

# Changes in Cognition and Hemodynamics 1 Year after Carotid Endarterectomy for Asymptomatic Stenosis

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## Abstract

**Objectives** The impact of a change in hemodynamics on cognitive skills in patients with asymptomatic carotid stenosis (ACS) after carotid endarterectomy (CEA) remains unclear. The aim of this study was to evaluate the results of CEA for ACS at 1 year by assessing the changes in anterior, middle, and posterior cerebral artery blood flow in tandem with changes in cognitive efficiency.

**Methods** Flow volume in cerebral arteries using quantitative magnetic resonance angiography was measured in a group of 14 males and 5 females before and at 1 year after CEA for ACS. Cognitive efficiency was assessed by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The values of flow volume were processed using simple ratio (SR) and were used for covariance analyses with changes in cognitive skills after CEA.

**Results** A significant improvement in cognitive efficiency indexes of immediate memory and visuospatial perception at 1 year after CEA for ACS was observed. Simultaneously, a significant deterioration of speech index was noted. During the analysis of association between flow and cognition, the highest correlation could be

## Keywords

- ▶ carotid endarterectomy
- ▶ carotid stenosis
- ▶ cognitive dissonance
- ▶ quantitative magnetic resonance angiography

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seen between the middle cerebral artery (MCA) flow and the visuospatial perception. A change in posterior cerebral artery (PCA) flow was associated with an increase in immediate memory index and anterior cerebral artery (ACA) flow change with the speech index.

**Conclusion** Convergence of data supporting the association between revascularization and cognitive improvement were added in a small, single-center cohort of ACS patients undergoing CEA. No significant differences in cognition were seen between preoperative findings and at 1 year after CEA. Visuospatial perception improvement was linked to flow change in MCA, immediate memory improvement to flow change in PCA, and speech index change to flow change in ACA. Methodical limitations of this small study preclude formulating larger generalizations. Hemodynamic factors in CEA should be assessed in a larger-scale study.

## Introduction

Asymptomatic carotid stenosis (ACS) is a risk factor of acute ischemic stroke (AIS).<sup>1,2</sup> In view of this, several large trials have examined the role of carotid endarterectomy (CEA) in primary stroke prevention. The Asymptomatic Carotid Artery Surgery Trial (ACST-1) found that a successful CEA in asymptomatic patients reduces the 10-year stroke risk,<sup>3</sup> while the currently enrolling ACST-2 has established an acceptable overall serious event rate of periprocedural disabling stroke and death at 30 days of 1.0%.<sup>4</sup> Carotid artery stenting (CAS) in ACS also reduces stroke risk; however, in a meta-analysis of five trials, CAS was associated with a higher risk of periprocedural stroke than the ACST-2 rate (2.6 vs. 1.3%, respectively;  $p = 0.04$ ).<sup>5</sup>

Despite the demonstrated reduction in stroke risk, as advances in optimal medical therapy (OMT) are being made, the role of any intervention in the primary prevention of stroke is a matter of an ongoing debate.<sup>2,4,6,7</sup> An additional factor gaining consideration is the potential to improve cognitive efficiency in asymptomatic patients with hemodynamic compromise.

Cognitive impairment is often described as a stepwise or progressive disease resulting from accumulated ischemic injury. It is not clear whether reduced cerebral blood flow in asymptomatic patients with high-grade carotid artery stenosis or occlusion has any influence on cognition.<sup>7-10</sup> The presence of unstable plaque, the degree of carotid stenosis, and the presence of brain microemboli all appear to represent minor risk factors of cognitive worsening in ACS patients.<sup>11</sup>

Cognitive outcome after CEA for ACS or flow augmentation using cerebral bypass for carotid artery occlusion is likely influenced by numerous factors.<sup>8,9,12-15</sup> Among these are sequelae of periprocedural embolization, possible periprocedural brain hypoperfusion in the setting of poor collateralisation,<sup>12</sup> elimination of the source of embolism from a plaque, and flow augmentation distal to endarterectomy site in the case of CEA.<sup>13,14</sup> Jussen et al<sup>15</sup> studied the hemodynamics of chronic occlusive cerebrovascular disease and observed that the cerebral cortex is able to reversibly reduce the reaction capacity of neuronal populations under the conditions of severe hemodynamic stress. At the same

time, they showed that brain revascularization by means of bypass surgery helps improve a specific motor function of neurons,<sup>15</sup> suggesting that restoration of blood flow reverses the neuronal effects of severe hemodynamic stress. Based on these results, further elucidation of the relationship between hemodynamics and cognitive efficiency is needed.

Quantitative magnetic resonance angiography (qMRA) is a special imaging technique that combines time-of-flight (TOF) MRA and 2D cine phase-contrast magnetic resonance imaging (MRI) to measure blood flow (in mL/min) in cervical and intracranial arteries. The technique was validated on a phantom and its clinical significance in assessment of vertebrobasilar pathology was established as well.<sup>16,17</sup> The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) neuropsychological battery is suitable for clinical practice in patients with extracranial atherosclerosis and has been used in other studies of cognitive deficit in CEA.<sup>14,18</sup> RBANS focuses on five cognitive domains: immediate memory, visuospatial/constructional, language, attention, and delayed memory. The applicability of both qMRA and the RBANS was tested in the pilot study.<sup>19</sup>

The aim of the present study was to evaluate cerebral hemodynamics with qMRA and cognitive efficiency with RBANS before and at 1 year after CEA for ACS.

## Methods

The study protocol was approved by the institutional ethical committee under the registration number 1/13. Participation in a study was offered to patients with ACS with best medical therapy and indicated for CEA during the period from March to October 2013.

### Inclusion Criteria

The inclusion criteria for the study were the following:

- Internal carotid artery (ICA) stenosis ( $\geq 60\%$ ) detected by ultrasound imaging, assessed according to the North American Symptomatic Carotid Endarterectomy Trial criteria and indicated for CEA, and confirmation of the presence of stenosis and ruling out of a high-riding bifurcation by CT angiography.

- Ability to undergo qMRA examination (absence of implanted stimulators, absence of any type of arrhythmia—patients with periprocedural arrhythmia due to paroxysmal atrial fibrillation were excluded).
- informed consent with psychological examination, and ability and willingness to undergo a psychological examination.

### Exclusion Criteria

The exclusion criteria for the study were the following:

- Stenosis of the first segment of MCA or ACA or stenosis of the second or third segment of PCA  $\geq 60\%$  confirmed by CT angiography.
- Confirmation of any stroke by MRI (diffusion-weighted imaging [DWI]/fluid-attenuated inversion recovery [FLAIR] sequences).
- Any symptomatology in the carotid distribution on the side indicated for CEA  $<6$  months prior to surgery.
- History of dementia, depression, and other conditions limiting the examination of cognition.

### Carotid Endarterectomy

Institutional protocol of CEA in ACS was described in 2011.<sup>20</sup> The indication for CEA was based on any ACS progression demonstrated by two consecutive ultrasonography examinations or presence of high-risk plaque, also demonstrated by ultrasonography. All surgeries were performed without temporary discontinuation of antiplatelet therapy (monotherapy by acetylsalicylic acid or by clopidogrel). CEA was performed under total intravenous anesthesia (TIVA). An intraluminal shunt was used selectively in cases of unilateral 50% decrease in amplitude of somatosensory evoked potentials (SSEPs) of the contralateral median nerve compared with the ipsilateral.<sup>21–24</sup> Clips were applied to the superior thyroid and external carotid arteries after minimizing the risk of peripheral embolization by intraoperative heparinization. Common carotid artery was clamped afterward. Only then was the ICA finally dissected. After the endarterectomy, the internal carotid clip was released temporarily to flush out potential emboli. After completion of the arterial suture, the external carotid clip was removed as the first one, followed by the common carotid clip. After the next 20 seconds, the internal carotid clip was released as the last one. All surgeries were performed by two surgeons according to this philosophy (J.F. and M.B.). Each patient was observed for 1 day postoperatively in the intensive care unit. Patients without complications were discharged 3 to 7 days after surgery.

### Flow Quantification in Cerebral Arteries

The 1.5-T Achieva (Philips Medical System, The Netherlands) MRI scanner was used for imaging. Any silent stroke was ruled out using initial FLAIR sequence. Data on arterial flow (mL/min) were obtained using qMRA (NOVA, VasSol, River Forest, Illinois, United States). A TOF MRA of intracranial and cervical arteries was used to reconstruct the 3D surface-rendered vessel images. After determining the optimal perpendicular scan plane and setting the baseline coordinates, a

retrospectively gated, fast 2D phase-contrast sequence was performed. Velocity encoding was automatically adjusted by the software and validated by a radiologist. Blood flow volumes in each individual arterial segment were calculated and recorded in the database system and evaluated by a physician blinded to the outcomes of the neuropsychological screening (J.F. and P.K.). Cerebral flow evaluations were performed on days 1 till 4 before surgery and on days 354 till 372 after surgery.

### Neuropsychological Examination

The RBANS test battery was used to examine cognitive efficiency.<sup>18,19</sup> Five RBANS cognitive indexes used as main indicators of mental functions are shown in **Table 1**. Preoperative neuropsychological battery testing was performed standardly 1 day before surgery and independently from MRI investigation. Postoperative testing was performed on the same day as the MRI flow evaluation, that is, on days 354 till 372 after surgery. Both neuropsychological examinations took place in a quiet and calm environment to ensure maximal patient comfort and prevent any additive preoperative stress load.

### Data Management and Statistical Evaluation

The crude score obtained from RBANS subtests was converted to an index score of individual cognitive skills according to age values and then assigned to flow volume values of corresponding patients. Considering the characteristics of the studied group, the nonparametric Wilcoxon signed-rank test was used for cognitive difference comparison before and at 1 year after the surgery.

The simple ratio (SR; ipsilateral flow volume/contralateral artery flow volume) of the selected intracerebral arteries was

**Table 1** Description of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) indexes

Immediate memory	Indicates the examinee's ability to remember information immediately after it is presented
Visuospatial/constructural	Indicates the examinee's ability to perceive spatial relations and to construct a spatially accurate copy of a drawing
Language	Indicates the examinee's ability to respond verbally to either naming or retrieving learned material
Attention	Indicates the examinee's ability to remember and manipulate both visually and orally presented information in short-term memory storage
Delayed memory	Indicates the examinee's anterograde memory capacity
Total scale	A total score that is calculated by summing the above five index scores

Source: RBANS manual.<sup>18</sup>

used to estimate the change in flow on the operated side. Absolute flow levels may vary over time as well. SR allows us to compare the changes in flow volumes in individual cerebral territories over time in repeated measurements. This ratio was employed by Ghogawala et al<sup>13</sup> and Douglas et al<sup>25</sup> in assessing the flow in the ICA. SR before and at 1 year after surgery for each artery was used for analysis of association with differences in individual cognitive skills using Spearman's correlation coefficient. Individual differences in laterality in the tested group were not taken into account due to a small study group size.

## Results

Five females and 14 males of an average age of 67.84 (48–80) years with ACS with no detectable ischemic lesion on MRI undergoing CEA participated in the study. In two patients, intraoperative SSEP amplitude drop under 50% occurred and the intraluminal shunt had to be inserted. One patient had postoperative signs of manipulation paresis of the marginal mandibular branch of the facial nerve with complete spontaneous recovery at 6 months. Another patient required temporary hospitalization in the postoperative intensive care unit due to exacerbation of chronic obstructive pulmonary disease.

At the 1-year follow-up, no mortality, stroke, or neurodegenerative disease that could influence cognitive efficiency was observed. No new ischemic lesions were observed on MRI as part of qMRA NOVA evaluation.

Change of cognitive skills at 1 year after surgery is summarized in ►Table 2 and change of flow in ►Table 3.

There was no statistically significant difference in total cognitive efficiency score before and after CEA. Postoperative improvement in the individual subtests of cognitive skills was observed in indexes of immediate memory ( $p = 0.02$ ) and visuospatial perception ( $p < 0.01$ ). Simultaneously, however, a significant worsening of speech index was recorded ( $p < 0.01$ ). Results are shown in ►Table 2.

Relationship of SR and RBANS cognitive performance changes before and after surgery is showed in ►Table 4. Postoperative increase of flow in the PCA ( $p = 0.03$ ) territory was associated with total RBANS score improvement. Analysis of cognitive indexes revealed the strongest correlation of blood flow in the MCA territory and visuospatial

skills ( $p = 0.01$ ). Change in blood flow in the PCA territory was associated with an increase in the index of immediate memory ( $p = 0.05$ ) and change in flow in the ACA territory with the index of speech ( $p = 0.03$ ). Unfortunately, hemispheric differences of the patients and laterality were not taken into account due to a small study group size. Therefore, the values of cognitive indexes of the visuospatial and immediate memory may differ between the CEA patients operated on the dominant versus the nondominant side.

## Discussion

In this study, preoperative cognitive skills of ACS patients were significantly reduced in RBANS battery (the lowest 10% of the population).<sup>18</sup> Values detected 1 year after the surgery are equal to or better than the lowest 14% of the population results report.<sup>18</sup> Despite this, no statistically significant difference can be seen in the overall cognition improvement observed in this group at 12 months after CEA. Cognitive skills analysis at 1 year after CEA showed improvement in the immediate memory and the visuospatial perception, and a change in language index. The improvement of the immediate memory index after CEA was also described by Takaiwa et al<sup>26</sup> and Kougiyas et al.<sup>27</sup> Improvement of the immediate memory and visuospatial perception in a group of symptomatic patients at 3 months after surgery was also described by Turk et al.<sup>28</sup> The results are in congruence with conclusions of metastudies identifying the influence of CEA on language and memory functions.<sup>13,29</sup>

Meta-analysis of 18 studies dealing with cognitive efficiency in both asymptomatic and symptomatic carotid stenosis in patients treated conservatively established a relationship between the diagnosis and cognitive deterioration in 14 of the studies.<sup>29</sup> Absence of a quality carotid model could be the reason for insufficient knowledge of the mechanism by which the cognitive deterioration manifests itself in ACS patients. Unstable plaque, degree of stenosis, least luminal diameter, plaque area, plaque echo lucency, and microembolization do not seem to have as much impact on cognitive impairment as the hemodynamic changes due to ACS.<sup>14</sup> Reductions of 40 to 50% in cerebral blood flow are sufficient to cause ischemic cell injury.<sup>12</sup> The characterization of the limit at which there is inadequate perfusion to

**Table 2** Cognitive skills before and at 1 year after surgery

Test RBANS	Preoperative mean (SD)	Postoperative mean (SD)	Z score	p value <sup>a</sup>
Total score	81.72 (10.85)	84.39 (7.91)	-1.04	0.30
Immediate memory	87.94 (13.07)	96.06 (12.80)	-2.33	0.02
Visuospatial/constructional	76.17 (9.2)	81.95 (15.91)	-3.59	0.01
Language	94.78 (7.98)	88.89 (7.95)	-2.45	0.01
Attention	82.28 (16.89)	82.17 (14.98)	-1.06	0.29
Delayed memory	88.72 (15.20)	93.11 (12.06)	-0.81	0.42

Abbreviation: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation.

<sup>a</sup>Wilcoxon signed-rank test.

**Table 3** SR indexes (ipsilateral/contralateral artery flow) before and at 1 year after CEA

Patient age and gender	ICA		MCA		ACA		ACA2		PCA	
	Pre-ICAr	Post-ICAr	Pre-MCAr	Post-MCAr	Pre-ACAr	Post-ACAr	Pre-ACA2r	Post-ACA2r	Pre-PCAr	Post-PCAr
67 M	–	–	0.73	0.76	–	–	0.85	1.37	1.51	0.89
74 M	–	–	1.73	–1.54	3.77	6.23	1.84	0.55	0.40	0.62
66 M	0.92	0.85	0.97	0.91	0.44	0.60	2.82	1.10	0.71	0.85
63 F	0.06	0.54	0.98	0.94	–	–	1.00	1.05	1.10	1.08
48 F	0.23	1.48	1.31	1.06	–0.79	1.35	0.79	0.40	1.02	1.12
65 F	1.18	0.90	0.93	1.06	1.04	1.20	1.23	0.48	0.99	1.16
74 M	1.15	1.19	0.90	0.92	1.08	1.16	1.17	0.73	1.25	1.20
61 F	0.80	1.11	1.36	1.29	1.15	1.44	1.32	0.62	1.04	1.02
65 M	8.68	5.76	0.75	0.71	–	–	1.19	0.82	0.96	0.76
67 M	1.12	0.97	1.02	0.91	1.54	1.23	1.32	0.84	1.08	1.10
73 M	0.93	1.05	1.23	0.95	0.41	0.68	1.05	2.40	0.72	0.70
71 M	0.93	1.05	1.23	0.95	0.41	0.68	1.05	2.40	0.72	0.70
66 M	1.24	1.37	1.37	1.04	1.62	1.40	0.73	1.05	0.94	0.84
60 M	0.71	1.42	1.20	1.19	0.76	1.15	0.94	1.05	1.08	1.05
71 M	0.74	0.90	1.09	1.14	0.52	1.04	1.02	1.07	1.24	0.80
75 M	0.90	1.21	1.29	0.85	0.74	1.52	1.17	0.49	0.77	0.77
63 M	–	–	1.05	0.85	–	–	1.08	1.24	0.93	1.53
80 M	–	–	1.34	1.22	–	–	0.79	0.95	0.83	0.77
80 F	1.11	1.23	0.92	0.97	0.86	1.05	0.58	1.43	1.19	1.29

Abbreviations: ACA, anterior cerebral artery; CEA, carotid endarterectomy; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SR, simple ratio.

maintain cognition with no physical signs and symptoms has yet to be defined.<sup>12</sup>

Blood flow quantification in the individual arteries of the circle of Willis with the use of qMRA was performed at precisely defined locations. Vessel flow measurement at 1 year after CEA was performed at identical points. SR calculation allowed us to compare the changes in flow volumes in individual cerebral territories over time. The difference in RBANS battery results exhibits certain correlations with the change in brain hemodynamics. Specifically, there was a statistically significant relationship between the values of the SR of PCA flow and both the total score of RBANS cognitive tests and the immediate memory index. There was a negative correlation between the language index and the change in MCA territory flow. A positive correlation was spotted between the language index and the change in ACA territory flow. Despite the expected correlation with PCA flow, the improvement in visuospatial skills showed significant correlation values with MCA flow instead. Based on the knowledge of flow of individual vessel territories, results indicated a partial match between functional brain specialization and relevant blood flow changes. The evaluation of cognitive results and hemodynamics after CEA was also studied by Ghogawala et al using qMRA to compare ipsilateral and contralateral MCA/ICA flow ratios in unilateral carotid stenosis.<sup>14</sup> Saito et al used a similar comparative technique with MR spectroscopy.<sup>30</sup> He assessed the hemodynamic effect of CEA in relationship to the N-acetyl aspar-

tate-to-choline ratio, N-acetyl aspartate-to-creatinine ratio, and choline-to-creatinine ratio. Investigation of the association between cognition and hemodynamics is already a part of other ongoing randomized studies.<sup>9</sup> Due to the varying methods used, no adequate comparison between the results of the studies is possible.

Cognitive deterioration in a symptomatic patient can be attributed to a direct effect of a strategically localized region of ischemia. So far, no evidence of the presence of ACS having a direct influence on cognitive efficiency has been established. It can be steadily interpreted only as a mere marker of intracerebral or generalized atherosclerosis.<sup>29,31</sup> Some articles point out the possibility of cognitive deficit persistence after an uncomplicated CEA in patients  $\geq 68$  years when compared with a younger age group.<sup>15</sup> Even the role of laterality in cognitive efficiency after CEA could be taken into account with an assumption that blood flow augmentation is beneficial for cognitive functions of the ipsilateral, that is, the operated side, rather than for the contralateral hemisphere. Results of these studies show wide variability.<sup>32</sup> Data indicate that symptomatic patients with an ischemic lesion in the left hemisphere had better outcome in tests of visuospatial and visual memory than patients with right-sided infarcts.<sup>33</sup> Conversely, patients with right hemisphere symptoms had better score in the verbal memory test than patients with left-sided strokes. Simultaneously, a correlation of the laterality of the operated side with the speech index was observed.<sup>34</sup> In the study, at 12 months after CEA, the laterality and hemispheric differences could not

**Table 4** Change in cognitive skills and in flow before and at 1 year after surgery

		ICAd	MCAd	ACAd	ACA2d	PCAd
RBANS total scale	$r_s$	0.08	-0.47*	0.20	-0.02	0.45*
	$p$	0.40	0.02	0.26	0.46	0.03
Immediate memory	$r_s$	-0.07	-0.30	0.41	0.12	0.41*
	$p$	0.40	0.11	0.08	0.32	0.05
Visuospatial/constructional	$r_s$	0.29	-0.70**	0.26	0.24	0.23
	$p$	0.16	0.01	0.20	0.16	0.18
Language	$r_s$	-0.15	0.03	-0.55*	0.22	0.27
	$p$	0.30	0.45	0.03	0.19	0.14
Attention	$r_s$	0.12	0.06	-0.11	0.19	0.15
	$p$	0.34	0.40	0.36	0.22	0.27
Delayed memory	$r_s$	0.11	-0.25	0.44	-0.010	-0.13
	$p$	0.35	0.16	0.07	0.36	0.30

Abbreviation: RBANS., Repeatable Battery for the Assessment of Neuropsychological Status.

\* $p < 0.01$ .

\*\* $p < 0.05$ .

be taken into account. A larger sample size study is warranted to include the laterality factor. An ongoing randomized study evaluates hemodynamics in ACS with MR perfusion imaging and its impact on cognition.<sup>7</sup>

### Limits of the Study

A small homogenous group of strictly selected ACS patients with the exclusion of dementia or an ischemic lesion on MRI underwent CEA at a center with an experience of over 2,000 CEAs with no serious neurologic sequelae at 1 year after surgery. The participation of asymptomatic patients eliminates many intervening factors of cognitive state; however, the patient group size and patient selection remain a significant limitation of the study, which precludes sufficient generalization. Due to a small study group size, no statistical correction for multiple analyses could be used. For the same reason, the laterality and hemispheric differences could not be taken into account. Vascular profile, comorbidities, and side not being taken into account in tested subjects represent another limitation of this study.<sup>11,13</sup>

### Conclusion

Previous studies investigating the effect of CEA on cognitive performance did not use qMRA for selected intracerebral arteries. This study shares the finding that the visuospatial perception skills are linked to flow changes in MCA, while the immediate memory improvement is associated with flow changes in PCA. Methodical limitations of this study preclude formulating wider generalizations. A larger qMRA study is desirable to evaluate hemodynamics and cognition in ACS patients.

#### Conflict of Interest

None declared.

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