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Mechanisms of Cognitive Improvement After Carotid Endarterectomy: Results of an Autopsy

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Abstract: To develop a clinically meaningful definition of cognitive change before and after carotid endarterectomy (CEA), we categorized patients with "improved postoperative function" and "non-improved postoperative function" based on subjective assessment and neuropsychological tests. The results showed that 11% of the patients showed an improvement in postoperative function. Through single-photon emission computerized tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), etc., it was found that improvement of cerebral blood flow by carcinoembryonic antigen (CEA) → improvement of cerebral metabolism → improvement of cerebral cortical neuroreceptor function and cerebral white matter microstructure → improvement of cognitive function. The degree of preoperative cerebral hemispheric white matter lesions was the rate-limiting factor for improvement in cognitive function.

Keywords: Carotid endarterectomy; Cognition; Cerebral blood flow; Cerebral metabolism; Small vessel diseases

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1. Introduction

Carcinoembryonic antigen (CEA) for severe stenosis of the cervical internal carotid artery is a well-established technique for preventing the onset or recurrence of ischemic attacks. Since the 1970s, there have been two schools of thought that cognitive function improves or remains the same after CEA [1-8]. However, no clear conclusion has been reached. Although there are many factors involved, such as differences in the case groups analyzed, the most important reason for this is that the definition of "improvement in cognitive function" for each case is different and has not been clearly defined. In this review, we will describe the concept and definition of improvement in cognitive function after CEA, and then outline the mechanism of improvement based on our own experience [1,9-17]. The study on which the following description is based was approved by the Ethics Committee of the University, including off-label use.

2. Concept of cognitive functional change after CEA

Neuropsychological testing is used to examine changes in cognitive function before and after surgery. Neuropsychological testing is an objective quantitative test of cognitive function, but it has several drawbacks, one of which is the practice effect: It was demonstrated that when the same neuropsychological test was repeated within 3 months, test scores were more likely to improve in patients under 75 years of age due to the practice effect [1,18]. To overcome this drawback, neuropsychological tests with two different test items were created. However, from the standpoint of the examinee, the first neuropsychological test is often more stressful, while the second time is often less stressful because the examinee has some understanding of the situation. Since neuropsychological tests using two different test items do not solve this problem, the practice effect should always be considered [18]. Moreover, neuropsychological tests include tests with no upper limit to the score, such as the Wechsler Adult Intelligence Scale (WAIS), and tests with an upper limit, such as the Hasegawa Simplified Scale for Dementia (HDS-R) or the mini mental state examination (MMSE). In tests with an upper limit, patients whose cognitive function is higher than the national average by nature cannot be detected before and after surgery. We believe that these tests are not suitable for observing pre- and post-operative changes. Therefore, we examined the changes in cognitive function before and after surgery. First, we performed the WAIS-Revised, WRS, and Rey–Osterrieth Complex Figure (ROCF) test, which are three neuropsychological tests with no upper limit to the scores, twice, in 40 normal subjects with no abnormal findings on MRI over a period of 3 months, and then determined the amount of change (postoperative vs. preoperative). More than 200 CEA cases were subjected to preoperative neuropsychological testing. Next, the surgeon and the patient's family members evaluated whether the patients' cognitive function improved postoperatively in each case. By this subjective definition, 11% of patients showed an improvement in postoperative function. In addition, a postoperative neuropsychological examination was conducted, and the amount of change in the pre- and postoperative neuropsychological scores was calculated. Here, the optimal pre- and postoperative score change for each neuropsychological test to detect postoperative improvement was determined by receiver operating characteristic (ROC) analysis. As a result, postoperative improvement in each case could be detected with a sensitivity and specificity of 80% and above, which means that the pre- and postoperative score change in one of the five items of the WAIS-R (verbal IQ, performance IQ), WRS (MQ), or ROCF test (copy, recall) was the mean change in score of normal subjects + 2 standard deviations or more. It should be noted that these optimal pre- and postoperative score changes are data for patients younger than 76 years of age, and that the practice effect becomes less significant for patients older than 76 years of age, resulting in a smaller difference between pre- and postoperative scores [9].

Subsequent data were based on this definition of neuropsychological testing, and each case was defined as "improved postoperative function" and "non-improved postoperative function".

3. Mechanisms of cognitive improvement after CEA

Theoretically, there is no mechanism for improvement of cognitive function after CEA other than improvement of cerebral blood flow as a result of the release of stenosis, as described at the beginning of this paper. Therefore, to prove this hypothesis, cerebral blood flow SPECT was performed before and after surgery [10]. As a result, the patients who showed postoperative improvement in cognitive function showed an increase in cerebral blood flow at the operated part, and it exceeded a certain threshold (**Figure 1**). However, the increase in cerebral blood flow at the operated part was not necessarily followed by an improvement in cognitive function," with a 50% chance of improvement [10]. This was true even when CEA was limited to asymptomatic lesions [11]. What then is the mechanism of cognitive function improvement when cerebral blood flow in the operated hemisphere increases? In this study, cerebral blood flow in the cerebellar hemisphere was measured in addition to cerebral blood flow in the cerebral hemisphere. In other words, we evaluated the relative postoperative changes in cerebral metabolism in the operated cerebral hemisphere by measuring pre- and postoperative changes in cerebral metabolic status or blood flow, crossed cerebellar diaschisis, or hypoperfusion in the contralateral cerebellar hemisphere, which reflects the cerebral metabolic status of the unilateral cerebral hemisphere. The results showed that in cases of postoperative improvement in cognitive function, in addition to an increase in cerebral blood flow in the operated cerebral hemisphere, there was a significant increase in the contralateral/affected ratio of cerebellar blood flow, that is, the disappearance of crossed cerebellar hypoperfusion (**Figure 1**). This indicates that in the operated cerebral hemisphere, cognitive function improves only when cerebral blood flow increases → cerebral metabolism improves.

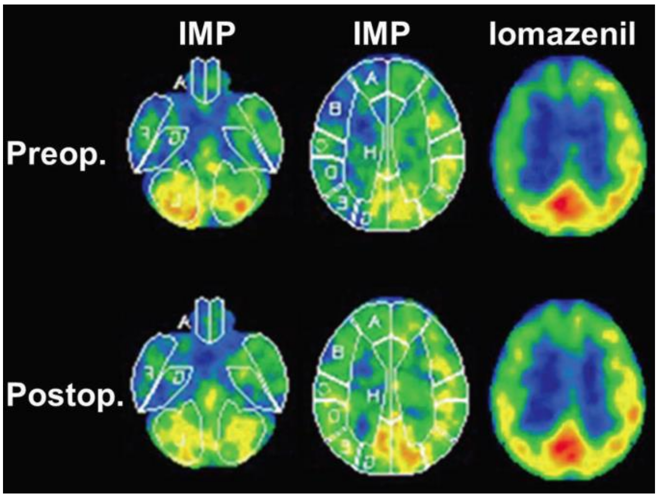

Figure 1 [10]**.** A 70-year-old man with symptomatic right internal carotid artery stenosis (95%) exhibited improvement in cognitive function after CEA. Brain perfusion (IMP) SCET images show postoperative decrease in asymmetry of tracer uptake between bilateral cerebral and cerebellar hemispheres. 123I-iomazenil SCET images showed a postoperative decrease in asymmetry of tracer uptake between bilateral cerebral and cerebellar hemispheres.

Therefore, we investigated three methods to directly measure cerebral hemispheric metabolism. The first method proton MRS, which can determine cerebral metabolism by using the NAA/creatinine ratio or choline/creatinine ratio. The NAA/creatinine ratio or choline/creatinine ratio significantly increased postoperatively in patients whose cognitive function improved after CEA compared to those whose cognitive function did not improve (**Figure 2**) [12]. Another study of glucose metabolism using 18F-FDG PET also demonstrated that patients with improved cognitive function after CEA had a significantly larger area of improved glucose metabolism in the operated cerebral hemisphere postoperatively than those without improvement (**Figure 3**) [13]. The third method was 18F-FRP170PET, which can detect tissues surviving under hypoxic conditions, before and after CEA [14]. The results showed that cognitive function was improved after CEA. As a result, the patients with improved cognitive function after CEA showed increased tracer accumulation in the operative cerebral hemisphere preoperatively, which disappeared postoperatively (**Figure 4**). This finding can be interpreted as the result of a hypoxic environment in which the nervous tissue voluntarily stopped functioning due to hypoperfusion and that oxygen metabolism was reduced as much as possible before surgery. The increased blood supply after CEA then caused the nervous tissue to begin functioning and oxygen metabolism to normalize [14,15].

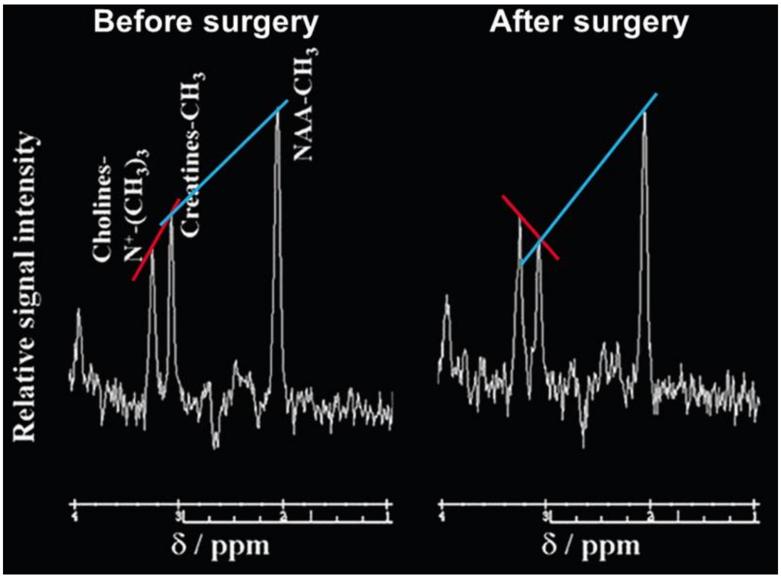

Figure 2 [12]**.** Proton magnetic resonance spectra obtained by using point-resolved spectroscopy in the region of interest in the cerebral hemisphere ipsilateral to the surgical site in a 62-year-old man with improved cognition after endarterectomy for symptomatic right internal carotid artery stenosis. Area for the NAA (cyan lines) or choline peak (red lines) to the area for the creatine peak is relatively increased after surgery (graph on the right) compared to the preoperative spectrum (graph on the left).

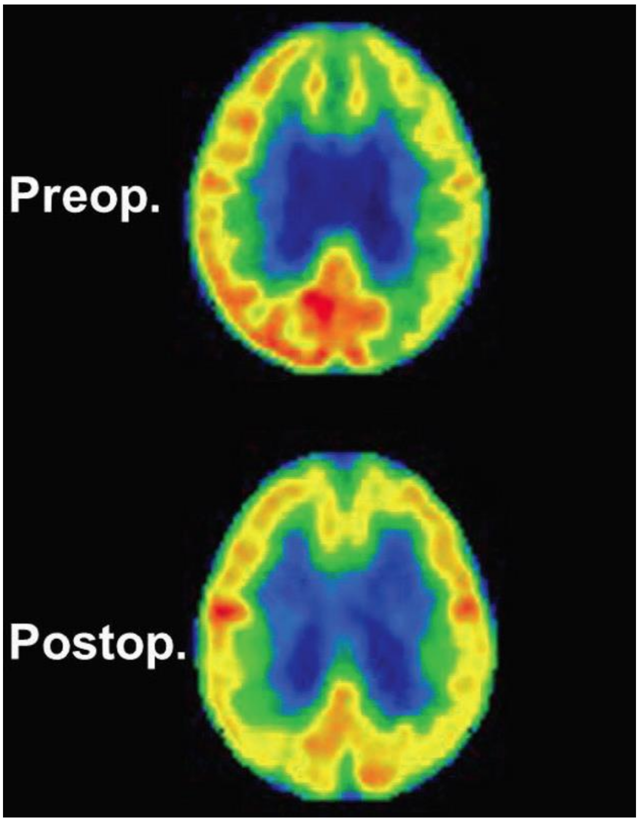

Figure 3 [13]**.** 18F-FDG PET obtained in a 69-year-old male with symptomatic left internal carotid artery stenosis exhibiting cognitive improvement after endarterectomy. Postoperative image reveals increased tracer uptake in the ipsilateral cerebral cortex as compared to preoperative images.

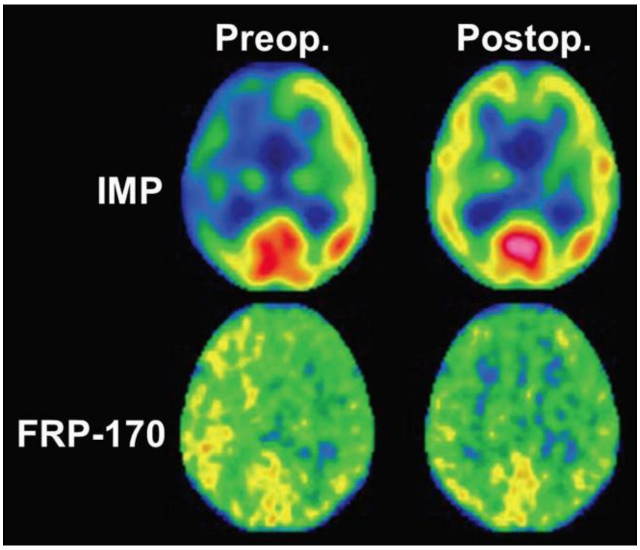

Figure 4 [14]**.** Brain perfusion SPECT (IMP) and FRP170 positron emission tomography images from a 72-year-old man with symptomatic right cervical internal carotid artery stenosis and improved cognition. Cerebral blood flow and FRP170 accumulation were reduced and increased, respectively, in the right cerebral hemisphere compared to the left cerebral hemisphere. These changes resolved after surgery.

We also examined cortical and white matter function in relation to cognitive improvement. We measured cortical neuroreceptor function using 123I-iomazenil, which binds to the abundant central benzodiazepine receptors in the cortex, and SPECT was used to visualize its binding ability [10]. The results showed that the cortical neuroreceptor binding capacity of 123I-iomazenil in the operated cerebral hemisphere increased in patients with improved cognitive function after CEA (**Figure 1**). Moreover, this phenomenon requires increased cerebral blood flow in the operated cerebral hemisphere and is strongly correlated with the disappearance of crossed cerebellar hypoperfusion [10]. For cerebral white matter, the fractional anisotropy (FA) values obtained from diffusion tensor magnetic resonance imaging (DTI) were quantitatively analyzed by tract-based spatial statistics analysis. Patients with improved cognitive function after CEA had a higher FA value than those who showed no improvement in cognitive function (**Figure 5**). Furthermore, this increase was demonstrated to extend to the frontal lobe of the contralateral cerebral hemisphere. The restructuring of cerebral white matter nerve fibers is thought to indicate remyelination of nerve fibers, and the main constituent of myelin is choline. We mentioned above that the choline/creatinine ratio in the operative cerebral hemisphere increased in patients with improved cognitive function after CEA, which is consistent with the increase in FA values using DTI [16].

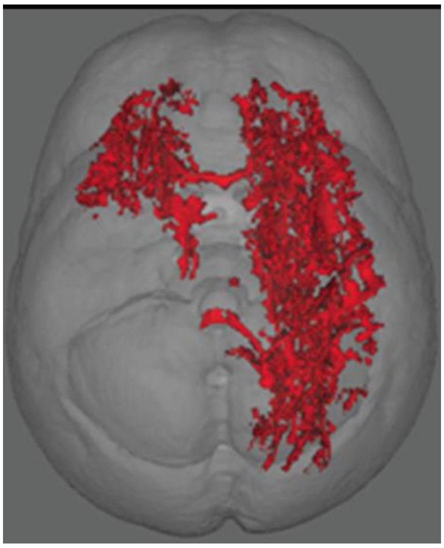

Figure 5 [16]**.** Voxels with significant postoperative increase in cerebral white matter fractional anisotropy in patients with cognitive improvement after carotid endarterectomy are expressed as red-yellow dots on three-dimensional images.

In summary, we can see that there is a flow of improvement of cerebral blood flow by CEA → improvement of cerebral metabolism → improvement of cortical neuroreceptor function and cerebral white matter microstructure → improvement of cognitive function. However, the biggest question here is why the first rate of speed, i.e., the rate at which cerebral blood flow improves with CEA and cognitive function improves thereafter, is so high in half of the cases, while the rate at which cerebral blood flow improves but cognitive function does not improve thereafter is so low in half of the cases? We hypothesized that this rate-limiting factor was irreversible dysfunction of the cerebral hemispheres that already existed prior to CEA. It is well known that small vessel diseases are an independent risk factor for cognitive dysfunction. Therefore, we compared the pre-operative presence of various small vessel diseases, pre- and post-operative changes in cerebral blood flow, and the presence of cognitive improvement, and found that post-operative increased cerebral circulation and pre-operative white matter lesion volume were significantly associated with cognitive improvement [17]. Specifically, if cerebral hemispheric white matter lesions are Fazekas grade 2 or 3, cognitive function does not improve even if there is an increase in cerebral blood flow [17]. Conversely, if cerebral hemispheric white matter lesions are light (Fazekas grade 0 or 1) and cerebral blood flow is increased, cognitive function improves by 89% [17].

4. Conclusion

CEA is a technique that drastically changes cerebral blood flow without touching the brain, and it is a model that allows us to examine changes in cerebral blood flow and brain function in detail. We hope that new discoveries will be made in the future.

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Disclosure statement

The authors have completed a COI self-report to the Japanese Neurosurgical Association.

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