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# Indocyanine green emission timing of the recipient artery in revascularization surgery for moyamoya disease

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## ABSTRACT

In superficial temporal artery to middle cerebral artery anastomosis with indirect revascularization for patients with moyamoya disease, the optimal method for selecting the most appropriate cortical artery for the recipient in anastomosis has not been established. We investigated the relationship between the fluorescence emission timing of the recipient artery in the preanastomosis indocyanine green videoangiography and operative outcomes. This retrospective study included 51 surgical revascularization procedures for 39 moyamoya disease patients. The enrolled surgical procedures were classified into three groups based on the fluorescence emission timing of the recipient artery in preanastomosis indocyanine green videoangiography: the EARLIEST, the INTERMEDIATE, and the LATEST. Clinical characteristics and operative outcomes were also collected. The occurrence of white thrombus at the anastomosis site and symptomatic hyperperfusion showed significant differences between the groups classified by the fluorescence emission timing of the recipient artery in preanastomosis indocyanine green videoangiography (white thrombus, $p = 0.001$; symptomatic hyperperfusion, $p = 0.026$). The development of white thrombi was significantly higher in the LATEST group, and all symptomatic hyperperfusion was observed in the EARLIEST group. These results indicated that the LATEST group had a significantly higher risk for developing white thrombus, and the EARLIEST group was prone to occur symptomatic hyperperfusion. Selecting the recipient artery based on evaluating the fluorescence emission timing in preanastomosis indocyanine green videoangiography may be useful in reducing perioperative complications.

Keywords: moyamoya disease, direct bypass surgery, indocyanine green, selection of recipient artery

Abbreviations:
CBF: cerebral blood flow
CI: confidence interval
DWI: diffusion-weighted imaging
ICG: indocyanine green
ICH: intracranial hemorrhage
MCA: middle cerebral artery
MMD: moyamoya disease
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
SD: standard deviation
STA: superficial temporal artery

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TIA: transient ischemic attack
VA: videoangiography



## INTRODUCTION

Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by progressive stenosis of the internal carotid artery and the secondary formation of collateral vessels. Superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis combined with various indirect methods (combined revascularization surgery) is known as an effective treatment for improving ischemic symptoms or intellectual functions and preventing intracranial hemorrhage recurrence.[1-4] Within the operating field of STA to MCA anastomosis in MMD patients, there are some cortical arteries that are candidates for bypass recipient. However, few studies have focused on how to choose the recipient artery,[5] and in most cases, the selection depends on the surgeon's decision. In indocyanine green videoangiography (ICG-VA) analyses using FLOW 800 (Carl Zeiss, Co.) or FlowInsight (Infocom Corporation) programs, some parameters have been shown to be useful for forecasting hyperperfusion or transient neurological events. However, these methods depend on the evaluation of the postanastomosis condition and require particular devices or programs.[6,7] Thus, an easier, more practical method for selecting the recipient artery is desired.

We focused on the differences in fluorescence emission timing among cortical arteries in preanastomosis ICG-VA (Fig. 1), which can be simply evaluated by surgeons in the operating room. We investigated the relationship between the ICG fluorescence emission timing in the recipient artery and outcomes regarding combined revascularization surgery in patients with MMD. This study aims to evaluate the usefulness of selecting the recipient artery by fluorescence emission timing in preanastomosis ICG-VA.

## MATERIALS AND METHODS

This study was carried out in agreement with the Declaration of Helsinki and approved by the Institutional Review Board of the Nagoya University Graduate School of Medicine (No. 2016, 0327). Informed consent was obtained from all study participants or their legal guardians.

*Enrolled surgical procedures*

We included in this study all combined revascularization surgeries for MMD patients between 2015 and 2020 in which preanastomosis ICG-VA were available. MMD was diagnosed according to the guidelines proposed by the Ministry of Health and Welfare of Japan,[8] and patients with moyamoya syndromes were not included in this study. As described later, to classify the recipient artery based on the fluorescence emission timing, two cases in which there was only one candidate for the bypass recipient in preanastomosis ICG-VA were excluded. Finally, 51 surgical procedures with 39 patients were retrospectively analyzed in this study. For symptomatic hyperperfusion, two cases were excluded because we were unable to evaluate cerebral blood flow (CBF).

*Surgical procedure, selection of the recipient artery, and ICG-VA*

In all surgeries, combined revascularization surgery for the MCA territory was performed by Y.A. or S.O. Specifically, after a frontotemporal craniotomy to reveal the gyruses around distal

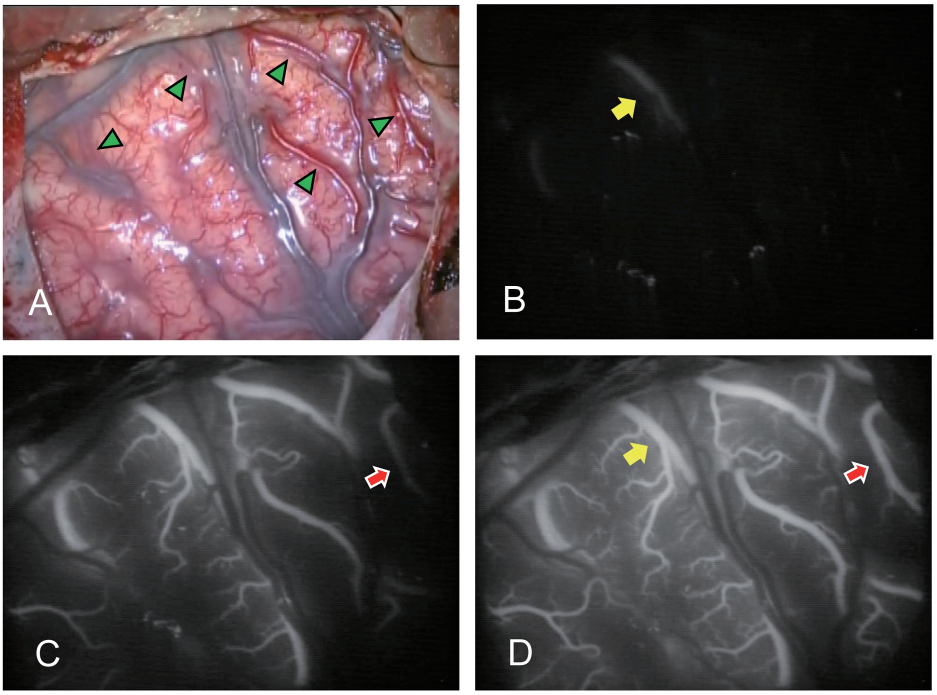


**Fig. 1** The classification of cortical arteries by indocyanine green videoangiography (ICG-VA)
**Fig. 1A:** Preanastomosis microscope photograph showing cortical arteries (green arrowhead) that could be the recipient in terms for the diameter.
**Fig. 1B:** Photograph of ICG-VA showing the cortical artery with the earliest fluorescence emission (yellow arrow).
**Fig. 1C:** Photograph of ICG-VA showing the cortical artery with the latest fluorescence emission (red arrow).
**Fig. 1D:** Photograph of ICG-VA showing the full cortical arteries.

part of the sylvian fissure, single STA to MCA (M4) anastomosis was performed in an end to side fashion. The primary bypass surgeon chose the recipient artery based on the decreased CBF region, the donor accessibility, the location within craniotomy area, and the vessel's visual characteristics under microscope such as redness, diameter, or the number of pial branches. When a white thrombus was developed at the anastomosis site and considered the cause of bypass failure, mechanical tapping, heparin injection, or resuture at the same site was performed as a rescue method. Final bypass patency was evaluated by ICG-VA or Doppler ultrasound. Indirect methods at the MCA territory (encephaloduromyosynangiosis or encephaloduromyopericranial-synangiosis) were also employed.

ICG-VA was performed with Leica M525 OH4 and FL800 (Leica, Co.) systems at the timing of pre and postanastomosis. Patients received ICG (Daiichi Sankyo, Co.) injection at a dose of 10 mg in each bolus.

During general anesthesia, PaCo2 was maintained between 36 and 40 mmHg.

*Classification of the recipient artery by fluorescence emission timing in preanastomosis ICG-VA*

The enrolled surgical procedures were classified into three groups according to the fluorescence emission timing of the anastomosed recipient artery in preanastomosis ICG-VA. This classification was performed using the following protocol (Fig. 1).

1. Under a microscope, we counted the total number of cortical arteries that could be the

recipient based on its diameter. In two cases, there was only one cortical artery and excluded from the study because there was no choice with regard to the recipient artery. In addition, there were no cases with two candidate cortical arteries.
2. Under preanastomosis ICG-VA, we evaluated the order of fluorescence emission in these cortical arteries.
3. We classified the patients into three groups according to the order of fluorescence emission in the anastomosed recipient artery: (A) the EARLIEST group included cases in whom the cortical artery with the earliest fluorescent emission was selected as the bypass recipient, (B) the LATEST group included cases in whom the cortical artery with the latest fluorescent emission was selected as the bypass recipient, and (C) the INTERMEDIATE group included all other cases.

For use in clinical practice similar to the situation in an operation room, these factors were evaluated by three neurosurgeons (F.K., Y.K., and K.U.) until a consensus was reached.

*Postoperative management*

All patients were managed to avoid hypovolemia and anemia. Systolic blood pressure was maintained between 80% to 120% of the preoperative value, and fibrinogen was maintained over 200 mg/dl. For the pediatric cases, to avoid severe crying, appropriate sedation using thiamylal sodium, diazepam, and/or dexmedetomidine were used for medical examination or procedures if necessary. 3.0T or 1.5T magnetic resonance imaging (MRI), including fluid attenuated inversion recovery imaging, diffusion weighted imaging (DWI), and magnetic resonance angiography (MRA), was performed routinely 2 or 3 days after surgery to check the infarction and bypass patency. Additional MRI was performed when the patients showed the neurological symptoms. CBF was evaluated 3 or 4 days after surgery by single photon emission computed tomography using 99mTc-ethylcyteinate dimer or 123I-iodoamphetamine.

*Evaluated outcomes*

As the potential outcomes were affected by the difference in fluorescence emission timing of the recipient artery in preanastomosis ICG-VA, we measured the following events.

- Intraoperative events: final bypass patency, clamp time, and development of white thrombus at anastomosis site (Fig. 2).
- Perioperative events: perioperative infarction and symptomatic hyperperfusion.
- Longterm events (over 3 months after surgery): stroke and the caliber change rate of the donor STA.

Symptomatic hyperperfusion was diagnosed according to all of the following criteria proposed by Fujimura et al[9]: (1) the presence of a significant increase in CBF at the site of the anastomosis responsible for apparent neurologic signs, including focal neurologic deficit and/or severe headache because of hemorrhagic changes; (2) apparent visualization of STA to MCA bypass by MRA and the absence of any ischemic changes by DWI; and (3) the absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, or seizure. The caliber change ratio of the donor STA was compared between preoperation and 3 to 6 months after the operation at the most proximal portion of the bifurcation on the MRA source images.[10] Additionally, we evaluated the following clinical parameters as possible confounding factors with respect to the outcomes: age, sex, clinical phenotype, MRA stage,[11] antiplatelet treatment, and operation side.

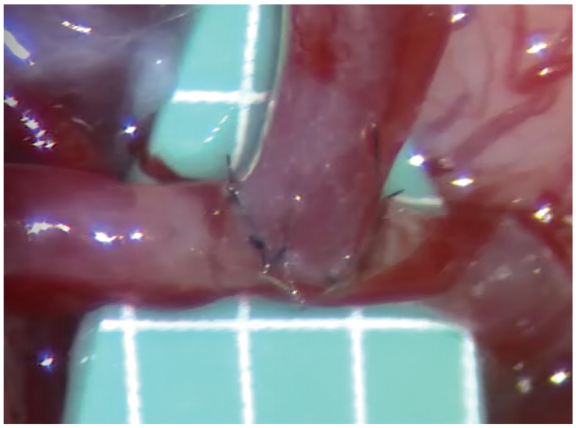

**Fig. 2** Intraoperative picture showing white thrombus development at the anastomosis site

*Statistical analysis*

Fisher's exact test for categorical variables and the t test for numerical variables were used to compare pairs of groups. For comparisons among 3 groups, Fisher's exact test for categorical variables and one way ANOVA for numerical variables were used, and if appropriate, the Bonferroni correction was applied for a post hoc analysis. Logistic regression analysis was used to test the effect of multiple variables on the occurrence of white thrombus. Significance was set at a P value $< 0.05$. Statistical analyses were performed in R 3.6.2 (R Foundation for Statistical Computing; https://www.r-project.org/).

## RESULTS

The clinical characteristics compared between the groups classified by the fluorescence emission timing of the recipient artery in preanastomosis ICG-VA are summarized in Table 1. The baseline characteristics of the study cases, including sex, age, clinical phenotype, and MRA stage, did not show significant differences between these 3 groups, but the operation side differed significantly.

*The relation between outcomes and fluorescence emission timing of the recipient artery in preanastomosis ICG-VA*

We first investigated the outcomes that were affected by the difference in fluorescence emission timing of the recipient artery in preanastomosis ICG-VA (Table 2). The development of white thrombus at the anastomosis site and the occurrence of symptomatic hyperperfusion differed significantly among the groups classified by fluorescence emission timing of the recipient artery in preanastomosis ICG-VA (white thrombus, $p = 0.001$; symptomatic hyperperfusion, $p = 0.026$). According to the post hoc analysis, significantly more white thrombi developed in the LATEST group than in the EARLIEST and INTERMEDIATE groups (EARLIEST vs LATEST, $p = 0.023$; INTERMEDIATE vs LATEST, $p = 0.004$; EARLIEST vs INTERMEDIATE, $p = 1.0$) (Fig. 3). All symptomatic hyperperfusion was observed in the EARLIEST group, but the post hoc analysis did not show significant differences between groups (EARLIEST vs LATEST, $p = 0.24$; INTERMEDIATE vs LATEST, $p = 1.0$; EARLIEST vs INTERMEDIATE, $p = 0.22$). Other

outcomes, including final bypass patency, clamp time, perioperative infarction, chronic stroke, and caliber change of STA, did not show significant differences.

**Table 1** Summary of the clinical characteristics compared with the fluorescence emission timing of the recipient artery in preanastomosis ICG-VA

| | Fluorescence emission timing | | | |
|---|---|---|---|---|
| | EARLIEST | INTERMEDIATE | LATEST | P Value |
| No. of surgical procedures | 24 | 13 | 14 | |
| Sex | | | | 0.843 |
| Male | 6 | 4 | 3 | |
| Female | 18 | 9 | 11 | |
| Mean age ± SD, yrs | 20.2 ± 16.1 | 20.9 ± 20.2 | 22.9 ± 16.9 | 0.902 |
| Operation side | | | | 0.047 |
| Right | 12 | 10 | 4 | |
| Left | 12 | 3 | 10 | |
| Clinical phenotype | | | | 0.272 |
| TIA | 15 | 10 | 7 | |
| Ischemic stroke | 0 | 1 | 3 | |
| ICH | 1 | 1 | 0 | |
| Headache | 3 | 1 | 3 | |
| Asymptomatic | 4 | 0 | 1 | |
| Others | 1 | 0 | 0 | |
| MRA stage | | | | 0.084 |
| 1 | 0 | 0 | 1 | |
| 2 | 16 | 10 | 4 | |
| 3 | 7 | 3 | 7 | |
| 4 | 1 | 0 | 2 | |
| Antiplatelet treatment | 18 | 10 | 11 | 1.00 |
| Total number of cortical arteries evaluated with ICG-VA | | | | 0.071 |
| 3 | 10 | 5 | 5 | |
| 4 | 9 | 3 | 8 | |
| 5 | 5 | 1 | 0 | |
| 6 | 0 | 2 | 1 | |
| 7 | 0 | 2 | 0 | |

ICG-VA: indocyanine green videoangiography
ICH: intracranial hemorrhage
SD: standard deviation
TIA: transient ischemic attack

**Table 2** The relation between the operative outcomes and fluorescence emission timing of the recipient artery in preanastomosis ICG-VA

| | Fluorescence emission timing | | | P Value |
|---|---|---|---|---|
| | EARLIEST | INTERMEDIATE | LATEST | |
| No. of surgical procedures | 24 | 13 | 14 | |
| Intraoperative outcome | | | | |
| Bypass patent (%) | 22 (91.7) | 13 (100.0) | 12 (85.7) | 0.362 |
| White thrombus (%) | 6 (25.0) | 1 (7.7) | 10 (71.4) | 0.001 |
| Mean clamp time ±SD, min | 49.7 ± 15.2 | 52.3 ± 16.1 | 52.9 ± 8.1 | 0.769 |
| Perioperative outcome | | | | |
| Perioperative infarction (%) | 2 (8.3) | 2 (15.4) | 3 (21.4) | 0.380 |
| Symptomatic hyperperfusion (%) | 6 (25.0) | 0 (0.0) | 0 (0.0) | 0.026 |
| Long-term outcome | | | | |
| Stroke 1 month after operation | 0 | 0 | 0 | Not available |
| The mean rate of caliber changes (mm) in STA ±SD | 1.05 ± 0.27 | 1.24 ± 0.25 | 1.19 ± 0.35 | 0.313 |

SD: standard deviation
STA: superficial temporal artery

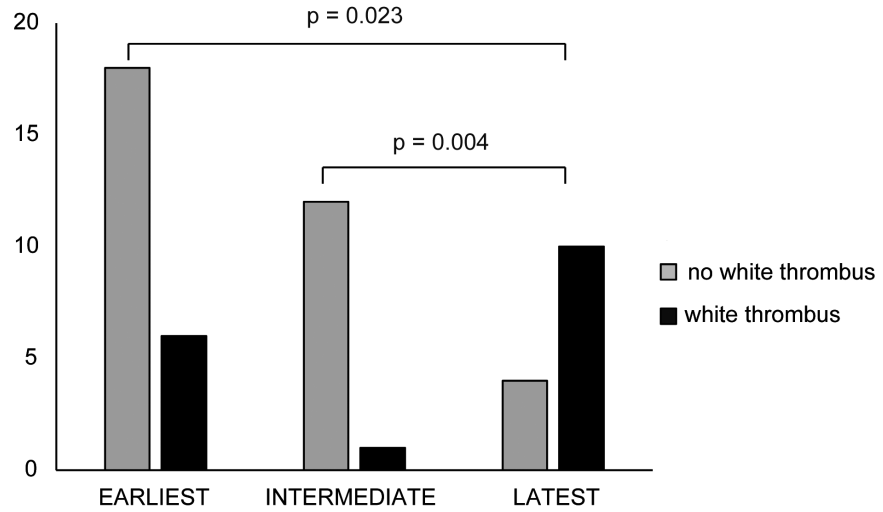


**Fig. 3** Bar graph showing the occurrence of white thrombus among groups classified by the fluorescence emission timing of the recipient artery in preanastomosis indocyanine green videoangiography
The P values were corrected by Bonferroni.

*Risk factors for white thrombus*

Next, we investigated other clinical factors that influenced the development of white thrombi at the anastomosis site (Table 3). Clinical factors, including age, operation side, clinical phenotype, MRA stage, antiplatelet treatment, and clamp time, did not differ significantly. Because the MRA stage corresponded to a P value less than 0.10, we performed multivariate analysis with

fluorescence emission timing of the recipient artery in the preanastomosis ICG-VA and MRA stages. Logistic regression analysis showed that being included in the LATEST group was a significant independent predictor for developing white thrombus compared with being incluced in the EARLIEST group (odds ratio 12.3, 95% CI 1.91–78.7; p = 0.008).

**Table 3** Risk factors for white thrombus

| | White thrombus | | Univariate | Multivariate | | |
|---|---|---|---|---|---|---|
| | Yes | No | P Value | Odds ratio | 95% CI | P Value |
| No. of surgical procedures | 17 | 34 | | | | |
| Mean age ± SD, yrs | 18.5 ± 14.6 | 22.4 ± 18.3 | 0.450 | | | |
| Operation side | | | 0.382 | | | |
| Right | 7 | 19 | | | | |
| Left | 10 | 15 | | | | |
| Clinical phenotype | | | 0.228 | | | |
| TIA | | 23 | | | | |
| Ischemic stroke | 3 | 1 | | | | |
| ICH | 0 | 2 | | | | |
| Headache | 4 | 3 | | | | |
| Asymptomatic | 1 | 4 | | | | |
| Others | 0 | 1 | | | | |
| MRA stage | | | 0.066 | | | |
| 1 | 0 | 1 | | control | | |
| 2 | 8 | 22 | | 1.71E+08 | 0-inf | 0.996 |
| 3 | 6 | 11 | | 9.27E+08 | 0-inf | 0.996 |
| 4 | 3 | 0 | | 6.22E+15 | 0-inf | 0.993 |
| Antiplatelet treatment | 11 | 28 | 0.181 | | | |
| Mean clamp time ±SD, min | 51.8 ± 13.4 | 51.0 ± 14.0 | 0.849 | | | |
| Fluorescence emission timing | | | 0.001 | | | |
| EARLIEST | 6 | 18 | | control | | |
| INTERMEDIATE | 1 | 12 | | 0.286 | 0.02–2.79 | 0.281 |
| LATEST | 10 | 4 | | 12.300 | 1.91–78.7 | 0.008 |

CI: confidence interval
ICH: intracranial haemorrhage
SD: standard deviation
TIA: transient ischemic attack

*Risk factors for symptomatic hyperperfusion*

We also investigated other clinical factors that influenced the occurrence of symptomatic hyperperfusion (Table 4). Clinical factors, including age, operation side, clinical phenotype, and MRA stage, did not differ significantly. Because only fluorescence emission timing of the recipient artery in preanastomosis ICG-VA corresponded to a P value less than 0.10 and the number of symptomatic hyperperfusions was small, multivariate analysis was not applied.

**Table 4** Risk factors for symptomatic hyperperfusion

| | Symptomatic hyperperfusion | | Univariate |
|---|---|---|---|
| | Yes | No | P Value |
| No. of surgical procedures | 6 | 43 | |
| Mean age ± SD, yrs | 15.3 ± 17.3 | 22.6 ± 17.2 | 0.341 |
| Operation side | | | |
| Right | 3 | 22 | 1.000 |
| Left | 3 | 21 | |
| Clinical phenotype | | | 0.115 |
| TIA | 4 | 27 | |
| Ischemic stroke | 0 | 4 | |
| ICH | 1 | 1 | |
| Headache | 0 | 6 | |
| Asymptomatic | 0 | 5 | |
| Others | 1 | 0 | |
| MRA stage | | | 1.000 |
| 1 | 0 | 1 | |
| 2 | 4 | 25 | |
| 3 | 2 | 14 | |
| 4 | 0 | 3 | |
| Fluorescence emission timing | | 0.026 | |
| EARLIEST | 6 | 18 | |
| INTERMEDIATE | 0 | 12 | |
| LATEST | 0 | 13 | |

ICH: intracranial haemorrhage
SD: standard deviation
TIA: transient ischemic attack

## DISCUSSION

In this study, we investigated the relationship between the operative outcomes of combined revascularization surgery in patients with MMD and the fluorescence emission timing of the recipient artery in preanastomosis ICG-VA. Comparing groups classified by the fluorescence emission timing of the recipient artery in preanastomosis ICG-VA revealed that the LATEST group had a significantly higher risk for white thrombus, and the EARLIEST group was prone to occur symptomatic hyperperfusion. By selecting the recipient artery based on evaluating the fluorescence emission timing in preanastomosis ICG-VA, neurosurgeons can reduce the development of white thrombus or prepare medical treatments for symptomatic hyperperfusion.

The difference in the fluorescence emission timing in preanastomosis ICG-VA might be induced by the difference in the hemodynamic source and the variety of stenoses. As the MMD stage progresses, stenoses of the major cerebral arteries worsen, and collateral arteries develop.[12] In progressed MMD, parasylvian arteries are hemodynamically supplied from not only the MCA but also other cerebral arteries, such as the posterior cerebral artery, the anterior cerebral artery, or other collaterals.[12,13] The length of the arterial route to the MCA territory influences the

fluorescence emission timing. The stenosis in MMD was caused by fibrous thickening of the intima, and these histopathological characteristics are also observed in the cortical arteries.[14,15] Thus, stenoses with various degrees can occur in any segment of cerebral arteries. The blood flow velocity of each cortical artery may depend on the degree of stenosis in its arterial route and may influence the fluorescence emission timing.

The occurrence of white thrombus should be avoided because it requires rescue treatment, leads to bypass failure, and requires a longer operation time. In general, for thrombus development at the site of vascular injury, platelet aggregation plays a key role because of the ability to form stable adhesive interactions under conditions of rapid blood flow.[16] The degree of increased shear stress and flow perturbation correlate with the magnitude of platelet aggregation.[16-18] Applying this theory to vessel anastomosis, vascular injury is caused by the arteriotomy procedure. The degree of increased shear stress and flow perturbation at the anastomosis site would correlate with the flow velocity difference between the recipient and the donor. The cortical artery with the latest fluorescence emission timing would have the slowest blood flow among the cortical arteries that had the same hemodynamic origin. Therefore, it was considered that the flow velocity differences between donor and recipient at the anastomosis site in the LATEST group tended to be relatively large, increasing the possibility of thrombogenesis. Mikami et al reported that white thrombi tended to occur in cases with a more severe degree of stenosis in major cerebral arteries.[19] As the stenosis degree of major arteries increases, the flow velocity of the cortical arteries slows. Thus, our assessment matched the aforementioned report.

Symptomatic hyperperfusion is a potential complication that can cause hemorrhagic events.[9,20] In patients with MMD, adult onset, hemorrhagic onset, increases in preoperative cerebral blood volume in adult patients, and selection of a recipient artery supplied by the MCA are known as risk factors for symptomatic hyperperfusion,[9,13,21] but the etiology is still unknown. In this study, all symptomatic hyperperfusion occurred in the EARLIEST group. The cortical artery with the earliest ICG fluorescence emission would have the largest perfusion area in the MCA territory among the cortical arteries that had the same hemodynamic origin. The hemodynamic change by direct bypass in the larger area of the MCA territory, which is responsible for neurological functions such as motor or language, can result in greater occurrence of symptomatic hyperperfusion.

This study has some limitations. First, the hemodynamical parameters of ICG were not analyzed quantitively. Obtaining these parameters needs the particular devices, however, those devises could not normally be used in our institution. The present study just aimed to find clues for selecting optimal recipient artery under this condition. To ensure accuracy and similarity to the real clinical practice, the ICG fluorescence emission timing was evaluated by three surgeons. Second, this study indicated that selecting the recipient among the INTERMEDIATE cortical arteries seems appropriate to avoid the occurrences of white thrombus and symptomatic hyperperfusion. However, there are technically difficult cases because of the graft length or the recipient location. Third, because two types of tracers with different measurement methods were used for single photon emission computed tomography, the CBF evaluation was qualitative but not quantitative.

In conclusion, comparing the groups classified by the fluorescence emission timing of the recipient artery in preanastomosis ICG-VA revealed that the LATEST group had a significantly higher risk for developing white thrombus, and the EARLIEST group was prone to occur symptomatic hyperperfusion. Selecting the recipient artery based on evaluating the fluorescence emission timing in preanastomosis ICG-VA can enable us to predict, prepare medical treatment for, and reduce the perioperative complications.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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