Significance of Cerebral Blood Flow Analysis in the Acute Stage after Revascularization Surgery for Moyamoya Disease

Miki FUJIMURA¹ and Teiji TOMINAGA¹

¹Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi

Abstract

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by steno-occlusive changes at the terminal portion of the internal carotid artery, either bilaterally or unilaterally, and an abnormal vascular network at the base of the brain. Surgical revascularization such as extracranial-intracranial (EC-IC) bypass is the preferred procedure for moyamoya disease. Despite the favorable long-term outcome, cerebral infarction and hyperperfusion syndrome are potential complications of this procedure, which can lead to neurological deterioration in the acute stage. In light of the similar clinical presentations between perioperative ischemia and hyperperfusion, it is essential to attempt a prompt cerebral blood flow (CBF) measurement in the acute stage after EC-IC bypass for moyamoya disease to differentiate these distinct pathologies, because the management of cerebral ischemia and hyperperfusion is contradictory to each other. Routine CBF analysis by single-photon emission computed tomography and/or magnetic resonance imaging not only facilitated a safer perioperative management but also provided important information about dynamic pathology of the hemodynamic conversion in the acute stage after revascularization surgery for moyamoya disease. We represent the current status of CBF analysis during the perioperative period of revascularization surgery for moyamoya disease, and sought to discuss its significance and efficacy to avoid surgical complications.

Key words: moyamoya disease, perioperative management, extracranial-intracranial bypass, cerebral blood flow, single-photon emission computed tomography

Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by steno-occlusive changes at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain.¹,² 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).²,³ More recently, EC-IC bypass was shown to have a potential role for reducing 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 between surgical and non-surgical groups of moyamoya disease presenting with hemorrhage.⁴ Therefore, surgical indication of the revascularization surgery for moyamoya disease is considered to be expanding in the neurosurgical practice. Long-term outcome of EC-IC 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.²,³ We sought to review the importance of CBF measurement in the acute stage after revascularization surgery for moyamoya disease, and would demonstrate optimal perioperative management to avoid these deleterious phenomena after surgery.

Diagnosis and Basic Pathology

Moyamoya disease has been defined as a chronic, occlusive cerebrovascular disease with unknown etiology characterized by steno-occlusive changes at the terminal portion of the internal carotid artery, either bilaterally or unilaterally, and an abnormal vascular network at the base of the brain.
etiology characterized by bilateral steno-occlusive changes at the terminal portion of the ICA and an abnormal vascular network at the base of the brain.\textsuperscript{1,2,5} In light of the increasing number of the patients with unilateral involvement\textsuperscript{6} as well as the evidence that substantial number of unilateral cases could progress to the bilateral presentation,\textsuperscript{7} diagnostic criteria of the definitive moyamoya disease was revised to include patients with both bilateral and unilateral presentation of terminal ICA stenosis with abnormal vascular network at the base of the brain 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.

Despite this revision of the diagnostic criteria, the concept of the basic pathology of moyamoya disease has not been changed during the past 50 years. Intrinsic nature of moyamoya disease, including the temporal profile of its angio-architecture, is clearly indicated in classic grading system of the Suzuki’s angiographic staging.\textsuperscript{1,2} This angiographic staging does not represent the severity of moyamoya disease, but it indicates the compensatory nature of this entity to convert their vascular supply from internal carotid (IC) system to external carotid (EC) system, which we called IC-EC conversion.\textsuperscript{3} Due to the insufficient conversion at the transitional stage, such as at stage 3 and stage 4 with the development of moyamoya vessels, most patients manifest as ischemic symptom and/or intracranial hemorrhage, while substantial number of patients may achieve favorable IC-EC conversion without undergoing surgical intervention, as often seen in asymptomatic adult patients.\textsuperscript{8} 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 and Indication of Revascularization Surgery for Moyamoya Disease**

Concept of revascularization surgery for moyamoya disease includes both microsurgical reconstruction by EC-IC bypass and the consolidation for future EC-IC vasculogenesis by indirect pial synangiosis.\textsuperscript{3} 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 as indicated by Suzuki’s angiographic staging.\textsuperscript{1} Thus the concept of revascularization surgery for moyamoya disease is based on the idea to support the intrinsic compensatory nature of moyamoya disease, rather than to eradicate the intrinsic nature of this entity.

Surgical revascularization prevents cerebral ischemic attack by improving CBF in patients with moyamoya.\textsuperscript{3,9} Direct revascularization surgery such as STA-MCA anastomosis is established as an effective procedure for the patients with ischemic symptoms, providing long-term favorable outcomes.\textsuperscript{2,3,9} Based on the guidelines for diagnosis and treatment of moyamoya disease, revascularization surgery is recommended for the patients with moyamoya disease manifesting as cerebral ischemic symptoms (Recommendation grade B).\textsuperscript{2} Regarding hemorrhagic-onset patients, revascularization could be considered but adequate scientific evidence has been lacking (Recommendation grade C1).\textsuperscript{2} Nevertheless, recent evidence by JAM trial strongly suggested that direct revascularization surgery has a potential role for reducing the risk of re-bleeding in adult moyamoya disease patients presenting with intracranial hemorrhage.\textsuperscript{4} Therefore, surgical indication for moyamoya disease in general is considered to be expanding also to the hemorrhagic-onset patients as had been indicated to ischemic-onset patients. Finally, revascularization surgery for asymptomatic patients with moyamoya disease is not attempted because the natural history of asymptomatic patients is undetermined.\textsuperscript{2} To address this critical issue, AMORE (asymptomatic moyamoya registry) study is currently undertaken in Japan, which is a multicenter observational study to clarify the natural history of asymptomatic moyamoya disease.\textsuperscript{10}

**Perioperative Pathology and Surgical Complications**

Revascularization surgery for moyamoya disease is based on the “physiological” concept in light of the patients’ pathophysiology, as explained by IC-EC conversion theory,\textsuperscript{3} but it includes potential issue of the rapid CBF increase in the chronic ischemic brain, which may underlay the surgical complications of this management. It is essential to avoid hypercapnia and hypocapnia during surgery to reduce the risk for ischemic complication.\textsuperscript{2} Because patients with moyamoya disease are considered to have significantly poorer pial network on the affected hemisphere,\textsuperscript{11,12} direct vascular reconstruction by STA-MCA bypass may temporarily lead to 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,\textsuperscript{13–15} while CBF does not always increase at the remote
These heterogeneous and complex pathologies in the acute stage of revascularization surgery for moyamoya disease have been extensively investigated by perioperative CBF study, as the underlying mechanism of the particular surgical complications after revascularization surgery for moyamoya disease.

I. Cerebral ischemia due to three distinct mechanisms

Surgical complications of moyamoya disease include both neurological and non-neurological complications (Table 1). Neurological complications include cerebral ischemia and hyperperfusion syndrome. Regarding cerebral ischemia in the acute stage after surgery, following pathologies are proposed as the possible mechanisms. First, Hayashi and colleagues proposed “watershed shift” phenomenon as an intrinsic hemodynamic ischemia at the adjacent cortex to the site of the direct STA-MCA anastomosis for pediatric moyamoya disease. Retrograde blood supply from STA-MCA bypass may conflict 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. Careful evaluation of the correlation between postoperative CBF images and clinical symptom is essential to make accurate differential diagnosis between watershed shift and cerebral hyperperfusion. The watershed shift could result in cerebral infarction during the perioperative period among pediatric moyamoya disease, while fluctuating focal neurological deficit due to this phenomenon could be spontaneously resolved in most of the adult patients without causing infarction. Besides hemodynamic ischemia due to watershed shift, thromboembolism from the anastomosed site and the mechanical compression by swollen temporal muscle flap could also cause cerebral ischemia in the acute stage. Regarding the characteristic findings of early CBF imaging, the thromboembolism is characterized by hyperperfusion at the peripheral vascular territory of the anastomosed site, while mechanical compression results in hyperperfusion at relatively wide cortical area under the swollen temporal muscle used for indirect bypass. Sufficient hydration, maintenance of prompt hemoglobin concentration, and anti-platelet administration is essential especially to avoid watershed shift and thromboembolic complication during and after surgery. Revision of indirect bypass such as encephalo-myo-synangiosis should be considered when compression by swollen temporal muscle pedicle causes apparent CBF decrease. It is essential to differentiate each pathology by CBF measurement and MR imaging/angiography in the acute stage to select prompt management.

II. Cerebral hyperperfusion syndrome in moyamoya disease

Cerebral hyperperfusion syndrome should be mentioned as one of the most serious complications of revascularization surgery for moyamoya disease, especially in adult patients (Fig. 1). It is well documented that hyperperfusion syndrome after STA-MCA anastomosis is much more common among moyamoya disease patients than the patients with atherosclerotic occlusive cerebrovascular diseases. Focal cerebral hyperperfusion can cause temporary focal neurological deficit such as aphasia, hemiparesis, and dysarthria in a blood pressure dependent manner. Although clinical manifestation is similar to that of transient ischemic attack, blood pressure dependent deterioration of the focal neurological sign convinces the diagnosis of symptomatic focal hyperperfusion. Diagnosis of hyperperfusion syndrome in moyamoya disease is summarized in Table 2. Because the symptoms due to hyperperfusion become evident between 2 days and 6 days after surgery in most cases, CBF study such as single-photon emission computed tomography (SPECT) is recommended within 48 hours after surgery. Recent studies also suggested the diagnostic value of fluid-attenuated inversion recovery MR imaging.

Table 1 Surgical complication of direct/indirect revascularization for moyamoya disease

| Complication                                | Manifestation                                      |
|---------------------------------------------|---------------------------------------------------|
| Neurological                                |                                                   |
| Cerebral ischemia (cerebral infarction, TIA)| Watershed shift (hemodynamic)                     |
|                                             | Thromboembolism                                   |
|                                             | Compression by EMS flap                           |
| Focal hyperperfusion (HP)                   | Focal neurological deficit                        |
|                                             | Delayed hemorrhage                                |
| Others                                      |                                                   |
| Seizure                                     |                                                   |
| Chronic subdural hematoma                   |                                                   |
| Vasogenic edema without HP                  |                                                   |
| Non-neurological                            |                                                   |
| Wound trouble etc.                          | Skin necrosis                                     |
|                                             | Delayed wound healing                             |
|                                             | CSF collection/leakage                             |
| Systemic complication                       | Cardiopulmonary complication                      |
|                                             | Activation of autoimmune diseases                 |
|                                             | (thyrotoxicosis etc.)                             |

CSF: cerebrospinal fluid, EMS: encephalo-myo-synangiosis, TIA: transient ischemic attack.
A B C D

Table 2 Diagnosis of cerebral hyperperfusion syndrome after revascularization surgery for moyamoya disease

| Diagnostic tools, examination | Findings |
|------------------------------|----------|
| CBF analysis                 |          |
| SPECT ($^{123}$I-IMP)        | Focal intense CBF increase at the site of anastomosis |
| SPECT etc.                   |          |
| PET, perfusion CT            |          |
| Neuro-imaging                |          |
| MRI (DWI, T2WI)              | Absence of ischemic lesion |
| MRI (FLAIR)                  | Enhanced ivy sign |
| MRA                          | STA as thick high signal |
| CT (plain)                   | Delayed hemorrhage |
| Bed-side monitoring          |          |
| Neurological examination     | BP-dependent deterioration of neurological symptoms |
| BP monitoring                |          |

BP: blood pressure, CBF: cerebral blood flow, CT: computed tomography, DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery, $^{123}$I-IMP SPECT: N-isopropyl-$^{123}$I-iodoamphetamine single-photon emission computed tomography, MRA/MRI: magnetic resonance angiography/imaging, PET: positron-emission tomography, STA: superficial temporal artery.

Fig. 1 Representative case of a 58-year-old woman manifesting as cerebral hyperperfusion. N-isopropyl-p-$^{[123]$I} iodoamphetamine single-photon emission computed tomography before (A) and 1 day (B) and 7 days (C) after left superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis demonstrating marked increase in cerebral blood flow at the site of the anastomosis (arrow in B) compared to preoperative status (A). Focal hyperperfusion was ameliorated 7 days after surgery (C). Magnetic resonance angiography demonstrated patent STA as thick high signal (arrow in D).

Peripheral Management Based on CBF Analysis in the Acute Stage

Concept of the perioperative management of moyamoya disease after direct/indirect revascularization surgery is to afford elegant and effective “IC-EC conversion” without causing deleterious impact to both neural and vascular structures on the affected hemisphere. Although the excessive blood pressure lowering may increase the risk for perioperative infarction at the remote area from STA-MCA bypass, the prophylactic mild blood pressure lowering was reported to reduce the risk for hyperperfusion syndrome without increasing the incidence of ischemic complication. We have shown that prophylactic blood pressure control

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between 110 mmHg and 130 mmHg with the use of antiplatelet agent 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. To further ameliorate the reperfusion injury to the affected brain at the site of the anastomosis as well as the remote area under blood pressure lowering, we also used minocycline hydrochloride, a neuroprotective antibiotic, to block the deleterious inflammatory cascade caused by the activation of matrix metalloproteinase-9 in an attempt to prevent both hyperperfusion syndrome and cerebral infarction at the remote area. By the intensive perioperative management with prophylactic blood pressure control in combination with minocycline hydrochloride, the incidence of hyperperfusion syndrome as characterized by fluctuating focal neurological deficit was markedly reduced without increasing the ischemic complication. Our perioperative management protocol is summarized in Fig. 2.

Limitations of Current Perioperative Management for Moyamoya Disease

Early CBF measurement by SPECT with MR imaging facilitated safer and more elegant perioperative management after direct/indirect revascularization surgery for moyamoya disease, but the following issues remained to be solved in the future investigation. First, the incidence of symptomatic hyperperfusion was markedly decreased by current perioperative management protocol (Fig. 2), but the hyperperfusion phenomenon shown by CBF analysis could not be prevented by current strategies. In fact, we observed delayed intracranial hemorrhage in 7 patients (6.9%) among 102 consecutive direct/indirect revascularization surgeries even after the introduction of minocycline hydrochloride, although most of them remained asymptomatic hyperperfusion with minor subarachnoid hemorrhage. Second, prophylactic blood pressure lowering is not allowed in some patients with cardio-pulmonary dysfunction and/or renal failure. In light of the increasing number of the elderly moyamoya disease associated with atherosclerotic background, 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. Alternatively, natural history of the elderly patients with moyamoya disease should be clarified to establish a definitive surgical indication for elderly patients with moyamoya disease.

Conclusion

Concept of revascularization surgery for moyamoya disease includes both microsurgical reconstruction by EC-IC bypass and the consolidation for the future vasculogenesis leading to EC-IC anastomosis by indirect pial synangiosis. The direct/indirect revascularization surgery is a safe and effective treatment for moyamoya disease, and its indication is expanding in the neurosurgical practice. Postoperative cerebral hyperperfusion and perioperative infarction are potential complications of this procedure, thus we recommend intensive postoperative care and CBF measurement in the acute stage to counteract with these deleterious phenomena, because the management of hyperperfusion is contradictory to that of ischemia.

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Conflicts of Interest Disclosure

The authors have no disclosures to report.

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*Address reprint requests to: Miki Fujimura, MD, PhD, Department of Neurosurgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan. e-mail: fujimur@nsg.med.tohoku.ac.jp*