THE STATE OF COGNITIVE FUNCTIONS AFTER ANGIORECONSTRUCTIVE OPERATIONS ON THE CAROTID ARTERIES

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Carotid artery stenosis is a risk factor for ischemic stroke. Surgical treatment is often used to improve cerebral perfusion and prevent the development of cerebrovascular pathology and related cognitive impairment. The aim of this prospective pilot study was to evaluate the cognitive functions (CF) of patients after surgery (open or endovascular intervention) on the internal carotid artery. The study included 90 patients (mean age 62 years, 71% of men) with atherosclerotic lesions of the carotid arteries. The CF was evaluated at four time points (before the intervention, 3, 6, and 9 months after) using cognitive scales and measuring cognitive evoked potentials. The state of the brain substance before and after the intervention was evaluated by the results of diffusion-weighted magnetic resonance imaging (DW-MRI). Three and six months after the operation, the patients demonstrated minor and varied CF alterations by the MMSE scale, but by the end of the observation period (9 months) the participants had their CF at the level close to that registered before the operation ($p = 0.43$). Thus, the intervention-associated changes in CF, regardless of the surgical approach, were primarily transient in nature. The rare cases of CF deterioration, as registered by the postoperative DW-MRI scans, were linked to the acute brain ischemia, both symptomatic and asymptomatic, and a perioperative stroke (1 case). Advanced age and altered cerebral arteries may be listed as the risk factors for the probable CF deterioration. Evaluation of the connections between CF alterations and multiple cases of intraoperative cerebral vascular embolism requires a longer observation period.

Keywords: carotid artery, stenosis, stent, endarterectomy, emboli, cognitive function, analysis of variance

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Compliance with ethical standards: the study was approved by the Research Center of Neurology Ethics Committee (protocol № 11/14 of November 19, 2014). All patients or their legally authorized representatives have signed the informed consent for surgery; the study followed the ethical principles of the Declaration of Helsinki (1975).

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СОСТОЯНИЕ КОГНИТИВНЫХ ФУНКЦИЙ ПОСЛЕ АНГИОРЕКОНСТРУКТИВНЫХ ОПЕРАЦИЙ НА СОННЫХ АРТЕРИЯХ

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Атеросклероз сонных артерий является фактором риска ишемического инсульта. Для улучшения мозговой перфузии и предотвращения развития цереброваскулярной патологии и связанных с ней когнитивных нарушений нередко используют хирургическое лечение. Целью данного проспективного поискового исследования было оценить когнитивные функции (КФ) пациентов после операции (открытого или эндоваскулярного вмешательства) на внутренней сонной артерии. В исследование было включено 90 пациентов (средний возраст — 62 года, 71% мужчин) с атеросклеротическим поражением сонных артерий. КФ оценивали в четырех временных точках (до вмешательства, через 3, 6 и 9 месяцев после него) с использованием когнитивных шкал и измерением когнитивных вызванных потенциалов. Состояние вещества головного мозга до и после вмешательства оценивали по результатам диффузионно-взвешенной магнитно-резонансной томографии (ДВ-МРТ). Через 3 и 6 месяцев после операции у пациентов наблюдали небольшие разнонаправленные изменения КФ (по шкале MMSE), но к концу срока наблюдения (9 месяцам) распределение оценок КФ у пациентов приблизилось к дооперационному ($p = 0{,}43$). Таким образом, ассоциированные с вмешательством (независимо от его вида) изменения КФ носили преимущественно транзиторный характер. Единичные случаи ухудшения (по данным ДВ-МРТ после операции) КФ были ассоциированы с острыми очагами ишемии (как симптомными, так и бессимптомными) в веществе мозга, а также с периоперационным инсультом (1 случай). К факторам риска неблагоприятного прогноза для КФ можно отнести: пожилой возраст и изменения в церебральных артериях. Для оценки связи КФ с множественными интраоперационными эмболиями сосудов мозга требуется более длительное наблюдение.

Ключевые слова: сонная артерия, стеноз, стент, эндартерэктомия, эмболия, когнитивные функции, дисперсионный анализ

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Vascular diseases are some of the leading causes of mortality and permanent disability, which makes their prevention and treatment an extremely urgent task from both medical and social viewpoints [1]. Average life expectancy is growing, as does the number of diagnosed vascular diseases and cognitive disorders associated with them. These factors call for further investigation of cerebrovascular pathology.

Cognitive dysfunction hinders social adaptation of the patients. It degrades their quality of life and, moreover, does the same to their ability to control the core disease and its comorbidities: arterial hypertension, atherosclerosis, diabetes mellitus.

The most important cause of the ischemic stroke is atherosclerotic stenosis of brachiocephalic arteries (BCA) and the internal carotid artery (ICA) in particular. The atherothrombotic subtype cerebral circulation failures cause over 30% of ischemic strokes, and up to 80% of them occur in the absence of preceding symptoms, which underlines the importance of thorough examination of atherosclerosis patients.

Embolism and cerebral hypoperfusion are the two major mechanisms distinguished in the pathogenesis of cognitive impairment (CI) associated with an ICA atherosclerosis [2]. Regardless of the presence or absence of signs of white matter lesions on the MRI scans, ICA stenosis is an independent marker of CI. A study that recruited over 4000 patients with asymptomatic ICA stenosis revealed CI in the group that had the disease in the pronounced form [3]. There is evidence of direct correlation between ICA intima-media thickness, which is the earliest atherosclerosis marker, and lower neuropsychological testing scores [4].

The current medical care doctrine prescribes shifting the focus from disease treatment to active health preservation pursued by each individual. In this context, guaranteeing adequate perfusion of the brain is the key preventive measure against development of a cerebrovascular pathology and CI.

Alongside antithrombotic therapy, surgery offers effective ways to normalize cerebral circulation. The methods are carotid endarterectomy (CEE) and transluminal balloon angioplasty with carotid artery stenting (CAS) [5–8]. Vascular bed correction undoubtedly improves cerebral circulation on the whole; however, with accumulation of practical clinical experience, some drawbacks peculiar to the surgery techniques were revealed. One of such drawbacks is the risk of intraoperative embolism and hemodynamic instability (up to a stagnation) and subsequent development of cerebral ischemia [9]. According to a randomized CREST study, the incidence of perioperative stroke after CEE and CAS was 2.3 and 4.1%, respectively [10]. DW-MRI scans reveal acute ischemia foci (AIF) in 21% of patients that underwent open surgery and 50% of those who had an endovascular intervention [11].

What links carotid revascularization and cognitive functions (CF) is still not entirely clear due to the large number of factors: 1) patients heterogeneity in stenosis clinical manifestations, localization and severity, initial status of cerebral perfusion, time between appearance of the symptoms and revascularization [12]; 2) types of neuropsychological tests used and timing of such assessments; 3) variability of surgical techniques and postoperative changes classification criteria [13]. In this study we aimed to identify and evaluate cognitive changes in surgery patients that had their ICA atherosclerosis operated on.

METHODS

The study included 90 patients (64 male and 26 female, age 47–83 years, average age 61 years) who were observed at the Department of General Angioneurology of the Research Center of Neurology (Moscow). The inclusion criteria were: any gender; an active chronic ischemic cerebrovascular disease (discirculatory encephalopathy, stage 1 or 2); ICA surgery performed from May 2015 to December 2018 at the Department of Vascular and Endovascular Surgery (27 patients underwent carotid endarterectomy (CEE), 63 patients underwent carotid angioplasty with stenting). The exclusion criteria were: a pronounced cardiac and somatic pathology; severe stroke; mental disorders; hemianopsia as a result of posterior cerebral artery circulation disorders; pronounced CI (MMSE score < 24 points) making neuropsychological testing impossible.

The carotid artery atherosclerosis diagnosis was confirmed with the help of the Viamo ultrasound examination system (Toshiba; Japan); we applied the NASCET (North American Symptomatic Carotid Endarterectomy Trial) examination algorithm [14].

All patients had their cognitive status assessed before surgery and 3, 6, and 9 months afterwards. We used the following CF assessment tools and methods: MMSE (Mini-Mental State Examination) [15]; 10 word memory trial, frontal assessment battery (FAB), clock-drawing test, digit span test (subtest of Wechsler Adult Intelligence Scale and Wechsler Memory Scales), conceptualization test, Schulte table and dynamic praxis [16]. The CF assessment tools and methods were selected based on their functional compatibility with the cognitive evoked potentials (CEP) examination.

We used the Neuro-MVP (Neurosoft; Russia) device and relied on the P300 wave to examine CEP; the results of the examination allowed objectification of changes in the participants' CF. 25 healthy individuals of the appropriate age provided baseline P300 potential data. We measured the P300 amplitude from the previous negative peak to the P300 peak.

Considering selection of the surgical treatment method, patients that had CEE contraindications according to the SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) [17] trial results and CAS indications according to the CREST [10] trial underwent endovascular surgery. Twenty-four hours after open or endovascular surgery, we initiated neurological examination that implied deficit assessment using the National Institutes of Health (NIH) stroke scale [18].

DW-MRI scans were used to evaluate the condition of the brain substance before and 24 hours after the intervention. We used a Siemens Magnetom Symphony 1.5T MRI system (1.5 Tesla magnet) to obtain the scans. The foci were predominantly small, therefore we relied on the diffusion-weighted scan images (b1000 diffusion coefficient) to assess damage to the brain substance [19].

At least 5 days before the surgery all patients received corrective antithrombotic, hypolipidemic, antihypertensive and antianginal therapy. After the surgery, all patients received basic drug therapy (antithrombotic, antihypertensive and lipid-lowering drugs). No nootropic drugs were prescribed.

Statistical analysis was performed using repeated measures ANOVA and analysis of contingency tables.

RESULTS

All patients participating in the study were diagnosed with arterial hypertension; every second patient exhibited two or more risk factors for vascular diseases. Sixty (67%) patients had cerebral circulation disturbances (ischemic) registered in their medical histories. Having analyzed the initial data, we learned that 33% of the patients scored 28-30 points on the MMSE scale, which indicates normal cognition, and 67% scored 25–27 points, which signals of mild CI. Analysis of the CF dynamics (MMSE scale) 3, 6 and 9 months after surgery revealed no notable deterioration: at 3 and 6 months, we detected multidirectional changes in CF (greater variety of scores, isolated cases of pronounced CF alterations), but at the 9-month time point, when the observation period ended, the said changes practically disappeared and all patients scored close to the pre-surgery values, the difference between pre- and post-surgery scores being insignificant ($p = 0.43$) (Fig. 1, 2). Thus, the post-surgery CF changes registered were primarily transient in nature.

Additional neuropsychological testing revealed baseline moderate impairments of verbal thinking, attention and short-term memory in some patients (Table 1). The development of CI was associated with the severity of BCA atherosclerosis, advanced age, arterial hypertension, coronary heart disease, diabetes mellitus, previous cerebral circulation failures.

Thorough post-surgery examination of these patients revealed a perioperative stroke (embolism of the middle cerebral artery) on the intervention side in one patient: the neurological deficit reached 6 points on the NIH stroke scale; the stroke manifested itself in the form of motor disorders. Further observation of this patient and verbal thinking and speech fluency tests revealed semantic memory deterioration that persisted throughout the study.

Positive changes were mainly observed in such neurodynamic processes as attention, fluency, operative and short-term memory (Fig. 3).

We found no correlation between the type of surgery performed and CF scores of the examined patients. Throughout the entire observation period, some patients older than 60 years exhibited more pronounced CI. Most patients younger than 60 years (86%) had their CF changing positively (MMSE scores) by the 6th month of the observation; by the 9-month time point, we registered a growing share of patients whose attention and short-term scores returned to norm, which was further confirmed by the P300 peak amplitude changes ($p = 0.05$). Previous ischemic strokes had no detectable effect on the post-surgery CF alterations.

The analysis of DW-MRI scans taken shortly after surgery revealed asymptomatic AIF embolic origin visualizing in 30 (33%) patients. The detected brain substance alterations were predominantly localized in the cortex (16 (53%)) on the intervention side (22 (73%)); the spots measured up to 5 mm. A separate analysis of DW-MRI scans and CEP data showed that the positive dynamics registered in patients without AIF at the 3- and 6-month time points and lack of such in patients with AIF allow considering the foci a factor preventing CF restoration post-surgery (Fig. 4).

Neuropsychological tests have also detected minor positive changes in the CF of patients without AIF 3, 6 and 9 months post-surgery.

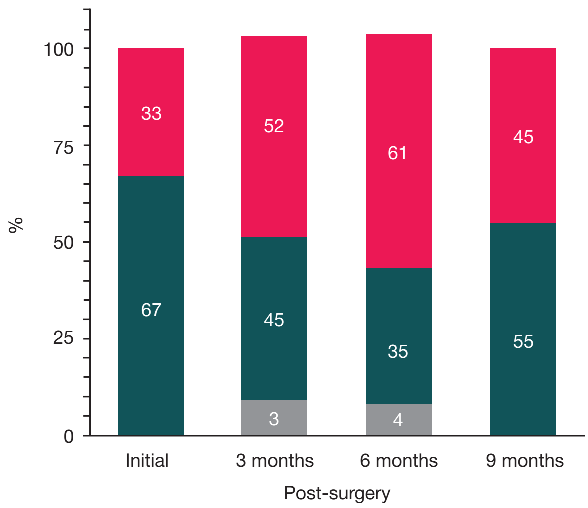

Fig. 1. Dynamics of the proportion of patients (Y axis, %) with different MMSE scores: no cognitive impairment (28–30 score) — upper fields, mild impairment (25–27 score) — middle fields, severe impairment (< 25 score) — two lower fields

Table 1. Patient CF assessment scores (based on screening tests)*

Neuropsychological tests	Screening tests			
	Before treatment	After 3 months	After 6 months	After 9 months
MMSE	27.1 ± 0.2	28.3 ± 0.1	28.2 ± 0.1	27.2 ± 0.1
FAB	13.1 ± 0.3	17.4 ± 0.1	18.1 ± 0.2	18.7 ± 0.3
Schulte table	57.3 ± 8.5	53.4 ± 13.1	47.7 ± 9.6	46.2 ± 10.3
Digit span test (direct)	5.1 ± 1.1	5.9 ± 1.1	6.1 ± 1.1	6.5 ± 1.2
Digit span test (reverse)	2.5 ± 1.1	3.7 ± 1.0	3.8 ± 1.1	3.8 ± 1.1
Dynamic praxis	1.6 ± 0.6	2.1 ± 0.7	2.2 ± 0.8	2.3 ± 0.6
Clock-drawing test	4.6 ± 2.2	5.7 ± 0.2	5.9 ± 1.1	5.8 ± 1.0
Conceptualization	2.3 ± 0.7	2.3 ± 0.1	2.2 ± 0.4	2.3 ± 0.3

Note: * — test results are presented as mean values with standard errors of mean (test result histograms are close to normal distribution).

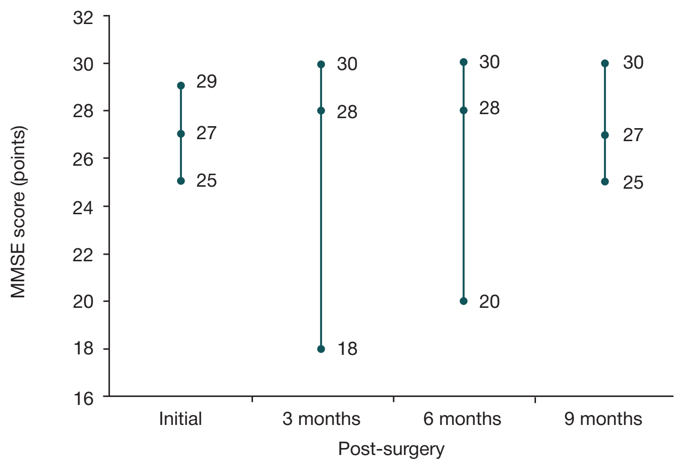

Fig. 2. Dynamics of MMSE scores describing cognitive functions (pre- and post-surgery at different time points); mean values (with minimum and maximum) are presented

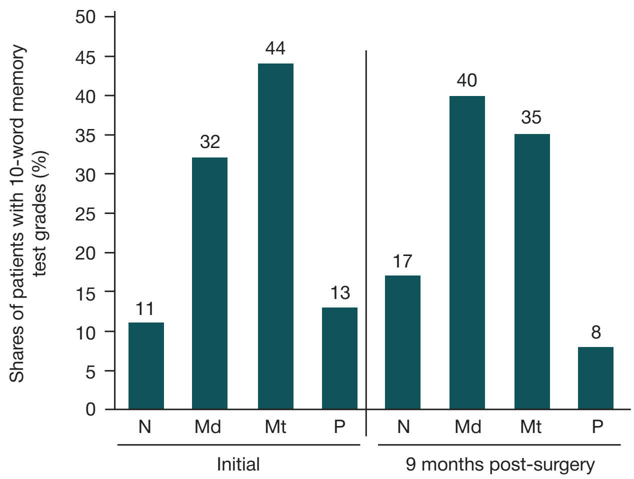

Fig. 3. Operative memory scores (10-word test) compared, pre-surgery (initial) and post-surgery (by the end of the observation period); N — norm (10 words); Md — mild impairments (8–9); Mt — moderate (6–7); S — severe (< 6). By the end of the observation period (9 months) all patients generally exhibited improvements of their operative memory

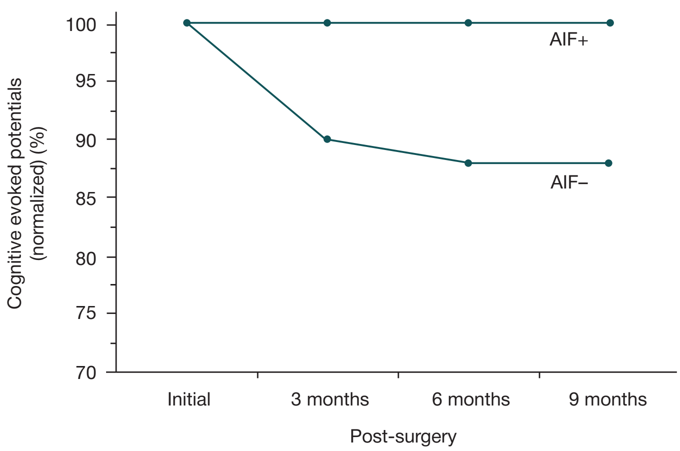

Fig. 4. CEP dynamics in patients with intraoperative acute ischemia foci (AIF+) and in patients without intraoperative acute ischemia foci (AIF–): during the observation period, the CEP level in the AIF+ group (n = 30) did not change, but in the AIF– group (n = 60) it decreased by 15% (p = 0.05). Normalized (divided by the initial levels) main CEP values (%) are given

There were no independent and significant predictors registered that were associated with the patient's condition 9 months after surgery.

The results of the P300 CEP study acquire particular importance in the context of studying CF. Initial testing of 90 patients showed that 22 (25%) of them had no changes in the features considered, while 68 (75%) patients exhibited the following deviations from the norm: 24 had no P300 peak, 25 had the peak latent, 19 had the P300 amplitude reduced. It should be noted here that the features of P300 (we give average values with standard deviations) registered in patients with arterial hypertension and without it were not significantly different from each other: 366.4 ± 29.6 versus 360.9 ± 51.1 ms (latency) and 5.4 ± 2.6 versus 5.4 ± 3.2 μV (amplitude). The P300 features revealed neither hemispheric asymmetry nor a correlation with the number of affected extracranial arteries (from one to four).

In the postoperative period, the average P300 latency and amplitude did not differ from the initial values. In the longer

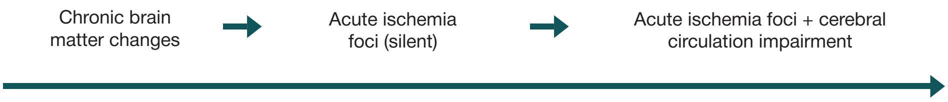

Fig. 5. Possible changes in the brain matter and post-surgery cognitive functions deterioration vector

term (9 months), P300 peak latency decrease and a slight response amplitude increase were registered in 55 (61%) patients. The average P300 potential latency values (with standard deviations) pre-surgery were 364.5 ± 37.5 ms, response amplitude — 5.4 ± 2.7 μV; post-surgery, the values were 349.5 ± 42.7 ms and 6.4 ± 3.3 μV, respectively.

DISCUSSION

The internal carotid artery system supplies about 2/3 of all the blood delivered to the namesake brain hemisphere. Atherosclerotic lesions in the extracranial arteries significantly hinder cerebral blood flow. The hemodynamic effect ICA stenosis has on cerebral circulation can lead to the development of a stroke with a clear neurological deficit or brain substance diffusion manifested in the form of diffused neurological symptoms. Post-surgery CF changes have been of interest to researchers for some time now. One of the early studies dedicated to psychopathological disorders following cardiac surgery reports the participants' impaired ability to focus attention, impaired delayed and fast memory, slowed psychomotor processes. The authors of this study concluded that it is advanced age and hypertension that are the risk factors for the development of postoperative cognitive complications [20].

The first research reports covering CI after carotid artery surgery were published in mid-1990s. The degree of intraoperative ischemia was assessed by monitoring somatosensory cortical evoked potentials during surgery. The alterations of neuropsychological indicators that depended on the degree of intraoperative ischemia were detected in patients that survived a stroke previously and had a more pronounced degree of damage to the arteries [21].

Further research efforts addressed the link between the stage of carotid stenosis and CI in patients showing no clinical signs of dementia. It was shown that CF deteriorate in patients that do not suffer from dementia but have stenosis at an advanced stage, while at the initial stages the disease does not affect the said functions. According to the psychometric tests, the revealed mild CI correlated with a change in latency of the P300 potential. The altered P300 potentials associated with mild CI were found in ICA stenosis patients, both asymptomatic and exhibiting symptoms locally [22]. In contrast to psychometric tests, CEP do not depend on the patient's motivation.

Given that the results of some studies indicate a significant improvement in CF after carotid artery interventions [23] while other papers provide evidence to the contrary [24, 25], the issue of identifying the factors driving change in cognitive abilities following surgery remains open.

We also studied CF after ICA surgery; in our work, we learned that the MMSE scores describing the state of CF in patients were most varied in the first 3 months post-surgery, which may have been a result of the patients' psychoemotional reaction to the operation [26]. The changes were mainly observed in such neurodynamic processes as attention, fluency, operative and short-term memory. After 9 months, CF have on average returned to the initial (pre-surgery) level. We can make an assumption that the long-term factors affecting the CF post-surgery are the initial status of the said functions and the adequacy of the secondary prevention measures aimed at vascular diseases. In addition, it is probable that restoration of perfusion and improvement of brain metabolism also cause a gradual recovery from the CI [27, 28].

The lack of connection between CF and the type of surgery performed (CEE or CAS) we have registered in our study is consistent with the findings reported by other researchers [29, 30].

At the 6-month time point, we detected a link between the patient's age (below 60 years) and the positive dynamics in CF restoration; moreover, at the 9-month time point we witnessed a growing number of patients whose short-term memory and attention indicators returned to norm, a finding consistent with other such findings published earlier [31, 32].

A feature of our work was the comparison of changes in the brain substance (as seen on DW-MRI scan) with the CF status at various time points post-surgery. We have detected some form of AIF in 33% of patients shortly after surgery. However, there was only one case of an acute ischemic stroke with hemiparesis on the contralateral side; the remaining AIF cases diagnosed were clinically asymptomatic.

Only a few studies [33, 34] did the DW-MRI-assisted correlation of acute ischemic lesions and neuropsychological outcome parameters, which is why there is still insufficient data to enable assessment of the forecast effect of detected lesions on cognitive status.

The clinical neuroimaging, neuropsychological and neurophysiological study we conducted allowed formulating a single CF component and establishing that the presence of AIF worsens the prognosis for cognitive functions. The dynamics of this single combined measure of CF in the remaining periods of observation depends on their clinical manifestations. In this connection, it is possible to suggest CF deterioration after CA stenosis surgery (Fig. 5).

The limitation of this study is the relatively short observation period (9 months). Continuation of the study would allow verifying the results.

CONCLUSIONS

1. One of the most important symptoms of chronic cerebrovascular disease in most patients with atherosclerotic pathology of the carotid arteries is cognitive dysfunction, which requires mandatory neuropsychological, neuroimaging and neurophysiological testing when planning angioreconstructive surgery. 2. Cognitive impairments in patients after angioreconstructive surgery on carotid artery are associated with the possible changes (symptomatic or asymptomatic) in the state of the brain substance.

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