema et al. (1) reported the postoperative patients received the early postoperative measurement could be very uncomfortable and fatiguing, and cognitive achievements were likely to be influenced by the discomfort. In our study, 3 patients who underwent CEA were excluded because they were very fatigued and it was too difficult to complete the postoperative early neuropsychological test. The early change of cognitive function was not observed in the control group. This indicated that CEA was associated with the early cognitive function decline in the patients with normal baseline cognitive function after CEA.

The potential various mechanisms that might affect cognitive performance in patients with CEA may be peri-procedural brain microembolic, cerebral hypoperfusion during CEA, and cerebral hyperperfusion after CEA (6,9,10,17,20). It is controversial that microembolic events lead to the cognitive impairment after CEA. The postoperative new cerebral hyperintense lesions on DWI obtained within a few days of CEA are found in 9-15% of patients with CEA (10-12,14, 23). Some authors (12,13,23) reported peri-procedural brain microembolic events leaded to postoperative cognitive decline, whereas other studies (8,10,11) showed the number of new cerebral ischemia lesions did not differ between patients with and without postoperative cognitive impairment, and the procedure-related microembolic events during CEA were not the main cause of postoperative cognitive impairment. Our results showed early significant cognitive decline following CEA, whereas there was no any evidence of postoperative new cerebral hyperintense lesions by DWI. It indicated that postoperative cognitive impairment might have no relationship with microembolic events during CEA. Hebb et al. (8) also reported similar results, and silent cerebral ischemia may be used erroneously in patients with normal neurological function who have cognitive impairment.

The low rate of procedure-related microembolic events is associated with well-selected patients and the meticulous

Table IV: Risk Factors for Cognitive Impairment Immediately After CEA

Variables value	Cognitive impairment		X^2	p
	Yes (n=11)	No (n=25)		
Age, y, mean (SD)	66 (9)	67 (8)		0.081*
Men, n (%)	8 (69)	17 (69)	0.080	0.777#
Years of education, y, mean (SD)	7 (3)	8 (4)		0.065*
Hypertension, n (%)	11 (100)	24 (96)	0.453	0.501#
Hypercholesterolemia, n (%)	10 (91)	24 (96)	0.377	0.539#
Cigarette smoking, n (%)	9 (82)	19 (76)	0.150	0.699#
Diabetes mellitus, n (%)	7 (64)	18 (72)	0.252	0.616#
Atrial fibrillation, n (%)	2 (18)	3 (12)	0.244	0.621#
Coronary heart disease, n (%)	4 (36)	8 (32)	0.065	0.798#
Degree of ICA stenosis (%), mean (SD)	93 (6)	81 (12)		0.029*
Duration of ICA clamping (min), mean (SD)	36 (9)	28 (5)		0.031*

**T-test for independent samples.*
#chi-square test. ***CEA:*** *Carotid endarterectomy.*

operative techniques. Meticulous carotid dissection and extirpation of intimal debris and air is fundamental to reduce the risk of procedure-related microembolic ischemic events during CEA (8). Selective shunting based on electroencephalographic or somatosensory evoked potential monitoring was associated with a stroke rate of 1% compared with a stroke rate of 4% in patients who received routine shunting (24). In our series, intraoperative shunting was performed in only 1 patient. To minimize the need for shunting, the temporary clamping of ICA was performed for 5 minutes before arteriotomy, and we prepared a shunt if the somatosensory evoked potentials deteriorated. Furthermore, we routinely raise the mean arterial pressure by 10% before clamping to increase the cerebral perfusion pressure. In the final stages of closing the arteriotomy, the technique to provide completely extirpation of intimal debris and air and the sequence of arterial release reduced the incidence of microembolic events during CEA.

The previous reports demonstrated the temporary hypoperfusion has been associated with transient cognitive dysfunction (2, 9, 16). Saito et al. (20) also reported that significant hypoperfusion of the cerebral hemisphere ipsilateral to the surgery during CEA is associated with postoperative cognitive deficits, even in the patients with normal performance of intraoperative electroencephalography monitoring. The findings of our study were largely in agreement with the reports. The results in our study showed the duration of ICA cross-clamping was associated with the postoperative early cognitive function decline after CEA. Although there was no intraoperative transcranial doppler (TCD) velocity or transcranial regional cerebral oxygen saturation analysis, and the findings of intraoperative electroencephalography were normal in our study, the postoperative cognitive impairment in 11 patients who had longer carotid artery clamping duration during CEA might be related to intraoperative temporary hypoperfusion.

The incidence of postoperative cognitive impairment was also significantly higher in patients with cerebral hyperperfusion than in those without (17). Hirooka et al. (11) reported all the patients with cerebral hyperperfusion syndrome developed postoperative cognitive impairment. Although perioperative cerebral blood flow was not measured, and cerebral hyperperfusion syndrome was not diagnosed in the present study, the results showed that the duration of ICA cross-clamping and extent of the carotid stenosis were significantly higher in patients with postoperative cognitive impairment than in those without. Development of cerebral hyperperfusion after CEA is associated with preoperative hemodynamic impairment (11), and the longer duration of ICA cross-clamping was independent predictor of postoperative hyperperfusion (17). It indicated the postoperative cognitive impairment in the patients who had more severe carotid artery stenosis and longer duration of ICA cross-clamping might also be related to postoperative hyperperfusion.

The results of this study also demonstrated 10 of 11 patients with postoperative cognitive impairment improved in cognitive function at 3 months after CEA. Permanent cognitive impairment developed in only 1 patient. It indicated cerebral blood flow was restored at 3 months after CEA, a restorative effect on cognitive function could be found. Various follow-up periods might explain the inconsistent result about the effect of CEA on cognitive function among many studies.

There are some limitations that should be addressed in this study. The subjects in the study were not consecutive patients because some patients were lost; moreover, the sample of the study was small. This might decrease the power of the study to detect further significant differences and limit the generalization of results. The study should include a control group consisting of patients who did not receive CEA. The reports have shown the efficacy of CEA in reducing the risk of stroke in patients with high-degree stenosis in 1991(4,15). A control group with significant carotid stenosis did not receive operation would ethically be controversial.

CONCLUSION

Our study demonstrated cognitive decline for the patients with unilateral carotid stenosis at early stage after CEA and a restorative effect on cognitive function at 3 months after CEA. Postoperative early cognitive impairment might be associated with the temporary hypoperfusion during the surgery and postoperative hyperperfusion, not the microembolic event. However, larger studies appropriately designed and powered to assess cognition following CEA are needed to confirm the conclusion.

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