Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 25, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.059

Association of the Recovery of Objective Abnormal Cerebral Perfusion With Neurocognitive Improvement After Carotid Revascularization

Ching-Chang Huang, MD,* Ying-Hsien Chen, MD,* Mao-Shin Lin, MD,*† Cheng-Hsin Lin, MD,†‡
Hung-Yuan Li, MD, PhD,* Ming-Jang Chiu, MD, PhD,§|| Chi-Chao Chao, MD,§
Yen-Wen Wu, MD, PhD,*¶#** Ya-Fang Chen, MD,†† Jen-Kuang Lee, MD,‡‡
Ming-Jiuh Wang, MD, PhD,§§ Ming-Fong Chen, MD, PhD,* Hsien-Li Kao, MD*

Taipei and New Taipei City, Taiwan

Objectives This study sought to report the effect of carotid artery stenting (CS) on neurocognitive function (NCF) in patients with severe carotid artery occlusive disease, depending on baseline brain perfusion status.

Background The effect of CS on NCF has been controversial.

Methods We prospectively enrolled 61 patients with carotid artery disease (22 with occlusion, 39 with severe stenosis) in whom CS was attempted. Computed tomography perfusion and NCF assessments including Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), verbal fluency, and Color Trails Test Parts 1 and 2 were applied before and 3 months after intervention.

Results Successful recanalization was achieved in 14 of 22 occlusion patients (64%) and in all 39 severe stenosis patients. Two cases were excluded due to procedural cerebral complications. The patients were divided into 3 groups: group 1 ($n = 8$) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS failed; group 2 ($n = 33$) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS was successful; and group 3 ($n = 19$) consisted of patients without abnormal baseline ipsilateral cerebral perfusion in whom CS was successful. The demographics and baseline NCF were similar among groups. Only in group 2 was there significant improvement in ADAS-Cog (pre-procedure median [interquartile range]: 6 [4 to 9] vs. post-procedure: 5 [3 to 7], $p = 0.002$), MMSE (pre-procedure: 27 [25 to 28] vs. post-procedure: 28 [25 to 29], $p = 0.004$) and Color Trails Test Part 1 (pre-procedure: 100 [78.5 to 136.5] s vs. post-procedure: 97 [60 to 128.5] s, $p = 0.003$) after CS. Significant difference in changes from baseline was observed only in the Color Trails Test Part 1 among groups (group 1 vs. 2 vs. 3: 1.5 [−14 to 11.5] vs. −12.5 [−36.5 to 0.5] vs. −0.5 [−11 to 27], $p = 0.0159$). Significant correlation between the change of ipsilateral brain perfusion and MMSE ($r = -0.33$, $p = 0.01$) was also identified.

Conclusions Successful CS for severe carotid stenosis/occlusion improves NCF, but only in patients with objective baseline abnormal cerebral perfusion. (J Am Coll Cardiol 2013;61:2503–9) © 2013 by the American College of Cardiology Foundation

Reducing embolic stroke by carotid artery stenting (CS) and carotid endarterectomy (CE) in patients with severe internal carotid occlusive disease has been well proven (1,2). In addition, neurocognitive function (NCF) is being increasingly recognized as an important outcome measure. Cognitive impairment and decline were found in patients with asymptomatic high-grade stenosis of the left internal carotid artery (ICA) (3), and hypoperfusion may be a potential cause (4). It is intuitive that reopening a stenotic vessel and restoring blood flow to the brain would certainly

From the *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; †Graduate Institute of Clinical Medicine, Medical College, National Taiwan University, Taipei, Taiwan; ‡Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan; §Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; ||Department of Psychology, National Taiwan University, Taipei, Taiwan; ¶Department of Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan; #Department of Nuclear Medicine and Cardiovascular Medical Center (Cardiology Division), Far Eastern Memorial Hospital, New Taipei City, Taiwan; **National Yang-Ming University School of Medicine, Taipei, Taiwan; ††Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan; ‡‡Department of Laboratory Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; and the §§Department of Anesthesiology, National Taiwan University Hospital, Taipei, Taiwan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first 3 authors contributed equally to this work and should be considered joint first authors.

Manuscript received June 6, 2012; revised manuscript received January 1, 2013, accepted February 14, 2013.

Abbreviations and Acronyms

ADAS-Cog = Alzheimer Disease Assessment Scale–Cognitive subscale

CBF = cerebral blood flow

CBV = cerebral blood volume

CE = carotid endarterectomy

CS = carotid artery stenting

CT = computed tomography

CTP = computed tomography perfusion

ICA = internal carotid artery

ICAO = internal carotid artery occlusion

MMSE = Mini-Mental State Examination

NCF = neurocognitive function

NIHSS = National Institutes of Health Stroke Scale

have favorable neurocognitive effects, but previous studies have provided inconsistent results (5–8). Several factors may contribute to the inconsistency, including the diversity of the patient population, the difference in baseline cerebral perfusion status, variability of surgical and endovascular techniques, the differences in neuropsychological testing methodology, and the possible learning effect on repeated tests. Procedural emboli, temporary flow interruption, and general anesthesia may also offset the benefit of improved cerebral hemodynamics.

Our previous work has demonstrated that successful CS can improve global cognitive functions as well as attention and psychomotor processing speed in patients with chronic internal carotid artery occlusion (ICAO) (9), even in asymptomatic patients (10). The results implied the reversibility of cognitive function in an ischemic hemisphere after restoring cerebral perfusion. Therefore, we conducted the present study with an expanded patient cohort to assess the neurocognitive change after CS in all patients with severe ICA disease, analyzed according to baseline perfusion status of the ipsilateral hemisphere and procedural result.

See page 2510

Methods

Patients. All patients were 18 years of age or older. From July 2008 to January 2010, endovascular intervention was attempted in 61 consecutive patients with severe ICA stenosis or ICAO. The indication was diameter stenosis >60% in symptomatic patients, and >80% in asymptomatic (2). Patients with documented ICAO would be followed up clinically for at least 2 months, and CS was only attempted in patients with ischemic symptom progression or objective hemisphere ischemia (11,12). We excluded patients with ischemic stroke within 2 weeks, vascular disease precluding catheter-based techniques, intracranial aneurysm or arteriovenous malformation, history of bleeding disorder, any surgery planned within 30 days, life expectancy <1 year, educational level below elementary school, aphasia, right-sided hemiparesis, marked depression, or at least moderate dementia. Brain computed tomography (CT) perfusion (CTP) with Diamox (acetazolamide) stress and a battery of neuropsychological tests were performed before and 3 months after carotid intervention.

NCF evaluation. Cognitive function evaluation was performed by an independent clinical psychologist, who was blinded to the outcomes of the intervention. Cognitive assessment of global measures included the Mini-Mental State Examination (MMSE) (13,14) and Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), a widely used rating instrument assessing memory, orientation, language, and ideational and constructional praxis. ADAS-Cog scores range from 0 to 70, with a higher score indicating lower performance (15,16). Additional tests covering neuropsychological functions, such as executive function, working memory, and attention, are compatible with the concept of VADAS-Cog and are suitable for our patients with vascular-related cognitive impairment (17,18). Relevant tasks included verbal fluency (category naming: fruits, vegetables, and fishes) and Color Trails Test Parts 1 and 2 (17,19). The Color Trails Test was used to replace the more educational-dependent conventional Trail Making Test.

Interventional procedure and clinical follow-up. Aspirin 100 mg and clopidogrel 75 mg/day were started 7 days before the procedure. CS procedure was done with techniques described in the literature (2,20). The definition of ICAO and the details of the interventional technique were also described previously (11,12). Technical success was defined as implantation of stents after recanalization of the lesion, with final residual diameter stenosis $\leq$20% and Thrombolysis In Myocardial Infarction flow grade 3 antegrade. All patients were sent to the intensive care unit for overnight hemodynamic and neurological monitoring, where systolic blood pressure was carefully maintained within 100 to 140 mm Hg. Aspirin and clopidogrel were continued for $\geq$3 months after successful intervention. Complete neurological examinations, including assessment of National Institutes of Health Stroke Scale (NIHSS) and Barthel Index, were done by an independent neurologist before, 1 week, and 3 months after the procedure. Neurological sequelae, intracranial hemorrhage, and death were recorded. Follow-up ultrasound examination was scheduled at 3 months after the intervention.

CT follow-up and analysis. CTP and CT angiography by a multidetector CT scanner was scheduled before and 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 using commercial software (CT Perfusion 3, Advantage 4.2, GE Healthcare, Little Chalfont, United Kingdom). Cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak, and mean transit time were calculated. The topographic pattern was categorized into absence of asymmetry, watershed zones, and vascular territory hypoperfusion. A grading system of qualitative assessment of brain perfusion in region of interest was applied as the following: 0 = complete perfusion; 1 = hypoperfusion with preserved CBV (a lower CBF, delayed time to peak, increased mean transit time, decreased