Impact of cerebral blood flow changes due to arterial bypass surgery on cognitive function in adult patients with symptomatic ischemic moyamoya disease

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OBJECTIVE Some adult patients with moyamoya disease (MMD) undergoing revascularization surgery show an improvement or decline in cognition postoperatively. Revascularization surgery for ischemic MMD augments cerebral blood flow (CBF) and improves cerebral oxygen metabolism. However, cerebral hyperperfusion, which is a short-term, major increase in ipsilateral CBF that is much greater than the metabolic needs of the brain, sometimes occurs as a complication. Cerebral hyperperfusion produces widespread, minimal injury to the ipsilateral white matter and cortical regions. The aim of the present prospective study was to determine how changes in CBF due to arterial bypass surgery affect cognitive function in adult patients with symptomatic ischemic MMD and misery perfusion.

METHODS Thirty-two patients with cerebral misery perfusion, as determined on the basis of ¹⁵O gas positron emission tomography, underwent single superficial temporal artery–middle cerebral artery (M₄ in the precentral region) anastomosis. Brain perfusion single-photon emission computed tomography (SPECT) studies were performed preoperatively, on the 1st postoperative day, and 2 months after surgery. Neuropsychological tests were also performed preoperatively and 2 months after surgery.

RESULTS Postoperative neuropsychological assessments demonstrated cognitive improvement in 10 cases (31%), no change in 8 cases (25%), and decline in 14 cases (44%). Based on brain perfusion SPECT and symptoms, 10 patients were considered to have cerebral hyperperfusion syndrome, and all of these patients exhibited a postoperative decline in cognition. Relative precentral CBF on the 1st postoperative day was significantly greater in patients with postoperative cognitive decline ($167.3\% \pm 15.3\%$) than in those with improved ($105.3\% \pm 18.2\%$; $p < 0.0001$) or unchanged ($131.4\% \pm 32.1\%$; $p = 0.0029$) cognition. The difference between relative precentral CBF 2 months after surgery and that before surgery was significantly greater in patients with postoperative cognitive improvement ($17.2\% \pm 3.8\%$) than in those with no postoperative change ($10.1\% \pm 2.4\%$; $p = 0.0003$) or with postoperative decline ($11.5\% \pm 3.2\%$; $p = 0.0009$) in cognition.

CONCLUSIONS Cerebral hyperperfusion in the acute stage after arterial bypass surgery impairs cognitive function. An increase in CBF in the chronic stage without acute-stage cerebral hyperperfusion improves cognitive function in adult patients with symptomatic ischemic MMD and misery perfusion.

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KEYWORDS moyamoya disease; arterial bypass surgery; cognition; cerebral hemodynamics; cerebral hyperperfusion syndrome; vascular disorders

MOYAMOYA disease (MMD) is a chronic, occlusive cerebrovascular disease of unknown etiology that is characterized by bilateral steno-occlusive changes in the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the

brain.^{27,32} When the patient experiences symptoms of ischemia, the typical treatment is revascularization surgery, which may involve anastomosis of the superficial temporal artery (STA) and the middle cerebral artery (MCA).⁸ Both adult and pediatric patients benefit from this procedure,

ABBREVIATIONS CBF = cerebral blood flow; ¹²³I-IMP = *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine; IQ = intelligence quotient; MCA = middle cerebral artery; MMD = moyamoya disease; OEF = oxygen extraction fraction; PET = positron emission tomography; POD 1 = postoperative day 1; RCBF_{atMCA} = relative CBF in the affected MCA ROI; ROC = receiver operating characteristic; ROI = region of interest; SPECT = single-photon emission computed tomography; STA = superficial temporal artery; WAIS-R = Wechsler Adult Intelligence Scale–Revised.

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which prevents further cerebral ischemic events.^{15,29,30,33} In particular, it is recommended for the symptomatic cerebral hemisphere that shows compromised hemodynamics such as misery perfusion.^{11,22}

A recent study has demonstrated that although the majority of adult patients undergoing revascularization surgery for MMD show no significant change in cognition compared with their preoperative performance, a small proportion of such patients show apparent improvement in cognition after surgery.³⁹ Revascularization surgery augments cerebral blood flow (CBF)^{9,22} and often improves cerebral oxygen metabolism,¹⁷ which may result in improved cognitive function.

In patients with adult-onset MMD, STA-MCA anastomosis may involve a complication called cerebral hyperperfusion, which is a short-term, major increase in ipsilateral CBF that is much greater than the metabolic requirements of the brain.^{4,14,26} This complication, which occurs in about 30% of patients, is characterized by temporary aphasia, hemiparesis, and dysarthria,^{4–6} as well as intracerebral and/or subarachnoid hemorrhage.^{6,7} Although patients who develop intracerebral hemorrhage have a poor prognosis, this condition has a low incidence (3%–5%).⁸

Postoperative cerebral hyperperfusion, which may show no symptoms, produces widespread, minimal damage to the ipsilateral white matter and cortical regions following carotid endarterectomy.^{2,21} This type of damage is the main reason for impaired postoperative cognition after carotid endarterectomy.^{2,21} Although a small proportion of patients exhibit cognitive improvement after revascularization surgery for adult-onset MMD, a similarly small proportion of patients show a postoperative decline in cognition in the absence of apparent parenchymal injury as seen on conventional neuroimaging.³⁹ Therefore, asymptomatic cerebral hyperperfusion or cerebral hyperperfusion syndrome after STA-MCA anastomosis may also cause a postoperative cognitive decline in patients with adult-onset MMD. However, the impact of these postoperative CBF changes on cognitive function in MMD has not been investigated systematically.

The aim of the present prospective study was to determine how CBF changes due to arterial bypass surgery affect cognitive function in adult patients with symptomatic ischemic MMD and misery perfusion.

Methods

This study was approved by the Iwate Medical University ethics committee.

Healthy Subjects

To record normal control values for the oxygen extraction fraction (OEF) on brain ¹⁵O gas positron emission tomography (PET), we recruited 10 healthy adult males who met the following inclusion criteria: age > 30 but < 60 years; no previous history of hypertension, diabetes mellitus, or dyslipidemia; and no leukoaraiosis or asymptomatic lacunar infarction as seen with conventional brain MRI.

Patients

Patients were diagnosed with MMD when they met the

criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Japanese Ministry of Health, Labour and Welfare. These patients were prospectively enrolled in this study if they met the following inclusion criteria: age > 30 but < 60 years; modified Rankin Scale score of 0 or 1; symptoms of carotid territory ischemia that were present $\leq$ 3 months prior to visiting our hospital; and no major cerebral infarction on MRI. Enrolled patients underwent brain ¹⁵O gas PET as described in the *Brain ¹⁵O Gas PET Study* section. Patients were considered candidates for arterial bypass surgery if they had misery perfusion in the symptomatic cerebral hemispheres as described in the *Definition of Preoperative Misery Perfusion and Data Analysis* section; these patients were also included in this study. Patients who had new cerebral ischemic lesions on MRI performed on the 1st postoperative day were excluded from the study.

The ethics committee at our institution reviewed and approved this study protocol. Each participant or a family member provided written informed consent prior to participation.

Brain ¹⁵O Gas PET Study

To define cerebral misery perfusion, PET studies were performed using a SET-3000GCT/M scanner (PET/CT; Shimadzu) for healthy subjects.²⁹ To detect cerebral misery perfusion, patients underwent the same PET studies more than 3 weeks after the last ischemic event.²⁹ Before emission scans, a transmission scan (3 minutes) with a ¹³⁷Cs point source was performed using a bismuth germanate transmission detector ring coaxially attached to the gadolinium silica oxide emission detector ring.²⁹ Measurements of the OEF were obtained during continuous inhalation of ¹⁵O₂. Data were collected for 5 minutes. A single breath of C¹⁵O was used to measure cerebral blood volume. OEF was calculated using the steady-state method³ and was corrected by cerebral blood volume.¹⁸

Brain ¹²³I-IMP SPECT Study

To assess CBF changes before and after surgery, *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine (¹²³I-IMP) SPECT studies were performed in patients using a triple-head gamma camera (GCA-9300R; Toshiba Medical Systems)²⁹ within 5 days after preoperative PET, on the 1st postoperative day, and 2 months after surgery. After intravenous infusion of 222 MBq of ¹²³I-IMP, data acquisition was performed at a midscan time of 30 minutes for a duration of 20 minutes.^{6,29}

Definition of Preoperative Misery Perfusion and Data Analysis

Linear and nonlinear transformation with SPM2 (FUJIFILM RI Pharma) were used to convert PET and SPECT images to anatomically standardize the size and shape of the brain and to create the same anatomical format across subjects.^{23,29} A 3D stereotaxic region of interest (ROI) template was used to automatically select constant ROIs (n = 318) in the cerebral and cerebellar hemispheres with SPM2.^{29,34} These ROIs were classified into one of 10 segments according to arterial supply (callosomar-

ginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampal, or cerebellar) in each hemisphere.²⁹ Five of these 10 regions (precentral, central, parietal, angular, and temporal), which were supplied by the MCA, as well as the cerebellar ROI, were analyzed.²⁹

Mean OEF values obtained from PET images were measured in the 5 ROIs in both cerebral hemispheres. In each ROI for each patient, an OEF that was higher than the upper limit of the 95% confidence interval of the control value was considered to be abnormally increased.²⁹ If at least 1 MCA ROI in the symptomatic hemisphere demonstrated an abnormally increased OEF, the patient was considered to exhibit symptomatic misery perfusion.²⁹

In patients, mean radioactive counts obtained from ¹²³I-IMP SPECT images were determined in the above 5 MCA ROIs in both the cerebral and cerebellar ROIs.²⁹ We defined the relative CBF in the affected MCA ROI ($RCBF_{afMCA}$) (%) as $100 \times (\text{mean radioactive count in an MCA ROI with an anastomosed STA}) / (\text{mean radioactive count in the cerebellar ROI ipsilateral to surgery})$.²⁹ The $RCBF_{afMCA}$ was calculated preoperatively, on the 1st postoperative day, and 2 months after surgery. Differences in $RCBF_{afMCA}$ between each time point were also calculated as follows: 1st postoperative day (POD 1) value minus preoperative value, described as $\Delta RCBF_{afMCA(POD\ 1-preop)}$; value obtained 2 months after surgery minus POD 1 value, described as $\Delta RCBF_{afMCA(2\ mos-POD\ 1)}$; and value obtained 2 months after surgery minus preoperative value, described as $\Delta RCBF_{afMCA(2\ mos-preop)}$.

Neuropsychological Evaluation

Each patient was assessed with the following neuropsychological tests: the Wechsler Adult Intelligence Scale-Revised (WAIS-R),³¹ which measures verbal and performance intelligence quotient (IQ); the Wechsler Memory Scale;¹⁶ and the Rey-Osterreith Complex Figure test (Rey test),¹⁹ in which patients must copy and recall a complex figure. Their cognitive abilities were evaluated according to scores on these 5 tests (WAIS-R verbal IQ, WAIS-R performance IQ, Wechsler Memory Scale, Rey copy, and Rey recall).

The neuropsychological tests were performed within 7 days before surgery and 2 months after surgery. All examinations were administered by a trained neuropsychologist who was blinded to the patients' clinical information.

Control values were obtained from a previously published study in which healthy subjects were assessed with the same neuropsychological tests on 2 separate dates.³⁷ For each patient, postoperative cognitive status was classified as showing improvement, no change, or decline based on results of the neuropsychological tests for healthy subjects and the definition as described previously.³⁷

Management of Patients During and After Surgery

During surgery, a single STA-MCA anastomosis was performed 1–4 months after the last ischemic event. The recipient artery was the M_4 that supplied the MCA ROI that had misery perfusion in the symptomatic cerebral hemisphere. For patients who exhibited misery perfusion in both cerebral hemispheres and in whom ischemic symp-

toms were present in both carotid territories ≤ 3 months prior to visiting our hospital, surgery was first performed in the hemisphere with the greater OEF. Surgery was then performed in the other hemisphere 3 months later.

Hypovolemia and anemia were strictly prevented in all patients after surgery. Systolic blood pressure was maintained between 110 and 130 mm Hg as much as possible. Cerebral hyperperfusion was suspected if a patient had a focal major increase in CBF in at least 1 MCA ROI on the surgically treated side as demonstrated with ¹²³I-IMP SPECT images on the day after surgery.³⁵ It was also suspected if a patient had headache, seizures, altered consciousness, and/or focal neurological symptoms, including aphasia, hemiparesis, or new or worsening dysarthria between 12 hours and 30 days postoperatively, and in such cases, a propofol coma was induced. The systolic blood pressure was maintained between 110 and 130 mm Hg even during propofol coma to the extent possible. If the focal increase in CBF on the day after surgery disappeared on ¹²³I-IMP SPECT images obtained 2 months after surgery, the patient was considered to have had cerebral hyperperfusion syndrome.

On the 1st postoperative day, MRI and MR angiography were performed to look for the development of new postoperative cerebral ischemic lesions and confirm patency of the arterial bypass.

Statistical Analysis

Data are expressed as the mean $\pm$ SD. Incidences or differences in each characteristic or value among 3 groups (patients with cognitive improvement, no change, or cognitive decline after surgery) were evaluated using the chi-square test followed by Bonferroni's inequality correction or Scheffe's F test. Chronological changes in $RCBF_{afMCA}$ were evaluated using Scheffe's F test. Significance was set at the $p < 0.05$ level for all statistical analyses except the chi-square test, followed by Bonferroni's inequality correction, for which differences were deemed statistically significance if $p < 0.05/3 = 0.0167$. The accuracies of the $RCBF_{afMCA}$ and $\Delta RCBF_{afMCA}$ for predicting postoperative cognitive improvement or decline were evaluated by receiver operating characteristic (ROC) curve analyses. The cutoff point lying closest to the left upper corner of the ROC curve for the prediction of postoperative improvement or decline was determined. Exact 95% confidence intervals for sensitivity, specificity, and positive and negative predictive values at the cutoff point were computed using binomial distributions.

Results

Over the course of 99 months, 120 patients satisfied the clinical inclusion criteria. Of these 120 patients, 5 patients refused arterial bypass surgery and did not undergo brain ¹⁵O gas PET. Thus, 115 patients underwent brain ¹⁵O gas PET.

Ten healthy adult males with a mean age of 42 ± 7 years (range 30–55 years) participated in the study and underwent brain ¹⁵O gas PET to provide normal control values. For PET-OEF in the precentral, central, parietal, angular, and temporal ROIs, the 95% confidence intervals in con-

TABLE 1. Comparison of basic characteristics among patients with cognitive improvement, no change in cognitive function, or cognitive decline after surgery

Characteristic	All Pts	Subgroup			p Value		
		A (imprvmt)	B (no Cx)	C (decline)	A vs B	B vs C	C vs A
Total no. of pts	32	10	8	14			
Age in yrs, mean	45.4 ± 8.7	39.2 ± 8.1	49.1 ± 9.0	47.6 ± 7.0	0.0423	NS	0.0488
Male sex	7 (22)	2 (20)	2 (25)	3 (21)	NS	NS	NS
Hypertension	6 (19)	1 (10)	2 (25)	3 (21)	NS	NS	NS
Diabetes mellitus	4 (13)	0 (0)	2 (25)	2 (14)	NS	NS	NS
Dyslipidemia	6 (19)	2 (20)	2 (25)	2 (14)	NS	NS	NS
TIA alone	25 (78)	8 (80)	7 (88)	10 (71)	NS	NS	NS
Suzuki angiographic stage 3	9 (28)	3 (30)	2 (25)	4 (29)	NS	NS	NS
Suzuki angiographic stage ≥ 4	23 (72)	7 (70)	6 (75)	10 (71)	NS	NS	NS
Time from 1st ischemic event to op in mos, mean	7.5 ± 7.6	8.2 ± 8.6	10.0 ± 9.7	5.6 ± 5.4	NS	NS	NS
Preop OEF (%) in precentral region, mean	52.7 ± 0.8	52.7 ± 0.9	52.6 ± 0.4	52.8 ± 0.9	NS	NS	NS
Duration of intraop temp occl in mins, mean	31.4 ± 6.3	31.1 ± 5.0	33.3 ± 6.8	30.5 ± 7.1	NS	NS	NS
Mean sys BP for 7 days after op, mm Hg	122 ± 14	124 ± 19	122 ± 13	121 ± 17	NS	NS	NS

BP = blood pressure; Cx = change; imprvmt = improvement; NS = not significant; occl = occlusion; pts = patients; sys = systolic; temp = temporary; TIA = transient ischemic attack.

Values are n (%) unless otherwise indicated. Mean values are presented with SDs.

trols were 33.5–51.8, 33.3–52.1, 33.4–52.2, 33.7–51.3, and 33.9–51.3, respectively. In patients, symptomatic misery perfusion was defined as at least 1 MCA ROI that was above the upper limit of the 95% confidence interval for PET-OEF in the symptomatic hemisphere. According to this definition, 36 patients were determined to have misery perfusion in the symptomatic hemispheres and 79 patients were determined to not have it. Arterial bypass surgery was recommended for the former group, but 2 of the 36 patients refused the surgery. The remaining 34 patients underwent arterial bypass surgery; 2 of these patients developed new ischemic lesions in the cerebral hemisphere ipsilateral to surgery as seen on MRI performed on the 1st postoperative day and were excluded from the present study. The 32 remaining patients were included in the present study and completed the ¹²³I-IMP SPECT studies and neuropsychological testing. Two of these 32 patients met all the inclusion criteria in both cerebral hemispheres and underwent bilateral arterial bypass procedures. However, the second surgery was done more than 6 months after the last ischemic event, and therefore we only analyzed data from the first surgery in these patients.

Table 1 shows basic characteristics of the 32 patients whose data were analyzed. In all 32 patients, the STA and M₄ in the precentral region were anastomosed. No other M₄ arteries were used as the recipient artery. Postoperative MR angiography demonstrated that the arterial bypass was patent in all 32 patients.

¹²³I-IMP SPECT imaging on the day after surgery showed a focal prominent increase in CBF in the precentral region in 17 of the 32 patients (53%). The precentral MCA ROI and the MCA ROI supplied by the anastomosed M₄ of the MCA were the same. Cerebral hyperperfusion syndrome was suspected in 10 of the 17 patients, including 4 who developed aphasia, 3 who developed seizures, and 3 who developed hemiparesis, all 2–10 days postoperatively.

The propofol coma lasted for 3–7 days. No new neurological deficits occurred in 7 patients after the coma. The other 3 patients exhibited hemiparesis or aphasia after the coma. Slight deficits remained 2 months after surgery. No patient exhibited intracranial hemorrhage during the postoperative course. In 17 patients with a focal increase in CBF on ¹²³I-IMP SPECT imaging on the 1st postoperative day, including 10 patients with suspected cerebral hyperperfusion syndrome, a focal increase in CBF was no longer evident on ¹²³I-IMP SPECT images obtained 2 months after surgery, and the 10 patients were ultimately determined to have had cerebral hyperperfusion syndrome.

In 10 patients with cerebral hyperperfusion syndrome, the second neuropsychological assessments were performed 6 weeks or more after termination of propofol coma. Apparent disturbances in consciousness were not observed in any of the patients during these neuropsychological assessments, although 3 of the patients with cerebral hyperperfusion syndrome exhibited slight hemiparesis or aphasia. All patients successfully underwent neuropsychological testing. Based on the neuropsychological assessments before and after surgery, 10 (31%), 8 (25%), and 14 (44%) patients were considered to have, respectively, improvement, no change, and decline in cognitive function postoperatively. All 10 patients with cerebral hyperperfusion syndrome exhibited a decline in cognitive function postoperatively. Table 2 shows the changes in each neuropsychological test score between the 2 tests (second test score minus first test score) in controls³⁷ and patients. Although there were no statistically significant differences between the controls and the overall study cohort with respect to the change in test scores, comparison of the values for controls and individual patient groups showed a number of statistically significant differences.

Table 1 shows a comparison of the basic characteristics among patients with improvement, no change, or a decline

TABLE 2. Differences in each neuropsychological test score between 2 tests (2nd test score minus 1st test score) in controls and patients

Test	Ctrls (n = 40)*	All Pts (n = 32)	Subgroup			p Value			
			A (imprvmt, n = 10)	B (no Cx, n = 8)	C (decline, n = 14)	Ctrls vs All Pts	Ctrls vs A	Ctrls vs B	Ctrls vs C
WAIS-R verbal IQ	3.4 ± 4.5	4.1 ± 9.0	13.4 ± 3.6	6.3 ± 4.1	-3.8 ± 6.4	NS	<0.0001	0.0314	0.0038
WAIS-R performance IQ	4.9 ± 5.0	4.9 ± 9.0	13.9 ± 4.1	6.4 ± 3.1	-2.4 ± 7.4	NS	0.0001	NS	0.0041
WMS	4.7 ± 6.1	6.5 ± 7.8	14.1 ± 3.1	8.6 ± 4.4	-0.2 ± 5.6	NS	0.0010	0.0286	0.0283
Rey copy	0.4 ± 1.1	0.6 ± 1.8	2.5 ± 0.7	0.5 ± 0.8	-0.6 ± 1.6	NS	<0.0001	NS	0.0312
Rey recall	2.9 ± 3.5	4.6 ± 5.5	9.8 ± 2.5	5.5 ± 2.6	0.3 ± 4.6	NS	<0.0001	0.0369	NS

Ctrls = controls; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS = Wechsler Memory Scale.

* Control values were obtained from a previously published study³⁷ in which healthy volunteers underwent testing on 2 separate occasions.

in cognitive function after surgery. Patients with improved cognition were younger than those who had no change or cognitive decline. There were no other statistically significant differences between the 3 subgroups.

Figure 1 and Table 3 show chronological changes of RCBF_{afMCA} in the precentral region (precentral RCBF_{afMCA}) in patients who showed improvement, no change, or a decline in cognitive function after surgery. Precentral RCBF_{afMCA} in all patients and in patients with postoperative improvement or decline differed significantly among the 3 times: RCBF_{afMCA} was highest on the 1st postoperative day, followed by 2 months after surgery, and then before surgery. Although precentral RCBF_{afMCA} in patients with unchanged cognition was significantly greater on the 1st postoperative day than before surgery and 2 months after surgery, RCBF_{afMCA} before surgery and 2 months after surgery did not differ significantly. Although precentral RCBF_{afMCA} before surgery and 2 months after surgery did not differ among patients in the 3 categories of postoperative cognition, precentral RCBF_{afMCA} on the 1st postoperative day was significantly greater in patients with postoperative cognitive decline than in those with improved or unchanged cognition; RCBF_{afMCA} did not differ between patients with improved and unchanged cognition. According to ROC curve analysis, sensitivity, specificity, and positive and negative predictive values for the precentral RCBF_{afMCA} on the 1st postoperative day at the cutoff point (142.0%) lying closest to the left upper corner of the ROC curve for the prediction of postoperative cognitive decline were 100% (95% CI 100%–100%), 83% (95% CI 66%–100%), 82% (95% CI 64%–100%), and 100% (95% CI 100%–100%), respectively (Fig. 1).

Figure 2 and Table 4 show precentral Δ RCBF_{afMCA} in patients with improvement, no change, and decline in cognitive function after surgery. Precentral Δ RCBF_{afMCA}(POD 1–preop) and Δ RCBF_{afMCA}(2 mos–POD 1) were significantly greater and lower, respectively, in patients with postoperative cognitive decline than in the other 2 subgroups (patients with improved or unchanged cognition); these 2 RCBF change values did not differ significantly between the subgroups with improved and unchanged cognition. Precentral Δ RCBF_{afMCA}(2 mos–preop) was significantly greater in patients with postoperative improvement than in those with no change or decline; precentral Δ RCBF_{afMCA}(2 mos–preop) did not differ significantly between the no-change and cognitive decline subgroups. According to ROC curve analyses,

sensitivity, specificity, and positive and negative predictive values for the precentral Δ RCBF_{afMCA}(2 mos–preop) at the cutoff point (11.3%) lying closest to the upper left corner of the ROC curve for the prediction of postoperative cognitive improvement were 100% (95% CI 100%–100%), 73% (95% CI 54%–91%), 63% (95% CI 39%–86%), and 100% (95% CI 100%–100%), respectively (Fig. 2).

Figures 3 and 4 show ¹²³I-IMP SPECT images in a patient with postoperative cognitive improvement and a patient with postoperative cognitive decline, respectively.

Discussion

The present study demonstrated that cerebral hyperperfusion in the acute stage after arterial bypass surgery impairs cognitive function and that an increase in CBF in the chronic stage without acute-stage cerebral hyperperfusion improves cognitive function in adult patients with symptomatic ischemic MMD and misery perfusion.

Cognition is reportedly impaired in 20%–30% of adult MMD patients without conventional MRI evidence of stroke when compared with cognitive function in healthy

FIG. 1. Chronological changes in RCBF_{afMCA} in the precentral region (precentral RCBF_{afMCA}) in patients with cognitive improvement, no change, and cognitive decline after surgery. Each symbol represents 1 patient. The dashed horizontal line denotes the cutoff point (142.0%) lying closest to the upper left corner of the ROC curve to predict impaired cognition after surgery. HPS = cerebral hyperperfusion syndrome.

TABLE 3. Chronological changes in RCBF_{afMCA} (%) in the precentral region in patients with cognitive improvement, no change in cognitive function, or cognitive decline after surgery

Description	All Pts (n = 32)	Subgroup			p Value		
		A (imprvmt, n = 10)	B (no Cx, n = 8)	C (decline, n = 14)	A vs B	B vs C	C vs A
Preop RCBF _{afMCA}	79.9 ± 5.9	77.3 ± 5.3	83.1 ± 6.4	79.8 ± 5.5	NS	NS	NS
POD 1 RCBF _{afMCA}	139.0 ± 34.2	105.3 ± 18.2	131.4 ± 32.1	167.3 ± 15.3	NS	0.0029	<0.0001
2 mos postop RCBF _{afMCA}	92.8 ± 4.3	94.5 ± 3.0	93.2 ± 5.5	91.3 ± 4.2	NS	NS	NS
Preop vs POD 1	p < 0.0001	p < 0.0001	p = 0.0014	p < 0.0001			
POD 1 vs 2 mos postop	p < 0.0001	p = 0.0067	p = 0.0086	p < 0.0001			
2 mos postop vs preop	p = 0.0492	p = 0.0326	NS	p = 0.0126			

RCBF_{afMCA} = relative CBF in the affected MCA ROI.

subjects.¹² Subtle but widespread disruption of cerebral white matter due to hemodynamic compromise may play a pivotal role in the development of cognitive dysfunction in adult MMD patients.¹³ A recent study also showed that the majority of adult MMD patients showed neither significant decline nor significant improvement in cognitive performance after arterial bypass surgery.³⁹ Based on neuropsychological assessments before and after surgery, 31% of our patients were considered to have postoperative improvement in cognitive function and 44% were considered to have postoperative cognitive decline. Both incidences were approximately 3-fold higher than those reported previously.³⁹ These discrepancies may be due to differences in methodological factors, including the sample size, types of patient and control groups, range of neuropsychological testing, and timing of postoperative assessment. However, the preoperative condition of cerebral hemodynamics in the patient population may influence cognitive outcomes most strongly. The previous study did not describe the presence or absence of such conditions in detail.³⁹ Because misery perfusion in the symptomatic hemisphere increases the risk of additional ischemic events in patients with

symptomatic chronic internal carotid artery or MCA occlusive disease caused by atherosclerosis,^{10,36} only patients with MMD and misery perfusion were considered candidates for arterial bypass surgery in our study.

Cerebral hyperperfusion syndrome after arterial bypass surgery for MMD can often be prevented by strict blood pressure control after surgery.⁸ However, intracranial hemorrhage develops in approximately 10% of MMD patients with cerebral hyperperfusion syndrome despite strict postoperative control of blood pressure.⁸ Other investigators showed that propofol coma in addition to strict postoperative control of blood pressure prevents the development of intracranial hemorrhage due to cerebral hyperperfusion after carotid endarterectomy.²⁵ Thus, in the present study, a propofol coma was induced for patients who were suspected to have cerebral hyperperfusion syndrome despite strict postoperative control of blood pressure, and none of the 10 patients with cerebral hyperperfusion syndrome developed intracranial hemorrhage. On the other hand, a propofol coma usually induces further reduction of blood pressure. This may result in hypoperfusion in cerebral regions without hyperperfusion, causing cognitive impairment. Therefore, we maintained systolic blood pressure between 110 and 130 mm Hg as much as possible, even during the propofol coma. As a result, systolic blood pressure after surgery did not differ significantly among patients with improvement, no change, or decline in cognitive function postoperatively. Propofol also reduces cerebral function, with a decrease in metabolism in the cerebral cortex.¹ However, after termination of long-term continuous infusion, the blood concentration of propofol declines rapidly, with a half-life of 24 hours at the longest.¹ In patients with cerebral hyperperfusion syndrome, the second neuropsychological assessments were performed 6 weeks or more after termination of propofol coma. At these neuropsychological assessments, none of the patients exhibited any apparent disturbances in consciousness. Thus, propofol coma minimally affected postoperative systolic blood pressure and cognitive results in our patients.

We will first describe possible mechanisms that may explain the development of cerebral hyperperfusion after arterial bypass surgery for MMD,^{6,8,29} and then we will comment on the relationship between misery perfusion before surgery and reduced cognitive function after surgery. Perfusion pressure will decrease in the cerebral hemisphere distal to the affected artery in the presence of

FIG. 2. Comparison of each precentral ΔRCBF_{afMCA} in patients with cognitive improvement, no change, and cognitive decline after surgery. Each symbol represents 1 patient. The dashed horizontal line denotes the cutoff point (11.3%) lying closest to the upper left corner of the ROC curve for the precentral ΔRCBF_{afMCA}(2 mos–preop) to predict postoperative cognitive improvement.

TABLE 4. Percentage change in RCBF_{afMCA} in the precentral region in patients with cognitive improvement, no change in cognitive function, or cognitive decline after surgery

Description	All Pts (n = 32)	Subgroup			p Value		
		A (imprvmt, n = 10)	B (no Cx, n = 8)	C (decline, n = 14)	A vs B	B vs C	C vs A
POD 1 – preop	59.1 ± 34.9	28.0 ± 18.7	48.3 ± 36.4	87.5 ± 16.3	NS	0.0031	<0.0001
2 mos postop – POD 1	–46.2 ± 36.0	–10.9 ± 17.1	–38.2 ± 35.3	–76.0 ± 16.0	NS	0.0030	<0.0001
2 mos postop – preop	12.9 ± 4.3	17.2 ± 3.8	10.1 ± 2.4	11.5 ± 3.2	0.0003	NS	0.0009

steno-occlusive changes in the terminal portion of the internal carotid artery that demonstrates insufficient collateral circulation. When perfusion pressure is reduced below the ability of autoregulatory mechanisms to compensate for the change, maximal dilation of resistance vessels and misery perfusion occur. Arterial bypass surgery restores perfusion pressure, but chronically impaired autoregulatory mechanisms may not adjust to the new steady state for several days, leading to temporary but persistent hyperperfusion. All patients in the present study had such critical conditions of cerebral hemodynamics, and 31% of them (10/32) developed cerebral hyperperfusion syndrome. On the 1st postoperative day, 7 other patients (22% of the overall group of 32) also had an increase in CBF that was equal to that in patients with cerebral hyperperfusion syndrome, although they remained asymptomatic. More than 80% of the patients (14 of 17) with such prominently increased CBF on the 1st postoperative day showed a reduction in cognitive function. These data are consistent with findings observed in patients treated with carotid endarterectomy.²⁵ Postoperative cerebral hyperperfusion, which may show no symptoms, produces widespread, minimal damage to the ipsilateral white matter and cortical regions following carotid endarterectomy, resulting in postoperative cognitive impairment.^{2,21} A case of an adult patient with the same phenomenon in MMD has also been reported: this patient developed cognitive decline accompanied by a decrease in cerebral oxygen metabolism due to cerebral hyperperfusion syndrome after arterial bypass surgery.²⁴ Postoperative cognitive decline in our patients with prominently increased CBF in the acute stage after surgery may thus be caused by such a mechanism.

Consistent with our data, arterial bypass surgery to treat the cerebral hemisphere that exhibits MMD-induced misery perfusion also produces an increase in CBF after surgery in the chronic postoperative stage.^{9,17,22} However, the degree of the increase in CBF in the postoperative chronic stage differed among cognitive outcomes when compared with preoperative CBF: the increase was greater in patients with postoperative cognitive improvement than in those with no change or cognitive decline. A previous study showed that revascularization surgery for the cerebral hemisphere with misery perfusion due to MMD improves cerebral oxygen metabolism accompanied by improvement in CBF in younger adult patients without development of postoperative parenchymal lesions.¹⁷ Our patients with postoperative cognitive improvement satisfied all these conditions for improvement in cerebral oxygen metabolism. Further, several investigators demonstrated that a postoperative increase in cerebral metabolism is associated with cognitive improvement after carotid endarterectomy.^{28,38} Therefore, arterial bypass surgery in the cerebral hemisphere that demonstrates misery perfusion may improve cerebral metabolism, increase CBF in the chronic stage after surgery, and improve cognitive ability.

Even in patients with improved cognition after surgery, CBF was transiently increased on the 1st postoperative day, although the degree of this CBF increase was lower in such patients than in patients with postoperative cognitive decline. The transient and slight increase in CBF in the acute postoperative stage may not damage neural tissues in the affected cerebral hemisphere.

Our study has several limitations. First, as mentioned above, we hypothesized that the level of increase in CBF

FIG. 3. Images obtained in a 35-year-old woman with ischemic MMD who exhibited improved cognition after surgery. The preoperative PET image demonstrates an increase in the OEF in the right precentral region (A). The preoperative brain perfusion SPECT image shows a reduction in CBF in the right precentral region (B), where CBF is slightly increased on the 1st postoperative day (C) and is further increased 2 months after surgery (D).

FIG. 4. Images obtained in a 44-year-old woman with ischemic MMD who exhibited cognitive decline after surgery. The preoperative PET image demonstrates an increase in the OEF in the right cerebral hemisphere including the precentral region (A). The preoperative brain perfusion SPECT image shows a reduction in CBF in the right cerebral hemisphere (B). A focal prominent increase in CBF is observed in the right precentral region on the 1st postoperative day (C). This increase in CBF had resolved 2 months after surgery (D).

following arterial bypass surgery would affect cerebral metabolism and improve cognitive ability. However, cerebral metabolism was not assessed in the present study. Second, we only assessed patients with misery perfusion caused by MMD who underwent arterial bypass surgery. Post-revascularization changes in cognitive function in MMD patients without misery perfusion³⁵ or with the onset of intracerebral hemorrhage²⁰ remain unknown.

Conclusions

Cerebral hyperperfusion in the acute stage after arterial bypass surgery impairs cognitive function, and an increase in CBF in the chronic stage without acute-stage cerebral hyperperfusion improves cognitive function in adult patients with symptomatic ischemic MMD and misery perfusion.

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Disclosures

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Conception and design: Ogasawara, Kobayashi. Acquisition of data: Yanagihara, Kobayashi, Terasaki. Analysis and interpretation of data: Yanagihara, Kobayashi, Kubo, Terasaki. Drafting the article: Ogasawara, Chida. Critically revising the article: Chida, Kubo, Yoshida. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ogasawara. Statistical analysis: Yoshida.

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