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Preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease

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Abstract

The present study examined whether preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with development of cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease. Among 65 adult patients with ischemic moyamoya disease, 19 had misery perfusion in the precentral region on preoperative ^{15}O positron emission tomography and underwent arterial bypass surgery for that region. Brain technetium-99 m-labeled ethyl cysteinate dimer single-photon emission computed tomography (SPECT) was preoperatively performed with and without hyperventilation challenge and relative cerebrovascular contractile reactivity to hypocapnia ($RCVCR_{hypocap}$) (%/mmHg) was calculated in the precentral region. Development of cerebral hyperperfusion syndrome was determined using perioperative changes of symptoms and brain N-isopropyl-p-[^{123}I]-iodoamphetamine SPECT performed after surgery. $RCVCR_{hypocap}$ was significantly lower in the 6 patients with cerebral hyperperfusion syndrome (-2.85 ± 1.10%/mmHg) than in the 13 patients without cerebral hyperperfusion syndrome (0.18 ± 1.97%/mmHg; $p = 0.0050$). Multivariate analysis demonstrated low $RCVCR_{hypocap}$ as an independent predictor of cerebral hyperperfusion syndrome (95% confidence interval, 0.04–0.96; $p = 0.0433$). Preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with development of cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease.

Keywords

Moyamoya disease, hyperperfusion syndrome, hypocapnia, misery perfusion, single-photon emission computed tomography

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Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease of unknown etiology 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.[1,2] Arterial bypass surgery, such as superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis, is generally employed as the standard surgical treatment for moyamoya disease with the onset of ischemic symptoms as well as intracerebral hemorrhages.[3] This procedure prevents further cerebral ischemic attacks in the former[4,5] and reduces the risk of rebleeding in the latter.[6]

Cerebral hyperperfusion following arterial bypass surgery is known as a surgical complication of moyamoya disease and is defined as an acute substantial increase in ipsilateral cerebral blood flow (CBF) well above the metabolic demands of the brain tissue.[7–9] Cerebral hyperperfusion syndrome after arterial bypass surgery for moyamoya disease is a complication of cerebral hyperperfusion, with an incidence of approximately 30% and with characteristic features including transient aphasia, hemiparesis, and dysarthria.[7,10,11] Cerebral hyperperfusion also leads to intracerebral hemorrhage and/or subarachnoid hemorrhage.[11,12] The incidence of such hemorrhage ranges from 3 to 5%, which could potentially result in permanent neurological deficit and/or mortality.[3] Furthermore, the incidence of cerebral hyperperfusion syndrome including hemorrhage is considerably greater in adult patients than in pediatric patients.[10,13]

Mechanisms to explain the development of cerebral hyperperfusion after arterial bypass surgery for moyamoya disease have been proposed.[11,13] When steno-occlusive changes at the terminal portion of the internal carotid artery develop with deficient collateral circulation, perfusion pressure is decreased in the cerebral hemisphere distal to the affected artery. Reduction of perfusion pressure below the compensatory capacity of autoregulatory mechanisms leads to maximal dilation of resistance vessels and misery perfusion. When the perfusion pressure is restored following arterial reconstructive surgery, several days may be required for chronically impaired autoregulatory mechanisms to adjust to the new steady state, resulting in temporary ongoing hyperperfusion. Thus, absent or insufficient contraction of maximally dilated resistance vessels in response to restored perfusion pressure may cause cerebral hyperperfusion after arterial bypass surgery for moyamoya disease. However, whether this hypothesis is correct remains unclear.

In the healthy human brain, hypocapnia induced by hyperventilation contracts the arterioles, resulting in reduced CBF.[14] This phenomenon can be displayed using positron emission tomography (PET).[15] Technetium-99 m-labeled (^{99m}Tc) ethyl cysteinate dimer (ECD), an accumulative radioligand, is used as a brain perfusion tracer for single-photon emission computed tomography (SPECT) to image reduced blood flow in the cerebral hemisphere with internal carotid artery or MCA occlusive disease.[16] Use of ^{99m}Tc-ECD SPECT can also image CBF changes by hypocapnia induced by hyperventilation in patients with moyamoya disease.[17]

The purpose of the present study using PET and SPECT was to determine whether preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with development of cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease.

Materials and methods

Healthy subjects

Twenty healthy male adults meeting the following criteria were prospectively enrolled to obtain normal control values of brain ^{15}O gas PET and ^{99m}Tc-ECD SPECT: age >30 years but <60 years; absence of any history of hypertension, diabetes mellitus or dyslipidemia; absence of leukoaraiosis or asymptomatic lacunar infarction on conventional brain magnetic resonance (MR) imaging. These 20 healthy subjects were assigned to one of two groups ($n = 10$ each) who underwent ^{15}O-gas PET or ^{99m}Tc-ECD SPECT, respectively.

Patients inclusion criteria

Patients who were diagnosed with moyamoya disease according to the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan were prospectively selected for the present study if they satisfied the following clinical inclusion criteria: age >30 years but <60 years; useful residual function (modified Rankin disability scale 0 or 1); presence of episodes of ipsilateral carotid territory ischemic symptoms that had occurred ≤3 months before presentation to our department; and absence of major cerebral infarction on MR imaging. These selected patients first underwent brain ^{15}O-gas PET according to the methods described below (see "Preoperative brain ^{15}O-gas PET study" section). When a patient showed symptomatic misery perfusion on the ^{15}O PET study (see "Data analysis and definition of preoperative misery perfusion and postoperative hyperperfusion" section), the patient was considered a candidate for

arterial bypass surgery and was finally included into the present study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee Iwate Medical University School of Medicine (H22-3) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, and written, informed consent was obtained from all subjects or their next of kin prior to the patient participation.

Preoperative brain ^{15}O-gas PET study

PET studies were performed using an SET-3000GCT/M scanner (PET/CT; Shimadzu, Kyoto, Japan) for healthy subjects and patients. In the latter group, these studies were performed more than three weeks after the last ischemic event. Before emission scans, a transmission scan (3 min) with a ^{137}Cs point source was performed using a bismuth germanate transmission detector ring coaxially attached to the gadolinium silica oxide emission detector ring. CBF was determined while the subject continuously inhaled $C^{15}O_2$ through a mask. Measurements of the cerebral metabolic rate of oxygen ($CMRO_2$) and oxygen extraction fraction (OEF) were obtained during continuous inhalation of $^{15}O_2$. Data were collected for 5 min. A single breath of $C^{15}O$ was used to measure cerebral blood volume (CBV). CBF, $CMRO_2$ and OEF were calculated using the steady-state method,[18] and $CMRO_2$ and OEF were corrected by CBV.[19]

Preoperative brain ^{99m}Tc-ECD SPECT study with and without hyperventilation

Within five days after PET, ^{99m}Tc-ECD SPECT studies were performed for patients using a triple-head gamma camera (GCA-9300R; Toshiba Medical Systems, Tochigi, Japan). The spatial resolution of the gamma camera with a high-resolution fan-beam collimator was 8.5 mm full width at half maximum. The SPECT acquisition protocol consisted of a matrix size of 128×128 and 30-min continuous acquisition (5 min/rotation) over 360° in 4° steps. Post-acquisition, data were corrected for scatter with the triple energy window method and then reconstructed by filtered back-projection. A Butterworth preprocessing filter was applied, with a cutoff frequency of 0.08 cycles per pixel (1 pixel = 1.72 mm). For attenuation correction, the iterative Chang method was used, and the attenuation map was generated by extracting the skin contour and assuming the inner region side as a uniform attenuation body. The attenuation coefficient was 0.146 cm^{-1}.

First, each patient was given an intravenous bolus injection of 740 MBq of ^{99m}Tc-ECD from a commercially supplied kit and scanning with the above-mentioned collimator was started 5 min after tracer injection with a scanning duration of 10 min. Two days later, the same patient underwent ^{99m}Tc-ECD SPECT with hyperventilation challenge. Under transcutaneous CO_2 partial pressure (PCO_2) monitoring using a single earlobe sensor (SENTEC Digital Monitor System; SENTEC, Ringstrasse, Switzerland), hyperventilation was performed for 90 s and ^{99m}Tc-ECD was administered immediately after the end of hyperventilation. Five minutes later, SPECT was performed in the same manner as at resting state. For each patient, PCO_2 at the end of hyperventilation and the lowest PCO_2 within 1 min after stopping were averaged, and the averaged value was subtracted from a pre-hyperventilation value. This difference was defined as ΔPCO_2 (mmHg).

Postoperative brain N-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) SPECT study

To detect postoperative cerebral hyperperfusion, ^{123}I-IMP SPECT studies were performed using the same scanner as ^{99m}Tc-ECD SPECT studies at one day and at one month after surgery. After intravenous infusion of 222 MBq of ^{123}I-IMP, data acquisition was performed at a mid-scan time of 30 min for a scan duration of 20 min.

Data analysis and definitions of preoperative misery perfusion and postoperative hyperperfusion

All PET and SPECT images were transformed into the standard brain size and shape by linear and nonlinear transformation using SPM2 for anatomic standardization.[20] Brain images from all subjects thus had the same anatomic format. A total of 318 constant regions of interest (ROIs) were automatically placed in both the cerebral and cerebellar hemispheres using a three-dimensional stereotaxic ROI template (3DSRT) with SPM2 (FUJIFILM RI Pharma, Tokyo, Japan).[21] ROIs were grouped into 10 segments (callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, posterior, hippocampal, and cerebellar) in each hemisphere according to the arterial supply. Of these 10 segments, five (precentral, central, parietal, angular, and temporal) perfused by the MCA and cerebellar ROI were used for the following analyses (Figure 1).

Mean values of CBF, CBV, $CMRO_2$ and OEF on PET images were measured in the five MCA ROIs in bilateral cerebral hemispheres. In each MCA ROI of each patient, when CBF or $CMRO_2$ was lower than the lower limit of the 95% confidence interval (CI) of control values obtained from 10 healthy subjects, this ROI was defined as displaying abnormally reduced

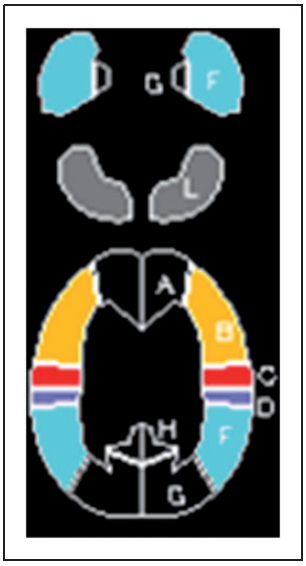

Figure 1. Diagrams showing the regions of interest (ROIs) of a three-dimensional stereotaxic ROI template. Orange, red, blue, cyan, and grey ROIs indicate precentral, central, parietal, temporal, and cerebellar regions, respectively.

CBF or $CMRO_2$, respectively; when CBV or OEF was greater than the upper limit of the 95%CI of the control values, this ROI was defined as having abnormally elevated CBV or OEF, respectively. Furthermore, when one or more MCA ROIs in the symptomatic hemisphere exhibited abnormally elevated OEF, the patient was defined as having symptomatic misery perfusion.

The mean value of radioactive counts on preoperative ^{99m}Tc-ECD SPECT images was measured in the five MCA ROIs in bilateral cerebral hemispheres and bilateral cerebellar ROIs. For each patient, the ratio of the mean radioactive count in each MCA ROI with misery perfusion in the symptomatic cerebral hemisphere to that in the ipsilateral cerebellar ROI was calculated. Relative cerebrovascular contractile reactivity to hypocapnia ($RCVCR_{hypocap}$) (%/mmHg) was defined as follows: $100*(Ratio_{rest} - Ratio_{HV})/ Ratio_{rest} *\Delta PCO_2$), where, $Ratio_{rest}$ and $Ratio_{HV}$ are the ECD SPECT ratios at resting state and with hyperventilation challenge, respectively. In each MCA ROI of each patient, when $RCVCR_{hypcap}$ was lower than the lower limit of the 95%CI of control values obtained from 10 healthy subjects, this ROI was defined as having abnormally reduced cerebrovascular contractile reactivity to hypocapnia; when $RCVCR_{hypocap}$ was greater than the upper limit of the 95%CI of control values, this ROI was defined as having abnormally increased cerebrovascular contractile reactivity to hypocapnia; and ROIs with other values of $RCVCR_{hypocap}$ were defined as having normal cerebrovascular contractile reactivity to hypocapnia.

When a focal increase in CBF was visually observed in one or more MCA ROIs ipsilateral to surgery and a ratio (defined as $RCBF_{postope}$) of the mean radioactive count in those MCA ROIs to that in the cerebellar ROI ipsilateral to surgery was >1.5 on ^{123}I-IMP SPECT images one day after surgery, the patient was suspected as having cerebral hyperperfusion.[13] Such patients were finally defined as having cerebral hyperperfusion when the focal increase in CBF at one day after surgery visually resolved on ^{123}I-IMP SPECT images one month after surgery. Cerebral hyperperfusion syndrome was determined using the following criteria: (1) headache, seizure, alteration in level of consciousness, and/or focal neurologic signs such as aphasia, hemiparesis, and dysarthria that newly developed or worsened between 12 h and 30 days after surgery; and (2) presence of cerebral hyperperfusion on ^{123}I-IMP SPECT.

Intra- and postoperative management

Patients underwent a single STA-MCA anastomosis without indirect revascularization between one month and four months after the last ischemic event. The M4 perfusing an MCA ROI with the misery perfusion in the symptomatic cerebral hemisphere was selected as a recipient artery. For patients with misery perfusion in bilateral cerebral hemispheres and bilateral carotid territory ischemic symptoms that had occurred ≤3 months before presentation to our department, the hemisphere with the MCA ROI with the higher OEF underwent surgery first; and three months later, the contralateral hemisphere underwent the surgery.

Postoperatively, all patients were strictly managed to avoid hypovolemia and anemia. Attempts were made to keep the systolic blood pressure between 110 and 130 mmHg. When a patient was suspected as having cerebral hyperperfusion on ^{123}I-IMP SPECT images one day after surgery and headache, seizure, alteration in level of consciousness, and/or focal neurologic signs newly developed or worsened after surgery, a propofol coma was induced.

One month after surgery, MR angiography was performed to confirm patency of the arterial bypass.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD). The results of ^{15}O-gas PET and ^{99m}Tc-ECD SPECT were compared between controls and patients using the Mann–Whitney U test. The relationship between each variable and development of cerebral hyperperfusion on postoperative ^{123}I-IMP SPECT imaging or cerebral hyperperfusion syndrome was evaluated with univariate analysis using the Mann–Whitney U test or χ^2 test. A multivariate statistical

analysis of factors related to development of cerebral hyperperfusion on postoperative ^{123}I-IMP SPECT imaging or cerebral hyperperfusion syndrome was also performed using logistic regression modeling. Variables showing values of $p < 0.2$ in univariate analyses were selected for analysis in the final model. Statistical significance for all analyses was set at the $p < 0.05$ level.

Results

From May 2010 to December 2015, a total of 65 patients satisfied the clinical inclusion criteria and underwent brain ^{15}O-gas PET. Of these 65 patients, 20 were determined as having misery perfusion in the symptomatic hemispheres, and 19 subsequently underwent preoperative ^{99m}Tc-ECD SPECT, arterial bypass surgery and postoperative ^{123}I-IMP SPECT. The remaining patient refused these further examinations and arterial bypass surgery, and was excluded from the present analyses. Of the 19 patients included, one satisfied all the inclusion criteria in bilateral cerebral hemispheres. Although this patient eventually underwent arterial bypass surgery in bilateral hemispheres, the second surgery was consequently performed more than six months after the last ischemic event. Thus, only data from the first surgery were analyzed in this patient.

Mean age of the 19 patients (4 men, 15 women) was 44 ± 8 years (range, 32–57 years). Concomitant disease states and symptoms were recorded, including four patients with hypertension, two patients with diabetes mellitus, and four patients with dyslipidemia; 14 patients had TIA alone and 5 had minor stroke with or without preceding TIA. The STA was anastomosed to the M4 in the precentral region in all 19 patients. The M4 of the other regions was not selected as a recipient artery. Duration of intraoperative temporary occlusion for the recipient artery ranged from 21 to 40 min (mean, 30 ± 5 min)

Mean age of the 10 healthy male adults who were enrolled to obtain normal control values of brain ^{15}O-gas PET was 42 ± 7 years (range, 30–55 years). Mean, SD and 95% CI of PET-CBF, CBV, $CMRO_2$ and OEF in the MCA ROI of the precentral region in controls and patients are shown in Table 1. CBF was significantly lower in patients than in controls. CBV and OEF were significantly greater in patients than in controls. $CMRO_2$ did not differ between controls and patients. The MCA ROI of the precentral region in all 19 patients exhibited abnormally reduced CBF and abnormally elevated CBV, and none of the MCA ROIs of the precentral region exhibited abnormally reduced $CMRO_2$.

The mean age of the 10 healthy male adults who were enrolled to obtain normal control values of $RCVCR_{hypocap}$ on ^{99m}Tc-ECD SPECT was 43 ± 8 years (range, 30–55 years). None of the healthy subjects or patients experienced the new development or deterioration of neurological symptoms during the hyperventilation challenge. In patients, ΔPCO_2 was 8 ± 3 mmHg (range, 5–15 mmHg). Mean, SD and 95%CI of $RCVCR_{hypocap}$ in the MCA ROI of the precentral region in controls and patients are shown in Table 1. $RCVCR_{hypocap}$ did not differ between controls and patients. The MCA ROI of the precentral region in nine and five patients exhibited abnormally reduced and increased cerebrovascular contractile reactivity to hypocapnia, respectively.

Of the 19 patients analyzed, 10 (53%) were suspected as having cerebral hyperperfusion on ^{123}I-IMP SPECT imaging one day after surgery. All these patients were finally determined as having cerebral hyperperfusion on ^{123}I-IMP SPECT images one month after surgery. In these 10 patients, the MCA ROI perfused by an

Table 1. Comparison of ^{15}O-gas PET and ^{99m}Tc-ECD SPECT values in MCA ROI of the precentral region in 20 cerebral hemispheres of 10 healthy subjects as controls and in 19 affected cerebral hemispheres of 19 patients.

	Controls ($n = 20$)	Patients ($n = 19$)	p
CBF (ml/100 g/min)			<0.0001
Mean	46.7	34.0	
SD	4.6	2.8	
95% CI	37.5 to 55.9	27.9 to 40.1	
CBV (ml/100 g)			<0.0001
Mean	3.74	5.50	
SD	0.59	0.30	
95% CI	2.47 to 5.01	4.85 to 6.15	
$CMRO_2$ (ml/100 g/min)			0.3185
Mean	3.50	3.31	
SD	0.55	0.27	
95%CI	2.32 to 4.68	2.73 to 3.89	
OEF (%)			<0.0001
Mean	42.6	54.7	
SD	4.3	2.6	
95%CI	33.5 to 51.8	49.2 to 60.2	
$RCVCR_{hypocap}$ (%/mmHg)			0.2021
Mean	−0.14	−0.77	
SD	0.47	2.24	
95%CI	−1.12 to 0.86	−5.26 to 3.70	

PET: positron emission tomography; ^{99m}Tc-ECD: technetium-99 m-labeled ethyl cysteinate dimer; SPECT: single-photon emission computed tomography; MCA: middle cerebral artery; ROI: region of interest; CBF: cerebral blood flow; SD: standard deviation; CI: confidence interval; CBV: cerebral blood volume; $CMRO_2$: cerebral metabolic rate of oxygen; OEF: oxygen extraction fraction; $RCVCR_{hypocap}$: relative cerebrovascular contractile reactivity to hypocapnia.

anastomosed M4 of the MCA was identical to the MCA ROI with cerebral hyperperfusion. Six (60%) of these 10 patients had cerebral hyperperfusion syndrome (Table 2). Three, two and one patients developed aphasia, seizure and hemiparesis, respectively. These symptoms developed two to nine days after surgery. Duration of propofol coma ranged from three to five days. Five patients recovered from this coma without new neurological deficits. The systolic blood pressure during propofol coma in the remaining patient (Patient 1) was kept between 110 and 130 mmHg of the systolic blood pressure, but that patient developed right hemiparesis after recovering from the coma (Figure 2). This hemiparesis remained one month after surgery,

Table 2. Clinical data in patients with cerebral hyperperfusion syndrome after surgery.

				Hyperperfusion syndrome		
Patient no.	Age (years)	Sex	Symptoms at onset	Symptoms	Onset (POD)	Duration of propofol coma (days)
1	52	W	TIA	Aphasia	3	5
2	55	M	Stroke	Seizure	5	3
3	32	W	TIA	Hemiparesis	2	4
4	47	M	TIA	Aphasia	9	4
5	57	W	Stroke with TIA	Seizure	6	3

POD: postoperative day; W: woman; M: man; TIA: transient ischemic attack.

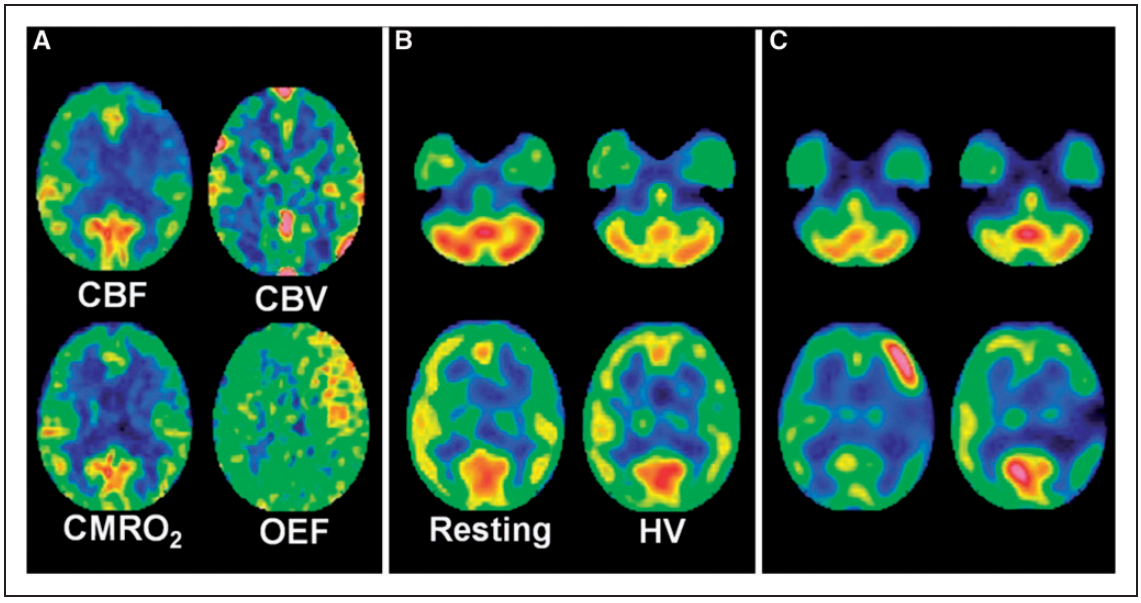

Figure 2. A 52-year-old woman with transient ischemic attacks of right hemiparesis and motor aphasia due to moyamoya disease. (a) Preoperative ^{15}O gas positron emission tomography images show a decrease in cerebral blood flow (CBF) and an increase in cerebral blood volume (CBV) in the left precentral and central regions where cerebral metabolic rate of oxygen ($CMRO_2$) and oxygen extraction fraction (OEF) are slightly decreased and markedly increased, respectively. (b) Preoperative Technetium-99 m-labeled (^{99m}Tc) ethyl cysteinate dimer (ECD) single-photon emission computed tomography (SPECT) images at rest (left) show a decrease in tracer uptake in the left precentral and central regions relative to that in the left cerebellar region. This difference in tracer uptake is decreased on ^{99m}Tc-ECD SPECT images with hyperventilation challenge (right). The left-to-right precentral and central differences in tracer uptake are also decreased on ^{99m}Tc-ECD SPECT images with hyperventilation challenge when compared with those at rest. (c) N-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) SPECT images one day after arterial bypass surgery reveal a focal increase in CBF in the left precentral region perfused by an anastomosed M4 of the left middle cerebral artery (left). Aphasia developed three days after surgery and propofol coma continued for five days. Right hemiparesis developed after recovery from this coma. This hemiparesis remained at one month after surgery when ^{123}I-IMP SPECT images demonstrate resolution of a focal increase in CBF in the left precentral region and development of a focal decrease in CBF in the left central region (right).

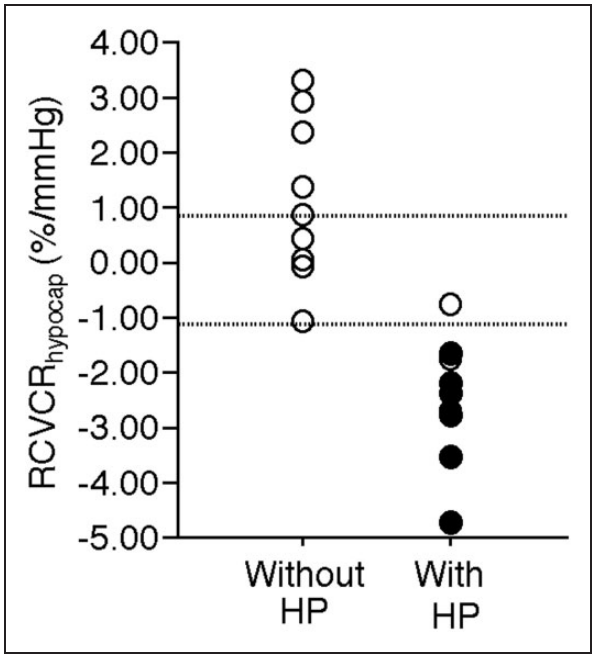

Figure 3. Relationship between cerebral hyperperfusion (HP) on postoperative ^{123}I-IMP SPECT imaging or cerebral hyperperfusion syndrome and preoperative RCVCR$_{hypocap}$ in the MCA ROI of the precentral region perfused by an anastomosed MCA. Closed and open circles denote patients with and without cerebral hyperperfusion syndrome, respectively. Upper and lower dotted horizontal lines denote upper and lower limits of the 95% confidence interval of control values obtained from healthy subjects, respectively.

when ischemic lesions developed in the left central region on MR imaging. An arterial bypass was patent on postoperative MR angiography in all 19 patients.

Figure 3 shows the relationship between the development of cerebral hyperperfusion on postoperative ^{123}I-IMP SPECT imaging or cerebral hyperperfusion syndrome and the preoperative RCVCR$_{hypocap}$ in the MCA ROI perfused by an anastomosed M4 of the MCA in patients. The RCVCR$_{hypocap}$ was significantly lower in patients with postoperative cerebral hyperperfusion than in those without postoperative cerebral hyperperfusion (Table 3) and in patients with cerebral hyperperfusion syndrome than in those without cerebral hyperperfusion syndrome (Table 4). Cerebral hyperperfusion showed abnormally reduced and normal cerebrovascular contractile reactivities to hypocapnia in 9 and 1 of the 10 patients, respectively; no patients with abnormally increased cerebrovascular contractile reactivity to hypocapnia experienced cerebral hyperperfusion. All six patients with cerebral hyperperfusion syndrome displayed abnormally reduced cerebrovascular contractile reactivity to hypocapnia.

Table 3 shows the results of univariate analyses of factors related to the development of cerebral hyperperfusion on postoperative ^{123}I-IMP SPECT. No variables other than RCVCR$_{hypocap}$ in the MCA ROI perfused by an anastomosed M4 of the MCA were associated with development of postoperative cerebral hyperperfusion. After closely related variables were eliminated in

Table 3. Factors related to development of cerebral hyperperfusion on postoperative SPECT in patients.

	Postoperative hyperperfusion		Univariate analysis	Multivariate analysis	
Risk factor	Yes ($n=10$)	No ($n=9$)	p	p	95% CI
Age (years)	46.1 ± 8.8	41.9 ± 7.8	0.1902	0.7302	0.62 to 1.80
Male sex	2 (20%)	2 (22%)	>0.9999		
Hypertension	2 (20%)	2 (22%)	>0.9999		
Diabetes mellitus	1 (10%)	1 (11%)	>0.9999		
Dyslipidemia	2 (20%)	2 (22%)	>0.9999		
TIA alone before surgery	7 (70%)	7 (78%)	>0.9999		
Preoperative PET-CBF (ml/100 g/min)	33.1 ± 3.2	35.0 ± 2.0	0.2358		
Preoperative PET-CBV (ml/100 g)	5.46 ± 0.31	5.55 ± 0.29	0.4618		
Preoperative PET-CMRO$_2$ (ml/100 g/min)	3.27 ± 0.35	3.36 ± 0.17	0.2701		
Preoperative PET-OEF (%)	55.5 ± 3.2	53.8 ± 1.3	0.4140		
Preoperative RCVR$_{hypocap}$ (%/mmHg)	-2.50 ± 1.08	1.13 ± 1.47	0.0003	0.1276	0.07 to 4.12
Duration of intraoperative temporary occlusion	30 ± 7	29 ± 5	0.7126		

Values represent number and percentage, or mean $\pm$ SD.

Table 4. Factors related to development of postoperative cerebral hyperperfusion syndrome in patients.

	Hyperperfusion syndrome		Univariate analysis	Multivariate analysis	
Risk factor	Yes ($n=6$)	No ($n=13$)	p	p	95% CI
Age (years)	46.0 ± 11.0	43.2 ± 7.3	0.4817		
Male sex	2 (33%)	2 (15%)	0.5573		
Hypertension	2 (33%)	2 (15%)	0.5573		
Diabetes mellitus	1 (17%)	1 (8%)	>0.9999		
Dyslipidemia	2 (33%)	2 (15%)	0.5573		
Only TIA before surgery	4 (67%)	10 (77%)	>0.9999		
Preoperative PET-CBF (ml/100 g/min)	33.6 ± 3.2	34.2 ± 2.8	0.7922		
Preoperative PET-CBV (ml/100 g)	5.60 ± 0.34	5.46 ± 0.28	0.3340	0.1740	0.24 to 99.12
Preoperative PET-$CMRO_2$ (ml/100 g/min)	3.34 ± 0.35	3.30 ± 0.24	0.5986		
Preoperative PET-OEF (%)	55.9 ± 3.7	54.2 ± 1.8	0.4827		
Preoperative $RCVR_{hypocap}$ (%/mmHg)	-2.85 ± 1.10	0.18 ± 1.97	0.0050	0.0433	0.04 to 0.96
Duration of intraoperative temporary occlusion	29 ± 7	30 ± 6	0.7250		

Note: Values represent number and percentage or mean ± SD.

univariate analyses, the following confounders ($p < 0.2$), age and $RCVCR_{hypocap}$ in the MCA ROI perfused by an anastomosed M4 of the MCA were included in the logistic regression model for multivariate analysis. No factors included in multivariate analysis were identified as independent predictors of the development of postoperative cerebral hyperperfusion.

Table 4 shows the results of univariate analyses of factors related to the development of cerebral hyperperfusion syndrome. No variables other than $RCVCR_{hypocap}$ in the MCA ROI perfused by an anastomosed M4 of the MCA were associated with development of cerebral hyperperfusion syndrome. Likewise, no closely related variables showed values of $p < 0.2$ in univariate analysis except $RCVCR_{hypocap}$. To eliminate closely related variables in univariate analyses, CBV with $p = 0.3340$ in addition to $RCVCR_{hypcap}$ was included in the logistic regression model for multivariate analysis. On multivariate analysis, a low $RCVCR_{hypocap}$ was an independent predictor of the development of cerebral hyperperfusion syndrome.

Discussion

The present study demonstrated that preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with development of cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease.

In the brain, ^{99m}Tc-ECD reaches a maximum within 1 min after tracer injection and remains that level for the next 15 min, even when the distribution of CBF is changed several minutes after tracer injection.[22] Thus, ^{99m}Tc-ECD SPECT with hyperventilation challenge in the present study displayed brain perfusion images within 1 min after the end of hyperventilation. Conversely, ^{99m}Tc-ECD SPECT enables imaging of a "snapshot" of regional CBF in this way,[23] but underestimates high CBF due to the limited first-pass extraction fraction.[24] We measured relative CBF reduction by hypocapnia on ^{99m}Tc-ECD SPECT and this CBF might be reduced below that at rest. Underestimation of ^{99m}Tc-ECD SPECT was therefore considered to have minimally influenced the present results. In contrast, because ^{123}I-IMP is a good first-pass extraction fraction near ^{15}O in the brain,[24] SPECT using this tracer was performed to detect postoperative cerebral hyperperfusion.

In patients with symptomatic chronic internal carotid artery or MCA occlusive disease due to atherosclerosis, presence of misery perfusion in the affected hemisphere reportedly increases the risk of further ischemic events.[25,26] Based on this finding, only patients with misery perfusion were considered as candidates for arterial bypass surgery for the present study period in our institution. As a result, all patients included into the present study had MCA ROIs with abnormally reduced CBF and abnormally elevated CBV.

The present study enrolling patients with such critical conditions of cerebral hemodynamics showed that preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation was significantly associated with the development of cerebral hyperperfusion syndrome, supporting the hypothesis that contraction of maximally dilated resistance vessels insufficient to restore perfusion pressure may cause

cerebral hyperperfusion syndrome after arterial bypass surgery. In contrast, preoperative CBV was not an independent predictor of cerebral hyperperfusion syndrome, which differed from results of a previous study.[13] Whereas only half of the patients included in the previous study exhibited an abnormal increase in CBV, all our patients were determined as having an abnormal increase in CBV. Furthermore, a quarter of patients with abnormal increases in CBV showed increased cerebrovascular contractile reactivity to hypocapnia, while half showed reduced cerebrovascular contractile reactivity to hypocapnia. Only the latter may have had resistant vessels that either do not contract or contract insufficiently to restore perfusion pressure, resulting in cerebral hyperperfusion syndrome. An abnormal increase in CBV may thus be a necessary but not sufficient condition for the development of cerebral hyperperfusion syndrome. This may be one reason for the discrepancies between the previous and present results.

In children with ischemic moyamoya diseases, marked reduction of CBF was reportedly observed on the ischemic region during re-build-up phenomenon on electroencephalography after hyperventilation,[17,27] suggesting relatively increased cerebrovascular contractile reactivity to hypocapnia in that region. These findings differed from our data of relatively decreased cerebrovascular contractile reactivity to hypocapnia in the ischemic region in adult patients with ischemic moyamoya diseases. This difference may explain why the incidence of cerebral hyperperfusion syndrome is considerably greater in adult patients than in pediatric patients.[10,13]

Several investigators have demonstrated that postoperative prophylactic blood pressure control (systolic blood pressure, 110–130 mmHg) combined with intra- and postoperative administration of minocycline hydrochloride, a neuro-protective antibiotic, blocking the deleterious inflammatory cascade by the activation of matrix metalloproteinase-9, significantly reduce the incidence of cerebral hyperperfusion syndrome.[3,28] On the other hand, routine use of blood pressure control for moyamoya disease may induce development of ischemia in the regions that are not perfused via an anastomosed STA like our one patient. Thus, such perioperative preventative treatments should be applied for only patients who are determined as having reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation.

The present study has several limitations that require discussion. First, we used cerebrovascular contractile reactivity to hypocapnia by hyperventilation as an indicator of the vasoconstrictive capacity of dilated resistance vessels to restore perfusion pressure. Dilatation and constriction of the small arterioles or intraparenchymal vessels contribute to CBF change with PCO_2 change,[14] and these vessels differ from the resistance vessels that play a main role in cerebrovascular autoregulation: the former is peripheral to the latter. Cerebrovascular contractile reactivity to hypocapnia by hyperventilation is thus not strictly an indicator of the vasoconstrictive capacity of resistance vessels. However, Tajima et al. recently reported a significant negative correlation between autoregulatory vasodilation and diameter response to hypercapnia in mouse arterioles, indicating that arterioles play key roles in both autoregulatory and hypercapnic vasodilation.[29] These findings support our data, suggesting that the reactivity to hypocapnia in the small arterioles or intraparenchymal vessels may correlate with the vasoconstrictive capacity of resistance vessels to increases in perfusion pressure under special hemodynamic conditions as in the patients in the present study. Second, among adult patients with histories of ischemic symptoms due to moyamoya disease, only patients with misery perfusion were considered as candidates for arterial bypass surgery for the present study period in our institution. This surgical indication is based on the finding regarding ICA or MCA occlusive diseases due to atherosclerosis.[25,26] Whether the finding is correctly applied for adult patients with a history of ischemic symptoms due to moyamoya disease remained unclear and the validity of this determination should be validated. We will analyze long-term outcomes of adult patients without misery perfusion despite the presence of histories of ischemic symptoms due to moyamoya disease who did not undergo arterial bypass surgery. Lastly, as described above, because only patients with misery perfusion were included into the present study, the sample size was small.

In conclusion, the present study demonstrated that preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation is associated with development of cerebral hyperperfusion syndrome after arterial bypass surgery for adult patients with cerebral misery perfusion due to ischemic moyamoya disease.

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Authors' contributions

All authors approved the version of the paper to be published. Shinpei Sato has contributed to the conception, design and implementation of the study. He analyzed and interpreted the data and drafted the article. Daigo Kojima has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Yasuyoshi Shimada has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Jun Yoshida has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Kentaro Fujimato has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Shunrou Fujiwara has contributed to the design, implementation of the study and revised the manuscript critically for important intellectual content. Masakazu Kobayashi has contributed to the design, implementation of the study and revised the manuscript critically for important intellectual content. Yoshitaka Kubo has contributed to the design, implementation of the study and revised the manuscript critically for important intellectual content. Kenji Yoshida has contributed to the design, implementation of the study and revised the manuscript critically for important intellectual content. Kazunori Terasaki has contributed to the design, implementation of the study and revised the manuscript critically for important intellectual content. Shouta Tsutsui has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Kenya Miyoshi has contributed to the analysis of the data and revised the manuscript critically for important intellectual content. Kuniaki Ogasawara has contributed to the conception, design and implementation of the study, and interpretation of the data. He has also revised the manuscript critically for important intellectual content.

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