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Carotid Artery Stenting Ameliorates the Cognitive Impairment in Patients with Leukoaraiosis, the Ischemic Change of Cerebral White Matter

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Leukoaraiosis (LA) is a leading cause of gait disturbance in the elderly and well known as a type of cerebrovascular diseases. LA is mainly caused by the focal ischemic damage in cerebral white matter. Cognitive impairment in patients with LA is difficult to treat. Carotid artery stenting (CAS) has been reported to improve the cognitive function in patients with cognitive impairment. However, whether CAS can ameliorate the cognitive impairment in patients with LA remains unknown. To address this problem, we prospectively enrolled 105 LA patients with carotid stenosis and 206 healthy subjects, who are free of carotid artery stenosis and brain diseases or injuries, as the control. Neuropsychological functions were tested in these LA patients before and after 1-, 6- and 12-month CAS, and compared with the data of control subjects. Mini-Mental State Examination (MMSE) and Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) scores were lower in LA patients than those in healthy controls ($P < 0.05$), indicating the cognitive impairment in the LA patients. Compared with the scores before CAS, there is a time-dependent increase in MMSE and WAIS-RC scores after 1-, 6- and 12-month CAS ($P < 0.05$). Moreover, CAS treatment reduced Clinical Dementia Rating scale in LA patients. The cognitive impairment of LA patients with carotid stenosis was severe, but their cognitive impairment was ameliorated with carotid stenosis ($P < 0.01$). Thus, CAS can improve cognitive function of the LA patients with carotid stenosis.

Keywords: carotid artery stenting; clinical dementia rating; cognitive impairment; leukoaraiosis; neuropsychological tests
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Introduction

Leukoaraiosis (LA) is a leading cause of gait disturbance in the elderly (Kaski et al. 2013) and attracts more researchers to explore the efficient methods for the therapy of LA. LA is well known as a kind of cerebrovascular diseases and mainly caused by the focal ischemic damage in cerebral white matter (Grueter and Schulz 2012; Yamada et al. 2012; Shimizu et al. 2014). LA is related to lacunar infarct, which is associated with an intracranial athermanous branch disease or an occlusion of a single penetrating artery by microathermanous or lipohyalinosis (Arboix et al. 2005, 2014). A previous report demonstrated that LA was not related to the cognitive performance in the acute phase until after the acute phase (Blanco-Rojas et al. 2013). LA needs to be analyzed at 6 months after lacunar infarct, while LA is indicative of greater diffuse vascular damage, which can account for the cognitive impairment.

Carotid stenosis is one of main factors responsible for LA (Saba et al. 2009). Multiple small vessel infarcts have been considered as a risk factor for LA (Putaala et al. 2009, 2011; Folsom et al. 2012). Additionally, there are many common factors such as hypertension, history of brain hemorrhage, ischemic heart disease and enhanced triglycerides, also contribute to the pathogenesis of LA (Gouw et al. 2008; Folsom et al. 2012; Shimizu et al. 2014).

The internal carotid arteries (ICAs) are the main vessels supplying oxygen-rich blood to brain. ICA occlusion is considered as the pathogenesis of LA (Streifler et al. 2002; Saba et al. 2011). For ICA occlusion, carotid artery stenting (CAS) is well known surgical techniques for the therapy of the blockade of the arteries (Oka et al. 2013). LA can cause the cognitive impairment and difficult to be treated. CAS has been widely reported to improve the cog-

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nitive function. However, whether CAS can improve cognitive impairment in the patients with LA remains unknown. To close the gap, CAS was performed to clarify whether the technique could ameliorate the risk of LA. Meanwhile, we evaluated whether CAS could improve the cognitive impairment of LA patients.

Materials and Methods

Participants

The study of human subjects was reviewed and approved by the Human Research Ethic Committee from Shandong Provincial Hospital affiliated to Shandong University (Jinan, China). The study protocol was conformed to the Helsinki Declaration. All the subjects and their families agreed to join the research and had the right to withdraw at any time. From March 7th, 2008 to September 6th, 2012, a total of 175 LA patients were recruited by Shandong Provincial Hospital affiliated to Shandong University. In the same period, 237 healthy volunteers were also recruited. All patients were diagnosed according to AHA/ASA Guideline (Goldstein et al. 2006). All the patients were suitable for the treatment of CAS.

According to the assessment by Magnetic Resonance Imaging (MRI) and computed tomography (CT), there were no brain diseases or injuries in healthy subjects. The healthy participants were selected if they had no history or current symptoms of ischemic or hemorrhagic stroke. The patients and healthy subjects were from the same area and also met the criteria: unrelated ethnic Han Chinese, similarly cultural and economic background, healthy liver and kidney. The normal results were shown in all participants for blood tests, pulmonary function tests, electrocardiography, chest radiography, and carotid Doppler ultrasonography.

The LA patients may have subcortical dementia syndrome (Lee 2011) and lacunar syndrome (Hassan et al. 2002) due to occlusion of single perforating vessel (Fisher 1965), slow mental process and failure memory. Internal carotid artery stenosis was examined by MR angiography (Hartkamp et al. 2012). All the patients were detected with in excess of 70% of internal carotid artery stenosis while all healthy subjects were free of ICA stenosis. Brain CT scan showed a focal infarction with a diameter of ≤ 15 mm located in the arterial territory of the branches of the basilar artery. The patients with atrial fibrillation, other major sources of cardioembolism, arterial stenosis ≥ 50%, neoplasms, hematological disorders, or brain trauma were excluded. Meanwhile, demographics, and vascular risk factors were estimated in patients and controls following the criteria, which included diabetes (fasting blood glucose levels of ≥ 145 mg/dl), hyperlipidemia (plasma cholesterol of ≥ 250 mg/dl), hypertension (> 165 mmHg systolic or > 95 mmHg diastolic), tobacco smoking (≥ five cigarettes per day) and heart disease. The exclusion criteria included present serious medical, psychiatric and neurologic disorders. The patients with severe communication problems are often difficult to be examined clinically. All the patients with the factors were not considered either in the study.

LA scale

LA was assessed with Scheltens scale (Morimoto et al. 2009). Every cerebral region was scored according to the size and the number of the lesions. In accordance with this scale, there are three regions for the scores of the periventricular white matter hyperintensity: the frontal and occipital caps, and the periventricular bands. The score is 0 if there is no lesion; the score is 1 if the size of lesion is 5 mm or less; the score is 2 if confluent lesions is more than 5 mm. There are four subcortical regions (frontal, parietal, temporal and occipital lobes) for the score of the deep white matter hyperintensity. The score is 0 if there is no lesion; the score is 1 if the number of 3-mm or smaller lesions are 5 or fewer; the score is 2 if the number of 3- mm or smaller lesions are 6 or more; the score is 3 if the number of from 4- to 10- mm lesions are 5 or fewer; the score is 4 if the number of from 4- to 10- mm lesions are 6 or more; the score is 5 if the number of 10- mm or larger lesions are 1 or more; and the score is 6 if there are large confluent lesions. The total LA score is the scores of the periventricular white matter intensities plus deep white matter hyperintensity.

Clinical lacunar syndromes

The frequency of the different clinical lacunar syndromes in the study sample (pure motor hemiparesis, pure sensory, sensorimotor syndrome, ataxic-hemiparesis, dysarthria-clumsy hand, atypical lacunar syndromes) was determined according to a previous report (Grau-Olivares et al. 2007).

Cerebral blood flow analysis

Blood flow volume (BFV) was examined using an extracranial segment of the ICA via a Doppler ultrasound system (Multiflow; DWL Elektronische Systeme, Singen, Germany) according to a report previously described (Lucas et al. 2013). The values for global cerebral blood flow were calculated using an equation from a previous report (Henriksen et al. 2012).

Cerebral metabolism analysis

The internal jugular vein was retrograde catheterized in all LA patients. A four Fr catheter was placed in the jugular bulb and the location was verified via X-ray. After the cerebral blood flow (CBF) measurements and therapeutic tests, blood samples were taken from an arterial line for baseline evaluation each day. Samples were collected with two-cc syringes rinsed with heparin and processed in our lab as soon as possible. For each sample, blood saturation, blood gases, hematocrit, hemoglobin, pH values, lactate plasma concentrations and glucose concentration were examined. All the parameters were calculated according to a previous report (Soustiel et al. 2006).

Clinical dementia rating (CDR) scale

CDR scale is frequently used to detect memory impairment (Inoue et al. 2012). More importantly, CDR is used not only to detect memory impairment but also to quantify the severity of symptoms of dementia. The aim of the clinical diagnosis for some dementia (as a frontal) is not the memory impairment on the acute phase (Pirani et al. 2010). CDR is used to assess three domains of cognition (memory, orientation, problem solving) and functions (community affairs, home and hobbies, personal care) (Cedarbaum et al. 2013). All LA individuals had an overall CDR of 0.5 or over 0.5. All healthy subjects had a CDR score of 0 (Table 1).

Effects of age, education level and gender on MMSE scores

Mini-Mental State Examination (MMSE) score is affected by age, gender and education level. Thus, the effects of age, education level and gender on MMSE scores were examined in LA patients and healthy subjects. The MMSE scores were given in the form of percent distributions specific for age, gender and educational level.

Carotid artery stenting (CAS)

Before the CAS, the brains of all subjects were examined by CT, MRI, Positron Emission Tomography (PET), carotid artery ultrasonography and brain vessels angiography. From the results, carotid artery stenosis was evaluated. According to the three dimensional image correlations of CT, MRI, and PET, the degree, location and length of vessel stenosis were assessed. Thus, the location and length of the stent could be determined.

CAS was performed by an experienced surgeon using Seldinger's needle techniques (Stone et al. 2013). The correct length and diameter of carotid stents were selected before the operation. Lesions were treated with a WallStent (Boston Scientific Corp, Natick, USA). All stents were implanted under the guidance of roadmap. After deployment, it was necessary for that all stents were dilated with a 5.5 mm balloon (Falcon Grande, Invatec, Roncadelle, Italy). The filter was retrieved through an 8F dedicated catheter. Patients were taken care of in the recovery room for 7 days. The procedure was performed by the same operator with the same stent to keep any potential bias as low as possible.

Neuropsychological test

After CAS, CDR was estimated using above method. Neuropsychological test was performed according to the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) (Yao et al. 2007). The measure consists of performance IQ, verbal IQ and Full IQ. There are 13 subtests for the measures (Verbal Comprehension: Information, Similarities, and Vocabulary; Perceptual Organization: Block Design, Picture Completion and Matrix Reasoning; Working Memory: Arithmetic, Digit Span and Letter-Number Sequencing; Processing speed: Digit Symbol-Coding and Symbol Search; and others: Picture Arrangement and Comprehension). Meanwhile, MMSE was performed according to a previous report (Schweizer et al. 2012). The levels of impairment have been classified: none, score = 24-30; mild, score = 18-24; and severe, score = 0-17 (Tombaugh and McIntyre 1992).

Statistical analysis

For the statistical analysis, all the variables were compared via the χ^2 test or *t*-test. Clinical characteristics were analyzed before and after CAS. The multivariate analyses for age, gender, and educational levels (school years more than 9, 5-8 and less than 4 years), were performed to evaluate the independent factor contributing to MMSE scores. A value of $P < 0.05$ was regarded as statistically significant. SPSS was used for the data analysis finally.

Results

Characteristics of participants

All patients had the obvious symptoms of lacunar syndromes for the LA. Of which, there were 30 cases for pure motor hemiparesis, 15 pure sensory, 8 sensorimotor syndrome, 16 ataxic-hemiparesis, 17 dysarthria-clumsy hand and 19 atypical lacunar syndromes (Table 1). Based on the comparison of healthy controls and LA patients on WAIS-RC, all the LA patients with carotid stenosis had lower scores than those from the healthy subjects (Table 2).

Four hundred and twelve subjects were evaluated for CBF and cerebral metabolism, and 101 subjects (70 LA patients and 31 healthy participants with a family history of high blood pressure) were excluded. Thus, the study included 105 patients with LA and 206 cases as healthy control. Table 1 showed the average value of CBF and cerebral metabolism for the patients and healthy ones. As expected, CBF values were lower in the LA patients compared with the controls. Similarly, cerebral metabolism was significantly lower in the patients compared with healthy ones. Glucose metabolism was also lower in patients than that from healthy ones.

Effects of age, education level and gender on MMSE scores

MMSE score can be affected by gender, age and education level (Piccinin et al. 2013). Thus, the effects of age, education level and gender on MMSE scores were investigated in LA patients. A decreased MMSE score was closely related with age and educational levels, regardless of gender. Inter-gender differences were not statistically significant ($P > 0.05$) (Table 3). In age groups > 39 years, over 63% of patients had a MMSE score ≤ 23. The MMSE scores were affected by both age and educational level. There was an inverse relationship between MMSE scores and age or education levels, ranging from a median of 27 for those less than 39 years, to 20 for individuals over 70 years. The median MMSE score was 26 for individuals with more than 9 years of schooling, 22 for those with 5 to 8 years of schooling, and 20 for those with less than 4 years of schooling. For all healthy subjects, no MMSE score was less than 23. The mean MMSE scores were 28. There was no significant statistical difference in healthy subjects ($P > 0.05$) (Table 4).

CAS treatment increases MMSE scores

Patients allocated into CAS treatment and control group were compared in their MMSE score before CAS treatment ($P > 0.05$). After six-month and twelve-month treatment, MMSE score increased significantly compared with those from the controls ($P < 0.05$) (Table 5).

CAS treatment causes a decline in CDR scale

Before CAS treatment, LA individuals had an overall CDR scale of 0.5 or over 0.5 and none was zero. After one-month CAS treatment, two patients had CDR scale of 0. Correspondingly, the number of CDR scale of 0.5 or over 0.5 was also reduced (Table 5). The change became obvious after six- and twelve-month CAS treatment. After twelve-month CAS treatment, five patients had CDR scale of 0. The number of CDR of 1 and 2 plus was reduced while the number of CDR of 0.5 was increased (Table 5). Thus, CAS treatment caused a decline in CDR scale.

CAS treatment ameliorates cognitive impairment of LA patients

The MMSE scores of LA patients after CAS were significantly better than those before CAS ($P < 0.05$) (Table 4). Based on the WAIS-RC scores (Full Scale IQ, Verbal IQ and Performance IQ), before the CAS treatment, LA indi-

Table 1. Demographic and clinical characteristic of study patients and healthy subjects.

	LA Patients (n = 105)	Healthy Subjects (n = 206)	Statistical value	P value
Gender (male/female)	65/40	117/89	0.897[a]	0.235
Age (years)	59.89 ± 32.37	60.10 ± 28.92	1.212[b]	0.123
Diabetes/Non-diabetes	15/90	25/181	0.204[a]	0.515
High blood pressure/Normal blood pressure	20/85	44/162	0.461[a]	0.350
Coronary heart disease/Non-coronary heart disease	18/87	30/176	0.127[a]	0.415
Smoker/Non-smoker	24/81	44/162	0.140[a]	0.371
Drinker/Non-drinker	23/82	43/163	0.001[a]	0.887
Educational years	10.81 ± 2.31	10.31 ± 3.55	1.283[b]	0.266
Left-handed/Right handed	13/92	16/190	1.801[a]	0.201
During of illness (years)	8.8 ± 4.7	-	-	-
Pathological MRI (%)	60 (57.1%)	-	-	-
Neuropsychological impairment (2 T-scores 35) (%)	75 (71.4%)	-	-	-
Leukoaraiosis score	12.3 ± 8.5	-	-	-
Lacunar syndromes				
Pure motor hemiparesis	30	-	-	-
Pure sensory	15	-	-	-
Sensorimotor syndrome	8	-	-	-
Ataxic-hemiparesis	16	-	-	-
Dysarthria-clumsy hand	17	-	-	-
Atypical lacunar syndromes	19	-	-	-
CBF [ml/(100 g × min)]	41.1 ± 7.3	45.61 ± 17.26	14.53[b]	< 0.01
$AVDO_2$ (ml/dl)	4.85 ± 1.45	6.82 ± 0.24	2.02[b]	< 0.01
$CMRO_2$ [ml/(100 g × min)]	1.93 ± 0.56	3.22 ± 0.21	1.14[b]	< 0.01
AVDGlc (ml/dl)	9.38 ± 0.34	9.74 ± 0.28	0.45[b]	< 0.05
CMRglc [ml/(100 g × min)]	3.04 ± 2.19	5.01 ± 0.50	2.08[b]	< 0.01
CDR scale				
CDR 0	0	206	-	-
CDR 0.5	55	0	-	-
CDR 1	30	0	-	-
CDR 2+	20	0	-	-

CBF, cerebral blood flow; $AVDO_2$, arteriovenous oxygen difference; $CMRO_2$, cortical metabolic rate of oxygen consumption; AVDGlc, arteriovenous glucose difference; CMRglc, cerebral metabolic rates of glucose; $^a\chi^2$ test and $^b t$-test.

viduals were identified with cognitive impairment with lower scores compared with healthy subjects (Table 5). There was greater improvement for the cognitive impairment after one-, six- and twelve-month CAS treatment (P < 0.05) (Table 5). Similarly, there was also a greater trend for improvement in neuropsychological assessments (P < 0.05) after one-, six- and twelve-month CAS treatment (P < 0.05) (Table 5).

Discussion

Our results indicated that the presence of cognitive impairment was higher in LA patients when compared to healthy ones. After CAS treatment, there was significant improvement for cognitive impairment of LA patients. The scores generated on the cognitive tests in both groups were not biased by literacy level. Neuropsychological abnormalities are closely associated with LA disease (Grau-Olivares et al. 2007). Thus, CAS may improve neuropsychological abnormalities of LA patients by carotid revascularization (Huang et al. 2013).

Persisting carotid stenosis can be a great contributor to disability in affected individuals. This may have implications on the general well-being of the individual as often vascular risks is usually missed and hence is left untreated. Carotid stenosis greatly affects the recognition function of an individual. This can be made worse by the lack of detection and non-treatment, and relevant individuals may be cognitively impaired. Such a situation works against successful treatment of LA patients, making it imperative to diagnose and effectively treat LA to improve the quality of therapy. Thus, carotid stenosis can be improved via CAS. However, given the burden of disease the condition brings about, it should be treated whenever it is detected in an individual.

Table 2. Comparison of healthy controls and LA patients on WAIS-RC.

	Healthy controls (n = 206)		LA patients (n = 105)		t-test		
	Mean	S.D.	Mean	S.D.	t	d.f.	P value
Full Scale IQ	103.7	13.8	80.7	12.9	15.63	269.3	2.76×10^{-26}
Verbal IQ	106.4	16.2	91.1	17.2	12.31	292.8	2.94×10^{-22}
Performance IQ	108.1	13.5	81.0	14.4	16.55	273.9	1.43×10^{-37}
Indices							
Verbal Comprehension	107.6	11.2	95.7	13.1	8.66	278.4	3.45×10^{-18}
Perceptual Organization	102.5	11.8	83.4	14.2	12.16	281.7	4.41×10^{-27}
Working Memory	108.1	16.3	89.5	15.7	12.33	354.2	1.84×10^{-26}
Processing Speed	105.5	12.8	76.7	11.7	18.7	265.4	5.65×10^{-61}
Subtests							
Vocabulary	10.9	4	7.2	3.8	8.55	288.5	2.31×10^{-15}
Similarities	12	2.8	8.2	3.0	8.41	282.9	1.43×10^{-17}
Information	11.3	2.1	8.0	2.8	6.12	300.3	4.18×10^{-11}
Comprehension	13.5	3.1	8.5	3.2	14.16	245.9	3.11×10^{-32}
Arithmetic	12.8	2.7	7.8	2.3	10.91	346	4.21×10^{-29}
Digit Span	10.6	2.5	9.1	2.2	8.24	317.2	5.22×10^{-9}
Letter-Number Sequencing	10.1	2.6	7.1	3.8	8.99	287.1	3.18×10^{-21}
Picture Arrangement	10.9	3.6	7.8	3.1	9.56	323.6	4.32×10^{-19}
Picture Completion	10.7	2.8	7.1	2.6	8.76	277.4	2.79×10^{-18}
Block Design	11.6	3.7	8.1	3.4	8.33	312.9	7.23×10^{-17}
Matrix Reasoning	11.9	2.7	7.4	2.5	11.53	266.9	6.55×10^{-25}
Digit Symbol Coding	12.1	2.4	6.9	2.2	16.87	351.3	3.17×10^{-60}
Symbol Search	10.9	2.6	5.2	3.0	18.2	319.4	8.12×10^{-51}

d.f., distribution function.

Table 3. The MMSE scores of LA patients.

	Male (n = 65)				Female (n = 40)				P value
	cases	MMSE score (≤ 23)			cases	MMSE score (≤ 23)			
		No	%	Mean ± S.D.		No	%	Mean ± S.D.	
Age group									
30-39	6	0	0	26.9 ± 3.3	4	0	0	27.0 ± 3.4	0.38
40-49	8	4	50	23.9 ± 4.8	6	3	50	22.2 ± 3.1	0.87
50-59	28	18	64	23.8 ± 4.3	17	10	60	21.9 ± 2.2	0.18
60-69	12	8	67	21.3 ± 3.1	8	6	75	23.3 ± 3.5	0.08
70-	11	8	73	20.6 ± 2.4	5	3	60	21.5 ± 3.1	0.21
Education level (years)									
≥ 9	16	8	50	26.0 ± 2.7	10	5	50	25.8 ± 2.3	0.92
5-8	32	18	56	22.3 ± 2.7	17	10	56	21.9 ± 3.0	0.88
≤ 4	17	10	56	20.2 ± 1.6	13	7	54	21.0 ± 2.1	0.67

Mini-Mental State Examination (MMSE) was performed according to a previous report (Schweizer et al. 2012). It is often considered that there is significant cognitive dysfunction if MMSE ≤ 23.

CDR scale is widely accepted as a staging measure for dementia. Previous reports identify and provide item parameters for the CDR that can be used for greater precision when estimating dementia severity. The aim of the study was to test CAS reliability and control LA better using the standard dementia assessments. WAIS-RC has been used for the study of cognitive functions and neuropsychiatric symptoms of some brain diseases. Here, the

Table 4. The MMSE scores of healthy subjects.

	Male (n = 117)				Female (n = 89)				P value
	cases	MMSE score (≥ 28)			cases	MMSE score (≥ 28)			
		No	%	Mean ± S.D.		No	%	Mean ± S.D.	
Age group									
30-39	11	8	73	30.8 ± 2.6	7	5	70	30.2 ± 2.9	0.78
40-49	15	9	60	28.2 ± 4.8	10	7	70	28.1 ± 3.3	0.83
50-59	53	25	47	27.2 ± 5.0	44	25	57	27.4 ± 3.1	0.91
60-69	22	11	50	25.9 ± 4.3	19	7	37	26.9 ± 3.5	0.18
70-	16	7	44	24.1 ± 2.4	9	4	44	25.0 ± 2.3	0.32
Education level (years)									
≥ 9	29	21	73	30.1 ± 3.2	11	8	70	29.6 ± 2.1	0.67
5-8	68	39	58	28. 5 ± 2.9	25	15	60	28.8 ± 3.6	0.87
≤ 4	20	10	50	25.3 ± 2.3	53	25	47	25.1 ± 3.5	0.61

MMSE was performed according to a previous report (Schweizer et al. 2012). It is often considered that there is normal cognitive function if MMSE ≥ 28.

Table 5. CAS treatment improves cognitive impairment of LA patients.

	Healthy subjects (n = 206)	LA patients (n = 105)			
		Before CAS	One-month CAS	Six-month CAS	Twelve-month CAS
MMSE scores	28.67 ± 4.72	22.75 ± 4.68[a]	23.97 ± 4.66	24.56 ± 3.22[c]	25.99 ± 3.37[c]
CDR scale					
CDR 0	206	0	2	4	5
CDR 0.5	0	55	60	65	70
CDR 1	0	30	25	25	20
CDR 2+	0	20	18	11	10
Full Scale IQ	103.7 ± 13.8	80.7 ± 12.9[a]	82.3 ± 11.5	86.5 ± 13.1[b]	91.1 ± 13.5[c]
Verbal IQ	106.4 ± 16.2	91.1 ± 17.2[a]	93.4 ± 16.0	95.2 ± 17.8[b]	97.3 ± 18.0[c]
Performance IQ	108.1 ± 13.5	81.0 ± 4.4[a]	83.0 ± 2.4	88.0 ± 3.8[b]	95.0 ± 5.2[c]
Indices					
Verbal Comprehension	107.6 ± 11.2	95.7 ± 13.1[a]	97.8 ± 12.5	99.2 ± 13.5[b]	102.3 ± 13.1[c]
Perceptual Organization	102.5 ± 11.8	83.4 ± 14.2[a]	85.1 ± 13.6	87.9 ± 15.1[b]	93.4 ± 15.7[c]
Working Memory	108.1 ± 16.3	89.5 ± 15.7[a]	91.2 ± 14.4	92.2 ± 16.1[b]	94.4 ± 14.9[c]
Processing Speed	105.5 ± 12.8	76.7 ± 11.7[a]	78.3 ± 13.1	80.1 ± 12.5[b]	88.9 ± 15.1[c]
Subtests					
Vocabulary	10.9 ± 4	7.2 ± 3.8[a]	8.1 ± 2.9	8.8 ± 3.5[b]	9.2 ± 3.1[c]
Similarities	12 ± 2.8	8.2 ± 3.0[a]	8.6 ± 2.0	9.2 ± 3.2[b]	9.9 ± 2.7[c]
Information	11.3 ± 2.1	8.0 ± 2.8[a]	8.9 ± 1.9	9.3 ± 2.4[c]	9.7 ± 2.9[c]
Comprehension	13.5 ± 3.1	8.5 ± 3.2[a]	9.0 ± 2.2	9.2 ± 3.4[b]	9.8 ± 3.6[c]
Arithmetic	12.8 ± 2.7	7.8 ± 2.3[a]	8.4 ± 2.5	8.8 ± 2.0[b]	9.5 ± 2.4[c]
Digit Span	10.6 ± 2.5	9.1 ± 2.2[a]	9.3 ± 2.1	9.5 ± 2.7[b]	9.7 ± 2.4[c]
Letter-Number Sequencing	10.1 ± 2.6	7.1 ± 3.8[a]	7.9 ± 2.7	8.4 ± 3.3[b]	9.1 ± 3.5[c]
Picture Arrangement	10.9 ± 3.6	7.8 ± 3.1[a]	8.3 ± 2.8	8.8 ± 3.2[b]	9.4 ± 3.6[c]
Picture Completion	10.7 ± 2.8	7.1 ± 2.6[a]	7.8 ± 2.3	8.6 ± 2.8[b]	9.1 ± 2.4[c]
Block Design	11.6 ± 3.7	8.1 ± 3.4[a]	8.9 ± 3.1[b]	9.1 ± 2.9[b]	9.6 ± 3.7[c]
Matrix Reasoning	11.9 ± 2.7	7.4 ± 2.5[a]	8.0 ± 2.3	8.4 ± 2.6[b]	9.2 ± 2.1[c]
Digit Symbol Coding	12.1 ± 2.4	6.9 ± 2.2[a]	7.4 ± 2.1	7.8 ± 2.7[b]	8.9 ± 2.8[c]
Symbol Search	10.9 ± 2.6	5.2 ± 3.0[a]	5.8 ± 3.2	6.2 ± 3.1[b]	7.2 ± 3.7[c]

[a]$P < 0.01$ vs. controls; [b]$P < 0.05$ and [c]$P < 0.01$ vs. before the CAS.

techniques were used for the examination of cognitive impairment of LA patients. From the decline of CDR scale and increase of 13 subtests of WAIS-RC (Table 5), CAS can ameliorate the cognitive impairment of LA patients ($P < 0.05$).

An important strength of this study was the assessment of patients for LA by chart review. Evaluation of the diagnostic accuracy of the MMSE scores against these data provides the most robust evidence of its validity. Additional strengths of this study include the test of CDR scale and relatively large sample size. However, the results of our study cannot be generalized to all patients with LA, but only to the subgroup of the patients with lacunar stroke associated with carotid stenosis greater than 70%. In fact, most of the enrolled patients are not associated with severe stenosis or carotid occlusion. On the other hand, some patients might have been misclassified because not all cases were independently reviewed. However, we consider any underestimation to be slight because physicians accessed to all documentation including the patient's medical record. The comparative group included 206 individuals for statistical and practical reasons. Practically it was more difficult to recruit the LA individuals and retain them in the follow-up. They had no reason to return to our hospital, as they had no ailment or need for medication. Secondly, these individuals with normal neurological activity, as a group, exhibited less variability on the outcome measures.

Finally, the techniques of CAS have been widely used. However, understanding the key mechanisms resulting in cognitive impairment will help to limit the injury during the process of carotid revascularization (Ghogawala et al. 2008). For example, brain connectivity may provide a useful mechanism for the understanding (Cheng et al. 2012). Although CAS can reduce the risk of stroke, its neurocognitive effects are still unclear. Further comprehensive evaluation is necessary to determine the benefit of CAS interventions (Zhou et al. 2012).

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Conflict of Interest

The authors declare no conflict of interest.

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