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

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**Abstract**

**Background:** Hypoxic but viable neural tissue is seen on 1-(2-\textsuperscript{18}F-fluoro-1-[hydroxymethyl]ethoxy) methyl-2-nitroimidazole (\textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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-
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.

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 reduced cerebral metabolism and that such tissue may be viable in hypoxic conditions [6].

Brain SPECT and PET Studies

To assess cerebral perfusion, a brain N-isopropyl-p-(123I)-io-
doamphetamine (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
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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] 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. Thirty 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...
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 18F-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 18F-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 18F-FRP170 ratio (cut-off point = 1.072) respectively (Fig. 1). In 7 patients with a

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

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

WAIS-R, Wechsler Adult Intelligence Scale revised; IQ, intelligence quotient; ns, not significant; WMS, wechsler memory scale; MQ, memory quotient.
preoperative $^{18}$F-FRP170 ratio $>1.072$, the ratio was significantly decreased after surgery ($1.001 \pm 0.093$) when compared to the preoperative value ($1.110 \pm 0.066$; $p=0.0180$); in 11 patients with a preoperative $^{18}$F-FRP170 ratio $\leq1.072$, the ratio did not differ between pre- ($1.028 \pm 0.029$) and postoperative ($1.020 \pm 0.045$) states ($p=0.4769$).

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

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

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.
Hypoxic neural tissue seen with \(^{18}\text{F}-\text{FRP170}\) 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 patients 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]. \(^{15}\text{O}-\text{gas PET}\) detects misery perfusion as an increased oxygen extraction fraction in the ipsilateral MCA territory in a patient with unilateral ICA stenosis and postoperative improved cognition. CBF and \(^{18}\text{F}-\text{FRP170}\) accumulation are preoperatively reduced and increased, respectively, in the right cerebral hemisphere compared to the left cerebral hemisphere (a, c). These changes resolved after surgery (b, d). CBF; Cerebral blood flow.

In our patients, the preoperative \(^{18}\text{F}-\text{FRP170}\) ratio was higher in patients with postoperative improved cognition than in those without postoperative improved cognition, and the cutoff point of the preoperative \(^{18}\text{F}-\text{FRP170}\) 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 \(^{18}\text{F}-\text{FRP170}\) ratio was reduced after surgery in patients with a preoperative \(^{18}\text{F}-\text{FRP170}\) ratio > the cut-off point, it did not change after surgery in patients with a preoperative \(^{18}\text{F}-\text{FRP170}\) ratio ≤ the cut-off point. These results suggest that the cutoff point of the preoperative \(^{18}\text{F}-\text{FRP170}\) 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 \(^{18}\text{F}-\text{FRP170}\) ratio was correlated with the degree of the increase in the postoperative CBF ratio, and the greater reduction in the \(^{18}\text{F}-\text{FRP170}\) 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 \(^{18}\text{F}-\text{FRP170}\) 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
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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 18F-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 patients 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.

References


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 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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