Table 6 Summary of genetic studies combining several methods to specify the susceptibility gene for moyamoya disease (MMD)

Author (Year)	Methods	Subject	Ethnicity	Coverage	Result
Nanba et al. (2005)[47]	sequence analysis and bioinformatics analysis	9 individuals from one family, including 4 patients	Japanese	the 9-cM region within 17q25 and 26753 EST with significant similarity to the sequences of 17q25	no MMD related variation
Mineharu et al. (2008)[43]	genome-wide parametric linkage analysis, haplotype and mutation analysis of candidate genes	15 highly affected families, including 55 patients	Japanese	382 markers for 22 autosomes and 18 markers for the X chromosome	17q25.3 with a MLS 8.07 (broad classification) and 6.57 (narrow classification) at D17S704
Liu et al. (2009)[38]	parametric multi-point linkage analysis, sequence analysis of candidate 3 genes, segregation and linkage confirmation	194 Japanese in 36 families, including 109 patients; 5 Koreans in one family, including 2 patients	Japanese and Korean	13 markers at 5.1-Mb intervals in the 17q25-qter linkage region	17q25.3 with the LOD score 9.67 and Raptor ss161110142 (G/A) SNP with the LOD score 14.2
	followed by case-control study	90, 41, 23, and 25 non-familial patients and 384, 223, 100, and 164 controls (Japanese, Korean, Chinese, and Caucasian, respectively)	Japanese, Korean, Chinese, and Caucasian	SNPs of Raptor gene	Raptor ss161110142 (G/A) polymorphism in Asian cases with an OR 52.2
Kamada et al. (2011)[29]	genome-wide association study and locus-specific association study	72 patients, including 8 familial cases and 45 normal controls	Japanese	genome-wide 785720 SNPs and 335 SNPs in the 17q25-ter region	a single haplotype consisting of 7 SNPs at the RNF213 locus was tightly associated with MMD
	followed by mutational analysis of RNF213 and FLJ35220				p.R4859K (a founder mutation of RNF213) was found in 95% of familial MMD, 73% of non-familial MMD, and 1.4% of controls
Liu et al. (2011)[39]	genome-wide linkage analysis and haplotype and segregation analysis	8 three-generation families with MMD	Japanese	382 markers for 22 autosomes and 18 markers for the X chromosome	linkage at 17q25.3 ($p<10^{-4}$) with the MLS 8.46 at D17S784
	whole genome-exome analysis	8 index cases in above families	Japanese	the 1.5-Mb region on 17q25.3	p.N321S in PCMTD and p.R4810K in RNF213
	segregation confirmation	41 Japanese and one Korean families	Japanese and Korean		p.R4810K in RNF213 segregated in all 42 families
	association study	161, 384 Japanese cases and controls; 38, 223 Korean cases and controls; 52, 100 Chinese cases and controls	east Asian	ss179362673 (p.R4810K in RNF213)	strong association of pR4810K (OR338.9 in Japanese cases, OR135.6 in Korean cases, and OR14.7 in Chinese cases)
	confirmation study by cloning, biochemical and functional analysis			transcription level, ubiquitination activity of RNF213 and RNF213-knockdown zebrafish	RNF213 involves in genetic susceptibility to MMD

EST: expressed sequence tag, LOD: logarithm of odds, MLS: maximal LOD score, OR: odds ratio, SNP: single nucleotide polymorphism.

V. EPC

Since Asahara et al. first described the presence of EPCs in the peripheral blood in 1997, their biological features have been widely investigated.[5] EPCs are also expected to be donor cells in cell therapy for several ischemic vascular diseases, because they are known to contribute to vasculogenesis and endothelial repair under pathological conditions. Recently, participation of EPCs has been introduced in the pathogenesis of moyamoya disease.

Firstly, Yoshihara et al. found a significant increase of circulating $CD34^+$ cells in the peripheral blood in patients of major cerebral artery occlusion with angiographic moyamoya vessels.[78] Subse-

quently, Rafat et al. reported a significant increase of circulating EPCs ($CD34^+CD133^+VEGFR2^+$ cells) in adult patients with moyamoya disease.[51] They also found increasing plasma levels of VEGF and granulocyte-macrophage colony-stimulating factor, which were thought to mediate mobilization of EPCs. Likewise, Ni et al. reported an increase of circulating $CD34^+CXCR4^+$ cell number and plasma level of stromal cell-derived factor-1α in patients with moyamoya disease.[48] On the other hand, Kim et al. reported a significant decrease of circulating EPCs ($CD34^+CD133^+VEGFR2^+$ cells) in child patients with moyamoya disease.[32] A future discussion would be necessary whether this discrepancy might be originated from the age of the patients or stages of the disease. In both cases, these studies were quite important in a point that EPCs may participate in the formation of extensive collateral vessels (moyamoya vessel) in moyamoya disease.

As an another viewpoint, Jung et al. have found disturbed function of the circulating EPCs isolated from the peripheral blood of adult patients with moyamoya disease.[28] Similar findings were also observed in pediatric moyamoya disease.[32] However, the question still remains whether EPCs participate in the progressive occlusive lesion of the internal carotid artery, which is a 'primary' initiation site of moyamoya disease.

As mentioned above, EPCs contribute to vasculogenesis and endothelial repair. However, recent laboratory studies point that some circulating progenitor cells also participate in vascular remodeling including the development and progression of atherosclerotic plaque.[55] Since the existence of smooth muscle progenitor cells (SMPCs) was described by Simper et al., attention has focused on the finding that SMPCs have opposite role to EPCs in the development of several vascular diseases.[59]

Recently, our laboratory found that the $CD34^+$ $VEGFR2^+$ cells were closely involved in the intimal thickening of the supraclinoid internal carotid artery collected from adult patients with moyamoya disease.[61] This study was interesting in that certain progenitor cells also participated in the progressive occlusive lesion in moyamoya disease. However, the roles and the identity of such cells are still unknown.

As mentioned above, vascular progenitor cells (VPCs) such as EPC and SMPC might shed new light on the pathogenesis of moyamoya disease. However, there are several issues in such 'progenitor cell' research. These 'progenitor cells' were mostly defined by surface cell markers such as CD34, CD133, and VEGFR2, but definitive specific cell markers of such 'progenitor cell' have not been identified so far. Moreover, in this field, there were some discrepancies among studies. Further detailed study with different viewpoints would be necessary to elucidate the role of the VPCs in the pathogenesis of moyamoya disease.

Discussion

The classical and contemporary concepts shown in this review may cause confusion. None of the studies introduced can explain, by themselves, the particular aspects of pathology and clinical presentation, or the epidemiological features of moyamoya disease. None, for example, can answer the simple question of whether or not the primary lesions of moyamoya disease are localized to the terminal portion of the internal carotid artery.[1,35,49,62,63]

Probably some studies, such as those of the abnormal value of cytokines, may reflect the secondary phenomena accompanying moyamoya disease rather than its essential cause. In addition, some phenomena, such as infection and HLA alleles abnormality, may be correlated to some trigger or enhancer of the disease. Among these phenomena, the genetic abnormality and the EPC hypothesis seem to come closest to identifying the primary cause of moyamoya disease since they have a chance of rationally explaining its particular epidemiological features. However, as mentioned, the simplest but most difficult question is the particular location of the lesion seen in the terminal portion of the internal carotid arteries. One hypothesis that may provide an answer is that, in children, the carotid bifurcation is the portion first exposed to hemodynamic shearing stress.

Consequently, it is clear that none of these hypotheses completely explains the pathological processes and clinical and epidemiological presentations of moyamoya disease.[1] Inevitably, we must consider the possibility that multiple causes are involved to the etiology of moyamoya disease.[35,49,63]

A "double hits hypothesis" combining existing hypotheses is shown in Fig. 1. The primary causes of moyamoya disease are considered to be multiple gene abnormalities. Some of those abnormalities may be related to qualitative and/or quantitative abnormalities in EPC. However, some triggers, such as infection or immune disorder, seem to be indispensable in starting the first step in the pathological process of the disease. Hemodynamic stress is probably also important in booting up the first mechanism.

Needless to say, the hypothesis presented in Fig. 1 is not an original one, but has simply combined existing hypotheses and arbitrarily assembled parts of existing hypotheses that are consistent with the

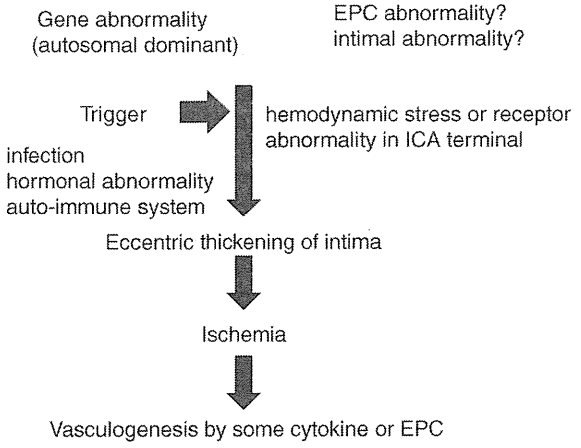

Fig. 1 Double hit hypothesis. EPC: endothelial progenitor cell, ICA: internal carotid artery.

complicated aspects of moyamoya disease. However, the double-hit hypothesis offers an attractive thesis since it can rationally explain the complicated aspects of moyamoya disease.

We may still not understand the true etiology of moyamoya disease. As shown in this review paper, a breakthrough is not visible. However, past basic studies offer important hints for new research. It is quite important that future work on moyamoya disease pays careful attention to past and present studies.

Disclosure and Conflict of Interest

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Predictors and Clinical Features of Postoperative Hyperperfusion after Surgical Revascularization for Moyamoya Disease : A Serial Single Photon Emission CT/Positron Emission Tomography Study

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Predictors and Clinical Features of Postoperative Hyperperfusion after Surgical Revascularization for Moyamoya Disease

A Serial Single Photon Emission CT/Positron Emission Tomography Study

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Background and Purpose—Clinical features and pathophysiology of postoperative hyperperfusion in moyamoya disease are still unclear. This study was aimed to clarify the incidence and time course of postoperative hyperperfusion and to determine the independent predictors of postoperative hyperperfusion in moyamoya disease.

Methods—This prospective study included 41 patients who underwent surgical revascularization for moyamoya disease. Using ^{15}O-gas positron emission tomography, hemodynamic and metabolic parameters were quantified before surgery. Using single photon emission CT, cerebral blood flow was serially measured just after surgery and on 2 and 7 days postsurgery. A multivariate logistic regression analysis was conducted to test the effect of multiple variables on postoperative hyperperfusion.

Results—Postoperative hyperperfusion was observed in 29 (50.0%) of 58 operated hemispheres. The incidence of both radiological and symptomatic hyperperfusion was significantly higher in adult patients than in pediatric ones (P=0.026 and P=0.0037, respectively). Hyperperfusion just after surgery more often led to subsequent neurological deficits (P=0.033). A multivariate analysis revealed that preoperative cerebral blood volume increase was an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya disease (OR, 6.6 and 12.3, respectively).

Conclusions—Postoperative hyperperfusion after surgical revascularization is not rare in moyamoya disease. Adult patients with a cerebral blood volume increase may be at high risk for radiological and symptomatic hyperperfusion after surgery. Careful perioperative management would reduce surgical complications and improve long-term outcome in moyamoya disease. (***Stroke*. 2012;43:00-00.**)

Key Words: bypass surgery ■ hyperperfusion ■ moyamoya disease ■ PET ■ SPECT

Moyamoya disease is an uncommon cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery and its main branches, resulting in the formation of a fine vascular network (the "moyamoya" vessels) at the base of the brain.[1–3] Surgical revascularization is the most successful therapy to improve cerebral hemodynamics and reduce the risk of subsequent ischemic stroke.[4–7] Direct bypass procedures such as superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis are quite useful to improve cerebral hemodynamics immediately after surgery.[4–8] The procedures also have the advantage to reduce the incidence of ischemic complications in the perioperative period.[4]

However, it should be reminded that direct bypass procedures possibly carry the risk of their specific complications.[9–12] Of these, postoperative hyperperfusion is recently recognized to occur after direct bypass surgery for moyamoya disease.[9,11,13,14] Postoperative hyperperfusion may lead to transient or permanent neurological deficits. Recent studies have shown that symptomatic hyperperfusion develops in 15% to 27.5% of patients who underwent direct bypass surgery for moyamoya disease.[15–17] Neurological deficits usually resolve within 7 days but may persist in some patients.[10,18] Regardless of symptomatic or silent, however, the incidence of postoperative hyperperfusion is still unclear, and the risk factors also remain obscure. Furthermore, there are few studies that denote its chronological feature.

Therefore, this study was aimed to clarify its incidence and clinical features in pediatric and adult patients with moyamoya disease by serially measuring blood flow for 1 week

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after surgery. Furthermore, this study aimed to determine the predictors of postoperative hyperperfusion in moyamoya disease using ^{15}O-gas positron emission tomography.

Methods

Patients

This prospective study included 41 patients who underwent surgical revascularization for moyamoya disease at our hospital between April 2006 and February 2011. All of them met the guideline for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor and Welfare of Japan. There were 12 males and 29 females. Their mean age was 33.7±19.6 years, ranging from 3 to 71 years. There were 13 children (<20 years) and 28 adults. Their clinical diagnosis included transient ischemic attack in 26 patients, ischemic stroke in 6, intracranial bleeding in 3, and asymptomatic in 6. This study was approved by an Institutional Review Board at Hokkaido University Hospital.

Preoperative Radiological Examinations

All patients underwent MRI, MR angiography, and cerebral angiography before surgery. MRI and MR angiography were performed using a 1.5- or 3.0-T apparatus. Disease stage was classified into 6 stages according to Suzuki's angiographic stage.[3] Using [^{123}I] *N*-isopropyl-*p*-iodo-amphetamine single photon emission CT (SPECT), cerebral blood flow (CBF) before and after intravenous injection of 10 mg/kg acetazolamide was quantitatively measured in all patients.[8,19–22] Cerebrovascular reactivity (CVR) to acetazolamide was determined as follows: CVR (%)=100×(CBF_{ACZ}−CBF_{rest})/CBF_{rest}, where CBF_{rest} and CBF_{ACZ} represent CBF before and after intravenous injection of acetazolamide, respectively.[23,24] CBF and CVR were rates as reduced when they were <27 mL/min per 100 g and <14%, respectively.[19] In this study, the involved hemisphere was considered as the candidate for surgical revascularization when having impaired reactivity to acetazolamide.[8,12]

In 33 of 41 patients, ^{15}O-gas positron emission tomography was also performed to determine CBF, cerebral blood volume (CBV), cerebral metabolic rate of oxygen, and oxygen extraction fraction (OEF).[19–22] Normal positron emission tomography values were obtained from 10 normal volunteers: CBF, 44±4 mL/min/100 g; CBV, 3.7±0.7 mL/100 g; cerebral metabolic rate of oxygen, 3.3±0.6 mL/min/100 g, and OEF, 0.43±0.05 (mean±SD). The values were rated as decreased when any of them were less than mean−2 SD and rated as increased when any of them were more than mean+2 SD.

Surgical Procedures

Totally 58 hemispheres of 41 patients underwent STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis.[8]

Postoperative Management

All patients were strictly managed to avoid hypovolemia and anemia. Systolic blood pressure was maintained between 100 and 140 mm Hg. Using [^{123}I] *N*-isopropyl- *p*-iodo-amphetamine SPECT, CBF was qualitatively determined 3 times within 1 week postsurgery. The first CBF measurement was performed immediately after surgery. Subsequent measurements were repeated 2 and 7 days postsurgery. MRI and MR angiography were also performed within 7 days after surgery.

Definition of Hyperperfusion

Postoperative hyperperfusion was defined as focal and intense increase of CBF followed by its normalization on subsequent SPECT studies (Figure 1). On qualitative SPECT studies during 1 week after surgery, the ipsilateral cerebellum was referred as to the inner normal control. Recent study has shown that CBF in the cerebral cortex ranges from 70% to 114% of that in the cerebellum in 11 normal volunteers (mean, 42.5±18.2 years).[25] In this study, therefore, CBF was rated as increased when CBF in the operated middle cerebral artery territory was >150% of the ipsilateral cerebellum. The patients were judged as developing radiological hyperperfusion when they did not develop any neurological deficits regardless radiological hyperperfusion on postoperative SPECT. On the other hand, they were judged as developing symptomatic hyperperfusion when they developed severe headache and/or focal neurological deficits corresponding to the area where hyperperfusion occurred after surgery.

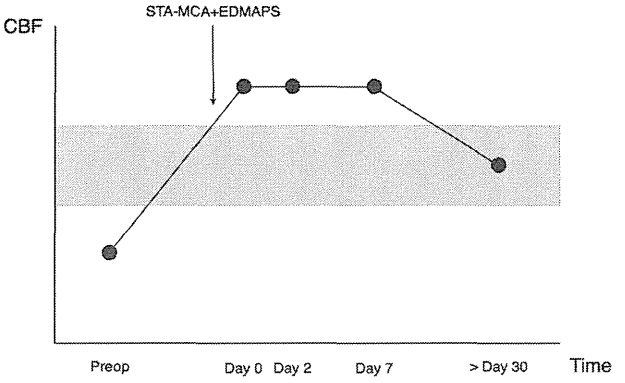

Figure 1. A line graph showing a typical course of postoperative hyperperfusion after surgery for moyamoya disease. Dashed area represents the normal range of cerebral blood flow (CBF).

Statistical Analysis

All continuous data were expressed as mean±SD. The data between 2 groups were compared by use of χ^2 test or unpaired *t* test as appropriate. A multivariate logistic regression analysis was conducted to test the effects of various clinical parameters on the occurrence of symptomatic hyperperfusion. A forward stepwise model-building procedure was performed for the parameters using $P<0.15$ achieved in univariate analysis. The level of significance was set at $P<0.05$.

Results

Incidence of Postoperative Hyperperfusion

On postoperative MR angiography, STA-MCA anastomosis was patent in all operated hemispheres. Repeated SPECT studies identified radiological hyperperfusion in 29 (50%) of 58 operated hemispheres. Of these, 13 hemispheres (44.8%) were symptomatic.

In pediatric cases, hyperperfusion was detected in 4 (20%) of 20 operated hemispheres. Of these, only one (5%) developed temporary neurological deficits. In adult cases, however, hyperperfusion was detected in 25 (65.7%) of 38 operated hemispheres (Figure 2). Of these, 12 hemispheres (31.5%) were symptomatic (Table 1). The incidence of both symptomatic and radiological hyperperfusion was significantly higher in adult patients than in pediatric ones ($P=0.0037$ and $P=0.026$, respectively).

Clinical Features of Symptomatic Hyperperfusion

Clinical features of 13 patients who developed symptomatic hyperperfusion after surgery widely varied (Table 2). In 8 (61.5%) of 13 patients, hyperperfusion was observed just after surgery. In 4 (30.8%) of 13 patients, hyperperfusion persisted for at least 1 week after surgery. No neurological deficits developed in other 28 patients in this study.

Neurological symptoms included motor weakness in 2 patients, motor aphasia in 7, dysarthria in 3, and seizure in 2

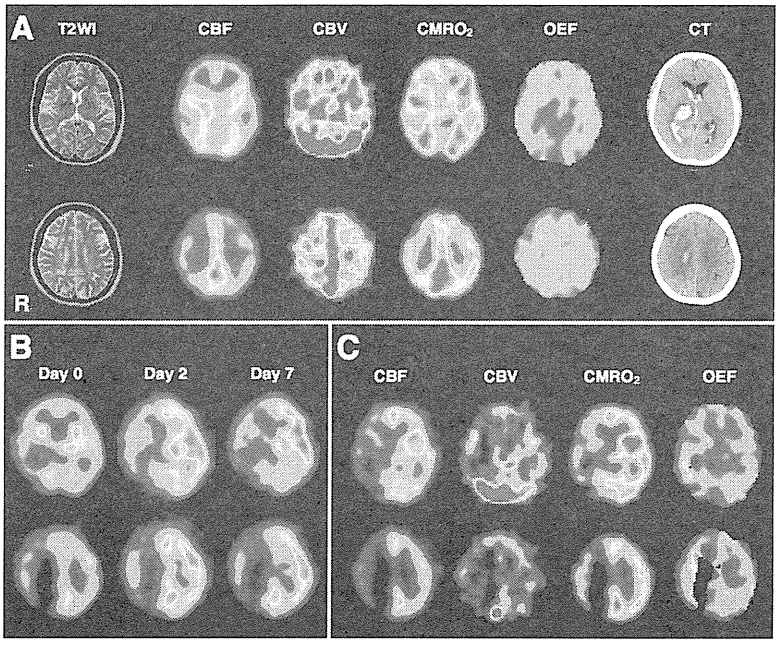

Figure 2. Radiological finding of a 52-year-old woman who was diagnosed as moyamoya disease because of transient weakness of bilateral extremities. **A**, Preoperative examinations revealed a marked decrease of cerebral blood flow (CBF) and an increase of cerebral blood volume (CBV) and oxygen extraction fraction (OEF) in the bilateral frontal lobes, although MRI demonstrated no cerebral infarction. Several days later, she developed intracerebral hemorrhage in the right thalamus. Approximately 6 months later, she underwent bypass surgery on the left side. **B**, Postoperative serial single photon emission CT (SPECT) reveals significant improvement of CBF just after surgery, but a marked hyperperfusion in the left frontal lobe 2 days and 7 days after surgery. She developed motor aphasia 2 days after surgery. **C**, One month after surgery, positron emission tomography scan showed the normalization of CBF, CBV, and OEF in the left hemisphere.

(Table 2). Their onset varied from 0 to 9 days after surgery (mean, 3.5±3.5 days). Neurological symptoms disappeared within 24 hours in 10 (76.9%) of 13 patients but persisted for 2 to 14 days in another 3 (23.1%). A mean duration of hyperperfusion-related symptoms was 2.2±3.6 days. Subsequently, all of them completely disappeared (Figure 2).

Early Onset of Hyperperfusion May Cause Neurological Signs

SPECT studies just after surgery identified radiological hyperperfusion in 9 adult patients. Of these, 7 patients (77.7%) developed hyperperfusion-related deficits. As shown in Table 2, the onset of their neurological deficits varied from immediate to 11 days postsurgery. However, hyperperfusion-related neurological deterioration developed in only 5 (31.3%) of 16 patients in whom radiological hyperperfusion occurred thereafter. Therefore, the adult patients with hyperperfusion just after surgery are at significantly higher risk for subsequent neurological deterioration (P=0.033, χ^2 test). There was no significant difference in clinical features between the patients with immediate hyperperfusion and those with delayed hyperperfusion.

Independent Predictors of Hyperperfusion in Adults

The effects of various factors on postoperative hyperperfusion in adult patients are shown in Table 3. The logistic regression analysis indicated CBV increase as the independent predictor of postoperative hyperperfusion in adult moyamoya disease (OR, 6.6; 95% CI, 1.1–39.0; P=0.0349).

Likewise, the effects of various factors on postoperative symptomatic hyperperfusion are shown in Table 4. The logistic regression analysis also revealed that CBV increase could predict symptomatic hyperperfusion in adult moyamoya disease (OR, 12.3; 95% CI, 1.1–131.6; P=0.0368).

Table 1. Incidence of Postoperative Hyperperfusion in Moyamoya Disease

	Adult Patients	Pediatric Patients	*P* Value
No.	38	20	
Age, y	46.2±11.1	10.1±4.3	<0.001
Male/female	10/28	6/14	
Symptomatic hyperperfusion	12 (31.5%)	1 (5.0%)	0.0037
Silent hyperperfusion	13 (34.2%)	3 (15.0%)	0.026

Discussion

This study demonstrates that radiological hyperperfusion occurs in 50% of patients with moyamoya disease after surgery. The incidence of both radiological and symptomatic hyperperfusion is much higher in adult patients than in pediatric ones. Majority of hyperperfusion-related symptoms disappeared within 24 hours but persisted for 2 to 14 days in approximately 25% of patients. Serial SPECT studies demonstrate that hyperperfusion just after surgery may easily lead to subsequent neurological deficits. Finally, multivariate analysis reveals that CBV increase may be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya disease.

Historically, postoperative hyperperfusion is known as one of the serious complications after carotid endarterectomy (CEA), leading to temporary or permanent neurological deteriorations. Of these, intracerebral hemorrhage is often fatal.[26,27] Cognitive impairment is also accepted as one of prolonged complications.[28] Excessive proliferation and edema of endothelial and smooth cells are found in the arteriolar walls of patients who develop cerebral edema and hemorrhage after CEA.[29] Previous studies strongly suggest that long-lasting and dense cerebral ischemia may play a key role to induce postoperative hyperperfusion. Thus, critical reduction of cerebral perfusion pressure may induce a persistent maximal dilatation of the arterioles, leading to postoperative hyperperfusion in response to a rapid recovery of cerebral perfusion pressure after CEA. Experimental studies show medial hypertrophy, loss of contractile strength,

Table 2. Clinical Data in Patients With Symptomatic Hyperperfusion After Surgery

Patient No.	Age, y/Sex	Clinical Diagnosis	Side	Hyperperfusion on SPECT			Symptoms	Onset and Duration
				POD 0	POD 2	POD 7		
1	34/F	TIA	L	No	Yes	No	Hemiparesis	POD 3
2	52/F	TIA	L	No	No	Yes	Aphasia, facial palsy	POD 6
3	41/F	TIA	R	No	No	Yes	Seizure	POD 9
4	58/F	TIA	L	No	Yes	No	Aphasia, seizure	POD 4
5	35 M	TIA	L	Yes	No	No	Dysarthria	POD 3–4
6	36/F	TIA	L	Yes	Yes	Yes	Aphasia	POD 2–16
7	43/M	Ischemic stroke	L	Yes	No	No	Aphasia	POD 0
8	52/F	Bleeding	L	No	Yes	Yes	Aphasia	POD 2
9	40/F	Bleeding	L	Yes	Yes	No	Aphasia	POD 0
10	40/F	Bleeding	R	Yes	Yes	Yes	Dysarthria	POD 0–2
11	16/F	Asymptomatic	R	Yes	Yes	Yes	Dysarthria	POD 5
12	38/M	Asymptomatic	L	Yes	Yes	No	Seizure	POD 1
13	55/M	Asymptomatic	L	Yes	Yes	Yes	Aphasia	POD 11

SPECT indicates single photon emission CT; POD, postoperative day; F, female; M, male; L, left; R, right.

and decreased resistance in the arterioles of chronically hypoperfused vascular beds.[30,31] Recent studies reveal that impaired acetazolamide reactivity can highly predict the occurrence of post-CEA hyperperfusion.[32–34] A similar phenomenon can be observed after STA-MCA anastomosis for patients with severely disturbed cerebral hemodynamics.[35,36] Interestingly, the reduction of both CBF and CVR can also anticipate the occurrence of hyperperfusion after STA-MCA anastomosis.[32,37]

However, clinical significance of postoperative hyperperfusion has not been recognized in moyamoya disease until recently. Thus, Uno et al[11] reported an adult case that developed symptomatic hyperperfusion after surgery for moyamoya disease. Subsequently, several studies have evaluated its clinical features in moyamoya disease. Thus, the incidence of symptomatic hyperperfusion ranges from 15% to 28% in adult patients with moyamoya disease but was very low (5.9%) in pediatric patients, correlating very well with the present results.[14–17,38] Therefore, adult patients with moyamoya disease are at high risk for symptomatic hyperperfusion after surgery. More importantly, this study first demonstrates that the incidence of radiological hyperperfusion is much higher, 20% and 67.5% in pediatric and adult patients, respectively. Therefore, the potential risk for postoperative hyperperfusion syndrome is much higher than considered before. In addition, this study reveals that 7 of 13 patients develop motor aphasia due to postoperative hyperperfusion, although previous reports have not pointed out this fact. There are several explanations for this finding. First,

Table 3. Predictors for Postoperative Hyperperfusion in Adult Moyamoya Disease

	Hyperperfusion		Univariate Analysis	Multivariate Analysis	OR (95% CI)
	Yes	No			
No.	25	13			
Age, y	44.9±11.0	48.7±10.9	*P*=0.1586		
Male sex	7	3	*P*=0.5323		
Clinical diagnosis (hemisphere, no.)			*P*=0.6397		
TIA	14	5			
Ischemic stroke	2	3			
Intracranial bleeding	3	1			
Asymptomatic	6	4			
Suzuki's stage (≥4	19	8	*P*=0.1244	*P*=0.1244	
PET parameters					
CBF decrease	22	12	*P*=0.5764		
CBV increase	21	7	*P*=0.0165	*P*=0.0349	6.6 (1.1–39.0)
$CMRO_2$ decrease	12	10	*P*=0.4949		
OEF elevation	16	9	*P*=0.5200		
CVR decrease	20	10	*P*=0.9999		

TIA indicates transient ischemic attack; PET, positron emission tomography; CBF, cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CVR, cerebrovascular reactivity.

Table 4. Predictors for Postoperative Symptomatic Hyperperfusion in Adult Moyamoya Disease

	Symptomatic Hyperperfusion		Univariate Analysis	Multivariate Analysis	OR (95% CI)
	Yes	No			
No.	12	13			
Age, y	43.6±8.3	48.7±10.9	P=0.1013	P=0.2837	
Male sex	4	3	P=0.4497		
Clinical diagnosis (hemisphere, no.)			P=0.3474		
TIA	7	5			
Ischemic stroke	1	3			
Intracranial bleeding	3	1			
Asymptomatic	1	4			
Suzuki's stage (≥4)	9	8	P=0.2180		
PET parameters					
CBF decrease	10	12	P=0.4687		
CBV increase	11	7	P=0.0283	P=0.0368	12.3 (1.1–131.6)
$CMRO_2$ decrease	5	10	P=0.5704		
OEF elevation	7	9	P=0.4400		
CVR decrease	10	10	P=0.9999		

TIA indicates transient ischemic attack; PET, positron emission tomography; CBF, cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CVR, cerebrovascular reactivity.

cerebral hemodynamics are severely impaired in the frontal lobe in the majority of patients with moyamoya disease.[39] Second, language function may be exclusively sensitive to hyperperfusion relative to other area of the brain.

Serial SPECT studies reveal that adult patients with radiological hyperperfusion just after surgery more often develop neurological signs than those with delayed onset. This is the first study that systemically analyzes chronological course of hyperperfusion after surgery in moyamoya disease. However, all neurological symptoms are transient and resolve within several days by strictly controlling blood pressure within normal limits. Therefore, serial SPECT studies are quite useful to predict symptomatic hyperperfusion and avoid permanent neurological sequelae.

In this study, multivariate analysis is used to explore the predictors of postoperative hyperperfusion in adult patients. Pediatric patients were not included because of their low incidence. As the results show, clinical diagnosis at onset was not related to the occurrence of postoperative hyperperfusion. Previously, Ohue et al[14] stated that symptomatic hyperperfusion more often occurs in ischemic-onset patients than in hemorrhagic-onset patients. In contrast, Fujimura et al[17] concluded that adult-onset and hemorrhagic-onset patients are at higher risk for symptomatic hyperperfusion. Therefore, there is a distinct discrepancy among these studies. Larger studies would be necessary to decide whether the onset type is closely related to its occurrence.

As aforementioned, CVR is accepted as a useful parameter to predict the occurrence of post-CEA hyperperfusion. However, the hemispheres with reduced CVR per se are the candidates for surgical revascularization in moyamoya disease.[8] This study clearly shows that preoperative CBV increase can be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya patients (OR, 6.6 and 12.3, respectively). Theoretically, an increased CBV strongly suggests an autoregulatory vasodilatation in response to the cerebral perfusion pressure reduction.[40] On the other hand, OEF elevation cannot predict the occurrence of both radiological and symptomatic hyperperfusion after bypass surgery. Derdeyn et al[41] precisely evaluated clinical significance of CBV increase in hemodynamic impairment due to occlusive cerebrovascular disease. They found that an OEF increase in the territory of an occluded carotid artery often occurs in the absence of a CBV elevation and that patients with both increased OEF and increased CBV are at much higher risk for subsequent stroke than those with increased OEF and normal CBV. Based on these observations, they have concluded that increased CBV may indicate pronounced vasodilatation due to exhausted autoregulatory vasodilatation in patients with chronic carotid occlusion and increased OEF.[41] Recently, Hokari et al[21] also reported the importance of CBV measurement to predict an increased OEF in patients with both decreased CBF and decreased CVR due to occlusive carotid artery disease using SPECT. Furthermore, Fukuda et al[42] demonstrated that an increased CBV was the only significant predictor of post-CEA hyperperfusion. Therefore, preoperative measurement of CBV may be useful to predict the occurrence of postoperative hyperperfusion in adult moyamoya disease.

As aforementioned, pediatric patients with moyamoya disease were not included in multivariate analysis. As previously reported, however, CBV is known to be often elevated in most of them.[43,44] Indeed, all pediatric patients had a CBV increase on positron emission tomography scans, although most of them did not show hyperperfusion after surgery. This finding strongly suggests pathophysiological differences in a CBV increase in response to cerebral perfusion pressure reduction between pediatric and adult patients with moyamoya dis-

ease. Thus, autoregulatory vasodilatation may quickly recover after STA-MCA anastomosis starts to supply blood flow in pediatric patients. However, such vasodilatation may require longer time to recover in adult patients probably because of long-lasting cerebral ischemia. The difference in the caliber of STA may be another explanation for the discrepancy between them. Thus, the caliber of STA largely determines blood flow just after STA-MCA anastomosis.[45]

In conclusion, radiological hyperperfusion occurs in 50% of patients with moyamoya disease after surgery, being higher than considered before. Adult patients are at much higher risk for postoperative hyperperfusion than pediatric patients. Preoperative CBV increase may be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult patients.

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Disclosures

None.

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Lessons Learned From Moyamoya Disease: Outcome of Direct/Indirect Revascularization Surgery for 150 Affected Hemispheres

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Abstract

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain. Recent advances in molecular biology and genetic research have provided better understanding of the pathophysiology of moyamoya disease, but surgical revascularization still remains the preferred treatment for this entity. The present study investigated the clinical course of 106 consecutive patients with moyamoya disease who underwent superficial temporal artery-middle cerebral artery anastomosis with indirect pial synangiosis in 150 hemispheres. The outcomes of surgery on the operated hemisphere were favorable, with no cerebrovascular event during the outpatient follow-up period (mean 58.4 months) in 89.3% (134/150). Two patients suffered hemorrhagic events on the operated hemisphere during the follow-up period (2/150, 1.33%), one of whom suffered deteriorated neurological status after hemorrhage. Despite the favorable long-term outcome, the incidence of temporary neurological deterioration due to cerebral hyperperfusion was 18.0% (27/150), but no patients suffered permanent neurological deterioration directly caused by hyperperfusion. In conclusion, direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease, although the issue of bleeding/re-bleeding remains to be solved. Postoperative cerebral hyperperfusion and peri-operative infarction are potential complications of this procedure, so we recommend intensive postoperative care and cerebral blood flow measurement in the acute stage, because the management of hyperperfusion is contradictory to that of ischemia.

Key words: moyamoya disease, surgical management, extracranial-intracranial bypass, surgical complication, long-term outcome

Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain.[9,28] Extracranial-intracranial (EC-IC) bypass such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is generally employed as the standard surgical treatment for moyamoya disease to prevent cerebral ischemic attacks by improving cerebral blood flow (CBF).[7,11,13,23] Recent advances have been made in understanding the molecular biology and pathophysiology of moyamoya disease, and new genetic mutations and deletions have been identified,[14,18] but surgical revascularization remains the preferred treatment for moyamoya disease patients with ischemic symptoms.[7,11,13,23] The present study investigated the long-term outcomes of combined (direct/indirect) revascularization procedures in a single institute performed under standardized surgical indications and postoperative management protocol. The concept of revascularization surgery for moyamoya disease is discussed based on its intrinsic genetics and histological background.

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Patients and Methods

The present study included 106 consecutive patients

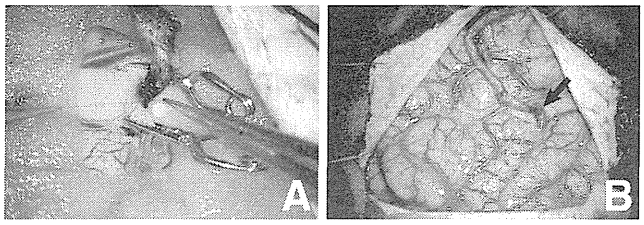

Fig. 1 Intraoperative photographs of left superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis. A: The M_4 segment of the right MCA was explored, and anastomosis between the STA stump and MCA was performed. B: Low power magnification view after anastomosis (*arrow*).

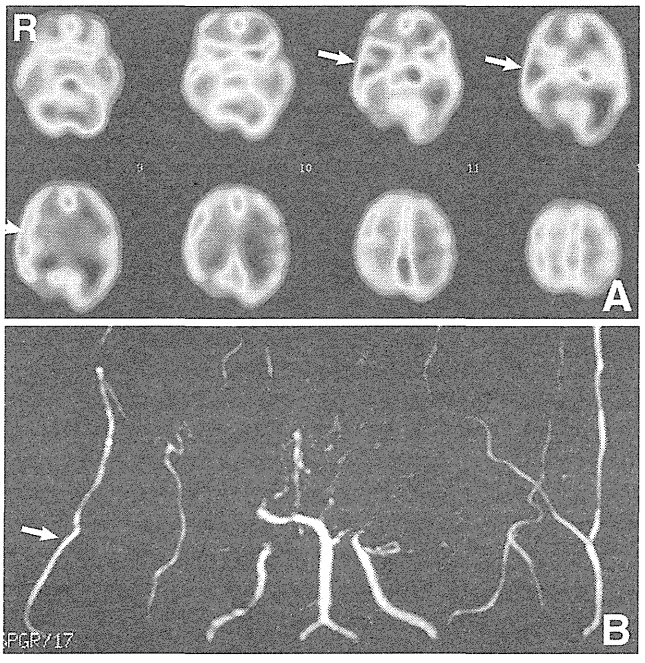

Fig. 2 Representative case of a 31-year-old woman presenting with cerebral infarction. A: N-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography scans in the acute stage after right superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis demonstrating marked increase in cerebral blood flow on the hemisphere operated on (*arrows*). B: Magnetic resonance angiogram after revascularization surgery demonstrating the STA-MCA bypass as a thick high signal (*arrow*).

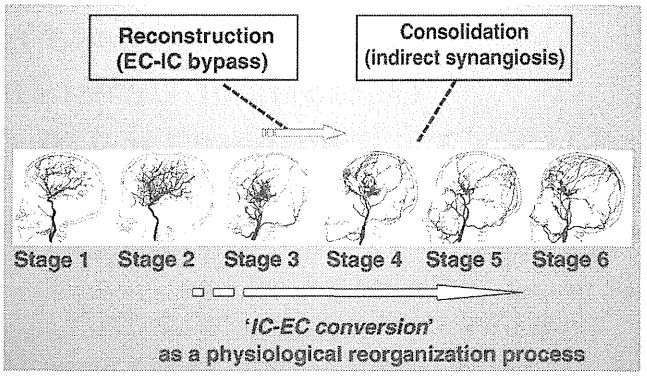

Fig. 3 Status of revascularization surgery for moyamoya disease in the intrinsic physiological reorganization system. Suzuki's grading could indicate the compensatory nature of moyamoya disease, so called *'intracranial carotid to extracranial carotid system (IC-EC) conversion'* as a physiology of moyamoya disease. Concept of revascularization surgery for moyamoya disease includes both vascular reconstruction by extracranial-intracranial (EC-IC) bypass and consolidation for future arteriogenesis by indirect pial synangiosis.

with moyamoya disease, 30 men and 78 women aged 2–69 years (mean 33.1 years), surgically treated in 150 hemispheres between March 2004 and November 2010. The inclusion criteria of this study, corresponding to our surgical indications for STA-MCA anastomosis, included all of the following items: presence of ischemic symptoms, apparent hemodynamic compromise on N-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography (^{123}I-IMP SPECT), independent activity of daily living (modified Rankin scale scores 0–2), and absence of major cerebral infarction.[2,4,5] All hemispheres that did not match these criteria were excluded from the initial surgery. Once hemodynamic compromise was confirmed, the patients underwent revascularization surgery. All patients underwent STA-MCA (M_4) anastomosis with encephalo-duro-myo-synangiosis (Fig. 1).[2,4,5] All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis, of the Ministry of Health, Labour and Welfare, Japan, except for four patients with 'probable moyamoya disease' showing unilateral involvement.[9] All patients were strictly followed up in our institutes for more than 12 months with a mean follow-up period of 58.4 months. The presence or absence of cerebral ischemic symptoms including stroke and transient ischemic attack (TIA), and occurrence of any intracranial hemorrhagic event such as intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) were investigated based on the patient's records.

CBF was routinely measured by ^{123}I-IMP SPECT 1 and 7 days after surgery in all patients (Fig. 2A).[5] 1.5-T or 3-T magnetic resonance (MR) imaging and MR angiography were routinely performed within 2 days after surgery (Fig. 2B).[17] MR imaging included

diffusion-weighted, T_2-weighted, fluid-attenuated inversion recovery, and T_2*-weighted images. The diagnostic criteria for symptomatic cerebral hyperperfusion included all of the following items[2,4,5]: presence of a significant focal increase in CBF at the site of the anastomosis, which is responsible for the apparent neurological signs including focal neurological deficit and/or severe headache due to hemorrhagic changes; apparent visualization of STA-MCA bypass by MR angiography and the absence of any ischemic changes by diffusion-weighted MR imaging; and absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, TIA, and seizure. The occurrence of symptomatic cerebral hyperperfusion after revascularization surgery was evaluated by ^{123}I-IMP SPECT in the acute stage.

Results

No cerebrovascular events occurred in 134 of the 150 operated hemispheres (89.3%) of 106 patients during the outpatient follow-up period (Table 1). TIA was detected in 13 operated hemispheres (8.6%) during the outpatient follow-up period, but all patients with onset of TIA showed disappearance or improvement of ischemic attack during the follow-up period. One patient with ischemic onset (1/150, 0.66%) suffered minor completed stroke in the operated hemisphere during paroxysmal arterial fibrillation due to thyrotoxicosis 6 months after the revascularization surgery. One patient with ischemic onset (1/150, 0.66%) developed ICH of the ipsilateral thalamus 3 years after successful revascularization surgery, and suffered deterioration of modified Rankin scale score from 0 to 3 after the hemorrhage.

Table 1 Long-term outcome of superficial temporal artery-middle cerebral artery anastomosis with pial synangiosis during the outpatient follow-up period

Cerebrovascular event	No. of hemispheres	Incidence (%)	Neurological status
No cerebrovascular event	134/150	89.3	N/A
TIA	13/150	8.6	N/A
Cerebral infarction*	1/150	0.66	mRS 2→2
Hemorrhage	2/150	1.33	
SAH	1/150		mRS 0→0
ICH	1/150		mRS 0→3

*Minor completed stroke during paroxysmal arterial fibrillation due to thyrotoxicosis. ICH: intracerebral hemorrhage, mRS: modified Rankin scale before and after the cerebrovascular events, N/A: not applicable, SAH: subarachnoid hemorrhage, TIA: transient ischemic attack.

Two patients with hemorrhagic onset developed rebleeding (2/150, 1.33%), one from contralateral ICH and one from ipsilateral SAH, but neither patient suffered deterioration of their neurological status. Postoperative MR angiography showed the patency of the STA-MCA bypass in all 106 patients with 150 operated hemispheres.

None of the 106 patients suffered peri-operative cerebral infarction in any of the 150 hemispheres, except for the following four patients. Three patients (3/150, 2.0%) presented with pseudolaminar necrosis in part of the cerebral cortex supplied by the STA-MCA bypass in the sub-acute stage probably due to thrombo-embolism, which did not affect their long-term neurological status. One patient (1/150, 0.66%) with an atherosclerotic background presented with cerebral infarction 3 days after surgery in the ipsilateral occipital lobe during intensive blood pressure control for symptomatic SAH due to hyperperfusion. However, this infarction did not affect her long-term activity of daily living.

Twenty-six patients (27/150 hemispheres, 18.0%) demonstrated temporary neurological deterioration, including mild focal neurological signs, due to postoperative focal cerebral hyperperfusion between 2 and 14 days after surgery. Postoperative MR imaging/MR angiography did not show any ischemic changes, and showed the STA on the operated hemisphere as thick high signal intensity in all 27 hemispheres.[17] Postoperative SPECT demonstrated significant intense increases in CBF at the sites of anastomosis in all 27 hemispheres. Twenty-two patients (23/150 hemispheres, 15.3%) demonstrated transient focal neurological deficit due to focal hyperperfusion that mimicked ischemic attack, starting between 2 and 9 days after surgery and persisting for several days. The anatomical location and temporal profile of the hyperperfusion were completely in accordance with the transient neurological signs in all 22 patients. Four patients (4/150 hemispheres, 2.6%) complained of severe headache and demonstrated symptomatic cerebral hyperperfusion associated with SAH in three patients (2.0%) or with ICH at the right frontal sub-cortex in one patient (0.66%). No patient suffered permanent neurological deficit due to cerebral hyperperfusion. No patient suffered delayed neurological deterioration due to cerebral hyperperfusion during the follow-up period.

Discussion

Planning of revascularization surgery for moyamoya disease should especially consider the intrinsic anatomical and/or physiological background

of this rare entity. The histopathological characteristics of moyamoya disease include intimal hyperplasia and medial thinness.[22,29] These histopathological changes are known to be occur in the peripheral pial arteries[29] as well as major arterial trunks such as the carotid fork and proximal MCA, so the intrinsic fragility of the recipient artery must be appreciated during the anastomosis. Consideration of the macroscopic anatomy requires preservation of the transdural anastomosis via the middle meningeal artery, occipital artery, and STA during surgery, which have all spontaneously developed preoperatively due to the compensatory nature of moyamoya disease.[28]

The concepts of revascularization surgery for moyamoya disease include both microsurgical reconstruction by EC-IC bypass and consolidation for future EC-IC arteriogenesis by indirect pial synangiosis (Fig. 3).[7] Both procedures may attempt to convert the vascular supply for the brain from the intracranial carotid to the extracranial carotid system (IC-EC). The natural pathophysiological course of moyamoya disease, as demonstrated by Suzuki's angiographic staging,[28] suggests that *'IC-EC conversion'*[7] of the vascular supply is consistent with an intrinsic compensatory reorganization process of this entity. Therefore, the concept of revascularization surgery for moyamoya disease should be based on the idea to *support* the intrinsic compensatory nature of moyamoya disease,[28] rather than to *eradicate* the pathophysiology of this entity.

Surgical revascularization prevents cerebral ischemic attack by improving CBF in patients with moyamoya disease. Direct revascularization surgery such as STA-MCA anastomosis has been established as an effective procedure for patients with ischemic symptoms, providing long-term favorable outcomes.[7,11,13,23] A series of 450 revascularization procedures for moyamoya disease, in which the direct revascularization technique was used in 95.1% of adults and 76.2% of pediatric patients, obtained a surgical morbidity rate of 3.5%, mortality rate of 0.7%, and cumulative 5-year risk of perioperative or subsequent stroke or death of 5.5%, indicating that revascularization surgery in patients with moyamoya disease carries low risk and is effective at preventing future ischemic events.[11] In contrast to the promising effect of revascularization surgery for patients with ischemic onset, whether surgical revascularization has potential for preventing future re-bleeding in patients with hemorrhagic onset remains controversial.[19] This issue remains to be elucidated in the currently on-going Japan Adult Moyamoya trial.[19] In the present study, 150 direct revascularization procedures for patients with ischemic symptoms provided high cure/improvement rates of ischemic symptoms, with mortality rate of 0%. However, two patients developed intracranial hemorrhage on the operated hemisphere during the outpatient follow-up period, and one patient had significantly deteriorated activity of daily living due to thalamic hemorrhage. Therefore, surgical revascularization markedly ameliorates the risk of future ischemic stroke, but the effect for preventing hemorrhage remains to be clarified in a future study.

Table 2 Potential complications in the acute stage after superficial temporal artery (STA)-middle cerebral artery anastomosis with indirect pial synangiosis for moyamoya disease

Pathology	Procedure	Management
Cerebral ischemia		
thrombo-embolism[7]	direct	anti-platelet agent
hemodynamic ischemia[12]	direct/indirect	hydration/ antioxidant
watershed shift[12]	direct	anti-platelet agent
brain compression by EMS graft[3]	indirect	surgical decompression/ EMS revision
HP		
focal HP with transient neurological deficit[2,4,5,16,21]	direct	BP lowering/ antioxidant
hemorrhage due to HP[6]	direct	BP lowering/ ligation of STA
Others		
subdural hematoma	indirect > direct	hematoma evacuation
CSF leakage	indirect/direct	spinal drainage/ revision

BP: blood pressure, CSF: cerebrospinal fluid, EMS: encephalo-myo-synangiosis, HP: hyperperfusion.

Revascularization surgery for moyamoya disease provides favorable long-term outcome, but involves some potential complications,[2-7,10,12,16,17,20,21] as summarized in Table 2. Symptomatic cerebral hyperperfusion[24,26,27] after the direct revascularization technique is characterized by transient focal neurological deterioration mimicking ischemic symptoms.[2,16,21] Such cerebral hyperperfusion is a cause of transient neurological deterioration[2,5,16,21] or delayed ICH[6] during the acute stage after STA-MCA anastomosis for moyamoya disease. The incidence of temporary neurological deterioration due to hyperperfusion is 16.7% to 38.2%,[2,4,5,16,21] if mild focal neurological signs are included. Furthermore, our most recent study using routine postoperative CBF measurement by ^{123}I-IMP SPECT after STA-MCA (M_4) anastomosis for moyamoya and non-moyamoya disease patients showed that the incidence of symptomatic hyperperfusion was significantly higher in the moyamoya disease group

(26/121 hemispheres, 21.5%) than in the non-moyamoya disease group (0/28, 0%).[5] In the present study, the incidence of symptomatic hyperperfusion was as high as 18.0%, again indicating that symptomatic hyperperfusion should be recognized a possible complication of direct revascularization surgery for moyamoya disease.

The reason why moyamoya disease patients have higher risk for symptomatic cerebral hyperperfusion is undetermined. The intrinsic anatomical vulnerability of the pial artery structure, such as medial thinness and waviness and duplication of the internal elastic lamina,[22,29] may lead to fragility of the peripheral arteries in the vascular territory of the STA-MCA bypass. Excessive production of reactive oxygen species during revascularization may also affect the vascular permeability, and thus result in transient neurological deterioration and/or hemorrhagic complications.[1] Recent studies using dura mater, arachnoid membrane, and serum obtained from patients with moyamoya disease have demonstrated that the expression of vascular endothelial growth factor (VEGF)[25] and matrix metalloproteinase (MMP)-9[8,15] were significantly increased in moyamoya patients, so such increased expression of VEGF and MMP-9 in patients with moyamoya disease may contribute, at least in part, to the vulnerability to cerebral hyperperfusion.

The concepts of revascularization surgery for moyamoya disease include both microsurgical reconstruction by EC-IC bypass and consolidation for future arteriogenesis leading to EC-IC anastomosis by indirect pial synangiosis. The intrinsic pathology is important to understand such as anatomical fragility of the recipient artery and the presence of spontaneously developed transdural anastomosis during surgery. Direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease with ischemic symptoms, although the issue of bleeding/re-bleeding remains to be solved. Postoperative cerebral hyperperfusion and peri-operative infarction are potential complications of this procedure, so we recommend intensive postoperative care and CBF measurement in the acute stage, because the management of hyperperfusion is contradictory to that of ischemia.

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