Intraoperative EC-IC Bypass Blood Flow Assessment With Indocyanine Green Angiography in Moyamoya and Non-Moyamoya Ischemic Stroke

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Key words
- Cerebral blood flow
- Cerebral hyperperfusion syndrome
- EC-IC bypass
- Indocyanine green angiography
- Moyamoya disease

Abbreviations and Acronyms
CCD: Charge coupled device
$CoSO_2$: Cortical oxygen saturation
DSA: Digital subtractive angiography
EC-IC: Extracranial-intracranial
ICG: Indocyanine green
MD: Moyamoya disease
non-MD: Mon-moyamoya ischemic stroke
rCBF: Regional cerebral blood flow
ROI: Region of interest
SPECT: Single photon emission computed tomography
STA-MCA: Superficial temporal artery-middle cerebral artery
VLS: Visual light spectroscopy

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OBJECTIVE: **Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis has been used in moyamoya disease (MD) and non-moyamoya ischemic stroke (non-MD). It is important to monitor hemodynamic changes caused by bypass surgery for postoperative management. We evaluated the bypass blood flow during STA-MCA anastomosis by using indocyanine green (ICG) fluorescence angiography.**

METHODS: **We evaluated the bypass blood flow in 13 MD and 21 non-MD patients during STA-MCA anastomosis by means of ICG angiography with injection of ICG into the anastomosed STA. The ICG perfusion area was calculated when the ICG fluorescence intensity reached maximum. We measured cortical oxygen saturation before anastomosis by means of visual light spectroscopy.**

RESULTS: **ICG angiography demonstrated bypass blood flow from the anastomosed STA to the cortical vessels in all patients. The ICG perfusion area in MD (20.7 ± 6.6 cm^2) was significantly larger than that in non-MD (8.4 ± 9.1 cm^2, $P < 0.05$). The cortical oxygen saturation (58.9% ± 8.3%) in MD was significantly lower than that in non-MD (73.4% ± 9.5%, $P < 0.05$).**

CONCLUSIONS: **ICG angiography with injection of ICG into the bypass artery allowed quantitative assessment of bypass blood flow. The bypass supplies blood flow to a greater extent in MD than in non-MD during surgery. This might be caused by a larger pressure gradient between the anastomosed STA and recipient vessels in MD. These observations indicate that MD requires careful control of systemic blood pressure after surgery to avoid cerebral hyperperfusion syndrome. ICG angiography is considered useful for facilitating safe and accurate bypass surgery and providing information for postoperative management.**

INTRODUCTION

Moyamoya disease (MD) is a rare occlusive cerebrovascular disease characterized by progressive stenosis of bilateral terminal portions of the internal carotid arteries (16). Extracranial-intracranial (EC-IC) bypass, such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis, has become a standard surgical therapeutic option in MD to prevent recurrent ischemic events (8, 13). In addition, EC-IC bypass surgery has been performed to prevent stroke in patients with transient ischemic attack caused by hemodynamic compromise (1, 19). Neuroradiologic studies have demonstrated beneficial effects of bypass surgery on cerebral hemodynamic status in both MD (1, 13) and non-MD ischemic diseases (1).

To perform EC-IC bypass surgery safely and accurately, the following problems need to be considered and resolved during surgery. First, occlusion of the graft artery must be corrected during surgery. Intraoperative graft occlusion usually occurs for technical reasons or because of a hypercoagulable state. Second, cerebral ischemia due to the temporary occlusion of the recipient artery such as the MCA may result in cerebral infarction after surgery. Finally, an increased perfusion pressure induced by bypass blood flow may cause hyperperfusion syndrome in the chronically hypoperfused brain. Indeed, several studies have reported the occurrence of cerebral hyperperfusion syndrome after STA-MCA anastomosis in MD (2, 3, 10, 20).

To resolve the problems during bypass surgery, various intraoperative monitoring techniques have been developed to evaluate the hemodynamic changes or pa-

tency of the graft during surgery including EC-IC bypass (1, 2, 4, 13). Recently, we have developed an intraoperative visual light spectroscopy (VLS) system for continuous measurements of hemodynamic changes during bypass surgery (4). The VLS monitoring system could detect dynamic changes of cortical blood flow during bypass surgery in MD and non-MD. Interestingly, the increase of cortical blood flow induced by the STA blood flow was observed more frequently in MD than in non-MD, suggesting that the STA supplied more blood to the ischemic brain in MD than in non-MD after bypass surgery (5). These data obtained by VLS might be useful for postoperative management, such as control of systemic blood pressure, in patients undergoing bypass. However, it remains unclear to what extent the bypass serves to contribute to cortical blood flow in MD and in non-MD as the VLS system can measure the hemodynamic changes only at the recording point.

Recently, indocyanine green (ICG) fluorescence has been applied to intraoperative imaging of cerebral vessels during neurosurgical operations (12, 17). Intraoperative ICG angiography offers real-time information on the cortical blood flow with a high spatial resolute and excellent image quality, as ICG fluorescence is near-infrared fluorescence, which is highly transmittable in biological tissues compared with visible light fluorescence (14). ICG fluorescence has been applied to intraoperative angiography during EC-IC bypass surgery (11, 21). Peña-Tapia et al. (11) found ICG fluorescence angiography useful in the identification of the optimal cortical target point for EC-IC bypass surgery. Woitzik et al. (21) demonstrated that ICG fluorescence angiography provides a reliable and rapid intraoperative assessment of bypass patency. However, it was not clarified to what extent the bypass contributes to cortical blood flow during surgery in these studies, as ICG was given systemically through an intravenous bolus injection.

In the present study, we used ICG angiography to compare blood supply during the bypass to the cortex during STA-MCA anastomosis in MD and in non-MD patients. To assess the bypass blood flow selectively, ICG was injected into a branch of the anastomosed STA. In addition, using VLS, we compared the cortical oxygen saturation ($CoSO_2$) during surgery in the two groups.

MATERIALS AND METHODS

We investigated 34 patients undergoing craniotomy for STA-MCA anastomosis. The subjects included 13 patients with MD (mean age [mean ± SD], 27.3 ± 13.4 years) and 21 with non-MD (59.9 ± 9.2 years), including 13 patients with occlusion of the internal carotid artery and 8 patients with occlusion of the MCA. The mean age of MD was significantly younger than that of non-MD ($P = 0.00003$). **Table 1** summarizes the patient profiles. Digital subtractive angiography (DSA) was performed before and 1 week after bypass surgery in all patients. Preoperative DSA demonstrated that the principal routes of collateral circulation were mainly moyamoya vessels in MD, whereas leptomeningeal anastomosis supported the collateral circulation in non-MD. All MD patients had suffered multiple episodes of transient ischemic attack or cerebral hemorrahge; computed tomography demonstrated cerebral infarction in two patients and cerebral hemorrhage in four. The present study was approved by the Committee for Clinical Trials and Research on Humans. The ethical committee of our university hospital approved the protocol of the study.

In all patients, single photon emission computed tomography (SPECT, PRISM 2000XP, Shimadzu Co.; Kyoto, Japan) was used to measure the regional cerebral blood flow (rCBF) at rest and at 10 minutes after intravenous injection of acetazolamide (1.0 g). To evaluate the regional hemodynamics, regions of interest were designated in the cortical territory of the MCA. SPECT demonstrated a reduced rCBF at rest (≤30 ml/100 g/min) and reactivity to acetazolamide (%CVR ≤ 10%) before surgery in all MD and non-MD patients.

The parietal branch of the STA was carefully isolated from the reflected skin flap, and anastomosed end-to-side to the M4 portion of the MCA. In MD patients, encephalo-myo-synangiosis was also performed after the STA-MCA anastomosis. The physiologic parameters during surgery were within the normal ranges in all patients; there were no significant differences in physiologic parameters and blood flow of the STA between the MD and non-MD groups (**Table 1**).

Hemodynamic changes in the patients during STA-MCA anastomosis were evaluated with an ICG angiography system (Photodynamic Eye, C9830, Hamamatsu Photonics; Hamamatsu, Japan), which consists of a light source (780 nm) and a charge coupled device (CCD) camera with optical filter (840 nm). The CCD camera is mounted on a three-legged stool, which is fitted with sterilized plastic covers. The distance between the CCD camera lens and operative field was 10 cm. The lens of the CCD camera is a fixed-focus lens; the optical axis was set to be vertical to the brain surface.

The ICG solution contained 25 mg of ICG (Diagnogreen, Daiichi-Sankyo Company; Tokyo, Japan) in 10 ml of saline. An aliquot (0.1 ml) was injected into a branch vessel of the STA, which was clamped at the proximal portion after the STA-MCA anastomosis, then the clamp was released so that the ICG solution flowed into the cortical arteries.

We analyzed the time course of ICG fluorescence intensity at region of interest (ROI) on the cortex. In addition, to analyze the ICG perfusion area quantitatively, we calculated the perfusion area at the time point when the ICG fluorescence intensity reached the maximum level, using image analysis software (Image J 1.40g, National Institutes of Health; Bethesda, MD, USA) to analyze the static image at the maximal ICG fluorescence. The ICG perfusion area was calculated automatically based on the number of pixels that exceeded the background fluorescence intensity level.

For intraoperative VLS monitoring, we used our recently developed system (4). Briefly, VLS measures changes of oxyhemoglobin and deoxyhemoglobin concentration in the cerebral vessels based on the characteristic absorption spectra of hemoglobin in the visible light range; the analyzed wavelength range was 520 to 580 nm. The ratio of oxyhemoglobin to [oxyhemoglobin + deoxyhemoglobin] indicates the $CoSO_2$. The $CoSO_2$ was measured before STA-MCA anastomosis.

RESULTS

Figure 1A shows an example of ICG fluorescence angiography after an injection of

Table 1. Patient profiles, physiologic parameters, and STA blood flow in MD and non-MD patients

No.	Age/sex	Clinical diagnosis	SBP	DBP	BT	HR	SaO_2	PaO_2	PCO_2	Hb	Ht	STA-flow
1	45/m	CI (IC)	135	84	34.4	63	100	314.0	42.0	14.1	41.1	48
2	71/m	CI (IC)	143	80	35.0	65	100	170.5	38.0	13.5	40.5	28
3	74/m	CI (IC)	150	65	34.5	75	100	182.9	42.2	13.4	39.1	44
4	48/m	TIA(IC)	130	65	35.7	85	100	134.6	37.6	12.8	37.6	27
5	55/m	CI (IC)	140	80	35.1	55	100	168.5	44.2	14.5	43.1	24
6	48/f	CI (MCA)	115	68	35.0	60	100	189.2	44.8	13.1	37.8	50
7	49/f	CI (MCA)	130	75	35.7	69	100	213.1	36.0	10.7	31.8	24
8	61/m	CI (MCA)	165	80	35.0	58	100	244.2	37.0	13.4	39.4	26
9	49/f	TIA (MCA)	130	80	35.0	75	100	125.2	42.6	12.6	37.6	24
10	68/m	CI (IC)	130	60	36.0	55	100	151.4	40.1	10.4	32.2	12
11	52/m	SAH (IC)	152	74	36.5	74	100	134.5	38.4	13.5	41.5	36
12	63/m	TIA (MCA)	147	84	36.5	65	100	266.0	43.1	12.6	38.0	9
13	68/m	CI (IC)	164	82	35.9	56	100	174.0	38.5	13.1	39.2	60
14	72/f	TIA (MCA)	128	70	36.6	70	100	194.0	38.2	9.9	29.3	102
15	61/m	CI (IC)	177	90	36.5	68	100	(-)	(-)	14.0	43.2	54
16	64/m	TIA (IC)	148	78	36.6	88	100	191.0	40.9	13.7	41.2	10
17	53/f	TIA (MCA)	163	82	36.2	66	100	164.0	40.5	15.5	46.0	(-)
18	59/m	TIA (MCA)	154	81	36.1	65	100	303.0	35.2	15.1	43.7	47
19	62/f	CI (IC)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	12
20	72/m	CI (IC)	103	58	36.5	56	100	294.0	49.0	13.5	40.1	14
21	64/f	TIA (MCA)	140	86	36.5	72	100	192.0	39.8	13.0	37.8	(-)
22	35/m	MD	148	92	34.4	58	100	216.3	35.8	14.2	41.7	42
23	23/m	MD	148	62	34.3	65	100	241.6	38.7	13	39.4	16
24	14/f	MD	125	70	34.5	73	100	213.5	41.9	13.2	38.4	24
25	14/f	MD	120	65	35.1	58	100	293.0	38.0	12.4	36.4	16
26	23/f	MD	145	80	35.5	65	100	250.6	40.9	13.2	38.5	20
27	64/m	MD	120	65	36.0	62	100	188.4	39.6	11.5	33.8	44
28	26/f	MD	140	90	34.7	65	100	181.7	35.7	12.5	36.4	21
29	24/f	MD	127	76	36.5	77	100	337.0	36.0	12.3	36.9	12
30	20/f	MD	102	61	36.3	72	100	200.0	37.0	14.6	43	10
31	31/f	MD	126	72	36.1	80	100	251.0	37.0	13.6	41.6	21
32	19/f	MD	118	77	37.1	84	100	230.0	44.7	14.7	42.8	(-)
33	29/m	MD	127	76	(-)	77	100	335.0	41.1	12.3	36.9	(-)
34	32/m	MD	142	91	36.8	61	100	278.0	41.8	16	47.3	16

SDP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); BT, body temperature (°C); HR, heart rate; SaO_2, oxygen saturation (%); PaO_2, arterial oxygen partial pressure (mm Hg); $PaCO_2$, arterial carbon dioxide partial pressure (mm Hg); Hb, hemoglobin (mg/dl); Ht, hematocrit (%); STA, blood flow of the superficial temporal artery (ml/min); CI, complete stroke; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; MD, moyamoya disease; IC and MCA in parentheses, occlusion of internal carotid artery and middle cerebral artery, respectively.

ICG. We could obtain real-time images of the bypass flow from the graft to the cortical vessels, and confirmed patency of the bypass graft.

ICG fluorescence intensity rapidly increased to the maximum level and returned to the control level when the ROI was set within the perfusion area of ICG (**Figure 1B**). In contrast, when the ROI was set outside the perfusion area, no remarkable increase of ICG fluorescence intensity was observed.

Figure 2 shows examples of ICG angiography in MD and non-MD patients. The ICG perfusion area in MD patients was larger than that in non-MD patients when the ICG fluorescence intensity was maximum. The mean ICG perfusion area in MD patients

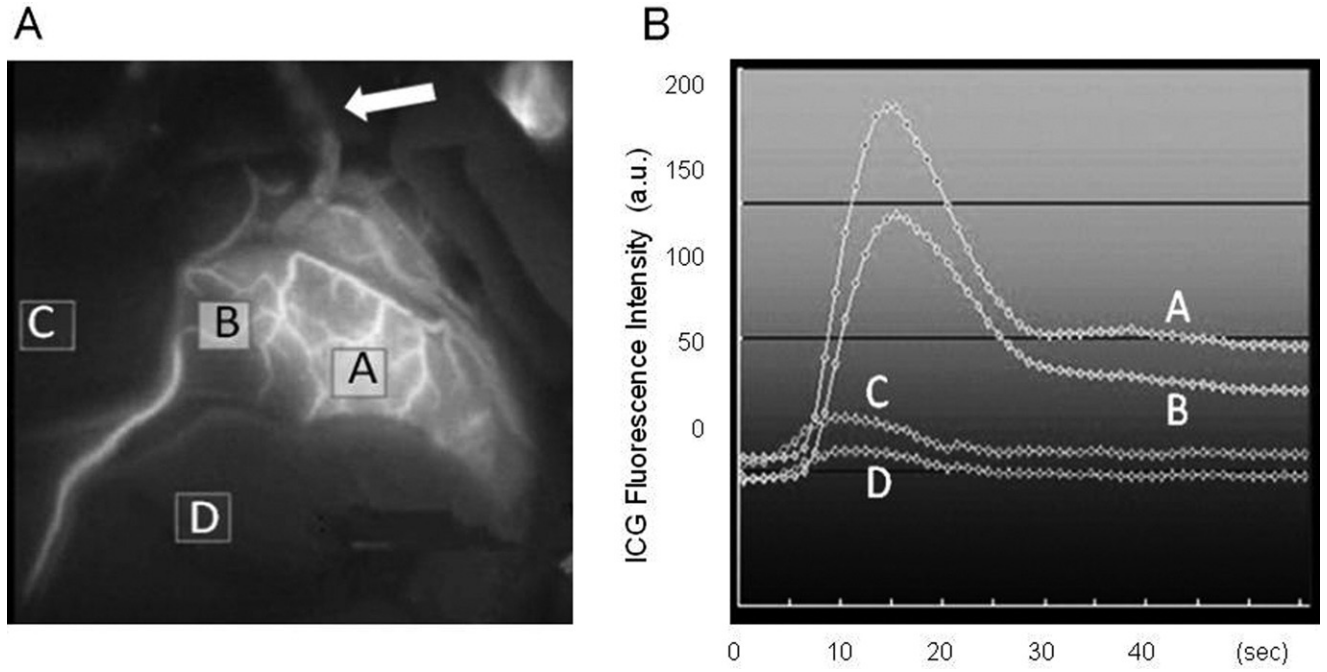

Figure 1. Intraoperative indocyanine green (ICG) angiography during superficial temporal artery-middle cerebral artery anastomosis. (**A**) An example of ICG fluorescence angiography at the time point when the ICG fluorescence intensity reached the maximum level. White arrow indicates the anastomosed superficial temporal artery. (**B**) Time courses of ICG intensity curve. A, B, C, D correspond to the ROIs in **A**, respectively.

(20.7 ± 6.6 cm^2) was statistically significantly larger than that in non-MD patients (8.4 ± 9.1 cm^2; $P<0.05$) (**Figure 3A**).

Although SPECT did not demonstrate differences in rCBF on the lesion side between MD and non-MD patients, VLS revealed significant differences in $CoSO_2$ between the two groups. The $CoSO_2$ (58.9% ± 8.3%) in MD patients was significantly lower than that in non-MD patients (73.4% ± 9.5%; $P < 0.05$) (**Figure 3B**). There was no significant difference in the STA blood flow before anastomosis between MD (22 ± 10 ml/min) and non-MD patients (33 ± 31 ml/min; $P > 0.05$) (**Table 1**).

Postoperative DSA demonstrated that the anastomosed STA supplied blood to the primary motor cortex on the lesion side 1 week after surgery (**Figure 4**). Note that ICG angiography had demonstrated only a small ICG perfusion area during surgery. We did not observe neurological symptoms or dysfunction after surgery in any of the patients.

DISCUSSION

The present results demonstrated that the ICG perfusion area in MD patients was significantly larger than that in non-MD patients. These findings were consistent with the results of our recent study, in which we used VLS for evaluation of hemodynamic changes induced by STA blood flow (5). We found that the STA blood flow increased the $CoSO_2$ more frequently in MD than in non-MD patients. This suggested that the STA supplied more blood flow to the cortex in MD than in non-MD patients, but was not conclusive, as the VLS allowed measurements at only a single point (4, 5). In contrast, ICG angiography allows two-dimensional imaging of STA blood supply to the cortex. Based on these results we conclude that the anastomosed STA supplied more blood to the cortex in MD than in non-MD patients during surgery.

Although the physiologic mechanisms underlying the difference in bypass blood flow remain unclear, the following possibilities should be considered. First, changes of the graft size after bypass could affect the bypass blood flow. Although the graft size could be enlarged after bypass surgery, this would be slow, and indeed, no change in graft size was evident under a surgical microscope. Second, possible differences in systolic blood pressures and blood gases during surgery between MD and non-MD patients might affect the bypass blood flow. However, both systemic blood pressure and blood gases were maintained within normal ranges during general anesthesia, as this is essential to avoid perioperative ischemic complications. Finally, a possible larger pressure gradient between the anastomosed STA and recipient vessels might cause a greater STA blood supply. Kawase and Tazawa (7) evaluated the relation between the bypass flow and the pressure gradient between the STA and MCA in non-MD patients, and found that the bypass flow was linearly correlated with the pressure gradient. Although they did not compare the pressure gradient between MD and non-MD patients, these findings suggest that MD might exhibit a larger pressure gradient between the bypass artery and recipient vessels. Indeed, in the present study, VLS revealed lower $CoSO_2$ before anastomosis in MD than in non-MD patients, suggesting that the pressure gradient between the anastomosed STA and recipient vessel in MD was larger than that in non-MD patients. However, preoperative SPECT did not

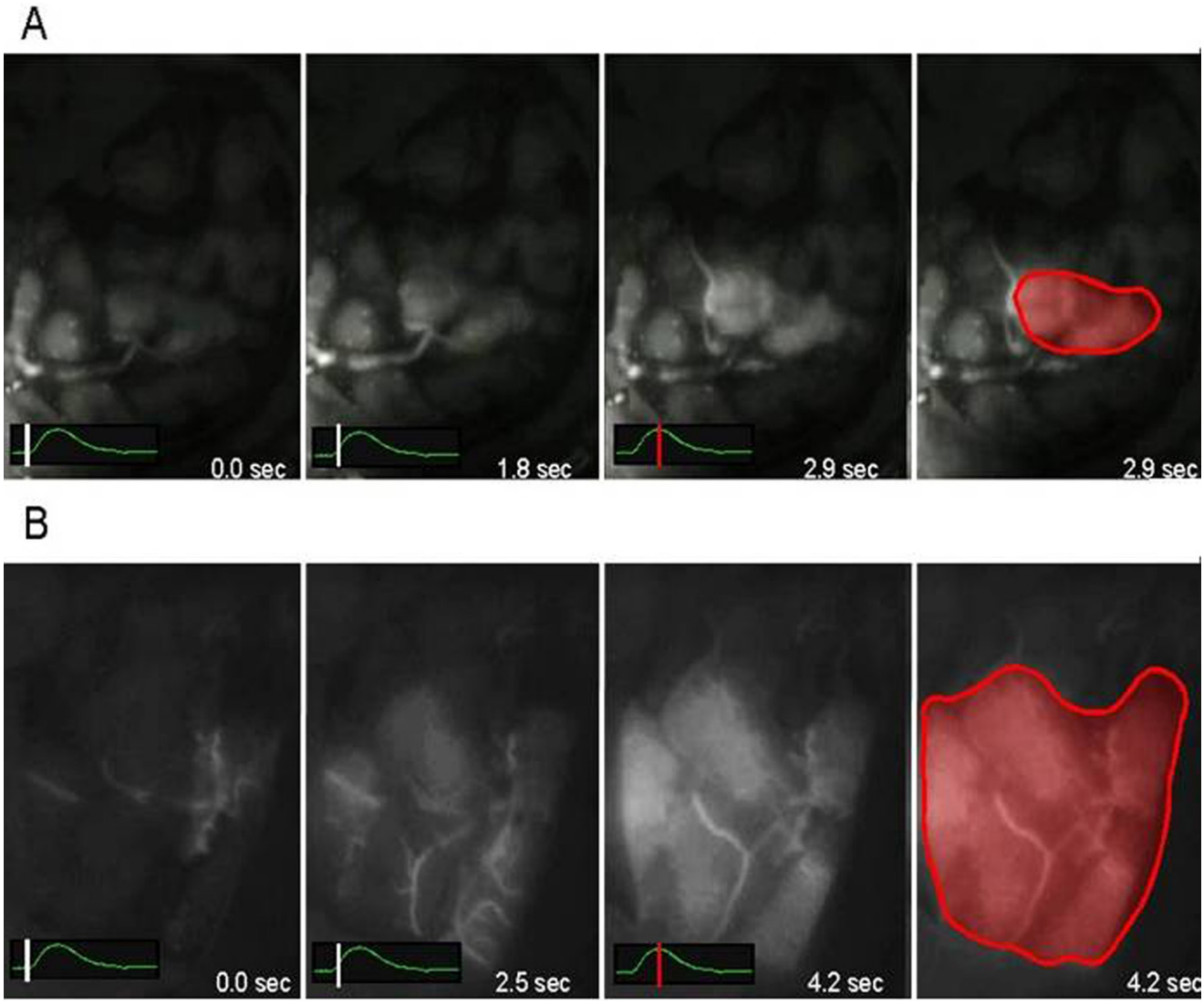

Figure 2. Serial pictures of indocyanine green (ICG) angiography in non-moyamoya disease (MD) (**A**) and MD (**B**). The time (seconds) after injection of ICG was superimposed in each picture. The ICG fluorescence intensity in non-MD and MD reached the maximum values at 2.9 seconds and 4.9 seconds, respectively. The read areas indicate the ICG perfusion areas when the ICG fluorescence intensity was maximum.

show significant differences in rCBF in these areas. This discrepancy may be caused by the differences in sensitivity and measurement volumes between VLS and SPECT. Further studies are necessary to clarify the physiologic mechanism of the difference in bypass blood supply between the two groups.

A number of studies have described the occurrence of hyperperfusion syndrome in MD patients after STA-MCA anastomosis (2, 3, 10, 20). Although the underlying physiologic mechanism is unclear, the present results suggest that blood flow through the anastomosed STA is larger in MD than in non-MD patients, and this may play a role in the occurrence of cerebral hyperperfusion syndrome in MD. It should be noted, however, that none of the MD patients complained of symptoms of cerebral hyperperfusion syndrome after surgery in the present study, therefore a large amount of bypass blood supply alone may not be sufficient to cause cerebral hyperperfusion syndrome. Several studies have demonstrated that extravasation of contrast materials in neuroradiologic examinations was associated with cerebral hyperperfusion after revascularization, indicating that a breakdown of the blood-brain barrier is involved (15, 18). These observations suggest that extravasation of ICG from cerebral vessels during surgery might be a predictor of the occurrence of cerebral hyperperfusion syndrome. Further studies are necessary to examine this hypothesis.

Postoperative DSA revealed that the anastomosed STA supplied blood to the primary motor cortex 1 week after surgery, whereas ICG angiography demonstrated that the ICG perfusion area was localized in the cranial window in both MD and non-MD patients during surgery. These findings indicate that the STA blood flow increased rapidly during 1

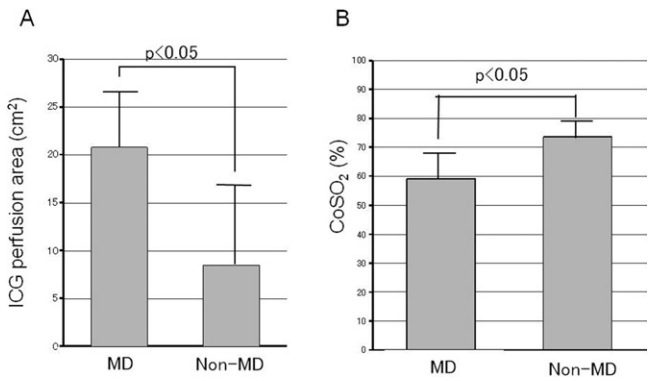

Figure 3. Comparison of indocyanine green perfusion area (**A**) and cortical oxygen saturation (**B**) between non-moyamoya disease (MD) and MD. (A) The indocyanine green perfusion area in MD was statistically larger than that in non-MD. (**B**) The cortical oxygen saturation in MD was significantly larger than that in non-MD. The error bars indicate standard deviation.

week after surgery. We previously observed a similar progressive increase in bypass blood flow during 1 week after surgery using near-infrared spectroscopy (5). That is, we measured the changes of cerebral blood oxygenation in the primary motor cortex during digital compression of the anastomosed STA. When decreases in oxyhemoglobin were observed, the bypass was considered to supply blood flow to the primary motor cortex, because decreases in oxyhemoglobin reflect cerebral ischemic changes. The degree of oxyhemoglobin reduction by the compression reflects the STA blood supply as changes in oxyhemoglobin reflect blood flow of the STA. Indeed, such a progressive increase in bypass blood flow may continue for more than a year after surgery (9). In agreement with this idea, postoperative repeated cerebral angiography demonstrated an increase in the size of the anastomosed STA (6). These observations indicate that bypass blood flow dynamically increases for a considerable time after surgery. It should be noted, however, that the increase of STA blood flow in the present study did not cause hyperperfusion syndrome, as no patient complained of symptoms related to hyperperfusion, such as headache after surgery.

CONCLUSION

The present results demonstrated that bypass blood flow through the anastomosed STA is larger in MD than in non-MD patients. The observation that $CoSO_2$ before anastomosis in MD was lower than that in non-MD patients suggested that the perfusion pressure in MD was lower than that in non-MD. This could cause a larger pressure gradient between the anastomosed STA and recipient vessels, resulting in the greater extent of bypass blood flow. These results may account, at least in part, for the occurrence of cerebral hyperperfusion syndrome in MD patients. Intraoperative ICG angiography with injection of ICG into the bypass artery is suggested to be useful for facilitating safe and accurate bypass surgery and providing useful information for postoperative management.

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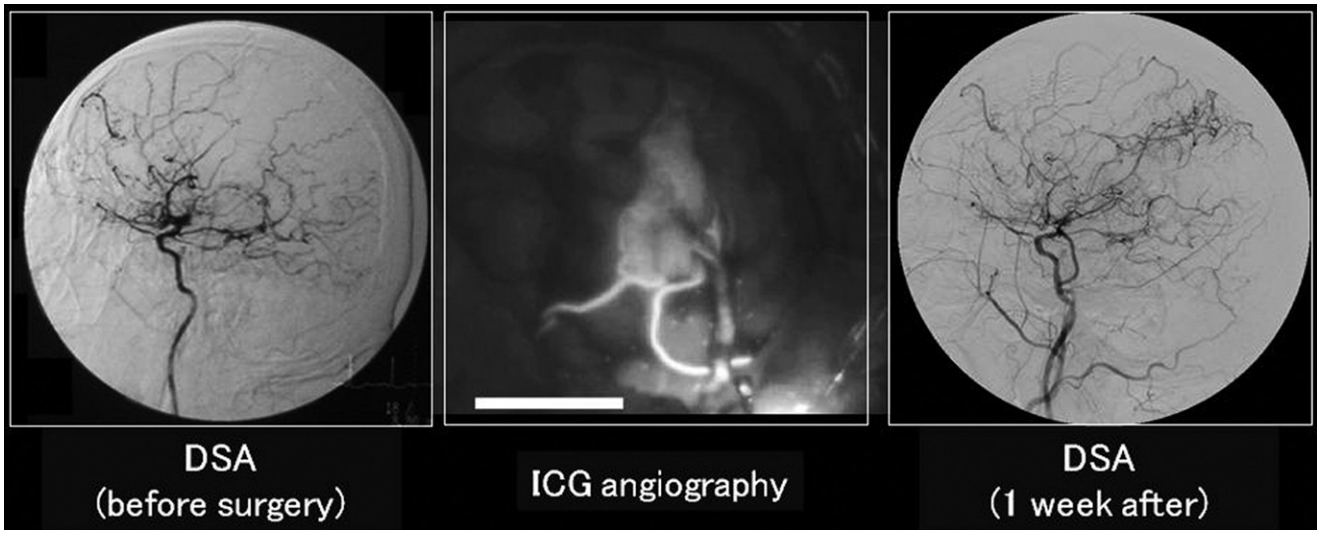

Figure 4. Comparison of intraoperative indocyanine green (ICG) angiography and digital subtractive angiography performed before and 1 week after surgery. ICG angiography demonstrated only a small ICG perfusion area during surgery, whereas postoperative digital subtractive angiography demonstrated that the superficial temporal artery supplied blood to the primary motor cortex 1 week after surgery. The white thick line in the ICG angiogram indicates 2 cm.

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