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Reduced Hypoxic Tissue and Cognitive Improvement after Revascularization Surgery for Chronic Cerebral Ischemia

Yasuyoshi Shimada[a, b] Masakazu Kobayashi[a, b] Kenji Yoshida[a]
Kazunori Terasaki[b] Shunrou Fujiwara[a] Yoshitaka Kubo[a] Takaaki Beppu[a]
Kuniaki Ogasawara[a, b]

[a]Department of Neurosurgery, Iwate Medical University, Morioka, Japan; [b]Cyclotron Research Center, Iwate Medical University, Morioka, Japan

Keywords

Hypoxic tissue · Cognition · Cerebral ischemia · Revascularization surgery

Abstract

Background: Hypoxic but viable neural tissue is seen on 1-(2–^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) positron emission tomography (PET) in patients with chronic cerebral ischemia with a combination of misery perfusion and moderately reduced oxygen metabolism. Cognitive function sometimes improves after revascularization surgery in patients with chronic cerebral ischemia. ***Objectives:*** We used brain perfusion single-photon emission computed tomography (SPECT) and ^{18}F-FRP170 PET to determine whether hypoxic tissue was reduced following the restoration of cerebral perfusion after carotid endarterectomy (CEA) in patients with severe stenosis of the cervical internal carotid artery (ICA) and whether the reduction in hypoxic tissue was associated with cognitive improvement. ***Method:*** Eighteen patients with abnormally reduced cerebral blood flow (CBF) in the affected cerebral hemispheres on preoperative brain perfusion SPECT underwent CEA. They underwent ^{18}F-FRP170 PET and neuropsychological tests preoperatively and 6 months postoperatively. Brain perfusion SPECT was also performed 6 months postoperatively. Regions of interest were placed in the bilateral middle cerebral artery territories on SPECT and PET images, and the ratio of values in the affected versus contralateral hemispheres was calculated. ***Results:*** The CBF ratio ($p = 0.0006$) and ^{18}F-FRP170 ratio ($p = 0.0084$) were significantly increased and reduced, respectively, after surgery compared to the corresponding ratios before surgery. The difference in the ^{18}F-FRP170 ratio (postoperative – preoperative value) was negatively correlated with the difference in the CBF ratio ($\rho = -0.695$; $p = 0.0009$). The difference in the ^{18}F-FRP170 ratio was significantly lower in patients with postoperative improved cognition compared to that in those without ($p = 0.0007$). The area under the receiver operating characteristics curve for the difference in the ^{18}F-FRP170 ratio for detecting postoperative improved cognition was significantly greater than that for the difference in the CBF ratio (difference between areas, 0.278; $p = 0.0248$). ***Conclusions:*** Hypoxic tissue is reduced following the resto-

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Kuniaki Ogasawara
Neurosurgery
Iwate Medical University
19-1 Uchimaru Morioka, 020-8505 (Japan)
E-Mail kuogasa@iwate-med.ac.jp

ration of cerebral perfusion with revascularization surgery in patients with severe atherosclerotic stenosis of the cervical ICA. The reduction in hypoxic tissue is associated with cognitive improvement in such patients.

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Introduction

Revascularization surgery such as carotid endarterectomy (CEA) for cervical internal carotid artery (ICA) stenosis is an effective method for preventing stroke in appropriately selected patients [1]. Furthermore, cognitive function sometimes improves after revascularization surgery in such patients [2, 3]. This cognitive improvement is reportedly related to postoperative restoration of brain perfusion that was reduced before surgery [4]. Restoration of perfusion may lead to improvement in cerebral metabolism, resulting in cognitive improvement [4, 5]. These findings suggest that functionally impaired but structurally intact tissue may exist in areas of chronic cerebral ischemia with reduced cerebral metabolism and that such tissue may be viable in hypoxic conditions [6].

A recent study using positron emission tomography (PET) with ^{15}O-gas and a new radiolabeled compound, 2-nitroimidazole, 1-(2–^{18}F-fluoro-1-[hydroxymethyl] ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170), demonstrated that tissues with abnormally elevated uptake of ^{18}F-FRP170, a direct marker of hypoxic but viable tissue, are present in patients with chronic cerebral ischemia with a combination of misery perfusion and moderately reduced oxygen metabolism due to major cerebral artery steno-occlusive disease [6]. One hypothesis is that oxygen metabolism may decrease in the late stages of misery perfusion due to chronic cerebral ischemia, leading to hypoxia in that cerebral region [6]. Several questions follow from this idea [6]. When cerebral perfusion is restored after revascularization surgery, does the hypoxic tissue remain? If the hypoxic tissue disappears, does cognitive function improve?

The purpose of the present study using brain perfusion single-photon emission computed tomography (SPECT) and ^{18}F-FRP 170 PET was to determine whether hypoxic neural tissue is reduced following restoration of cerebral perfusion after CEA in patients with severe atherosclerotic stenosis of the cervical ICA and whether the reduction in hypoxic neural tissue is associated with cognitive improvement in such patients.

Materials and Methods

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the Institutional Research Committee, and written informed consent was obtained from all patients or their next of kin before participation.

Subjects

The present study was a prospective observational study. Patients with the following conditions were considered candidates for inclusion in the present study. As specified in the North American Symptomatic CEA Trial criteria [7], patients were eligible for CEA if they had $\geq$70% stenosis in the unilateral ICA as seen with magnetic resonance (MR) angiography, computed tomography, or arterial catheterization, and if they showed a peak systolic velocity r200 cm/s with cervical color duplex ultrasound in the affected ICA [8]. Patients with complete absence of symptoms of ipsilateral carotid territory ischemia or no such symptoms for >6 months before visiting our hospital were considered asymptomatic. Patients with symptoms of ipsilateral carotid territory ischemia between 2 weeks and 6 months before visiting our hospital were considered symptomatic. Patients were eligible for our current study if they also met the following criteria: modified Rankin disability scale 0 or 1; no infarct in the entire region perfused by the M4 branch of the middle cerebral artery (MCA); a sulcal and ventricular grade $\leq$5 with MR imaging, which was used to determine brain atrophy on MR imaging [9]. Eligible patients underwent brain perfusion SPECT as reported in the "*Brain SPECT and PET Studies*" section below. When patients had abnormally reduced cerebral blood flow (CBF) in the affected cerebral hemispheres (see "*Brain SPECT and PET Studies*" section), they were finally included in the present study. Patients with cerebral hyperperfusion syndrome after surgery [5] (see "*Brain SPECT and PET Studies*" section) were excluded.

Brain SPECT and PET Studies

To assess cerebral perfusion, a brain N-isopropyl-p-(123I)-iodoamphetamine (IMP) SPECT study was performed using a triple-head gamma camera (GCA-9300R; Toshiba Medical Systems, Tochigi, Japan) [10]. For patients who experienced ischemic symptoms, this study was performed more than 3 weeks after the last ischemic event. After intravenous infusion of 222 MBq ^{123}I-IMP, data acquisition was performed at a mid-scan time of 30 min for a scan duration of 20 min. The SPECT acquisition protocol, post-acquisition processing, and correction were performed as described previously [10]. The brain ^{123}I-IMP SPECT study was also performed in the same manner 6 months after surgery.

Within 7 days after the brain ^{123}I-IMP SPECT study, ^{18}F-FRP170 PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu Corp.) [11]. ^{18}F-FRP170 was synthesized using on-column alkaline hydrolysis according to previously described methods [6, 12]. The final formulation for injection was prepared in normal saline containing 2.5% v/v ethanol using solid-phase extraction techniques. Sixty minutes after an intravenous injection of approximately 370 MBq ^{18}F-FRP170, data were collected for 10 min [6, 13].

All SPECT and PET images were transformed into the standard brain size and shape by linear and nonlinear transformation using SPM2 for anatomic standardization [14]. Thus, brain images from all subjects had the same anatomic format. Three hundred eighteen constant regions of interest (ROIs) were automatically placed in the bilateral cerebral hemispheres using a three-dimensional stereotaxic ROI template with SPM2 (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) [15]. Ten ROIs per hemisphere were set by artery supply: callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampus, and cerebellar. Five of these 10 ROIs were combined and considered the ROI that was perfused by the MCA: precentral, central, parietal, angular, and temporal.

In both MCA ROIs, we determined the mean radioactive count from SPECT and PET images. We then calculated the asymmetry ratio for the MCA ROI by dividing the value for the affected cerebral hemisphere by the value for the other hemisphere. The patient was considered to have abnormally reduced CBF in the affected cerebral hemisphere if the CBF ratio obtained preoperatively was <0.933 [16]; such patients were enrolled in this study. The difference in the ratios between the preoperative and postoperative studies (postoperative ratio – preoperative ratio) was defined as the Δ ratio.

Patients underwent additional brain ^{123}I-IMP SPECT if they experienced seizures, an altered level of consciousness, and/or focal neurologic signs such as new or worsened motor weakness that occurred 1–30 days after surgery. When a focally or globally prominent increase in CBF was visually observed in the affected cerebral hemisphere on this brain SPECT, the patient was determined to have cerebral hyperperfusion syndrome [5].

Definition of Cognitive Improvement

Each patient was assessed with the following neuropsychological tests: the Wechsler Adult Intelligence Scale Revised (WAIS-R) [17], which measures verbal and performance intelligence quotient (IQ); the Wechsler Memory Scale (WMS), which measures memory quotient (MQ) [18]; and the Rey-Osterreith Complex Figure test (Rey test) [19], in which patients must copy and recall a complex figure. Thus, cognitive abilities were evaluated according to scores on these 5 tests (WAIS-R verbal IQ, WAIS-R performance IQ, WMS MQ, Rey copy, and Rey recall).

The pre- and postoperative neuropsychological tests were performed within 7 days after the brain IMP SPECT study. Differences in each neuropsychological test score between the 2 tests (postoperative test score – preoperative test score) were calculated for each patient. A trained neuropsychologist who was blinded to the clinical data of the patients performed these tests.

For each patient, postoperative improved cognition was defined based on the difference in each neuropsychological test score between the 2 tests [20] tests on 2 separate occasions [20]. For the score of each test, the difference (second test score – first test score) was calculated. A significant change was defined as the mean + 2SD of the difference in controls: WAIS-R verbal IQ (12.4); WAIS-R performance IQ (14.9); WMS MQ (16.9); Rey copy (2.6); Rey recall (9.9) [20]. In patients, postoperative cognitive improvement was defined as a significant increase in the difference in at least one of these 5 tests [20].

Statistical Analysis

Data are expressed as the mean ± SD. Differences between variables before and after surgery were evaluated using the Wilcoxon signed-rank test. Differences in variables among 3 groups (controls, patients with postoperative improved cognition, and patients without postoperative improved cognition) were evaluated using the Scheffe's F test. The relationship between variables in patients with and without postoperative improved cognition was evaluated using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve was used to assess the accuracy of the preoperative CBF or ^{18}F-FRP170 ratio for predicting postoperative improved cognition. Correlations between 2 variables were determined using the Spearman's rank correlation coefficient. ROC curves were also used to assess the accuracy of the ΔCBF ratio and Δ^{18}F-FRP170 ratio for detecting the postoperative improved cognition. Pairwise comparisons of the area under the curve ROC for the ΔCBF ratio or Δ^{18}F-FRP170 ratio were performed. For all statistical analyses, significance was set at $p < 0.05$.

Results

During the 20 months of this study, 77 patients with cervical ICA stenosis satisfied the clinical inclusion criteria and underwent brain perfusion SPECT. Among these patients, 20 had abnormally reduced CBF in the affected cerebral hemispheres and underwent preoperative ^{18}F-FRP170 PET studies and neuropsychological testing. After CEA, one experienced cerebral hyperperfusion syndrome, and another did not undergo a postoperative ^{18}F-FRP170 PET study and neuropsychological testing. These 2 patients were excluded from the present study, and the remaining 18 patients were finally analyzed.

The mean age of the 18 patients (16 men, 2 women) was 72 ± 5 years (range 61–81 years). Among these patients, 17 patients had hypertension, 6 patients had diabetes mellitus, and 11 patients had dyslipidemia. Thirteen patients had ipsilateral carotid territory symptoms, and 5 patients showed asymptomatic ICA stenosis. The overall average degree of ICA stenosis was 94 ± 2% (range 90–95%). The mean duration of ICA clamping was 37 min (range 25–49 min). No patients underwent intraluminal shunt. The postoperative courses of all 18 patients were uneventful, and any ischemic events in the ipsilateral or contralateral cerebral hemisphere did not develop until postoperative PET and neuropsychological testing.

The CBF ratio was significantly increased after surgery (0.933 ± 0.076) compared to that before surgery (0.852 ± 0.066; $p = 0.0006$; Fig. 1). The ^{18}F-FRP170 ratio was significantly reduced after surgery (1.014 ± 0.066) compared to that before surgery (1.060 ± 0.061; $p = 0.0084$; Fig. 1).

Based on the neuropsychological assessments before and after surgery, 6 (33%) patients were determined to have postoperative improved cognition. Table 1 shows the differences in each neuropsychological test score between the 2 tests (second test score – first test score) in controls [20] and patients. Differences in all neuropsychological tests were significantly higher in patients with

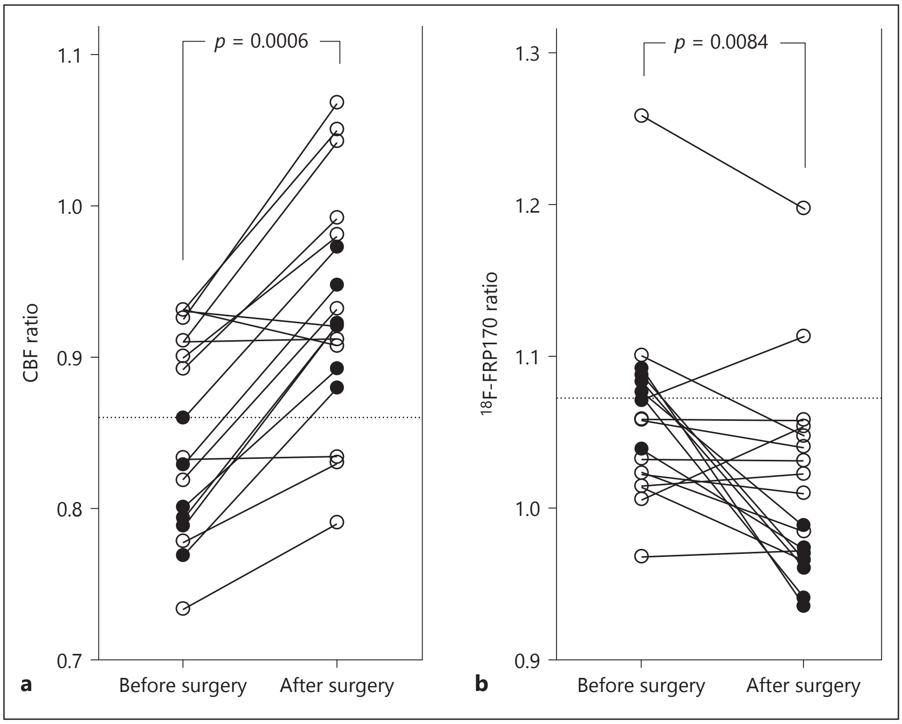

Fig. 1. Change in the CBF ratio (**a**) and 1-(2–^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) ratio (**b**) before and after surgery. Closed and open circles denote patients with and without postoperative improved cognition respectively. Each horizontal dotted line denotes the cut-off point lying closest to the upper left corner of the receiver operating characteristic curve for the preoperative CBF or ^{18}F-FRP170 ratio, respectively, for predicting postoperative improved cognition. CBF, cerebral blood flow.

Table 1. Differences in each neuropsychological test score between 2 tests (second test score – first test score) in controls and patients

Test	Controls [20], (*n* = 40)	Patients (*n* = 18)		*p* value		
		A cognition improved (*n* = 6)	B cognition not improved (*n* = 12)	controls vs. A	controls vs. B	A vs. B
WAIS-R verbal IQ	3.4±4.5	11.0±3.6	6.8±4.6	0.0009	ns	ns
WAIS-R performance IQ	4.9±5.0	14.7±3.0	7.0±5.8	0.0002	ns	0.0129
WMS MQ	4.7±6.1	12.9±7.5	7.4±4.9	0.0122	ns	ns
Rey copy	0.4±1.1	2.0±1.7	1.2±1.0	0.0103	ns	ns
Rey recall	2.9±3.5	9.0±3.0	2.7±3.8	0.0015	ns	0.0035

WAIS-R, Wechsler Adult Intelligence Scale revised; IQ, intelligence quotient; ns, not significant; WMS, wechsler memory scale; MQ, memory quotient.

postoperative improved cognition than in controls. None of these differences was statistically significant between controls and patients without postoperative improved cognition. Differences in WAIS-R performance IQ and Rey recall were higher in patients with postoperative improved cognition than in those without.

The preoperative CBF ratio was significantly lower in patients with postoperative improved cognition (0.807 ± 0.032) than that in those without (0.874 ± 0.067; $p = 0.0393$; Fig. 1). The preoperative ^{18}F-FRP170 ratio was significantly higher in patients with postoperative improved cognition (1.075 ± 0.019) than that in those without (1.052 ± 0.073; $p = 0.0482$; Fig. 1). Sensitivity, specificity, and positive- and negative-predictive values for the preoperative CBF or the ^{18}F-FRP170 ratio at the cut-off point lying closest to the upper left corner of the ROC curve for predicting postoperative improved cognition were 100% (6/6), 67% (8/12), 60% (6/10), and 100% (8/8) for the preoperative CBF ratio (cut-off point = 0.860) and 71% (5/7), 91% (10/11), 83% (5/6), and 83% (10/12) for the preoperative ^{18}F-FRP170 ratio (cut-off point = 1.072) respectively (Fig. 1). In 7 patients with a

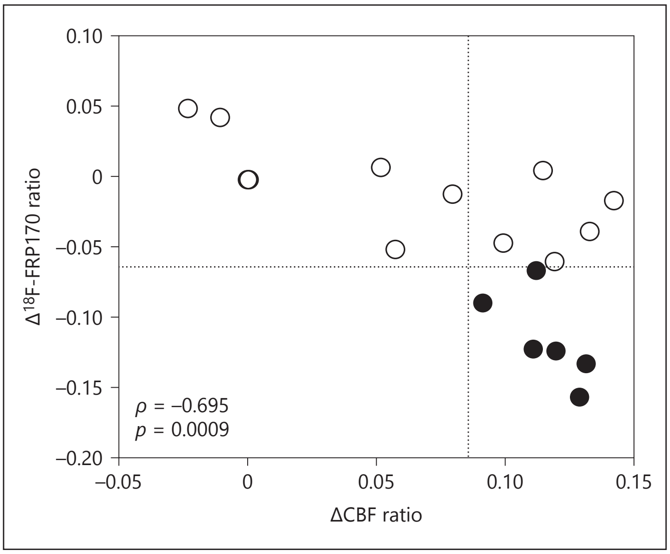

Fig. 2. Relationship among the ΔCBF ratio, Δ1-(2–^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) ratio, and postoperative cognitive changes. Closed and open circles denote patients with and without postoperative improved cognition, respectively. Vertical and horizontal dotted lines denote the cut-off point lying closest to the upper left corner of the receiver operating characteristic curve for the ΔCBF ratio and the Δ^{18}F-FRP170 ratio, respectively, for detecting postoperative improved cognition. CBF, cerebral blood flow.

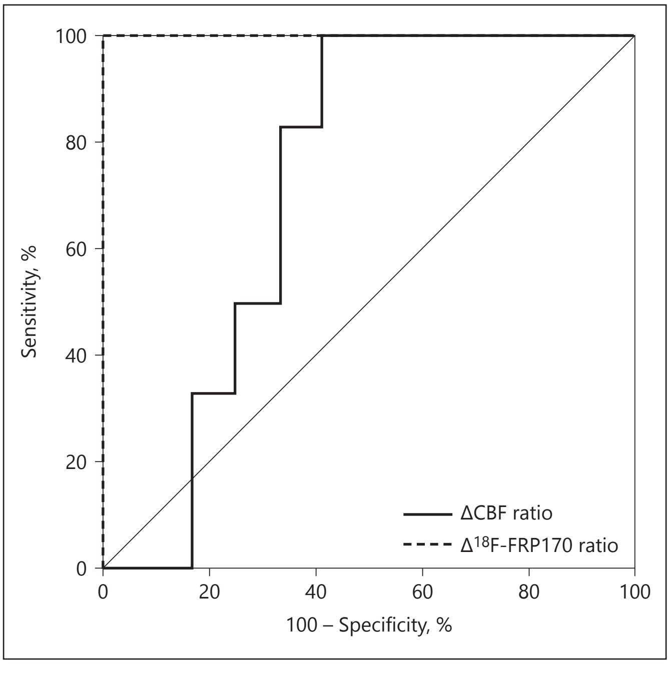

Fig. 3. Receiver operating characteristic curves for the ΔCBF ratio and Δ1-(2–^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) ratio for detecting postoperative improved cognition. CBF, cerebral blood flow.

preoperative ^{18}F-FRP170 ratio >1.072, the ratio was significantly decreased after surgery (1.001 ± 0.093) when compared to the preoperative value (1.110 ± 0.066; $p = 0.0180$); in 11 patients with a preoperative ^{18}F-FRP170 ratio ≤1.072, the ratio did not differ between pre- (1.028 ± 0.029) and postoperative (1.020 ± 0.045) states ($p = 0.4769$).

The relationship among the ΔCBF ratio, Δ^{18}F-FRP170 ratio, and postoperative cognitive change is shown in Figure 2. The Δ^{18}F-FRP170 ratio was negatively correlated with the ΔCBF ratio ($\rho = -0.695$; $p = 0.0009$). The ΔCBF ratio tended to be greater in patients with postoperative improved cognition (0.116 ± 0.015) than in those without (0.064 ± 0.060), but the difference was not significant ($p = 0.1340$). The Δ^{18}F-FRP170 ratio was significantly lower in patients with postoperative improved cognition (–0.115 ± 0.033) than in those without (–0.011 ± 0.035; $p = 0.0007$).

The ROC curves for ΔCBF ratio and Δ^{18}F-FRP170 ratio for detecting postoperative improved cognition are shown in Figure 3. The area under the curve for the Δ^{18}F-FRP170 ratio (1.000) was significantly greater than that for the ΔCBF ratio (0.722; difference between areas, 0.278; $p = 0.0248$). Sensitivity, specificity, and positive- and negative-predictive values for the ΔCBF ratio and Δ^{18}F-FRP170 ratio at the cut-off point lying closest to the upper left corner of the ROC curve were 100% (6/6), 58% (7/12), 55% (6/11), and 100% (7/7) for the ΔCBF ratio (cut-off point = 0.080) and 100% (6/6), 100% (12/12), 100% (6/6), and 100% (12/12) for the Δ^{18}F-FRP170 ratio (cut-off point = –0.066) respectively (Fig. 2). In a subgroup of 11 patients with ΔCBF ratio >0.080, the Δ^{18}F-FRP170 ratio was significantly lower in patients with postoperative improved cognition (–0.115 ± 0.033) than that in those without (–0.032 ± 0.025; $p = 0.0062$).

Pre- and postoperative brain perfusion SPECT and ^{18}F-FRP170 PET images in a patient with cognitive improvement after CEA are shown in Figure 4.

Discussion

The present study demonstrated that hypoxic neural tissues were reduced following the restoration of cerebral perfusion with revascularization surgery for patients with severe atherosclerotic stenosis of the cervical ICA and that the reduction in hypoxic neural tissue was associated with cognitive improvement in such patients.

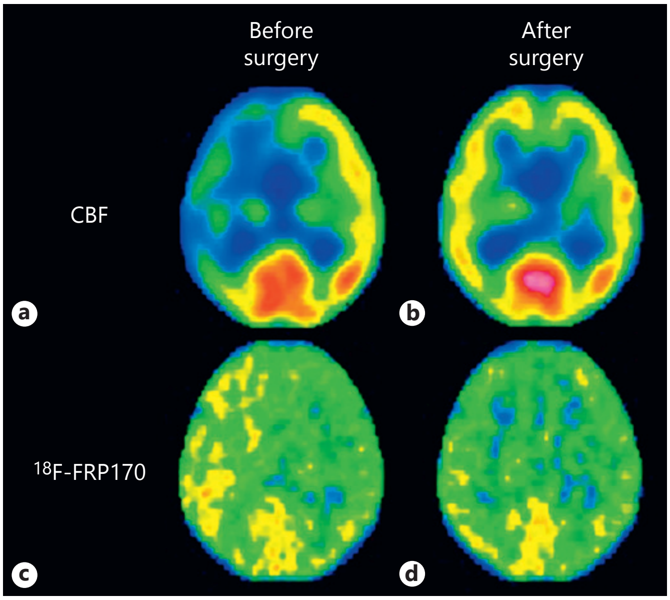

Fig. 4. Brain perfusion single-photon emission computed tomography (**a**, **b**) and 1-(2–^{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (^{18}F-FRP170) positron emission tomography (**c**, **d**) images from a 72-year-old man with symptomatic right cervical internal carotid artery stenosis and postoperative improved cognition. CBF and ^{18}F-FRP170 accumulation are preoperatively reduced and increased, respectively, in the right cerebral hemisphere compared with the left cerebral hemisphere (**a**, **c**). These changes resolved after surgery (**b**, **d**). CBF, Cerebral blood flow.

Hypoxic neural tissue seen with ^{18}F-FRP170 PET is absent in regions with severely reduced cerebral oxygen metabolism [6]. The degree of cerebral atrophy on MR imaging is correlated with that of cerebral metabolism [21, 22]. Thus, the present study included only patents without cerebral atrophy [9] to exclude those with severely reduced cerebral metabolism.

Hypoxic neural tissue is also present in chronic cerebral ischemia with misery perfusion [6]. ^{15}O-gas PET detects misery perfusion as an increased oxygen extraction fraction in the ipsilateral MCA territory in a patient with unilateral ICA steno-occlusive disease. In these patients, CBF was reduced in the affected MCA compared to the other MCA territory: the CBF ratio as seen with brain perfusion ^{123}I-IMP SPECT has been reported as <0.933 [16]. Therefore, we only enrolled patients with such a CBF ratio due to unilateral cervical ICA stenosis to include as many patients as possible with misery perfusion in the affected hemisphere. Actually, the CBF ratio was significantly increased after surgery in our patients, suggesting that many of them exhibited misery perfusion before surgery [23].

Cerebral hyperperfusion syndrome occasionally occurs within several days after CEA for cervical ICA stenosis, especially in patients with compromised cerebral hemodynamics [24]. This syndrome impairs cognitive function even when the cerebral tissue appears structurally intact on MR imaging [5]. To investigate the relationship between postoperative improved cognition and hypoxic neural tissue, patients with cerebral hyperperfusion syndrome were excluded from the present study.

In our patients, the preoperative ^{18}F-FRP170 ratio was higher in patients with postoperative improved cognition than in those without postoperative improved cognition, and the cutoff point of the preoperative ^{18}F-FRP170 ratio obtained from the ROC curve for predicting postoperative improved cognition was 1.072. This value represented mean+1.6 SD of the control value previously obtained from healthy subjects [6]. Furthermore, while the ^{18}F-FRP170 ratio was reduced after surgery in patients with a preoperative ^{18}F-FRP170 ratio > the cut-off point, it did not change after surgery in patients with a preoperative ^{18}F-FRP170 ratio ≤the cut-off point. These results suggest that the cutoff point of the preoperative ^{18}F-FRP170 ratio may be optimal for predicting postoperative improved cognition. They also showed that hypoxic neural tissue existing before surgery is reduced with cognitive improvement after revascularization surgery.

In the present study, the degree of postoperative reduction in ^{18}F-FRP170 ratio was correlated with the degree of the increase in the postoperative CBF ratio, and the greater reduction in the ^{18}F-FRP170 ratio was associated with postoperative improved cognition. These findings suggested that neural tissue in hypoxic conditions due to chronic hypoperfusion is viable but functionally impaired before surgery and that this neural tissue is no longer hypoxic following the restoration of cerebral perfusion after surgery. The tissue may begin to function again, resulting in cognitive improvement.

Hypoxic neural tissue seen with ^{18}F-FRP170 PET is absent in regions with no or slightly reduced cerebral oxygen metabolism as if those regions exhibit misery perfusion [6]. In those regions, cerebral metabolism is not significantly increased despite a great increase in CBF after revascularization, resulting in postoperative unchanged cognition. These observations may explain our data showing that approximately half of the patients with a significant increase in postoperative CBF ratio did not have postoperative improved cognition; and such patients had less of a decrease in the postoperative ^{18}F-FRP170 ratio.

The results of the present study supported the previously proposed hypothesis that oxygen metabolism may be reversibly decreased in the late stages of misery perfusion due to chronic cerebral ischemia, leading to hypoxia in that cerebral region [6]. However, the present study included only patents without morphologic changes such as cerebral atrophy. Cerebral hemodynamics deteriorates with the progression of ICA stenosis, which often results in misery perfusion. Long-standing misery perfusion reportedly leads to morphologic changes such as cortical neural damage and brain atrophy even if cerebral infarction does not develop [25, 26]. Thus, in patients who were included in the present study, misery perfusion may not persist for a long time. Hypoxic but viable neural tissue may also be present in this unique condition.

In conclusion, hypoxic neural tissue was reduced following the restoration of cerebral perfusion after revascularization surgery in patients with severe atherosclerotic stenosis of the cervical ICA, and the reduction in hypoxic neural tissue was associated with cognitive improvement in such patients.

Acknowledgment

None.

Ethics Statement

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional research committee, and written informed consent was obtained from all patients or their next of kin before participation.

Disclosure Statement

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Authors Contribution

Y.S. contributed to the conception, design and implementation of the study. He analyzed and interpreted data and drafted the article. M.K., K.Y., K.T., S.F., and Y.K. contributed to the design and implementation of the study and revised the manuscript critically for important intellectual content. T.B. contributed to the analysis of data and revised the manuscript critically for important intellectual content. K.O. contributed to the conception, design and implementation of the study, and interpretation of data. He also revised the manuscript critically for important intellectual content.

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