Characteristic Pattern of the Cerebral Hemodynamic Changes in the Acute Stage After Combined Revascularization Surgery for Adult Moyamoya Disease: N-isopropyl-p-[^{123}I] iodoamphetamine Single-Photon Emission Computed Tomography Study

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Introduction

Moyamoya disease (MMD) is a unique cerebrovascular disease with unknown etiology characterized by progressive stenosis of the terminal portion of the internal carotid artery (ICA) and abnormal vascular network formation at the base of the brain [1–3]. Surgical revascularization by superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis is a standard surgical procedure especially for adult patients with MMD [1, 3–6]. The STA-MCA anastomosis not only prevents cerebral ischemic attack by improving cerebral blood flow (CBF), but could also reduce the risk of re-bleeding in patients with posterior hemorrhage who were known to have extremely high re-bleeding risk [7, 8]. Regarding surgical procedure, recent study indicates the superiority of direct/indirect combined revascularization surgery such as STA-MCA anastomosis with indirect pial synangiosis [9]. Despite its long-term favorable outcome, however, local cerebral hyperperfusion syndrome and perioperative cerebral infarction are potential complications of this procedure [10–16]. Therefore, routine hemodynamic study and intensive perioperative management, including strict blood pressure control and administration of neuroprotective agents, are essential to provide favorable outcome [3, 17, 18]. In the present study, we sought to clarify the characteristic pattern of cerebral hemodynamic changes in the acute stage after combined revascularization surgery for adult MMD patients, who were treated by modern perioperative management protocol.

Materials and Methods

Inclusion Criteria of Patients and Surgical Procedure

The postoperative changes in CBF were investigated in 54 consecutive adult patients with MMD (21–76 years old, 43.1 average) surgically treated in 65 hemispheres by the same surgeon (M.F.) between July 2017 and June 2018. Surgical indication for MMD included all of the following items: the presence of ischemic symptoms (minor completed stroke and/or transient ischemic attack [TIA]) and/or posterior hemorrhage, the presence of hemodynamic compromise, independent activity of daily living (modified Rankin scale scores 0–2), and absence of major brain damage that exceed the vascular territory of one major branch of MCA.

Preoperative CBF was quantified by the autoradiographic method in most cases, and the CBF in each subregion using N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT) [10, 13]. All patients underwent STA-MCA (M4) anastomosis with encephalo-duro-myo-synangiosis (EDMS) [4]. Craniotomy was performed around sylvian fissure end, approximately 8 cm in diameter, and the stump of STA was anastomosed to the M4 segment of MCA, which was followed by EDMS. All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis, of the Ministry of Health, Labor, and Welfare, Japan [1, 3].

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G. Esposito et al. (eds.), *Trends in Cerebrovascular Surgery and Interventions*, Acta Neurochirurgica Supplement 132,
https://doi.org/10.1007/978-3-030-63453-7_8

Postoperative CBF Measurement and Perioperative Management Protocol

CBF was routinely measured by ^{123}I-IMP-SPECT at postoperative day (POD) 1 and 7 after surgery in all patients. The temporal profile of the postoperative cerebral hemodynamics was qualitatively classified into three patterns. First, the "local hyperperfusion-redistribution pattern" was defined as transient local hyperperfusion at the site of the anastomosis (POD1) and subsequent distribution of the improved CBF in wider vascular territory (POD7). Second, the "gradual CBF improvement pattern" was defined as none of minor improvement of CBF (POD1) which was followed by the moderate improvement of CBF on the affected hemisphere (POD7). All of the patterns that did not satisfied the above two patterns were defined as "others." Postoperative computed tomography (CT) scan was routinely performed immediately after surgery and one day after surgery in all cases. 1.5-T or 3-T magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed within three days after surgery. MRI included diffusion-weighted images (DWI), T2-weighted images, and T2*-weighted images in all cases. The fluid attenuated inversion recovery was also performed in most cases. The criteria for "local hyperperfusion" included all of the following items: (1) The presence of a significant local CBF increase at the site of the anastomosis that exceeded the CBF value of the other supratentorial region of the bilateral hemispheres. (2) Apparent visualization of STA-MCA bypass by MRA. (3) The absence of other pathologies such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis and CBF increase secondary to seizure.

All 54 patients operated on 65 hemispheres were prospectively subjected to prophylactic intensive blood pressure lowering (100–130 mmHg of systolic blood pressure) according to standardized postoperative management protocol to prevent cerebral hyperperfusion syndrome using 1–10 mg/h continuous intravenous drip infusion of nicardipine hydrochloride as previously described [17]. All patients were managed by intraoperative and postoperative intravenous administration of minocycline hydrochloride (200 mg/day) until 7 days after surgery, in order to avoid the deleterious effects of cerebral hyperperfusion, and to reduce the potential risk of cerebral ischemia at remote area [18]. To avoid the unfavorable effect of intensive blood pressure lowering on the contralateral hemisphere and/or ipsilateral remote areas, we routinely administered anti-platelet agents (100 mg aspirin/day) starting the day after surgery in all cases [17, 18]. Based on the temporal profile of ^{123}I-IMP-SPECT and MRI/MRA findings, we gradually allowed a return to normo-tensive conditions within 7–10 days after surgery [17, 18].

Table 1 Patterns of cerebral hemodynamic changes after 65 consecutive direct/indirect revascularization surgeries for adult moyamoya disease

	Hemisphere	Incidence
Local hyperperfusion (POD1)-redistribution (POD7)	37/65	56.9%
Gradual increase in CBF (POD1-POD7)	20/65	30.8%
Others	8/65	12.3%

CBF cerebral blood flow, *POD* postoperative day

Results

The outcome of 65 surgeries was favorable in all cases except for one (1.5%), which manifested as delayed intracerebral hemorrhage due to local hyperperfusion and did not affect the patient's long-term activity of daily living. The postoperative ^{123}I-IMP-SPECT revealed the characteristic CBF improvement pattern with local hyperperfusion (POD1) and subsequent distribution of CBF in wider vascular territory (POD7) on 37 hemispheres (56.9%, 37/65). "Gradual CBF improvement pattern" was found on 20 hemispheres (30.8%, 20/65), and eight hemispheres were classified into the "others" (12.3%, 8/65). The result is summarized in Table 1, and the representative case with "local hyperperfusion-redistribution pattern" is shown in Figs. 1 and 2. None of the patients developed perioperative cerebral infarction, while one patient suffered transient ischemic change by DWI at the cerebral cortex adjacent to the site of the anastomosis that resolved within 2 weeks.

Discussion

The present prospective study by routine ^{123}I-IMP-SPECT revealed the characteristic CBF improvement pattern in the acute stage after STA-MCA anastomosis with indirect pial synangiosis for adult MMD patients. We found that local hyperperfusion at the site of the anastomosis (POD1) and subsequent distribution of CBF in wider vascular territory (POD7), so-called "local hyperperfusion-redistribution pattern," was the most common hemodynamic pattern as evident on 37 hemispheres (56.9%, 37/65) after combined revascularization surgery for adult MMD. Under the strict perioperative management by blood pressure control (100–130 mmHg of systolic blood pressure) and the administration of neuro-protective/anti-inflammatory agent (minocycline hydrochloride) [17, 18], the outcome of 65 surgeries was generally favorable despite the presence of transient local hyperperfusion, except for one (1.5%, 1/65) manifesting as delayed intracerebral hemorrhage due to local hyperperfusion. We thus recommend intensive perioperative care with routine CBF measure-

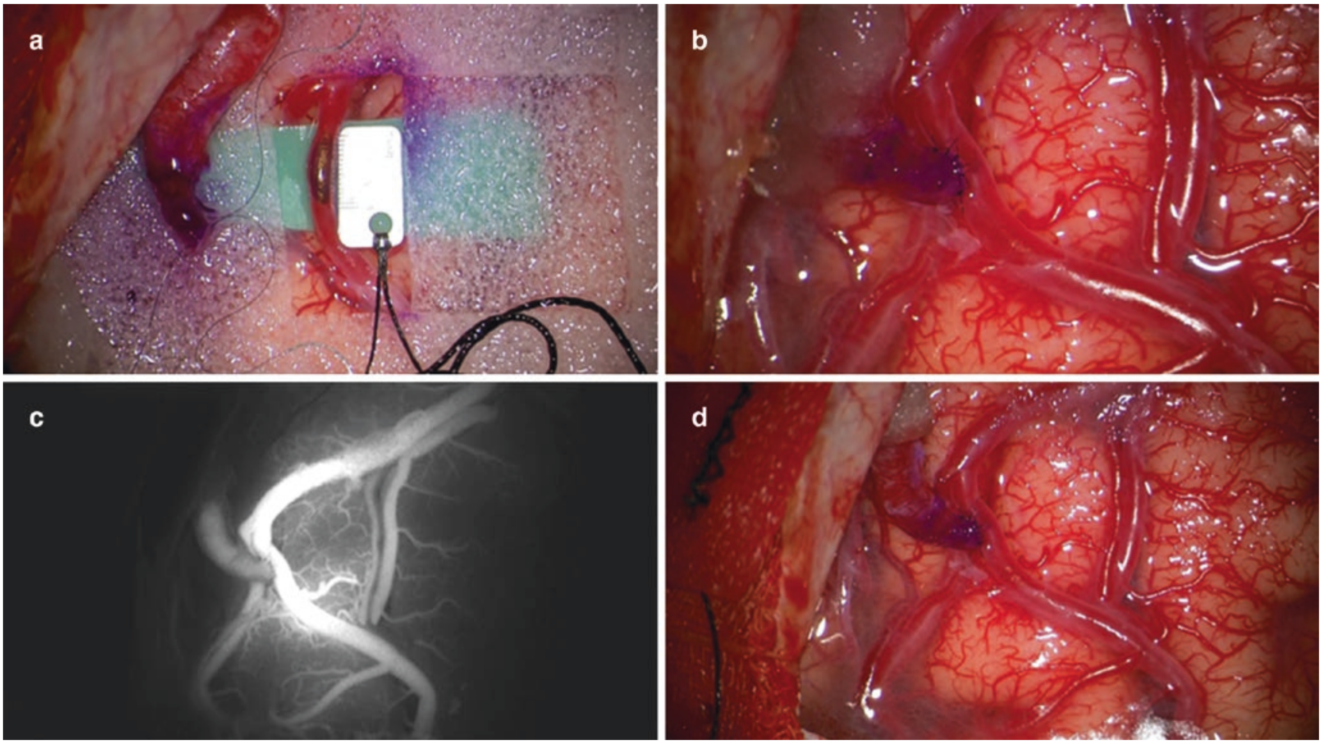

Fig. 1 Intraoperative microscopic view of right superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis for a 47-year-old patient. (**a**, **b**, **d**) The stump of STA was anastomosed to M4 segment of left MCA with 1.1 mm in diameter, with the temporary occlusion time of 26 min. (**c**) Intraoperative indocyanine green video-angiography after the anastomosis showing apparently patent STA-MCA bypass

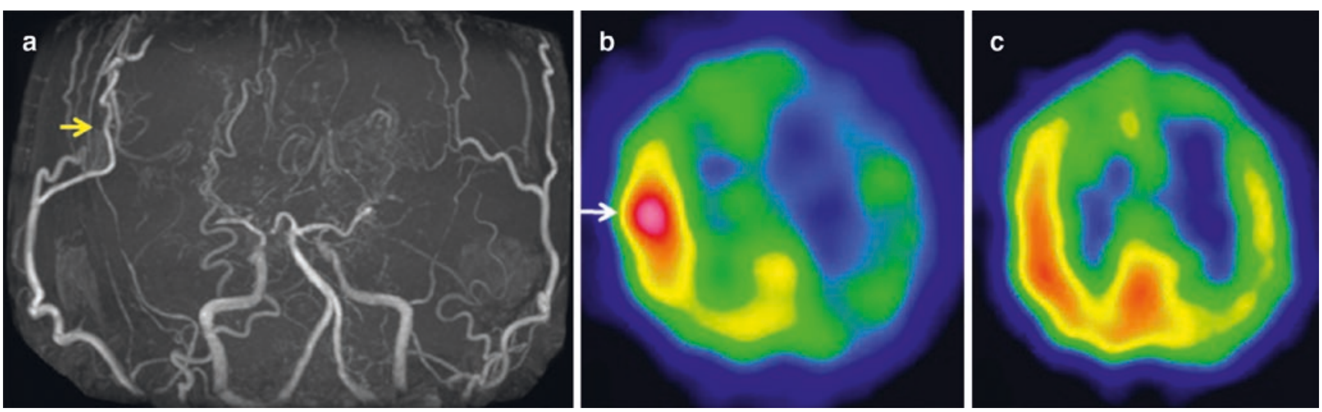

Fig. 2 (**a**) Magnetic resonance angiography on postoperative day 2 showing the patency of right STA-MCA bypass (arrow). (**b**, **c**) N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography on postoperative day 1 (**b**) showing focal cerebral hyperperfusion in the right frontal lobe (arrow), which is significantly relieved with favorable distribution 7 days after surgery (**c**)

ment to avoid the deleterious effect of transient local hyperperfusion within 7 days after STA-MCA anastomosis for adult MMD patients.

Surgical complications of MMD include perioperative cerebral ischemia and cerebral hyperperfusion syndrome [1, 3, 5]. Perioperative cerebral ischemia could be caused by at least three distinct mechanisms: "watershed shift phenomenon" [14, 19], thrombo-embolism at the site of the anastomosis [13], and mechanical compression of the brain surface by swollen temporal muscle used for indirect bypass procedure [20]. Besides perioperative cerebral ischemia, rapid local increase in CBF at the site of the anastomosis could result in focal hyperemia associated with vasogenic edema and/or hemorrhagic conversion, especially in adult MMD

[11–13, 15, 16]. We have reported that the incidence of cerebral hyperperfusion syndrome after STA-MCA bypass was significantly higher in MMD patients than that in patients with atherosclerotic occlusive cerebrovascular diseases [13]. Prognosis of the focal neurological deficit due to hyperperfusion is generally favorable, but it could lead to delayed intracerebral hemorrhage in a rare occasion [12]. In fact, the present study included one complication case with delayed intracerebral hemorrhage even under the modern perioperative management protocol. In light of the risk factors for hyperperfusion syndrome in MMD such as adult-onset [11, 16], increased preoperative cerebral blood volume [16], hemorrhagic-onset [11], operation on the dominant hemisphere [18], and smaller diameter of the recipient artery [18], it is particularly important to manage adult MMD patients with these factors promptly to avoid deleterious effects of hyperperfusion during the perioperative period.

In conclusion, the direct/indirect combined revascularization surgery is generally a safe and effective treatment for adult MMD under modern perioperative management. In light of the characteristic CBF improvement pattern with local hyperperfusion (POD1) and subsequent distribution of CBF in wider vascular territory (POD7) on 37 hemispheres in the present series (56.9%, 37/65), transient local hyperperfusion should be strictly managed by intensive perioperative care in adult MMD patients.

Acknowledgements *Funding*: This work was supported by MHLW Grant Number S17310031, AMED Grant Number J170001344 and JSPS KAKENHI Grant Number 17K10815.

Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Informed Consent Informed consent was obtained from individual participants included in the study.

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