Post-carotid endarterectomy changes in cerebral glucose metabolism on ^{18}F -fluorodeoxyglucose positron emission tomography associated with postoperative improvement or impairment in cognitive function

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OBJECT Cognitive function is often improved or impaired after carotid endarterectomy (CEA) for patients with cerebral hemodynamic impairment. Cerebral glucose metabolism measured using positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG) correlates with cognitive function in patients with neurodegenerative diseases. The present study aimed to determine whether postoperative changes in cerebral glucose metabolism are associated with cognitive changes after CEA.

METHODS In patients who were scheduled to undergo CEA for ipsilateral internal carotid artery (ICA) stenosis ($\geq 70\%$ narrowing), cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide were assessed preoperatively using brain perfusion single-photon emission computed tomography (SPECT). CBF measurement using SPECT was also performed immediately after CEA. For patients with reduced preoperative CVR to acetazolamide in the cerebral hemisphere ipsilateral to surgery, cerebral glucose metabolism was assessed using FDG-PET before surgery and 3 months after surgery and was analyzed using 3D stereotactic surface projection. Neuropsychological testing was also performed preoperatively and 3 months postoperatively.

RESULTS Twenty-two patients with reduced preoperative CVR to acetazolamide successfully underwent FDG-PET studies and neuropsychological testing before and after CEA. Seven, 9, and 6 patients were defined as showing improved, unchanged, and impaired postoperative cognition, respectively, based on the neuropsychological assessments. The cortical area with increased postoperative glucose metabolism was greater in patients with improved postoperative cognition than in those with unchanged ($p < 0.001$) or impaired ($p < 0.001$) postoperative cognition. The cortical area with decreased postoperative glucose metabolism was greater in patients with impaired postoperative cognition than in those with improved ($p < 0.001$) or unchanged ($p < 0.001$) postoperative cognition. All 7 patients with improved cognition exhibited postoperative hemispheric increases in glucose metabolism, while 5 of the 6 patients with impaired cognition exhibited postoperative hemispheric decreases in glucose metabolism. Brain perfusion SPECT revealed that the latter 6 patients experienced postoperative cerebral hyperperfusion, and 2 of the 6 patients exhibited cerebral hyperperfusion syndrome. The cortical area with decreased postoperative glucose metabolism in these 2 patients was greater than that in other patients.

CONCLUSIONS Postoperative changes in cerebral glucose metabolism, as measured using FDG-PET, are associated with cognitive improvement and impairment after CEA.

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KEY WORDS carotid endarterectomy; cognition; cerebral metabolism; ^{18}F -fluorodeoxyglucose; positron emission tomography; vascular disorders

ABBREVIATIONS AI = asymmetry index; CBF = cerebral blood flow; CCH = crossed cerebellar hypoperfusion; CEA = carotid endarterectomy; CVR = cerebrovascular reactivity; FDG = ^{18}F -fluorodeoxyglucose; ICA = internal carotid artery; MCA = middle cerebral artery; PET = positron emission tomography; Rey = Rey-Osterrieth Complex Figure test; ROI = region of interest; SPECT = single-photon emission computed tomography; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS = Wechsler Memory Scale; ^{123}I -IMP = *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine.

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CAROTID endarterectomy (CEA) is an effective means of preventing stroke in appropriately selected patients.³ It also improves cerebral hemodynamics through the surgical repair of carotid stenosis, which can lead to a recovery in the reduced cerebral metabolism seen before surgery.⁴ In contrast, blood flow in the cerebral hemisphere ipsilateral to the CEA sometimes substantially increases above the metabolic demands of the brain tissue immediately after surgery.³⁰ This phenomenon is defined as “postoperative cerebral hyperperfusion.”^{27,30} Cerebral hyperperfusion syndrome after CEA represents a complication of cerebral hyperperfusion and is characterized by unilateral headache, face and eye pain, seizure, and focal symptoms that occur because of cerebral edema or intracerebral hemorrhage.^{24,27,30} The post-CEA hyperperfusion phenomenon, even when asymptomatic, can cause a postoperative reduction in cerebral metabolism.^{5,23}

While CEA can improve cognitive function,^{7,18} 10%–30% of patients experience cognitive impairment following CEA.^{6,11,25} A recent study with a large sample size reported that postoperative cognitive function was improved (in 11% of patients studied) or impaired (in 11% of patients studied) among patients who underwent CEA.³³ Post-CEA recovery of cerebral metabolism may result in postoperative cognitive improvement.^{4,28} In contrast, post-CEA reductions in cerebral metabolism may result in postoperative cognitive impairment.^{5,23,28} In previous reports, cerebral metabolism in the cerebral hemisphere ipsilateral to the CEA was assessed using specific indicators such as crossed cerebellar hypoperfusion (CCH) or central benzodiazepine receptor-binding potential with single-photon emission computed tomography (SPECT) or as metabolites with magnetic resonance (MR) spectroscopy.^{4,5,23,28} The influence of CEA on more common cerebral metabolism, e.g., oxygen or glucose metabolism, has not been investigated, and postoperative changes in these metabolic indicators have not been compared with changes in cognitive function.

Glucose metabolism in the human brain has been measured using positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG). Cerebral glucose metabolism, as depicted on FDG-PET images, reportedly correlates with cognitive function in patients with mild cognitive impairment, Alzheimer’s disease, and Parkinson disease.^{1,2,15} Therefore, the aim in the present study was to determine whether postoperative changes in cerebral glucose metabolism, measured using FDG-PET, are associated with cognitive improvement or impairment after CEA.

Methods

Inclusion Criteria

Patients who were scheduled to undergo CEA and satisfied the following basic inclusion criteria were prospectively selected: age ≤ 75 years; ipsilateral cervical internal carotid artery (ICA) stenosis (≥ 70% narrowing, as calculated using the method of the North American Symptomatic Carotid Endarterectomy Trial²⁰) on angiography with arterial catheterization; preoperative useful residual function (modified Rankin Scale Score 0, 1, or 2); no ipsilateral carotid territory ischemic symptoms or symptoms

that had occurred > 6 months before presentation to our department (defined as asymptomatic), or symptoms that had occurred between 2 weeks and 6 months before presentation to our department (defined as symptomatic); and voluntary provision of written informed consent. Finally, according to the preoperative brain perfusion SPECT criteria described below, patients who had reduced cerebrovascular reactivity (CVR) to acetazolamide in the cerebral hemisphere ipsilateral to surgery were entered into the present study. Patients meeting the following criteria were excluded from the present study: development of further ischemic symptoms during the period between initial evaluation and surgical intervention; new neurological deficits lasting ≥ 2 months after surgery; or additional ischemic lesions identified by MRI, including T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences obtained at 3 months postoperatively, as compared with preoperative MRI.

This protocol was reviewed and approved by the institutional ethics committee.

Brain Perfusion SPECT Study

Brain perfusion *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine (¹²³I-IMP) SPECT studies with and without acetazolamide challenge were performed as described previously.²² Before surgery, patients underwent measurement of cerebral blood flow (CBF) without acetazolamide challenge, followed by SPECT with acetazolamide challenge 3 days later. The ¹²³I-IMP SPECT study without acetazolamide challenge was also performed immediately after surgery, and patients showing post-CEA hyperperfusion in that SPECT study underwent a third CBF measurement in the same manner 3 days after CEA. CBF images were assessed according to the ¹²³I-IMP autoradiography method.²²

All ¹²³I-IMP SPECT images were transformed into a 3D stereotactic region of interest (ROI) template comprising 318 constant ROIs in both the cerebral and cerebellar hemispheres.³¹ Five grouped ROIs (precentral, central, parietal, angular, and temporal) were combined and defined as a ROI perfused by the middle cerebral artery (MCA). The mean value of all pixels in the MCA ROI in the cerebral hemisphere ipsilateral to the CEA and the value in the bilateral cerebellar hemispheric ROIs were calculated. Preoperative CVR to acetazolamide in the cerebral hemisphere ipsilateral to the CEA was calculated as follows: CVR (%) = [(CBF with acetazolamide challenge – CBF at the resting state)/CBF at the resting state] × 100. When CVR in the MCA ROI ipsilateral to the CEA was less than the mean 2 SDs of the control values as described previously (18.4%), a patient was defined as having reduced CVR.²² When postoperative CBF in the ipsilateral MCA ROI was increased by greater than 100% (i.e., a doubling) compared with preoperative values, a patient was defined as having post-CEA hyperperfusion.^{26,27}

The asymmetry index (AI) of cerebellar blood flow was used to assess the postoperative development of CCH and was calculated as the interhemispheric difference in cerebellar blood flow (ipsilateral cerebellar hemispheric ROI – contralateral cerebellar hemispheric ROI) divided by the mean of the bilateral cerebellar hemispheric ROI

values and then multiplied by 100. The differences between the AI immediately after or 3 days after CEA and the AI before CEA (postoperative value – preoperative value) were calculated and defined as Δ AI. When the Δ AI value was greater than the mean +2 SDs as compared with normal volunteers (8.4), the patient was defined as having postoperative CCH.²³

FDG-PET Study

PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu).¹² Radiosynthesis of FDG was performed using a TRACERlab MX_{FDG} module (GE Healthcare) with the nucleophilic substitution method.⁸ All patients fasted for at least 4 hours, and blood glucose levels at the time of FDG injection were confirmed as $\leq$ 180 mg/dl. All FDG-PET scans were obtained after intravenous injection of 185 MBq of the tracer. Emission data were acquired in 6 decay-corrected, 5-minute frames for a total of 30 minutes, starting 30 minutes after FDG injection in the 3D mode. The FDG-PET studies were performed 7 days after the last preoperative SPECT study and 3 months after surgery.

All FDG-PET image data were transferred to a personal computer and converted to a binary format. Stereotactic normalization was performed to transform images into standardized 13,288 pixels using 3D stereotactic surface projection (NEUROSTAT).¹⁹ For each pixel in the FDG-PET images, the AI was calculated according to the following formula: $\text{FDG-AI} = (C_{\text{CEA}} - C_{\text{CON}}) / (C_{\text{CEA}} + C_{\text{CON}}) \times 100$, where C_{CEA} is the count for the pixel ipsilateral to the CEA, and C_{CON} is the count for the corresponding pixel on the contralateral side. FDG-AIs were calculated before and after surgery, and the difference between FDG-AIs (postoperative values – preoperative values) was calculated and defined as Δ FDG-AI. As a control, the mean and standard deviation of Δ FDG-AI were calculated for each pixel in a subgroup of patients with unchanged postoperative cognition. For each pixel in each patient, a Δ FDG-AI value greater than the mean +2 SDs or a value less than the mean –2 SDs, as compared with controls, was defined as having increased or decreased postoperative glucose metabolism, respectively. For each patient, the number of pixels with increased or decreased postoperative FDG in the cerebral hemisphere ipsilateral to CEA was calculated. In addition, the ratio (%) of the number of pixels with increased or decreased FDG to the total number of pixels of the entire unilateral cerebral hemisphere (6644 pixels) was calculated and defined as the area with increased or decreased postoperative glucose metabolism, respectively. Furthermore, a 95% confidence interval of the area with increased or decreased glucose metabolism was calculated for a subgroup of patients with unchanged postoperative cognition. When a patient had an area with increased glucose metabolism beyond the upper limit of the 95% confidence interval, that patient was defined as having a postoperative hemispheric increase in glucose metabolism. When a patient had an area with decreased FDG beyond the upper limit of the 95% confidence interval, that patient was defined as having a postoperative hemispheric decrease in glucose metabolism.

Neuropsychological Evaluation

For each patient, we administered a battery of neuropsychological tests consisting of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),²⁹ the Wechsler Memory Scale (WMS),¹⁴ and the Rey-Osterrieth Complex Figure test (Rey).¹⁷ The WAIS-R generates verbal and performance IQs. The Rey test evaluates copy and recall of a complex figure. Thus, 5 scores (WAIS-R verbal IQ, WAIS-R performance IQ, WMS, Rey copy, and Rey recall) were used to evaluate cognitive function.

All neuropsychological tests were performed within 7 days before surgery and 3 months after surgery. A trained neuropsychologist blinded to patient clinical information administered all examinations.

For each patient, postoperative cognition was determined to be improved, unchanged, or impaired, based on results of the neuropsychological tests and the definitions described previously.³³

Intraoperative Management

All patients underwent surgery under general anesthesia. No intraluminal shunt during ICA clamping was used in any patients.

Statistical Analysis

Data are expressed as the mean $\pm$ standard deviation. Differences in the change for each neuropsychological test score among patients and controls³³ were evaluated using the Mann-Whitney U-test. Differences or incidences of each characteristic among the 3 groups (patients with improved, unchanged, or impaired postoperative cognition; patients with postoperative hemispheric increases or decreases in glucose metabolism; or patients without postoperative hemispheric changes) were evaluated using the chi-square test followed by Bonferroni's inequality correction or Scheffé's F test. For all statistical analyses, significance was set at $p < 0.05$, with the exception of the chi-square test followed by Bonferroni's inequality correction for differences that were deemed statistically significant, which was set at $p < 0.05/3 = 0.0167$. All statistical analyses were performed using PASW Statistics for Windows, version 18 (SPSS).

Results

During the 24-month study period, 88 patients satisfied all of the inclusion criteria except for the preoperative brain perfusion SPECT criteria. Twenty-three of those 88 patients were found to have reduced CVR to acetazolamide in the cerebral hemisphere ipsilateral to CEA prior to surgery. Of these, 1 patient developed a new major neurological deficit immediately after surgery that lasted for 2 months and also exhibited additional ischemic lesions 2 months after surgery, which was determined through comparison of preoperative and postoperative MRI. That patient was excluded from the present study, but none of the remaining 22 patients satisfied any of the exclusion criteria. All of these 22 patients successfully underwent a postoperative brain perfusion SPECT study, pre- and postoperative FDG-PET studies, and pre- and postoperative neuropsychological testing.

The mean age of the 22 patients (19 men, 3 women) entered into the present study was 67 ± 6 years (range 53–75 years). Concomitant disease states and symptoms were recorded, including hypertension in 18 patients, diabetes mellitus in 10 patients, and dyslipidemia in 8 patients. Sixteen patients displayed ipsilateral carotid territory symptoms, and the remaining 6 patients had asymptomatic ICA stenosis. Preoperative MRI demonstrated infarction in the hemisphere ipsilateral to ICA stenosis in 11 patients and no infarction in the remaining 11 patients. Mean overall degree of ICA stenosis was $83 \pm 8\%$ (range 70%–99%), as calculated using the method of the North American Symptomatic Carotid Endarterectomy Trial.²⁰ The contralateral ICA was occluded in 2 patients, and 5 additional patients showed 60%–99% stenosis. Mean duration of ICA clamping was 33 minutes (range 24–45 minutes).

Eleven patients met the CBF criteria for post-CEA hyperperfusion using brain perfusion SPECT immediately after surgery. In 9 of these 11 patients, hyperperfusion resolved by postoperative Day 3, and all 9 patients showed uneventful postoperative courses. However, the remaining 2 patients with cerebral hyperperfusion immediately after CEA experienced a progressive increase in CBF by postoperative Day 3. One patient developed hyperperfusion syndrome with confusion and aphasia on postoperative Day 4, while the other patient experienced cerebral hyperperfusion syndrome with confusion and left motor weakness beginning on postoperative Day 5. Propofol coma was induced in both patients. Following termination of the propofol coma, both patients eventually experienced a full neurologically recovery.

Based on the neuropsychological assessments before and after surgery, 7 (32%), 9 (41%), and 6 (27%) patients were regarded as having improved, unchanged, and impaired postoperative cognition, respectively. All 6 patients with impaired cognition exhibited cerebral hyperperfusion immediately after surgery; 2 of these 6 patients experienced cerebral hyperperfusion syndrome. All 5 of the remaining patients with post-CEA hyperperfusion had unchanged cognition.

None of the 22 patients exhibited CCH immediately after surgery; of the 11 patients with cerebral hyperperfusion immediately after surgery, 7 (including 2 with cerebral hyperperfusion syndrome) showed CCH on postoperative Day 3; and 6 of the 7 patients with CCH on postoperative Day 3 exhibited impaired cognition.

Table 1 shows differences in each neuropsychological test score between the 2 testing periods (second test score – first test score) in control patients³³ and in patients who underwent CEA. While there were no differences between controls and all patients in the study or between controls and patients with unchanged postoperative cognition, all differences were higher in patients with improved postoperative cognition and lower in those with impaired cognition as compared with controls.

In the subgroup of 9 patients with unchanged cognition, the mean ± 2 SDs of the Δ FDG-AI value was 0.0 to 5.0 in 1569 pixels (23.6%), 5.0 to 10.0 in 4083 pixels (61.5%), 10.0 to 20.0 in 971 pixels (14.6%), and > 20.0 in 21 pixels (0.3%) in a total of 6644 pixels. The mean ± 2 SDs of the Δ FDG-AI value was 0.0 to -5.0 in 1551 pixels (23.4%),

TABLE 1. Differences in neuropsychological test scores between 2 testing periods in control patients and patients who underwent CEA

Test	Control Patients†	All Patients	Subgroup			p Value			
			Improved Cognition (Group A)	Unchanged Cognition (Group B)	Impaired Cognition (Group C)	Control vs All Patients	Control vs Group A	Control vs Group B	Control vs Group C
No. of patients	40	22	7	9	6				
WAIS-R verbal IQ	3.4 ± 4.5	3.0 ± 8.2	11.6 ± 5.0	3.0 ± 3.9	-6.8 ± 3.2	NS	<0.001	NS	<0.001
WAIS-R performance IQ	4.9 ± 5.0	3.2 ± 8.4	11.9 ± 5.7	3.1 ± 1.9	-6.7 ± 5.4	NS	0.001	NS	<0.001
WMS	4.7 ± 6.1	5.3 ± 10.6	14.7 ± 5.0	6.6 ± 4.1	-9.0 ± 6.3	NS	<0.001	NS	<0.001
Rey copy	0.4 ± 1.1	1.0 ± 2.6	3.3 ± 1.8	0.8 ± 1.0	-1.5 ± 2.7	NS	<0.001	NS	0.005
Rey recall	2.9 ± 3.5	3.3 ± 5.8	8.0 ± 4.1	4.4 ± 2.6	-4.2 ± 2.9	NS	0.003	NS	<0.001

NS = not significant.

* Values are expressed as the mean $\pm$ standard deviation, unless indicated otherwise.

† Control patients are described in Yoshida et al., 2012.

TABLE 2. Comparison of characteristics among patients with improved, unchanged, or impaired postoperative cognition

Parameter	Group			p Value		
	A	B	C	Group A vs B	Group B vs C	Group C vs A
Mean age in yrs	64.1 ± 5.8	70.3 ± 3.2	65.7 ± 7.3	NS	NS	NS
Male sex	86% (6/7)	89% (8/9)	83% (5/6)	NS	NS	NS
Hypertension	71% (5/7)	89% (8/9)	83% (5/6)	NS	NS	NS
Diabetes mellitus	28% (2/7)	44% (4/9)	67% (4/6)	NS	NS	NS
Dyslipidemia	28% (2/7)	44% (4/9)	33% (2/6)	NS	NS	NS
Symptomatic lesion	71% (5/7)	67% (6/9)	83% (5/6)	NS	NS	NS
Infarction on preop MRI	43% (3/7)	67% (6/9)	33% (2/6)	NS	NS	NS
% degree of ICA stenosis	83.9 ± 6.0	78.7 ± 7.5	87.2 ± 9.9	NS	NS	NS
Bilat lesions	28% (2/7)	33% (3/9)	33% (2/6)	NS	NS	NS
Duration in min of ICA clamping	35.1 ± 5.2	32.6 ± 7.5	32.7 ± 3.4	NS	NS	NS
% area w/ postoperatively increased FDG	12.3 ± 5.5	1.5 ± 1.2	1.0 ± 0.6	<0.001	NS	<0.001
% area w/ postoperatively decreased FDG	1.5 ± 1.5	3.1 ± 2.0	10.0 ± 3.2	NS	<0.001	<0.001

−5.0 to −10.0 in 4032 pixels (60.7%), −10.0 to −20.0 in 1039 pixels (15.6%), and < −20.0 in 22 pixels (0.3%) in a total of 6644 pixels.

Table 2 shows a comparison of patient characteristics among the 3 groups. The area with increased postoperative glucose metabolism was greater in patients with improved postoperative cognition than in those with unchanged or impaired cognition; no difference in values was observed between patients with unchanged and impaired cognition. The area with decreased postoperative glucose metabolism was greater in patients with impaired postoperative cognition than in those with improved or unchanged cognition; no difference in values was observed between patients with improved and unchanged cognition. Other variables did not differ among patients with improved, unchanged, or impaired postoperative cognition.

In the subgroup of 9 patients with unchanged cognition, the 95% CIs for the areas with increased or decreased postoperative glucose metabolism were −1.4% to 4.4% or −1.7% to 7.5%, respectively. When a patient had an area with a postoperative increase in glucose metabolism greater than 4.4%, the patient was defined as having a postoperative hemispheric increase in glucose metabolism. When a patient had an area with a postoperative decrease in glucose metabolism greater than 7.5%, the patient was defined as having a postoperative hemispheric decrease in glucose metabolism. All 7 patients with improved cognition were defined as having postoperative hemispheric increases in glucose metabolism (Fig. 1), while 5 of the 6 patients with impaired cognition were defined as having a postoperative hemispheric decrease in glucose metabolism (Fig. 2); all 5 patients exhibited CCH on postoperative Day 3. The decreased postoperative glucose metabolism in the 2 patients with postoperative cerebral hyperperfusion syndrome and impaired cognition was greater than that in other patients. Table 3 shows a comparison of characteristics among patients with postoperative hemispheric increases or decreases in glucose metabolism and patients without hemispheric changes. The incidence of improved postoperative cognition was greater in patients with postoperative hemispheric

ic increases in glucose metabolism than in patients with hemispheric decreases or in patients without hemispheric changes. The incidence of impaired postoperative cognition was greater in patients with postoperative hemispheric decreases in glucose metabolism than in patients with hemispheric increases or in patients without hemispheric changes. No other variables differed when comparing patients with hemispheric increases or decreases in glucose metabolism and patients without hemispheric changes.

¹²³I-IMP SPECT and FDG-PET images for each patient with postoperative improvement and impairment in cognitive function are shown in Figs. 3 and 4, respectively.

Discussion

The present study demonstrates that postoperative

FIG. 1. Comparison of area with increased postoperative FDG on PET among patients with improved, unchanged, and impaired postoperative cognition. Dashed horizontal line denotes the upper limit of the 95% confidence interval calculated in the subgroup of 9 patients with unchanged cognition. When a patient showed an area with increased FDG beyond the upper limit, the patient was defined as having a postoperative hemispheric increase in FDG. Arrows indicate patients with cerebral hyperperfusion syndrome.

FIG. 2. Comparison of area with decreased postoperative FDG on PET among patients with improved, unchanged, and impaired postoperative cognition. *Dashed horizontal line* denotes the upper limit of the 95% confidence interval calculated in the subgroup of 9 patients with unchanged cognition. When a patient shows an area with decreased FDG beyond the upper limit, the patient was defined as having a postoperative hemispheric decrease in FDG. Arrows indicate patients with cerebral hyperperfusion syndrome.

changes in cerebral glucose metabolism are associated with cognitive improvement or impairment after CEA.

A previous study reported that only patients with a significant increase in and normalization of blood flow in the ipsilateral cerebral hemisphere after CEA exhibit postoperative cognitive improvement, suggesting that the presence of preoperative cerebral hemodynamic impairment may be predictive of postoperative cognitive improvement.⁴ However, risk factors for post-CEA hyperperfusion, a primary cause of postoperative cognitive impairment,²⁵

also include preoperative hemodynamic impairment.^{11,26,34} Another previous study reported that preoperative CVR to acetazolamide appears to be the patient characteristic that most accurately predicts the development of cognitive improvement and impairment after CEA.³³ Preoperative CVR is significantly lower in patients with improved or impaired cognition after surgery than in patients with unchanged cognition.³³ Thus, only patients with reduced preoperative CVR in the cerebral hemisphere ipsilateral to CEA were included in the present study. As a result, the incidence of patients with improved and impaired cognition after surgery was considerably greater (more than 2-fold) in the present patient population than in the previous study.³³

Several investigators have demonstrated that decreased preoperative cerebral glucose metabolism, as measured using FDG-PET, is associated with some degree of patient recovery and improved cerebral perfusion in patients with chronic ICA or MCA occlusion who underwent superficial temporal artery–MCA bypass surgery.^{13,16} However, the effects of improved postoperative cerebral glucose metabolism on cerebral function and cognition have not been investigated in detail. One study using FDG-PET showed a correlation between increased cerebral glucose metabolism and improved cognitive function among patients with Alzheimer's disease who were treated with pharmacotherapy.¹ Additional studies have shown that progression in dementia in patients with Parkinson disease and longitudinal cognitive declines in patients with mild cognitive impairment are reportedly associated with reductions in cerebral glucose metabolism measured by FDG-PET.^{2,15} Data in the present study demonstrate that glucose metabolism in the cerebral hemisphere ipsilateral to CEA often increases or decreases after surgery in patients with hemodynamic impairment, and that these postoperative changes

TABLE 3. Comparison of characteristics among patients with postoperative hemispheric increases or decreases in glucose metabolism and patients without postoperative hemispheric changes

Parameter	Group			p Value		
	Postop Hemispheric Increase in Glucose Metabolism (Group A)	No Postop Hemispheric Change in Glucose Metabolism (Group B)	Postop Hemispheric Decrease in Glucose Metabolism (Group C)	Group A vs B	Group B vs C	Group C vs A
No. of patients	7	10	5			
Mean age in yrs	64.1 ± 5.8	70.2 ± 3.1	65.0 ± 7.9	NS	NS	NS
Male sex	86% (6/7)	90% (9/10)	80% (4/5)	NS	NS	NS
Hypertension	71% (5/7)	80% (8/10)	100% (5/5)	NS	NS	NS
Diabetes mellitus	28% (2/7)	50% (5/10)	60% (3/5)	NS	NS	NS
Dyslipidemia	28% (2/7)	50% (5/10)	20% (1/5)	NS	NS	NS
Symptomatic lesion	71% (5/7)	60% (6/10)	100% (5/5)	NS	NS	NS
Infarction on preop MRI	43% (3/7)	60% (6/10)	40% (2/5)	NS	NS	NS
% degree of ICA stenosis	83.9 ± 6.0	79.3 ± 7.3	87.6 ± 11.0	NS	NS	NS
Bilat lesions	28% (2/7)	30% (3/10)	40% (2/5)	NS	NS	NS
Duration in min of ICA clamping	35.1 ± 5.2	32.8 ± 7.1	32.2 ± 3.6	NS	NS	NS
Improved cognition	100% (7/7)	0% (0/10)	0% (0/5)	<0.001	NS	<0.001
Impaired cognition	0% (0/7)	10% (1/10)	100% (5/5)	NS	0.002	<0.001

FIG. 3. Images obtained in a 69-year-old male with symptomatic left ICA stenosis (90%) exhibiting cognitive improvement after CEA. **Left:** Postoperative FDG-PET (right) reveals increased tracer uptake in the ipsilateral cerebral cortex as compared with preoperative images (left). **Right:** Three-dimensional stereotactic surface projection images of the scans shown in the left panel demonstrate areas with increased postoperative FDG (red dots) occupying 20.5% of the entire ipsilateral cerebral cortex (upper) and those with decreased FDG (blue dots) occupying 1.3% of the entire ipsilateral cerebral cortex (lower). ANT = anterior; INF = inferior; LAT = lateral; MED = medial; POST = posterior.

in glucose metabolism are associated with postoperative improvements and impairments in cognition, respectively. Our findings correspond with previous data regarding post-CEA changes in cerebral metabolism assessed using specific indicators such as CCH or central benzodiazepine receptor-binding potential with SPECT analysis or as metabolites with MR spectroscopy.^{4,5,23,28} Our data also demonstrate that post-CEA recovery of cerebral metabolism results in postoperative cognitive improvement, and post-CEA reduction in cerebral metabolism results in postoperative cognitive impairment.

In the present study, while all 6 patients with impaired postoperative cognition experienced postoperative cerebral hyperperfusion and 5 of these 6 patients exhibited a postoperative hemispheric decrease in glucose metabolism, the 2 patients with cerebral hyperperfusion syndrome displayed a cortical area of decreased postoperative glucose metabolism that was greater than the area in other patients. These findings suggested that cerebral hyperperfusion syndrome may severely damage the ipsilateral cerebral cortex even if intracerebral hemorrhage does not develop.

FIG. 4. Images obtained in a 70-year-old male with symptomatic right ICA stenosis (95%) exhibiting cognitive impairment after CEA. Cerebral hyperperfusion syndrome with confusion and left motor weakness developed on postoperative Day 5. **Left:** Preoperative brain perfusion ¹²³I-IMP SPECT study shows reduced CBF in the ipsilateral cerebral hemisphere (first column on the left) where hyperperfusion developed immediately after surgery (second column). Postoperative FDG-PET images (fourth column) reveal decreased tracer uptake in the ipsilateral cerebral cortex as compared with preoperative images (third column). **Right:** Three-dimensional stereotactic surface projection FDG-PET images in left panel demonstrate areas with increased postoperative FDG (red dots) occupying 1.0% of the entire ipsilateral cerebral cortex (upper) and those with decreased FDG (blue dots) occupying 15.4% of the entire ipsilateral cerebral cortex (lower).

Cerebral damage due to hemispheric ischemia during ICA clamping may also be associated with postoperative cognitive impairment.¹⁰ In addition, while cognitive decline at Day 1 after surgery often resolves by 1 month, cognitive decline, as compared with cognitive function on postoperative Day 1, can also newly develop 1 month after surgery.⁹ CCH is defined as a reduction in blood flow in the cerebellar hemisphere contralateral to a supratentorial lesion, and the degree of CCH reportedly reflects the cerebral metabolic rate in the affected cerebral hemisphere relative to that in the contralateral cerebral hemisphere in patients with carotid artery occlusive disease.³² In 1 study, brain perfusion SPECT performed immediately after surgery did not reveal CCH in any patients with postoperative cerebral hyperperfusion. Despite the resolution or persistence of cerebral hyperperfusion on postoperative Day 3, most patients who exhibited CCH on postoperative Day 3 experienced cognitive impairment 1 month after surgery, while none of the patients without CCH on postoperative Day 3 developed postoperative cognitive impairment.²³ Our data correspond with these findings, although the interval between surgery and the second neuropsychological test was somewhat different (1 month in the previous study vs 3 months in the present study). Furthermore, another study reported that a patient with apparent cerebral hemispheric ischemia on intraoperative monitoring during ICA clamping exhibited cognitive impairment 2 months after surgery, despite the absence of either postoperative neurological deficits or new ischemic lesions identified by MRI.²¹ In that patient, brain perfusion SPECT performed immediately after surgery showed a decrease in blood flow in the affected cerebral hemisphere and CCH; PET performed 2 months after surgery revealed a decreased cerebral metabolic rate of oxygen in the affected cerebral hemisphere.²¹ Thus, cerebral damage might not have developed immediately after surgery in our patients, and the hemispheric decrease in glucose metabolism in postoperative Month 3 was unlikely to have been caused by intraoperative cerebral hemispheric ischemia. Cerebral hyperperfusion that lasts for ≤ 3 days after surgery may cause reductions to cerebral metabolism on postoperative Day 3, and the reduction may persist, resulting in cognitive impairment at 1–3 months after surgery.²³

The present study possesses several limitations that require consideration. The FDG-PET images were analyzed on a pixel-by-pixel basis using 3D stereotactic surface projection, and a Δ FDG-AI value greater than the mean +2 SDs or less than the mean –2 SDs in the subgroup of patients with unchanged postoperative cognition was defined as increased or decreased postoperative FDG, respectively. According to these definitions, the threshold was greater than 10.0 in 14.9% of the total number of pixels or less than –10.0 in 15.9% of pixels. Thus, increased or decreased postoperative FDG might be underestimated in such pixels. Further, a significant postoperative change in glucose metabolism in the cerebral cortex ipsilateral to surgery relative to that in the contralateral cerebral cortex was defined as changed glucose metabolism in the ipsilateral cerebral cortex. A previous study using MR spectroscopy indicated that cerebral metabolites in the contralateral cerebral hemisphere as well as those in the ip-

silateral cerebral hemisphere often increase or decrease in patients with improved or impaired postoperative cognition, respectively.²⁸ Therefore, the degree of postoperative increase or decrease in glucose metabolism might be underestimated with the present method. This underestimation may be a reason why 1 of the 6 patients with impaired cognition did not exhibit a postoperative hemispheric decrease in glucose metabolism.

Conclusions

Postoperative changes in cerebral glucose metabolism on FDG-PET are associated with cognitive improvement and impairment after CEA.

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