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Invited Review

Current Status of Revascularization Surgery for Moyamoya Disease: Special Consideration for Its 'Internal Carotid-External Carotid (IC-EC) Conversion' as the Physiological Reorganization System

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Moyamoya disease is a chronic cerebrovascular disease with unknown etiology, which is characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network formation at the base of the brain. Moyamoya disease is known to have unique and dynamic nature to convert the vascular supply for the brain from internal carotid (IC) system to the external carotid (EC) system, as indicated by Suzuki's angiographic staging established in 1969. Insufficiency of this 'IC-EC conversion system' may result in cerebral ischemia, as well as in intracranial hemorrhage from inadequate collateral vascular network, both of which represent the clinical presentation of moyamoya disease. Therefore, surgical revascularization by extracranial-intracranial bypass is the preferred procedure for moyamoya disease to complement 'IC-EC conversion' and thus to avoid cerebral infarction and/or intracranial hemorrhage. Long-term outcome of revascularization surgery for moyamoya disease is favorable, but rapid increase in cerebral blood flow on the affected hemisphere could temporarily cause unfavorable phenomenon such as cerebral hyperperfusion syndrome. We would review the current status of revascularization surgery for moyamoya disease based on its basic pathology, and sought to discuss the significance of measuring cerebral blood flow in the acute stage and intensive perioperative management.

Keywords: cerebral blood flow; extracranial-intracranial bypass; moyamoya disease; perioperative management; single-photon emission computed tomography
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Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by a unique and dynamic nature to convert the vascular supply for the cerebral hemisphere from internal carotid (IC) system to the external carotid (EC) system, so called 'IC-EC conversion disease' (Suzuki and Takaku 1969; Fujimura and Tominaga 2012b). In most of the literature, the characteristic of moyamoya disease is represented by its typical angiographic finding at the transitional state of 'IC-EC conversion', when steno-occlusive change at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain are evident (Fig. 1).

Extracranial-intracranial bypass, such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis, is generally employed as the standard surgical treatment for moyamoya disease to complement 'IC-EC conversion' and thus prevent cerebral ischemic attacks (Fukui 1997; Houkin et al. 1997). Recently, the extracranial-intracranial bypass was also shown to reduce the risk of re-bleeding in hemorrhagic-onset patients with moyamoya disease by the Japan Adult Moyamoya (JAM) trial: a multicenter randomized control trial to compare the incidence of re-bleeding rate between surgical and non-surgical groups of hemorrhagic-onset moyamoya disease (Miyamoto et al. 2014). Long-term outcome of the extracranial-intracranial bypass for moyamoya disease is favorable, but cerebral ischemia and hyperperfusion syndrome are potential complications of this procedure, which could lead to neurological deterioration in the acute stage (Fujimura et al. 2007; Kim et al. 2008; Ohue et al. 2008). We sought to review the current status of revascularization surgery for moyamoya disease based on its basic pathology, and sought to discuss the significance of measuring cerebral blood flow

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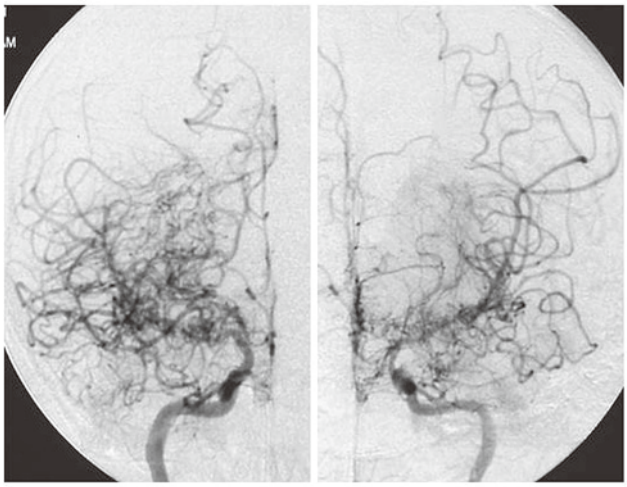

Fig. 1. Representative finding of the catheter angiography of moyamoya disease.
Bilateral carotid angiogram demonstrates steno-occlusive changes at the terminal ICA associated with the abnormal vascular network formation at the base of the brain.

(CBF) in the acute stage and intensive perioperative management after revascularization surgery.

Diagnosis of moyamoya disease

Diagnostic criteria

It had been required that steno-occlusive change at ICA should be evident bilaterally for the definitive diagnosis of moyamoya disease (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases 2012). In light of the increasing number of the patients with unilateral involvement (Hayashi et al. 2014) as well as the evidence that substantial number of unilateral cases could progress to the bilateral presentation (Kuroda et al. 2005), diagnostic criteria of the definitive moyamoya disease was revised to include patients, demonstrating both bilateral and unilateral involvement of terminal ICA stenosis associated with abnormal vascular network at the base of the brain with unknown etiology, as stated by the Research Committee of Moyamoya Disease of the Japanese Ministry of Health, Labour, and Welfare in 2015. Diagnostic criteria also state that definitive diagnosis of moyamoya disease requires catheter angiography in unilateral cases while bilateral cases could be promptly diagnosed by either catheter angiography or magnetic resonance (MR) imaging/angiography.

Modern supportive diagnostic tools

Definitive diagnosis of moyamoya disease is not always easy, especially in patients with early stage of Suzuki's angiographic grading (Suzuki and Takaku 1969), when abnormal vascular network is not yet evident. To resolve this critical issue, it is essential to understand the diagnostic value of high resolution MR imaging focusing on vascular wall anatomy of moyamoya disease. Kaku and colleagues (2012) recently proposed the constrictive remodeling theory that outer diameter narrowing of the affected intracranial vessels was the early characteristic change of moyamoya disease as demonstrated by three-dimensional (3D) constructive interference in steady-state (CIISS) MR image. Yuan et al. (2015) also reported that the vascular wall thinning and the arterial outer diameter narrowing shown by high resolution MR imaging could be the early morphological changes characteristic to moyamoya disease. Taken together, the high resolution MR imaging including 3D-CISS could provide the supportive information for the accurate diagnosis of moyamoya disease especially in the early angiographic stage. Alternatively, genetic analysis as described in the next paragraph would also provide supportive information for the diagnosis of moyamoya disease.

Etiology of moyamoya disease

Genetics: significance of RNF213 susceptibility gene

The etiology of moyamoya disease remains unknown, while recent findings suggest the importance of genetic factors (Ikeda et al. 1999; Inoue et al. 2000; Yamauchi et al. 2000; Sakurai et al. 2004). A more recent genome-wide association study identified the ring finger protein (RNF) 213 gene (*RNF213*) in the 17q25-ter region as a susceptibility gene for moyamoya disease among East Asian population (Kamada et al. 2011), although the exact function of *RNF213* is undetermined. We previously reported that a single-nucleotide polymorphism (SNP) of c.14576G>A in *RNF213* was detected in 95% of familial moyamoya diseases and 79% of sporadic cases among Japanese patients (Kamada et al. 2011). Although the mechanism underlying SNP of *RNF213* in moyamoya disease patients is undetermined, recent *in vivo* experiment using the *RNF213*-deficient mice may give clue to address this important question. We reported that the target disruption of *RNF213* did not develop moyamoya disease in the *RNF213*-deficient mice (Sonobe et al. 2014), but post-ischemic angiogenesis was significantly enhanced in mice lacking *RNF213* after chronic hind-limb ischemia (Ito et al. 2015), suggesting the potential role of the *RNF213* abnormality in the development of abnormal vascular networks in chronic ischemia. Further investigation with *RNF213*-deficient mice under variety of additional insults such as chronic brain ischemia and/or immune-adjuvants administration may provide new insight to clarify the etiology of moyamoya disease.

Environmental factors underlying moyamoya disease

As indicated by the basic research using genetic engineered mice of *RNF213,* moyamoya disease susceptibility gene, genetic abnormality is important but not the exclusive factor to develop moyamoya disease. Environmental factors as the secondary insults in addition to the genetic abnormality might be important to develop moyamoya disease, because *RNF213* polymorphism characteristic to moyamoya disease is also evident in 1.4% of the normal

control population (Kamada et al. 2011). Regarding the candidate of the secondary insults, infection, autoimmunity, other inflammatory conditions, and cranial irradiation are implicated in the etiology of moyamoya disease (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases 2012). Among them, autoimmune response could be the strongest candidate as the secondary insult to develop moyamoya disease, in light of the high prevalence of Graves' disease; autoimmune hyperthyroidism among East Asia patients with moyamoya disease (Kim et al. 2010). Alternatively, *RNF213* polymorphism could directly affect autoimmunity and thus contribute to the development of moyamoya disease, because RNF213 is predominantly expressed in white blood cells and spleen (Kamada et al. 2011).

Revascularization surgery for moyamoya disease

Concept of revascularization surgery

Due to the insufficiency of 'IC-EC conversion' at the transitional stage, such as at stage 3 and stage 4 of Suzuki's angiographic staging (Suzuki and Takaku 1969), substantial number of patients manifest as ischemic symptom and/or intracranial hemorrhage, while some patients may alternatively achieve favorable 'IC-EC conversion' without undergoing surgical intervention, as often seen in asymptomatic adult patients. While considering the pathological condition of each patient, it is essential to go back to Suzuki's angiographic staging and to consider the patients' angiographic and hemodynamic status.

Concept of revascularization surgery for moyamoya disease includes both microsurgical reconstruction by STA-MCA anastomosis and the consolidation for future vasculogenesis by indirect pial synangiosis such as encephalo-myo-synangiosis and encephalo-duro-arterio-synangiosis (Fujimura and Tominaga 2012b). Both concepts may attempt to convert the vascular supply for the brain from IC system to the EC system, which again match the physiological nature of moyamoya disease. Thus the concept of revascularization surgery for moyamoya disease is based on the idea to complement the intrinsic compensatory nature of moyamoya disease, rather than to eradicate the intrinsic nature of this entity (Fujimura and Tominaga 2012b). Alternatively, rapid increase in CBF provided by direct extracranial-intracranial bypass could provide temporary impact to the affected brain, because 'IC-EC conversion' is usually attempted during lengthy time period in the natural course of moyamoya disease.

Guideline recommendation

Surgical revascularization prevents cerebral ischemic attack by improving CBF. Direct revascularization surgery such as STA-MCA anastomosis is established as an effective procedure for the moyamoya disease patients with ischemic symptoms, providing long-term favorable outcomes. In fact, the Japanese Stroke Guideline recommends direct revascularization surgery for the patients with moyamoya disease manifesting as cerebral ischemic symptoms (Recommendation grade B) (Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases 2012). Intraoperative views are shown in Fig. 2. Regarding hem-

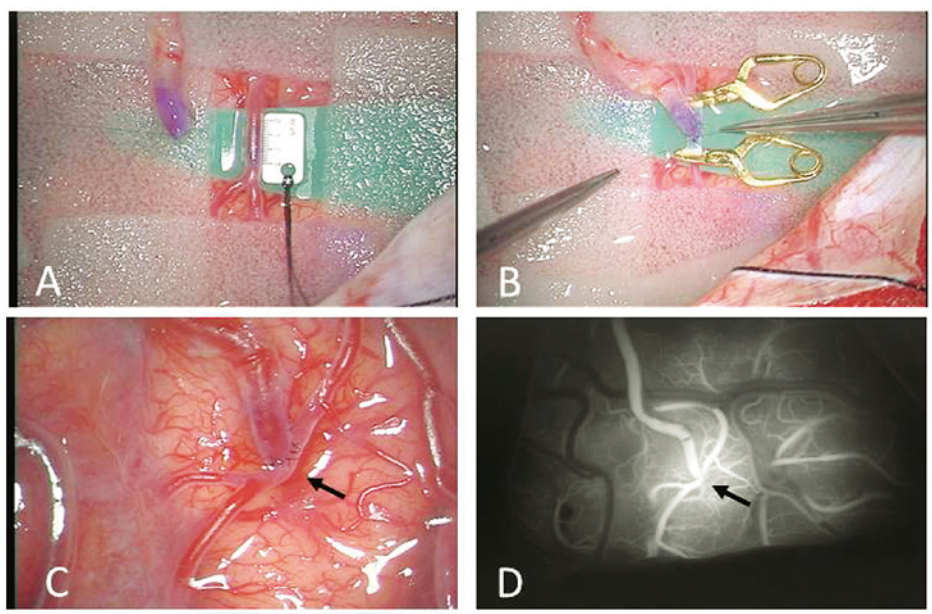

Fig. 2. Intra-operative view of STA-MCA anastomosis.
Surgical view before (A), during (B), and after right STA-MCA anastomosis (C, D). Arrows in C and D indicate the site of the anastomosis. Indocyanine green video-angiography demonstrated apparently patent bypass with favorable distribution of bypass flow.

orrhagic-onset patients, revascularization could be considered but adequate scientific evidence had been lacking (Recommendation grade C1). Nevertheless, recent evidence by JAM trial strongly encourages direct revascularization surgery for reducing the risk for re-bleeding in adult moyamoya disease patients presenting with intracranial hemorrhage (Miyamoto et al. 2014), although the statistical significance was marginal. Sub-group analysis of the JAM trial is currently undertaken to further clarify the patient population among hemorrhagic-onset moyamoya disease in which revascularization surgery exerts particular benefit by preventing re-bleeding. Finally, revascularization surgery for asymptomatic moyamoya disease patients is not recommended due to the uncertainty of the natural history of this patient population (Kuroda et al. 2007). To answer this important question, asymptomatic moyamoya registry (AMORE) study; multicenter observational study is currently undertaken in Japan to clarify the natural history of asymptomatic moyamoya disease (Kuroda et al. 2015).

Surgical complications

Cerebral ischemia such as peri-operative cerebral infarction

Revascularization surgery for moyamoya disease is based on the 'physiological' concept as indicated by 'IC-EC conversion' theory, but it includes potential issue of the rapid CBF increase in the chronic ischemic brain, which may underlay the surgical complications of this procedure (Fig. 3). Surgical complications of moyamoya disease include both neurological and non-neurological complications, and neurological complications include peri-operative cerebral infarction and cerebral hyperperfusion syndrome (Table 1). Regarding the perioperative cerebral infarction, following distinct pathologies are reported as the possible mechanisms underlying peri-operative ischemia. Firstly, Hayashi et al. (2010) proposed 'watershed shift phenomenon' as an intrinsic hemodynamic ischemia at the adjacent cortex to the STA-MCA bypass for child-onset moyamoya disease. Retrograde blood supply from STA-MCA bypass may interfere with the anterograde blood flow from proximal MCA, and thus result in the temporary decrease in CBF at the cortex supplied by the adjacent branch of MCA. The watershed shift phenomenon could lead to subsequent cerebral infarction among pediatric moyamoya disease (Hayashi et al. 2010). Besides hemodynamic ischemia due to watershed shift phenomenon, thrombo-embolic complication originated from the anastomosed site (Fujimura et al. 2008) and the mechanical compression by swollen temporal muscle flap could also cause cerebral ischemia in the acute stage (Fujimura et al. 2009a). Based on these observations, we believe that proper perioperative hydration, hemoglobin concentration maintenance, and routine use of anti-platelet agent are essential to avoid ischemic complications (Fujimura et al. 2012a). It is important to differentiate these distinct pathologies by CBF measurement and MR imaging/angiography in the acute stage for the accurate diagnosis and prompt perioperative management (Fig. 3). The management of each pathological condition is summarized in Table 1.

Cerebral hyperperfusion syndrome

Because the pial artery network is markedly affected in moyamoya disease patients (Kim et al. 2008; Nakagawa et al. 2009), the STA-MCA bypass may temporarily lead to

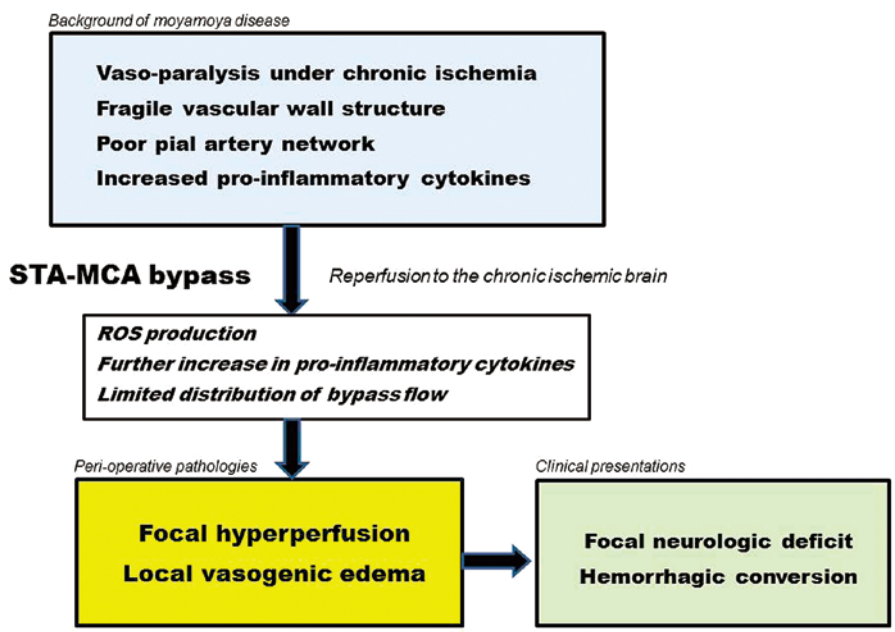

Fig. 3. Background of moyamoya disease and the peri-operative pathologies after STA-MCA anastomosis. The scheme also shows the potential risk factors responsible for the peri-operative pathologies, such as focal cerebral hyperperfusion and local vasogenic edema.

Table 1. Surgical complications of the revascularization surgery for moyamoya disease.

	Complication	Classification	Procedure	Management
Neurological complications	Ischemic complication (Cerebral infarction, TIA)	Watershed shift phenomenon	Direct bypass	Hydration, Antiplatelet, Edaravone
		Thrombo-embolism from anastomosis	Direct bypass	Antiplatelet, Edaravone
		Cortical compression by muscle pedicle	Indirect bypass	Revision of indirect bypass
	Cerebral hyperperfusion syndrome	Focal neurological deterioration	Direct bypass	BP lowering, Minocycline
		Delayed intracranial hemorrhage	Direct bypass	BP lowering
		Seizure	Direct/Indirect	Anti-epileptic agent
	Others	Chronic subdural hematoma	Direct/Indirect	Drainage
		Vasogenic edema without hyperperfusion	Direct bypass	BP lowering, Minocycline, Edaravone
Others	Aesthetic complication etc.	Skin necrosis	Direct/Indirect	Skin graft patch, Dressing
		Delayed wound healing	Direct/Indirect	Dressing
		CSF collection/leakage	Direct/Indirect	Spinal drainage
	Systemic complication	Cardiopulmonary complication	Direct/Indirect	Water balance correction etc.
		Activation of autoimmune diseases (Thyrotoxicosis etc.)	Direct/Indirect	Anti-thyroid therapy etc.

TIA, transient ischemic attack; BP, blood pressure; CSF, cerebrospinal fluid.

heterogeneous hemodynamic condition even within the hemisphere operated on. Rapid focal increase in CBF at the site of the anastomosis could result in focal hyperemia associated with vasogenic edema and/or hemorrhagic conversion in moyamoya disease (Fujimura et al. 2011). Now it is well known that cerebral hyperperfusion syndrome is one of the most serious complications of revascularization surgery for moyamoya disease, especially in adult patients (Fujimura et al. 2009b; Uchino et al. 2012). It had been believed for a long time that cerebral hyperperfusion was extremely rare after '*low flow bypass*' such as STA-MCA anastomosis, and the cause of the focal neurological deterioration after revascularization surgery for moyamoya disease had been exclusively attributed to cerebral ischemia. To counteract with this stereotype, we routinely measured CBF by N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP SPECT) in the acute stage of 257 consecutive surgical revascularization surgeries for moyamoya disease from 2004 operated by the single surgeon (M.F.), and found that that the incidence of symptomatic hyperperfusion, including mild focal neurological sign, was as high as 38.2% after STA-MCA anastomosis for adult-onset moyamoya disease in the initial series (Fujimura et al. 2007). Furthermore, the incidence of cerebral hyperperfusion syndrome after STA-MCA anastomosis was significantly higher in moyamoya disease patients than the patients with atherosclerotic occlusive cerebrovascular diseases (Fujimura et al. 2011). Focal cerebral hyperperfusion can cause temporary focal neurological deficit such as aphasia, hemiparesis, and dysarthria in a blood pressure dependent manner (Fujimura et al. 2007, 2009b, 2011). Although clinical manifestation is similar to that of transient ischemic attack, blood pressure dependent deterioration of the focal neurological sign convinced the diagnosis of symptomatic focal hyperperfusion. Because the symptoms due to hyperperfusion become evident between 2 to 6 days after surgery in most cases (Fujimura et al. 2011), we recommend routine CBF study within 48 hours after surgery (Fujimura et al. 2008). Prognosis of the focal neurological deficit is favorable in most cases, but focal hyperperfusion could also lead to delayed intracerebral hemorrhage and/or subarachnoid hemorrhage (Fujimura et al. 2009c, 2011). The incidence of delayed symptomatic hemorrhage due to hypeprerfusion is reported to be 3.3% (Fujimura et al. 2011), which could potentially result in permanent neurological deficit and/or mortality. Finally, the risk factors for hyperperfusion syndrome in moyamoya disease were reported as follows (Table 2); adult-onset (Fujimura et al. 2009b; Uchino et al. 2012), increased preoperative cerebral blood volume (Uchino et al. 2012), hemorrhagic-onset (Fujimura et al. 2009b), operation on the dominant (left) hemisphere (Hwang et al. 2013; Fujimura et al. 2014) and smaller diameter of the recipient artery (Fujimura et al. 2014). We also reported the predictive value of intraoperative brain surface monitoring by infrared thermography for postoperative hypeperfusion syndrome (Nakagawa et al. 2009). More recently, the predictive value of intraoperative indocyanine green videoangiography findings for post-operative hyperperfusion was reported from different institutes (Horie et al. 2014; Uchino et al. 2014). Representative findings of cerebral hyperperfusion are shown in Fig. 4.

Vasogenic edema without cerebral hyperperfusion

Besides cerebral ischemia and hyperperfusion, we recently reported local vasogenic edema without cerebral hyperperfusion in two cases of adult-onset moyamoya disease undergoing STA-MCA bypass (Sakata et al. 2015). Both patients exhibited apparent vasogenic edema at the site of the anastomosis, which prolonged over one month after revascularization surgery. Repeated CBF analysis failed to detect any evidence of either hyperperfusion or

Table 2. Risk factors for cerebral hyperperfusion syndrome (CHS) in moyamoya disease.

	Risk factors for CHS	References
Patients' age	Adult-onset Higher age	Fujimura et al. 2009b Uchino et al. 2012
Pre-operative hemodynamics	Increased CBV	Uchino et al. 2012
Onset-type	Hemorrhagic-onset	Fujimura et al. 2009b
Operation side	Dominant hemisphere Left hemisphere	Hwang et al. 2013 Fujimura et al. 2014
Vascular anatomy	Smaller diameter of the recipient artery	Fujimura et al. 2014
Intraoperative findings	Local temperature increase by infra-red thermography Restricted distribution by ICG video-angiography	Nakagawa et al. 2009 Horie et al. 2014, Uchino et al. 2014

CHS, cerebral hyperperfusion syndrome; CBV, cerebral blood volume; CVR, cerebrovascular reactivity; ICG, indocyanine green.

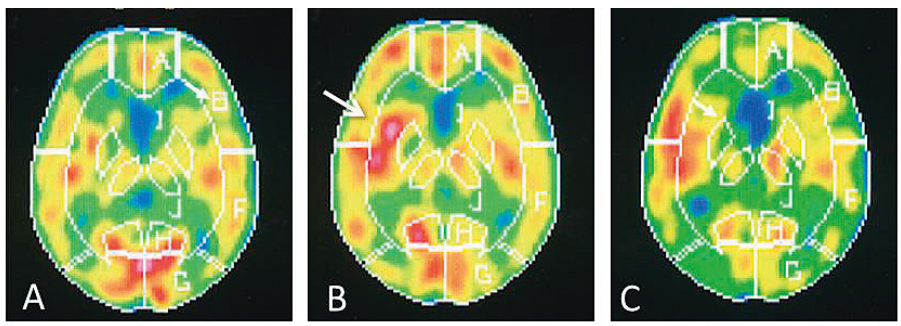

Fig. 4. Representative case of adult-onset moyamoya disease manifesting as focal cerebral hyperperfusion. N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography before (A) and one day (B), and seven days (C) after right STA-MCA anastomosis demonstrating marked increase in CBF near the site of the anastomosis (arrow in B) compared to pre-operative status (A). Focal hyperperfusion was ameliorated 7 days after surgery (C).

hypoperfusion. No neurological deterioration was found in these patients by intensive blood pressure control and minocycline administration, while increased vascular permeability as demonstrated by vasogenic edema formation might suggest the potential risk for hemorrhagic conversion (Sakata et al. 2015). Further evaluation is warranted to clarify the peri-operative pathologies after revascularization surgery for moyamoya disease to reduce the potential risk for surgical complications.

Establishment of peri-operative management protocol

Concept of the peri-operative care for moyamoya disease is to afford favorable 'IC-EC conversion' without causing deleterious impact to the affected brain. The excessive blood pressure lowering may increase the risk for peri-operative infarction at the remote area from STA-MCA bypass, but we found that prophylactic mild blood pressure lowering reduced the risk for hyperperfusion syndrome without increasing the incidence of ischemic complication, as long as adequate antiplatelet administration is attempted (Fujimura et al. 2012a). We have shown that prophylactic blood pressure control between 110 to 130 mmHg of the systolic blood pressure in the awake state significantly reduced the incidence of hyperperfusion syndrome after STA-MCA bypass in patients with moyamoya disease below that of the patients treated under normotensive conditions (Fujimura et al. 2012a). To further ameliorate the reperfusion injury to the affected brain, we additionally introduced minocycline hydrochloride, a neuro-protective antibiotic, to block the deleterious inflammatory cascade caused by the activation of matrix metalloproteinase-9 (MMP-9), which was implicated in moyamoya disease (Fujimura et al. 2009d; Kang et al. 2010), to prevent both hyperperfusion syndrome and cerebral infarction at the remote area. By the prophylactic blood pressure control combined with minocycline hydrochloride administration, the incidence of cerebral hyperperfusion syndrome as characterized by focal neurological deterioration was markedly reduced without increasing the ischemic complication (Fujimura et al. 2014). Our current protocol for peri-operative management of moyamoya disease is summarized in Fig. 5.

The CBF analysis in the acute stage facilitated safer and more elegant perioperative management after direct/indirect revascularization surgery for moyamoya disease, but the following limitation should be noted. Firstly, the hyperperfusion phenomenon shown by CBF analysis, either symptomatic or asymptomatic, could not be exclusively prevented even by current peri-operative management protocol. We observed delayed intracranial hemorrhage in 7 patients (6.9%) among 102 consecutive direct/indirect

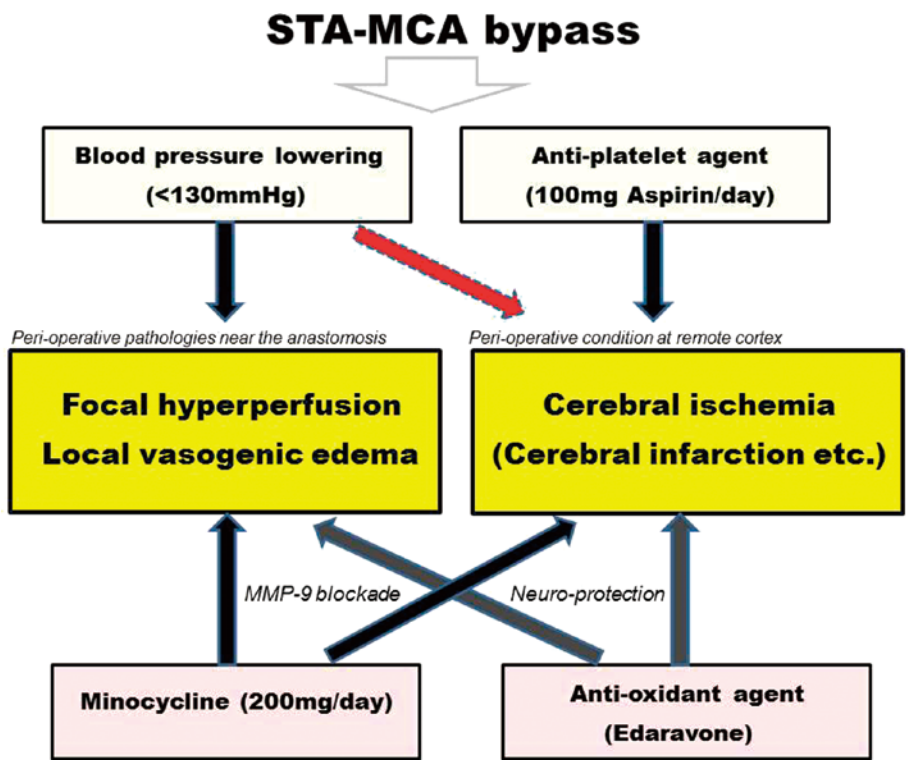

Fig. 5. Our peri-operative management strategy after STA-MCA anastomosis for moyamoya disease. The strategy attempts to avoid surgical complications including cerebral ischemia and hyperperfusion. Red arrow indicates the deleterious effect of blood pressure lowering to increase the potential risk for cerebral ischemia at remote area, including contralateral hemisphere and/or posterior circulation.

revascularization surgeries even after the introduction of minocycline hydrochloride, although most of them remained asymptomatic (Fujimura et al. 2015). It is essential to develop perioperative management of moyamoya disease based on the pharmacological strategies, by targeting molecular pathway underlying the early perioperative pathology after revascularization surgery.

Conclusion

Concept of revascularization surgery for moyamoya disease includes both microsurgical reconstruction by direct extracranial-intracranial bypass and the consolidation for the future vasculogenesis by indirect pial synangiosis. The direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease, while peri-operative cerebral infarction and cerebral hyperperfusion syndrome are potential complications of this procedure. Routine CBF measurement in the early postoperative period under strict blood pressure control between 110 to 130 mmHg (systolic) combined with the use of neuro-protective antibiotics minocycline hydrochloride facilitated safer and more elegant peri-operative management for moyamoya disease.

Conflict of Interest

The authors declare no conflict of interest.

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