Eur J Vasc Endovasc Surg (2015) 50, 5–12

Effects of Carotid Endarterectomy on Cerebral Reperfusion and Cognitive Function in Patients with High Grade Carotid Stenosis: A Perfusion Weighted Magnetic Resonance Imaging Study

Q. Wang [a,1], M. Zhou [a,1], Y. Zhou [a], J. Ji [a], D. Raithel [b], T. Qiao [a,*]

[a] Department of Vascular Surgery, Drum Tower Clinical Medical College of Nanjing Medical University, The Affiliated Drum Tower Hospital of Nanjing University, Nanjing, PR China
[b] Department of Vascular and Endovascular Surgery, Nuremberg Southern Hospital, Nuremberg, Germany

WHAT THIS PAPER ADDS

Carotid endarterectomy (CEA) is thought to reverse cognitive impairment in patients with high grade internal carotid artery stenosis by reversing the cerebral perfusion status. However, limited studies have investigated changes in cerebral perfusion and cognitive function in these patients before and after CEA. Using magnetic resonance perfusion weighted imaging (PWI) this study reports the correlation between reversion of perfusion and improvement in cognition in patients who underwent CEA. More patients than expected may benefit from CEA, including patients with mild cognitive impairment.

Objective: To investigate the influence of carotid endarterectomy (CEA) on cerebral perfusion and cognitive function in patients with internal carotid artery stenosis (ICA).
Methods: Patients were prospectively enrolled in this study. Shunted patients were excluded. Cerebral perfusion was measured by magnetic resonance (MR) perfusion weighted imaging (PWI) and diffusion weighted imaging (DWI) in 46 patients with $>$65% ICA (31 males, 64.5 $\pm$ 6.7 years) 1 week before and 6 weeks after CEA. Cognitive function was assessed using the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) 1 week before and 6 weeks after CEA.
Results: After CEA, perfusion parameters from PWI decreased, including mean transit time (MTT) (21.07 $\pm$ 7.36 vs. 14.27 $\pm$ 6.22, $p < .0001$), time to peak (TTP) (28.69 $\pm$ 8.54 vs. 23.45 $\pm$ 4.25, $p = .001$), arrive time (T0) (19.89 $\pm$ 7.32 vs. 15.20 $\pm$ 3.51, $p = .001$), and relative cerebral blood volume (rCBV) (11.48 $\pm$ 3.50 vs. 7.53 $\pm$ 3.17, $p < .0001$). A significant improvement was observed in MoCA (20.48 $\pm$ 1.70 vs. 22.04 $\pm$ 1.48, $p = .001$). Spearman's rank correlation analysis between TTP and MoCA scores demonstrated a linear relationship with an excellent correlation coefficient ($R = -.893$, $p < .001$). Linear regression indicated that diabetes was a risk factor for cognitive improvement in patients with ICA ($p = .014$). Further analysis showed that patients with DM performed worse in MoCA after the procedure (with-DM 21.15 $\pm$ 1.28 vs. non-DM 22.4 $\pm$ 1.46, $p = .010$) while the baselines were similar (non-DM: 20.3 $\pm$ 1.8 vs. with-DM: 20.9 $\pm$ 1.4, $p = .362$).
Conclusion: CEA could improve the cerebral perfusion and the cognitive function in un-shunted ICA patients. Cerebral reperfusion was an important factor for cognitive improvement. Diabetes had a negative effect on cognitive improvement after CEA.

Article history: Received 19 September 2014, Accepted 16 March 2015, Available online 29 April 2015
Keywords: Carotid endarterectomy, Carotid stenosis, Cognitive function, Perfusion weighted imaging

INTRODUCTION

Internal carotid artery stenosis (ICA) is known to have the potential for negative impact on patients' cognitive function.[1,2] The end stage of cognitive impairment is dementia, which, to date, has no effective treatment. Therefore, delaying the progression of any cognitive impairment arising from ICA stenosis could provide a strategy for preventing dementia.[3–5] Classical treatment for ICA stenosis is carotid endarterectomy (CEA), which has been proven effective in preventing future stroke as well as improving cerebral perfusion.[6–9] Although a number of clinical trials have been conducted to investigate changes in cognitive function after CEA, it remains unclear whether CEA can improve cognitive function.[10–15] Conflicting results have been attributed to various factors, including neuropsychological test methods, follow up schedule, limited sample

[1] The first two authors contributed equally to this work.
* Corresponding author. 321 Zhongshan Road, Nanjing, PR China.
E-mail address: qiaotongmail@aliyun.com (T. Qiao).
1078-5884/© 2015 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejvs.2015.03.032

size, and patient related variables such as the co-morbidity of other disorders, for example hypertension and diabetes.

Cerebral perfusion deficiency caused by hemodynamic changes and cerebral emboli was shown to have a key role in the process of cognitive impairment,[16] hence, it was suggested that the improved cerebral perfusion after CEA could be the main factor in reversal of cognitive impairment. However, studies assessing cerebral perfusion in ICA patients have been limited because of the lack of an overall quantitative approach other than cerebral blood flow.[17] Brain magnetic resonance imaging (MRI) was shown to be a potential method for detection of a decrease in cerebral perfusion in patients with ICA based on perfusion weighted imaging (PWI).[18] By comparison of perfusion parameters in PWI, cerebral perfusion status can be analyzed comprehensively and quantitatively.[19] In addition, MR diffusion weighted imaging (DWI) was also able to show ischemic lesion size based on the exhibition of cytotoxic cerebral edema, and this was a good imaging modality for detecting early ischemic brain lesions after CEA.[20] Therefore, changes in cerebral perfusion after CEA can be comprehensively evaluated using MRI, including PWI and DWI. A previous study[17] used qMRA, which reflected the cerebral blood flow (CBF), and suggested that improvement in blood flow was associated with greater cognitive improvement; however, use of an inappropriate neuropsychological test weakened the conclusion from that study. And, in addition, cerebral perfusion was not completely equal to CBF. As a result, further study is required, incorporating comprehensive evaluation of cerebral perfusion and approved neuropsychological scales.

The present study aimed to determine whether improvement in cerebral reperfusion is the main factor in cognitive improvement in patients with ICA stenosis. After CEA in patients with ICA stenosis, changes in cerebral perfusion were evaluated by MRI and changes in cognitive function by neuropsychological scales.

PATIENTS AND METHODS

Subjects

Patients diagnosed with ICA stenosis between January 2012 and January 2014 in the Department of Vascular Surgery, Nanjing Drum Towel Hospital were prospectively registered in the study. Each patient was screened with ultrasound for the need to receive revascularization. Eligibility requirements were (a) patients with symptomatic ICA $>50\%$ or asymptomatic ICA $>70\%$, measured by ultrasound according to the non-invasive equivalent of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria;[6] (b) no gender or age restrictions; and (c) patients understood and were willing to participate in the research.

Exclusion criteria were (a) patients with a history of psychosis or a score on the Hamilton Depression Rating Scale (HDRS) > 17;[21] (b) patients with Alzheimer's disease (AD) or any other concomitant neurological disorder potentially affecting cognitive function; (c) patients who had experienced a recent stroke (within 4 weeks, given the potential impact on cognitive function) or a stroke that had decreased social function; (d) patients with personal habits that have a negative impact on cognitive function, such as alcoholics and drug abusers; (e) patients unable to comply with the study assessment; and (f) patients having had surgical procedures that did not comply with the standardized surgical protocol, including use of a shunt.

Protocol approvals and patient consent

This study was approved by the institutional review board of the Drum Tower Hospital. All subjects and their caregivers provided informed consent.

Baseline data

Patient data were collected including demographic characteristics, presenting symptoms, and medical characteristics. Demographic data were composed of gender, age, and educational level (lower educational level refers to an education time ≤ 6 years; higher educational level refers to an education time >6 years). The severity of ICA stenosis was diagnosed by B-mode ultrasonography according to the NASCET method.[6]

Surgical procedure

Patients were treated pre-operatively with oral aspirin (BAYASPIRIN, Bayer, Germany) 100 mg/day for 3 days before the carotid endarterectomy (CEA), and received general anesthesia during the operation. The maximum carotid artery clamp time was 30 minutes. Low molecular heparin (Clexane, AVENTIS Pharma Specialites, France) was used at 10000 U/day after the operation, replaced by aspirin and/or clopidogrel (Plavix, Sanofi-Aventis, France) after 3 days which was then continued for 6 months.

Cerebral perfusion evaluation

Patients were examined by color Doppler ultrasound examination 6 weeks after CEA to evaluate the degree of stenosis of the carotid artery. To determine cerebral perfusion, MRI was performed 1 week before and 6 weeks after the operation on a 3.0-T MR system (Achieva 3.0T TX, Philips, the Netherlands). A standardized protocol was used in all patients for brain magnetic resonance angiography (MRA) (see supplementary material). Post processing of PWI was performed using specific software acquired from Philips with a semi-quantitative method for evaluating cerebral perfusion.[22] The relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), time to peak (TTP), mean transit time (MTT), and time of arrival (T0) were calculated (for detailed definition about these parameters, see supplementary material). A grading system was used for qualitative assessment of the cerebral perfusion. Baseline white matter changes were assessed semi-quantitatively by the sum of age related white matter changes (ARWMC) score as described previously.[23] Assessment of the PWI and DWI was performed by two independent researchers who were unaware of the angiographic and clinical outcomes.

Neuropsychological tests (NPTs)

Cognitive function was assessed 1 week before and 6 weeks after the operation. NPTs were performed by two trained clinical neuropsychologists, who were blinded to the outcome of the procedure, using the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). There was an interval of >1 hour between these two tests to avoid “benefit of study” effects. The Chinese versions were used for evaluation of MoCA (Beijing version MoCA) and MMSE. The MoCA was the version as recommended by Peking Union Medical College Hospital, and an additional 1 score was given to each subject who had educational experience of 11 years or less (≤11).

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows (Release 21.0; SPSS, Chicago, IL, USA). Continuous data are presented as mean ± SD. Discrete data are presented as counts and percentages. Student *t* tests were used for continuous data. Paired continuous data were compared by the Wilcoxon signed rank sum test. Discrete data were analyzed using either chi-square tests or Mann-Whitney *U* tests as appropriate. Correlation between perfusion recovery and improvement of cognitive function was performed by analysis of Spearman’s rank correlation coefficient. The association between cognitive function improvement and patient characteristics was analyzed by means of multivariate linear regression and expressed as standardized coefficients. Characteristic factors included age, hypertension, diabetes, prior ischemic event, asymptomatic, new lacunar infarcts, and ARWMC>4. All statistics were performed with a 0.05 level of significance.

RESULTS

One hundred and sixteen ICA stenosis patients were screened, of whom 82 were enrolled and received CEA. Technical success was achieved in 59 patients, with 23 patients excluded for being shunted. Cerebral hyperperfusion syndrome (CHS) occurred in one patient 3 days after the surgery, presenting as intense migraine like headache on the operated side, which recovered within 24 hours. No post-operative stroke occurred. Six patients refused the brain MRI after operation and NPTs could not be performed in seven patients after CEA. Thus, 46 patients finished this study. Their median educational experience was 9 years.

Table 1 details the characteristics of the patients included in the study. The mean operating CEA time was 82 ± 18.9 minutes, and the carotid artery clamp time was 11.7 ± 3.4 minutes. However, new lacunar infarcts were found in seven patients after CEA, with the average number in each patient being 2.03 ± 0.29, without symptoms. Six weeks after the operation, ultrasound examination was performed to detect technical defects. Blood flow in ICA was present in all patients, and no stenoses were found (Fig. S1A, B).

Table 1. Patient characteristics ($N = 46$).

Characteristic	$N = 46$
Age, years	64.5 ± 6.7
Gender	
Male	31 (67.4%)
Female	15 (32.6%)
Degrees of stenosis	
Bilateral	$N = 7$ (15.2%)
Stenosis side, %	75–95
Contralateral side, %	65–85
Unilateral	$N = 39$ (84.8%)
Stenotic side, %	65–95
Contralateral side, %	0–50
Side of operation	
Left	26 (56.5%)
Right	20 (43.5%)
Lower education level (≤6 years)	9 (19.6%)
Smoking	11 (23.9%)
Long-term antiplatelet therapy (>2 months)	14 (30.4%)
Hypertension	30 (65.2%)
Diabetes mellitus	13 (28.3%)
Coronary artery disease	10 (21.7%)
Prior ischemic events	
Transient ischemic attack	17 (37.0%)
Minor stroke	4 (8.7%)
Last event to revascularization, days	37.4 ± 16.2
Other medical status	
Peripheral vestibular disorder	8 (17.4%)
Syncope	7 (15.2%)
Asymptomatic	10 (21.7%)
Time from initial symptoms to revascularization (months)	2.7 ± 1.3
Pre-operation ARWMC scores	3.8 ± 2.0
Atrial fibrillation	1 (2.1%)

ARWMC = Age related white matter changes.

Perfusion status evaluation was performed by MRI. First, in 39 unilateral patients, cerebral perfusion was compared in the ipsilateral and contralateral sides. Pre-treatment PWI showed decreased cerebral perfusion in the ipsilateral side compared with the contralateral side, mainly reflected by the significant decrease in TTP ($p = .048$), MTT ($p = .02$), and rCBV ($p = .01$), but there were no significant differences in rCBF ($p = 0.37$) and T0 ($p = .08$) (Table. S1). Pre- and post-operative MRI examinations were performed. The differences in PWI and DWI pre- and post-operation suggested that CEA could reverse partly the impaired cerebral perfusion, mainly reflected in the decreased area of hypoperfusion in PWI (Fig. 1, A1, A2) and the decreased abnormal high signal on the ipsilateral side in DWI after the procedure (Fig. 1, B1, B2). Comparing the pre-operative and post-operative perfusion parameters, significant improvement was observed in cerebral perfusion in the ipsilateral side after CEA (Table 2). Improvement of rCBV, MTT, T0, and TTP in PWI, consistent with results of DWI, also indicated that CEA had positive effects on cerebral perfusion (Table 2).

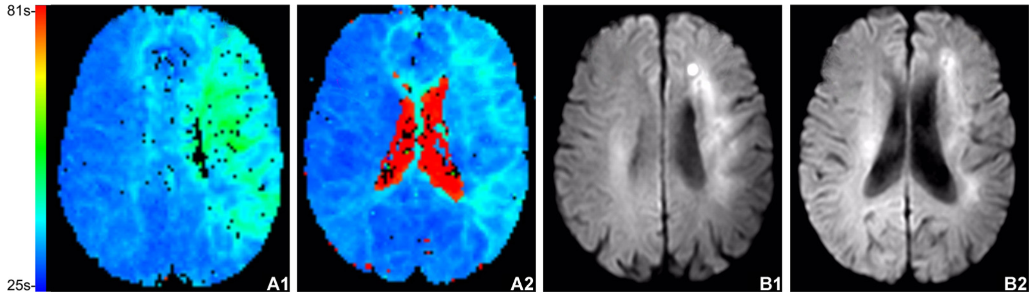

Figure 1. MRI including DWI and PWI was performed 1 week before and 6 weeks after CEA to evaluate cerebral perfusion. Changes in PWI pre- (A1) and post-CEA (A2) and in DWI pre- (B1) and post- (B2) CEA are shown. CEA = carotid endarterectomy; MRI = magnetic resonance imaging; PWI = perfusion weighted imaging; DWI = diffusion weighted imaging.

NPTs including MoCA and MMSE were completed in 46 patients. The total MMSE scores were similar in the pre- and post-operation groups, but post-operation patients performed better on the sub-test of "recall" compared with the baseline (Table 3). In contrast, as shown in Table 4, the total MoCA score improved significantly from 20.48 to 22.04 ($p < .001$) after CEA, as well as sub-tests including "visuo-executive", "naming," "attention," and "abstraction." But, interestingly, there was no improvement in "recall" in MoCA. In sub-tests of MoCA, "verbal fluency" and "orientation" showed the highest pre procedure scores, with "recall" and "visuo-executive" showing the lowest. After CEA, sub-tests of "abstraction," "attention," and "naming" in MoCA showed better improvement than other sub-tests (Fig. S2). The sub-test of "recall" also had the lowest score in MMSE. Differences in cognitive profile pre- and post-operation were more apparent in MoCA than MMSE (Fig. S2).

After evaluating changes in cerebral perfusion and cognitive function, analysis of Spearman's rank correlation coefficient was performed to explore any correlation between cerebral perfusion recovery and improvement of MoCA. TTP was selected as a representation of cerebral perfusion as it had been proved previously to be the best predictor of early cerebral ischemia.[24] The percentage changes in TTP (pre/post scores, %) and in MoCA (pre/post scores, %) are shown in Fig. 2. A linear relationship was found, with an excellent correlation coefficient ($R = -.893$, $p < .001$), between the variation of TTP and MoCA scores after the procedure. Fig. 2 also shows that the more TTP decreased after the procedure, the better the improvement in MoCA.

To investigate the influence of characteristic factors on improvement of MoCA, multivariate linear regression was performed. Cognitive function improvement (CI) was defined as "post-operation MoCA score/pre-operation MoCA score," then the relationship between the value of cognition improvement and characteristic factors in each patient was analyzed. Complication with diabetes was the only factor which was found to reduce the cognitive function improvement significantly (standardized coefficients: -.374, $p = .014$, Table S2).

Given the results of the linear regression, patients were divided into two groups based on whether or not they had diabetes. Ultrasound examination indicated that no re-stenosis was found after the procedure in either group. No significant decrease in perfusion parameters was found in patients with DM. Fig. 3A shows that DM had a negative effect on cerebral re-perfusion, mainly reflected in significantly elevated TTP (non-DM 22.54 ± 4.22 vs. with-DM 25.74 ± 3.94, $p = .023$) and significantly elevated rCBV (non-DM 6.89 ± 3.15 vs. with-DM 9.17 ± 3.06, $p = .031$) after the procedure. There were no significant differences between non- and with-DM groups in both pre-operative TTP (non-DM 28.02 ± 8.51 vs. with-DM 30.37 ± 8.70, $p = .407$) and rCBV (non-DM 11.67 ± 3.38 vs. with-DM 11 ± 3.87, $p = .567$). After comparing cerebral perfusion between these two groups,

Table 2. Change in perfusion parameter in ipsilateral side before and after CEA.

Perfusion parameter	Pre-CEA	Post-CEA	t value	p
MTT, s	21.07 ± 7.36	14.27 ± 6.22	4.24	<.0001
TTP, s	28.69 ± 8.54	23.45 ± 4.25	3.39	.001
rCBV	11.48 ± 3.50	7.53 ± 3.17	5.16	<.0001
T0, s	19.89 ± 7.32	15.20 ± 3.51	3.55	.001
rCBF	0.61 ± 0.25	0.53 ± 0.22	1.51	.136

CEA = carotid endarterectomy; rCBV = relative cerebral blood volume; rCBF = relative cerebral blood flow; TTP = time to peak; MTT = relative mean transit time; T0 = time of arrival.

Table 3. Change in MMSE before and after CEA.

Sub-tests	Pre-CEA	Post-CEA	t value	p
Orientation/10	9.07 ± 0.65	9.15 ± 0.79	−0.579	.564
Registration/3	2.83 ± 0.38	2.78 ± 0.41	0.521	.604
Calculation/5	4.57 ± 0.58	4.76 ± 0.43	−1.83	0.71
Recall/3	1.85 ± 0.60	2.11 ± 0.53	−2.22	.028
Naming/2	1.93 ± 0.25	1.98 ± 0.15	−1.017	.312
Repetition/1	0.89 ± 0.31	0.78 ± 0.42	1.411	.162
Reading/1	0.87 ± 0.34	0.83 ± 0.38	0.575	.567
Comprehension/3	2.41 ± 0.58	2.57 ± 0.50	−1.346	.182
Writing/1	0.78 ± 0.42	0.74 ± 0.44	0.484	.629
Drawing/1	0.83 ± 0.38	0.78 ± 0.42	0.521	.604
Total/30	26.02 ± 1.36	26.48 ± 1.49	−1.538	.128

MMSE = Mini Mental State Examination; CEA = carotid endarterectomy.

Table 4. Change in MoCA before and after CEA.

Sub-tests	Pre-CEA	Post-CEA	t value	p
Visuo-executive/5	2.43 ± 0.88	2.80 ± 0.78	−2.216	.036
Naming/3	2.02 ± 0.65	2.35 ± 0.57	−2.57	.012
Calculation/3	2.35 ± 0.53	2.41 ± 0.54	−0.587	.559
Attention/3	2.20 ± 0.62	2.52 ± 0.50	−2.77	.007
Verbal fluency/3	2.48 ± 0.66	2.52 ± 0.66	−0.317	.752
Abstraction/2	1.22 ± 0.63	1.54 ± 0.55	−2.654	.009
Recall/5	1.87 ± 0.65	2.00 ± 0.63	−0.973	.333
Orientation/6	5.72 ± 0.46	5.70 ± 0.51	0.215	.830
Total/30	20.48 ± 1.70	22.04 ± 1.48	−4.72	<.001

MoCA = Montreal Cognitive Assessment; CEA = carotid endarterectomy.

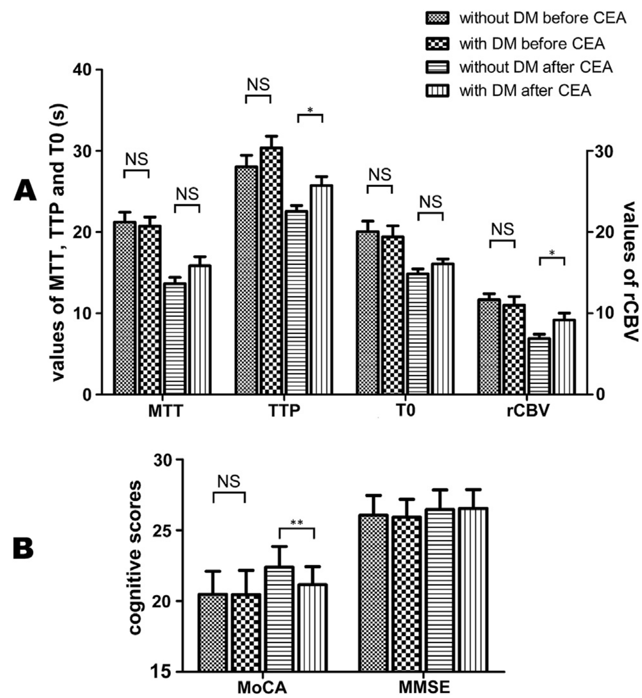

Figure 3. Comparison of perfusion parameters in patients with or without DM (A), and comparison of cognitive evaluation in patients with or without DM (B). CEA = carotid endarterectomy; DM = diabetes mellitus; rCBV = relative cerebral blood volume; TTP = time to peak; MTT = mean transit time; T0 = time of arrival; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination.

a comparison of cognitive function was performed in patients with or without DM. As expected, patients with DM performed worse in MoCA after the procedure (non-DM 22.4 ± 1.5 vs. with-DM: 21.2 ± 1.3, $p = .010$), while the baselines were similar (non-DM: 20.3 ± 1.8 vs. with-DM: 20.9 ± 1.4, $p = .362$).

DISCUSSION

Cerebral perfusion status in carotid stenosis

The present study demonstrated that CEA can result in improved cerebral perfusion 6 weeks after the operation. Post-CEA improvement in cerebral perfusion in symptomatic patients has been reported previously,[7,25] but improvement in asymptomatic patients was controversial, being identified as both significant[26] and non-significant.[27] Based on the results of the present study, the improved cerebral perfusion was observed in a general group. Being asymptomatic had no significant influence on cognitive improvement, which suggests that CEA could improve cerebral perfusion levels in both symptomatic and asymptomatic patients. Interestingly, in contrast with previous reports,[10,17] CBF in the present study did not increase significantly after the operation. This suggests that evaluating cerebral perfusion by CBF only might not be a suitable option in some cases. The present study was based on non-shunted patients, so patients with, theoretically, the largest increase of CBF after CEA were not studied, rendering this conclusion insufficient. Further study is required to

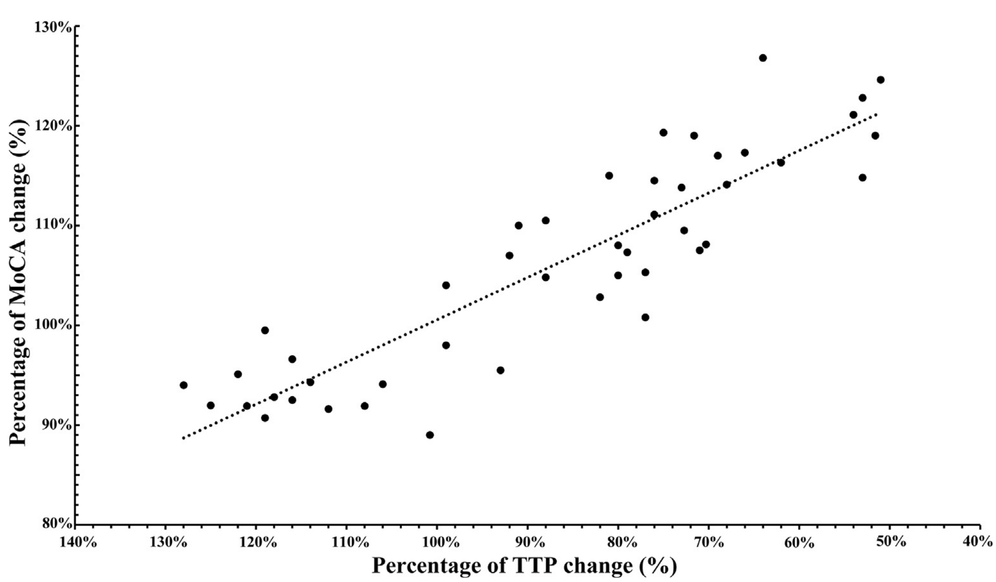

Figure 2. Scatter diagram of the percentage changes in TTP values and MoCA after the operation. MoCA = Montreal Cognitive Assessment; TTP = Time To Peak.

investigate this issue. Furthermore, in the present study, PWI was shown to be an optional and comprehensive method to detect cerebral perfusion improvement in symptomatic or asymptomatic patients at the early stage (6 weeks) after revascularization.

Neuropsychological changes after CEA

Previously, CEA was found to improve patient performance in the MMSE test,[28] but another study showed that MMSE was not suitable for detecting post-CEA cognition improvement.[29] Recently, a new neuropsychological test, MoCA, was developed to replace MMSE in screening mild cognitive impairment (MCI).[30] The Beijing version MoCA (MoCA-BJ) showed an excellent sensitivity of 90.4% and a fair specificity (31.3%). Even when the cut off score was lowered to 22, MoCA-BJ also showed sensitivity (68.7%) and specificity (63.9%).[31] Some studies have demonstrated the specificity of MMSE as relatively high, as well as the sensibility of MoCA in patients with cerebral ischemia both in the English[32] and Chinese versions.[33] In the present study, a combination of MMSE and MoCA was chosen to accurately detect change in patients' cognitive function. Consistent with the results of Watanabe et al.,[34] different evaluation results were observed after CEA between MMSE and MoCA. Different results between these two tests could partly be explained, according to a previous study,[35] by the different content. The sub-tests of "orientation," "registration," and "calculation," major proportions in the MMSE scale, were not significantly damaged in patients with mild cognitive impairment. MoCA included not only content evaluated by MMSE, but also focused on test items including "execution," "abstraction," "verbal fluency," and "visuo-executive," which were improved in MoCA after CEA in the present study.

Cerebral perfusion and neuropsychological changes

Scatter diagram and correlation analysis showed that improved cognitive function was related to improvement of cerebral perfusion. A previous study reported that chronic ischemia caused by bilateral carotid artery ligation significantly decreased the cognitive function of rats.[36] Whitten et al.[37] also reported that patients with 75% or greater stenosis of the ICA had significantly greater improvement in memory and mental abilities after CEA. Therefore, the improved cerebral perfusion was predicted as the reason for cognitive improvement in patients with ICA stenosis. Some previous clinical studies evaluated changes in CBF resulting from CEA, by single photon emission computed tomography (SPECT)[10] or qMRA,[17] and performed neuropsychological tests on these patients. They demonstrated that cognitive function improvement in ICA stenosis patients was related to CBF improvement. By more comprehensive evaluation of cerebral perfusion and use of an approved scale, the results of the present study proved the hypothesis that CEA reversed impaired cerebral perfusion by removing stenosis and, therefore, led to improved cognitive function.

Patient characteristics and cognitive impairments

Many factors can interfere with cerebral perfusion and cognitive function, including age, WML, hypertension, diabetes, etc., which might be responsible for the conflicting results of previous studies. In the present study, diabetes mellitus (DM) was the only factor found to have negative influence on post-CEA cognition improvement. As DM is known to be a risk factor for cardiovascular disease, it came as no surprise that multiple studies have described an association between DM and impaired cerebral perfusion on MRI.[38,39] The negative effect of chronic hyperglycemia on cerebral perfusion has been reported previously.[40] However, few studies have focused on the influence of DM on post-CEA cognition improvement. Patients with DM in the present study displayed a non-significant improvement in cerebral perfusion status, probably as a result of the microangiopathy caused by DM. On the other hand, hyperglycemia can also damage cognitive function.[41] Therefore, according to the present results and those of previous studies, the negative impact of DM on post-CEA cognition improvement might arise partly from the negative impact on cerebral perfusion. However, patients performed equally in MMSE and MoCA before CEA, so additional factors are involved. A previous study demonstrated that cognitive function deteriorated after carotid revascularization regardless of baseline ARWMC scores.[23] However, patients with ARWMC$>$4 in the present study benefited from CEA according to MoCA. This conflict could be explained by the relatively lower ARWMC scores (only ranging from 5 to 8) and the different scales compared to previous studies.

Despite the promising results, there are some limitations to this study. First, the number of patients who participated was small. Second, some patients might exhibit a "practice" effect as all patients took the examination twice; it is unclear how much this influenced the results. Third, no control group of non-operated patients was included in the present study. Further studies are required using not only MoCA and MMSE but also another scale to allow more detailed evaluation of patients' cognitive function.

In summary, the present study indicates that CEA can improve cerebral perfusion and promote recovery of cognitive function in non-shunted ICA patients, even at the early stage (just 6 weeks after CEA). By correlation analysis, the hypothesis that cerebral perfusion improvement from CEA is an important factor in the improvement of cognitive function was confirmed. In addition, this was the first demonstration of the inconspicuous revised cerebral perfusion and cognitive function in patients with DM undergoing CEA, which should be noted in future studies.

APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2015.03.032

CONFLICT OF INTEREST

None.

FUNDING

This study was funded by "High level Talents in Six Industries" in Jiangsu Province, P.R China. Project number: 2012-WS-094.

REFERENCES

1 Silvestrini M, Viticchi G, Falsetti L, Balucani C, Vernieri F, Cerqua R, et al. The role of carotid atherosclerosis in Alzheimer's disease progression. *J Alzheimers Dis* 2011;**25**(4):719–26.

2 Fergenbaum JH, Bruce S, Spence JD, Lou W, Hanley AJ, Greenwood C, et al. Carotid atherosclerosis and a reduced likelihood for lowered cognitive performance in a Canadian First Nations population. *Neuroepidemiology* 2009;**33**(4):321–8.

3 Li J, Wang YJ, Zhang M, Xu ZQ, Gao CY, Fang CQ, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology* 2011;**76**(17):1485–91.

4 Paulson GW, Kapp J, Cook W. Dementia associated with bilateral carotid artery disease. *Geriatrics* 1966;**21**(11):159–66.

5 Tatemichi TK, Desmond DW, Prohovnik I, Eidelberg D. Dementia associated with bilateral carotid occlusions: neuropsychological and haemodynamic course after extracranial to intracranial bypass surgery. *J Neurol Neurosurg Psychiatry* 1995;**58**(5):633–6.

6 North American Symptomatic Carotid Endarterectomy Trial C. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991;**325**(7):445–53.

7 Lukasiewicz A, Mindykowski R, Serafin Z. The influence of carotid endarterectomy on cerebral blood flow in significant carotid stenosis-perfusion computed tomography study. *Int Angiol* 2014;**33**(4):309–15.

8 Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**(9420):1491–502.

9 Luebke T, Aleksic M, Brunkwall J. Meta-analysis of randomized trials comparing carotid endarterectomy and endovascular treatment. *Eur J Vasc Endovasc Surg* 2007;**34**(4):470–9.

10 Kishikawa K, Kamouchi M, Okada Y, Inoue T, Ibayashi S, Iida M. Effects of carotid endarterectomy on cerebral blood flow and neuropsychological test performance in patients with high grade carotid stenosis. *J Neurolog Sci* 2003;**213**(1–2):19–24.

11 Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: the Tromso Study. *Neurology* 2004;**62**(5):695–701.

12 Takaiwa A, Kuwayama N, Akioka N, Kurosaki K, Hayashi N, Endo S, et al. Effect of carotid endarterectomy on cognitive function in patients with asymptomatic carotid artery stenosis. *Acta Neurochir (Wien)* 2013;**155**(4):627–33.

13 Paraskevas KI, Lazaridis C, Andrews CM, Veith FJ, Giannoukas AD. Comparison of cognitive function after carotid artery stenting versus carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2014;**47**(3):221–31.

14 Aleksic M, Huff W, Hoppmann B, Heckenkamp J, Pukrop R, Brunkwall J. Cognitive function remains unchanged after endarterectomy of unilateral internal carotid artery stenosis under local anaesthesia. *Eur J Vasc Endovasc Surg* 2006;**31**(6):616–21.

15 Picchetto L, Spalletta G, Casolla B, Cacciari C, Cavallari M, Fantozzi C, et al. Cognitive performance following carotid endarterectomy or stenting in asymptomatic patients with severe ICA stenosis. *Cardiovasc Psychiatry Neurol* 2013;**2013**:342571.

16 Alegret M, Cuberas-Borros G, Espinosa A, Valero S, Hernandez I, Ruiz A, et al. Cognitive, Genetic, and brain perfusion factors associated with four year incidence of Alzheimer's disease from mild cognitive impairment. *J Alzheimers Dis* 2014;**41**(3):739–48.

17 Ghogawala Z, Amin-Hanjani S, Curran J, Ciarleglio M, Berenstein A, Stabile L, et al. The effect of carotid endarterectomy on cerebral blood flow and cognitive function. *J Stroke Cerebrovasc Dis* 2013;**22**(7):1029–37.

18 Trivedi RA, Green HA, U-King-Im J, Graves M, Black R, Kirkpatrick PJ, et al. Cerebral haemodynamic disturbances in patients with moderate carotid artery stenosis. *Eur J Vasc Endovasc Surg* 2005;**29**(1):52–7.

19 Nuutinen J, Liu Y, Laakso MP, Karonen JO, Vanninen EJ, Kuikka JT, et al. Perfusion differences on SPECT and PWI in patients with acute ischemic stroke. *Neuroradiology* 2009;**51**(10):687–95.

20 Yamatogi S, Furukawa M, Iida E, Takahashi S, Ishihara H, Kato S, et al. Evaluation of small ischemic lesions after carotid artery stenting: the usefulness of thin-slice diffusion-weighted MR imaging. *Neuroradiology* 2011;**53**(4):255–60.

21 Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. *J Affect Disord* 2013;**150**(2):384–8.

22 Kim BJ, Kang HG, Kim HJ, Ahn SH, Kim NY, Warach S, et al. Magnetic resonance imaging in acute ischemic stroke treatment. *J Stroke* 2014;**16**(3):131–45.

23 Altinbas A, van Zandvoort MJ, van den Berg E, Algra A, de Borst GJ, Hendrikse J, et al. The effect of white matter lesions on cognition after carotid revascularization. *J Neurol Sci* 2013;**334**(1–2):77–82.

24 Yu J, Li J, Huang X. The Beijing version of the Montreal cognitive assessment as a brief screening tool for mild cognitive impairment: a community-based study. *BMC Psychiatry* 2012;**12**:156.

25 Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR, et al. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Comparative study between relative and quantitative measurements. *Radiology* 2002;**223**(2):361–70.

26 Shang Y, Cheng R, Dong L, Ryan SJ, Saha SP, Yu G. Cerebral monitoring during carotid endarterectomy using near-infrared diffuse optical spectroscopies and electroencephalogram. *Phys Med Biol* 2011;**56**(10):3015–32.

27 Telman G, Kouperberg E, Nitecki S, Karram T, Schwarz HA, Sprecher E, et al. Cerebral hemodynamics in symptomatic and asymptomatic patients with severe unilateral carotid stenosis before and after carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2006;**32**(4):375–8.

28 Soinne L, Helenius J, Tatlisumak T, Saimanen E, Salonen O, Lindsberg PJ, et al. Cerebral hemodynamics in asymptomatic and symptomatic patients with high grade carotid stenosis undergoing carotid endarterectomy. *Stroke* 2003;**34**(7):1655–61.

29 Fearn SJ, Hutchinson S, Riding G, Hill-Wilson G, Wesnes K, McCollum CN. Carotid endarterectomy improves cognitive function in patients with exhausted cerebrovascular reserve. *Eur J Vasc Endovasc Surg* 2003;**26**(5):529–36.

30 Baracchini C, Mazzalai F, Gruppo M, Lorenzetti R, Ermani M, Ballotta E. Carotid endarterectomy protects elderly patients from cognitive decline: a prospective study. *Surgery* 2012;**151**(1):99—106.
31 Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**(4):695—9.
32 Pendlebury ST, Markwick A, de Jager CA, Zamboni G, Wilcock GK, Rothwell PM. Differences in cognitive profile between TIA, stroke and elderly memory research subjects: a comparison of the MMSE and MoCA. *Cerebrovasc Dis* 2012;**34**(1):48—54.
33 Dong Y, Yean Lee W, Hilal S, Saini M, Wong TY, Chen CL, et al. Comparison of the Montreal cognitive assessment and the mini-mental state examination in detecting multi-domain mild cognitive impairment in a Chinese sub-sample drawn from a population-based study. *Int Psychogeriatr* 2013;**25**(11):1831—8.
34 Watanabe J, Ogata T, Hamada O, Nonaka M, Abe H, Higashi T, et al. Improvement of cognitive function after carotid endarterectomy-a new strategy for the evaluation of cognitive function. *J Stroke Cerebrovasc Dis* 2014;**23**(6):1332—6.
35 Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimers Dement* 2013;**9**(5):529—37.
36 Melo MC, Gadelha D, Mascena GV, Oliveira TK, Brandt CT. Translational realistic expectations of chronic cerebral hypoxemia in rat model after bilateral commom carotid artery ligation. Neurocognitive aspects. *Acta Cir Bras* 2014;**29**(1):53—8.
37 Whitten RH, Gee W, Kaupp HA, McDonald KM. Extracranial surgery for the low flow-endangered brain. *Arch Surg* 1981;**116**(9):1165—9.
38 Sarwar N, Aspelund T, Eiriksdottir G, Gobin R, Seshasai SR, Forouhi NG, et al. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik prospective study and systematic review. *PLoS Med* 2010;**7**(5):e1000278.
39 Brundel M, Kappelle LJ, Biessels GJ. Brain imaging in type 2 diabetes. *Eur Neuropsychopharmacol* 2014;**24**(12):1967—81.
40 Hou Q, Zuo Z, Michel P, Zhang Y, Eskandari A, Man F, et al. Influence of chronic hyperglycemia on cerebral microvascular remodeling: an in vivo study using perfusion computed tomography in acute ischemic stroke patients. *Stroke* 2013;**44**(12):3557—60.
41 Ho N, Sommers MS, Lucki I. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. *Neurosci Biobehav Rev* 2013;**37**(8):1346—62.