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Original Article

Quantitative cerebral perfusion assessment using microscope-integrated analysis of intraoperative indocyanine green fluorescence angiography versus positron emission tomography in superficial temporal artery to middle cerebral artery anastomosis

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Abstract

Background: Intraoperative qualitative indocyanine green (ICG) angiography has been used in cerebrovascular surgery. Hyperperfusion may lead to neurological complications after superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis. The purpose of this study is to quantitatively evaluate intraoperative cerebral perfusion using microscope-integrated dynamic ICG fluorescence analysis, and to assess whether this value predicts hyperperfusion syndrome (HPS) after STA-MCA anastomosis.

Methods: Ten patients undergoing STA-MCA anastomosis due to unilateral major cerebral artery occlusive disease were included. Ten patients with normal cerebral perfusion served as controls. The ICG transit curve from six regions of interest (ROIs) on the cortex, corresponding to ROIs on positron emission tomography (PET) study, was recorded. Maximum intensity (I_{MAX}), cerebral blood flow index (CBFi), rise time (RT), and time to peak (TTP) were evaluated.

Results: RT/TTP, but not I_{MAX} or CBFi, could differentiate between control and study subjects. RT/TTP correlated ($|r|$ = 0.534-0.807; $P < 0.01$) with mean transit time (MTT)/MTT ratio in the ipsilateral to contralateral hemisphere by PET study. Bland–Altman analysis showed a wide limit of agreement between RT and MTT and between TTP and MTT. The ratio of RT before and after bypass procedures was significantly lower in patients with postoperative HPS than in patients without postoperative HPS (0.60 ± 0.032 and 0.80 ± 0.056, respectively; $P = 0.017$). The ratio of TTP was also significantly lower in patients with postoperative HPS than in patients without postoperative HPS (0.64 ± 0.081 and 0.85 ± 0.095, respectively; $P = 0.017$).

Conclusions: Time-dependent intraoperative parameters from the ICG transit curve provide quantitative information regarding cerebral circulation time with quality and utility comparable to information obtained by PET. These parameters may help predict the occurrence of postoperative HPS.

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INTRODUCTION

The hemodynamic status of brain tissue can be classified into stage 0 (normal flow state), stage 1 (cerebral autoregulatory vasodilatation to compensate for a decrease in blood flow toward the brain), and stage 2 (autoregulatory failure, with a compensatory rise in oxygen extraction fraction [OEF]).[7] Positron emission tomography (PET) using oxygen-15-labeled tracers is the gold standard for measurement of such hemodynamic changes.[6]

Intraoperative indocyanine green (ICG) angiography has been in use for a decade and allows qualitative visualization of arterial, capillary, and venous systems and pathological vascular structures.[3-5,8,9,11,15,16,24-26,29,30] Recently, a microscope-integrated module (FLOW 800, Carl Zeiss, Oberkochen, Germany) has been developed to allow quantification of ICG transit in the surgical field. However, the reliability and clinical significance of such measurements have not yet been investigated.

Recent studies have clarified that postoperative hyperperfusion may cause serious neurological complications, such as brain swelling, seizure, and intracerebral hemorrhage, after superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis in patients with severe hemodynamic compromise.[13,18,31] However, reliable intraoperative parameters to predict the occurrence of postoperative hyperperfusion have not been identified.

Therefore, the purpose of this study was to determine whether integrated dynamic ICG fluorescence analysis could accurately detect impaired cerebral perfusion, and to compare the reliability and utility of such measurements with those obtained by PET using oxygen-15-labeled tracers. Further, we evaluated whether integrated dynamic ICG fluorescence analysis could predict onset of postoperative hyperperfusion syndrome (HPS) after STA-MCA anastomosis.

MATERIALS AND METHODS

Patients and subjects

Ten patients undergoing STA-MCA bypass surgery for unilateral major cerebral artery occlusive disease (two women and eight men; mean age, 63.8 years; age range, 45-74 years) who were referred to the Department of Surgical Neurology, Research Institute for Brain and Blood Vessels-AKITA, Japan, between June 2011 and March 2013 were enrolled in this study [Table 1]. Indications for STA-MCA bypass surgery for impaired cerebral perfusion were determined according to the Japanese EC-IC Bypass Trial study criteria.[22] In all surgeries, both the frontal and parietal branches of the STA were anastomosed to the branches of the MCA in an end-to-side fashion. Patients completed the PET protocol within 1 month before surgery and completed the intraoperative near-infrared ICG videoangiography (ICG-VA) protocol during surgery. Following surgery, systolic blood pressure was strictly controlled between 100 and 140 mmHg, and anticonvulsant medication was administered intravenously. Using single photon emission computed tomography with technetium-99m hexamethylpropylene amine oxime (99mTc-HM-PAO SPECT), cerebral blood flow (CBF) measurements were taken at 1 and 7 days after surgery. The postoperative state of the brain and the patency of bypass were also assessed by magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) at 1 and 7 days after surgery. Even when it was suspected that patient presented with

Table 1: Summary of clinical findings in six patients with occlusive disease

Case no.	Age/sex	Symptoms	Angiographic findings	Occlusion time (min)	Postoperative HPS
1	61/M	TIA	Lt ICA occlusion	18.7/20.6	None
2	70/M	TIA	Rt ICA occlusion	19.2/18.4	None
3	70/F	Central retinal artery occlusion	Rt MCA occlusion	16.3/31.3	Transient aphasia
4	71/M	Minor complete stroke	Lt ICA near occlusion	18.7/29.5	Transient paresis and dysarthria
5	64/M	Minor complete stroke	Rt MCA occlusion	34.0/36.2	None
6	53/M	Minor complete stroke	Rt MCA occlusion	15.9/24.5	None
7	74/M	Central retinal artery occlusion	Rt ICA occlusion	22.0/31.6	None
8	45/M	Minor complete stroke	Rt MCA occlusion	45.5/29.3	Headache and seizure
9	59/M	Minor complete stroke	Lt MCA occlusion	28.7/20.3	None
10	71/F	TIA	Rt MCA stenosis	17.3/24.0	None

M: Male, F: Female, TIA: Transient ischemic attack, Lt: Left, Rt: Right, ICA: Internal carotid artery, MCA: Middle cerebral artery, STA: Superficial temporal artery, HPS: Hyper perfusion syndrome

symptoms associated with hyperperfusion, evaluation by SPECT and MRI/MRA was performed.

Ten patients (seven women and three men; mean age, 61.3 years; age range, 32-70 years) undergoing craniotomy and clipping surgery for unruptured cerebral aneurysms served as control subjects. These subjects had no steno-occlusive disease, as assessed by intracranial MRA and neck MRA/neck ultrasonography, and these subjects completed the ICG-VA protocol just after fronto-temporal craniotomy.

The institutional medical review board of the Research Institute for Brain and Blood Vessels-AKITA approved the study protocol. All patients provided written informed consent.

Icg-va protocol and analysis

The recommended dose of ICG-VA is 0.1-0.3 mg/kg, and the daily dose should not exceed 5 mg/kg. In this series, all patients completed the ICG-VA study protocol just after fronto-temporal craniotomy, and the patients undergoing bypass surgery completed the same protocol just after bypass procedure. Subjects received a standard dose of 7.5 mg per injection dissolved in 3.0 ml of physiologic saline. The recording was started, and a calculated bolus of ICG was administered by the anesthesiologist at the surgeon's request. The ICG transit curves intensities were recorded by an automatic microscope-integrated algorithm using near-infrared light (λ = 800 nm; OPMI Pentero microscope with infrared fluorescence detection hardware and the Flow 800 software analysis tool; Carl Zeiss Meditec, Oberkochen, Germany). This tool features an algorithm for correcting shading and brain pulsation. Fluorescence intensities were measured in arbitrary intensity units (AIs) that corresponded to the intensity detected by the camera. The additional time needed for ICG angiography was approximately 90 s. The focal length and magnification of the microscope were set at the same level for comparison of flow analysis in all procedures. PaO_2, $PaCO_2$ and mean blood pressure were maintained within the normal range. Normal cardiac function (ejection fraction >55%) was also confirmed preoperatively in all patients.

The course of fluorescent intensities was measured by freely definable regions of interest (ROIs). The data from ROIs were exported as a Microsoft Excel file for further processing after surgery. This feature enabled calculation of various hemodynamic parameters. In this study, three facultative ROIs were defined on the superficial brain cortex of the frontal lobe (avoiding vascular structures), and three ROIs were defined on the superficial brain cortex of the temporal lobe in the same manner; thus, a total of six cortex ROIs were used for each patient. These ROIs were representative of the capillary compartment and were chosen for the absence of arterial or venous vessels traversing the respective territory. The following parameters were assessed [Figure 1]: maximum intensity (I_{MAX}); rise time (RT; i.e. the interval between 10% and 90% of maximum signal[17,27]); cerebral blood flow index (CBFi; i.e. the ratio of the fluorescent intensity to RT: CBFi = Δ fluorescence intensity/RT); and time to peak (TTP; i.e. the time interval between the initial appearance of fluorescence and I_{MAX}). A ratio of CBFi to control CBFi < 20% was defined as ischemic, between 20% and 40% was defined as penumbra, and between 40% to 80% was defined as oligemic zones, according to Blayev *et al*.[1] and Ginsberg.[10]

Pet protocol and imaging data analysis

PET was done with a three-dimensional PET scanner (SET-3000GCT/M; Shimadzu Corp., Kyoto, Japan), which provides 59 sections with a center-to-center distance of 2.6 mm. The axial field of view was 156 mm. The intrinsic spatial resolution was 3.5-mm full width at half maximum in-plane and 4.2-mm full width at half maximum axially. Filtered backprojection image reconstruction followed by 3D Gaussian smoothing with 6-mm full width at half maximum resulted in a final in-plane resolution of approximately 7-mm full width at half maximum. Each PET study included a transmission scan for attenuation correction. In our institution, three static emission scans with the inhalation of $C^{15}O$, the inhalation of $^{15}O_2$, and the injection of $H_2{}^{15}O$ were performed to obtain cerebral blood volume (CBV), cerebral metabolic rate of oxygen, OEF, and CBF maps,

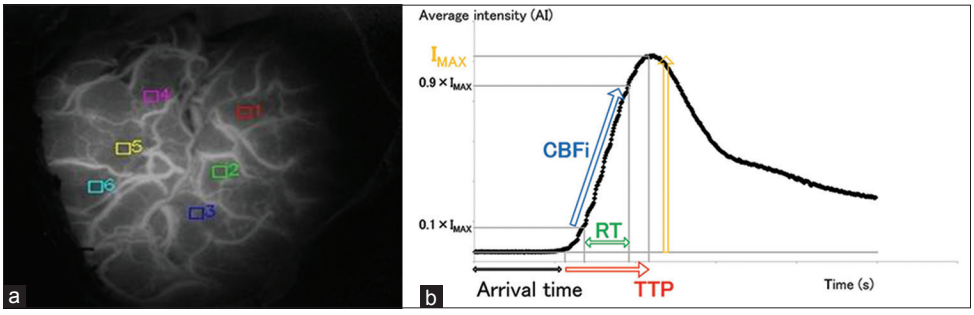

Figure 1: (a) Fluorescence intensity was measured in defined ROIs. Six facultative ROIs were defined on the cortex in the superficial brain tissue, avoiding vascular structures. (b) ICG transit curve showing the different parameters used to estimate perfusion. Parameters included IMAX (maximum intensity); TTP (time to peak); RT (rise time; i.e., the interval between 10% and 90% of maximum signal); and cerebral blood flow index (CBFi; i.e., the ratio of fluorescence intensity to RT: CBFi: Δ fluorescence intensity/RT)

respectively, according to the studies of Hatazawa *et al*.[12] and Ibaraki *et al*.[14] The interval between scans was approximately 15 min.

CBF, CBV, and OEF were analyzed with an automated ROI setting method developed by Ogura *et al*.[23] This method can be used to set the objective and reproductive ROIs and to analyze local cerebral hemodynamics and metabolism without distorting the individual PET images. Commercially available software (NEURO FLEXER version 1.0, Nihon Medi-Physics Co., Ltd., Tokyo, Japan) was used in this study. The volume of interest (VOI) template was constructed on the standardized brain generated by NEUROSTAT (Department of Radiology, University of Washington, Seattle, WA) to determine the areas in which the ROIs were set.[20,21] The VOI template was constructed so that the ROIs were drawn for major vascular regions and for 17 regions within the hemisphere, basal ganglia, thalamus, cerebellar cortex, cerebellar vermis, and pons. Using anatomic standardization of NEUROSTAT and inverse transformation, the automated ROI transformed the VOI template into individual brain shape on PET images, and the VOI template was extracted from each slice to determine ROIs.[23] The automated ROIs of the anterior/posterior branch of middle cerebral artery territory corresponding to the ROIs defined on cortex during surgery were used in this study. Mean transit time (MTT) was calculated as the ratio of CBV/CBF according to the central volume theorem;[19] this ratio yields MTT, which is the hypothetical mean time for a particle to pass through the cerebral circulation. CBF, CBV, MTT, OEF, and the ratios of ipsilateral to contralateral of each parameter (CBF ratio, CBV ratio, MTT ratio, and OEF ratio) were used in this study.

Statistical analysis

Numerical data are expressed as the mean ± standard deviation. Differences between measures of various parameters were examined by nonparametric tests, because the relatively small sample size undermines the distributional assumptions of a parametric test, such as the *t* test. Nevertheless, we confirmed that the same pattern of results was obtained when using t tests. The Mann–Whitney U-test was used to identify differences between measures of various ICG-VA parameters in patients with and without major cerebral artery occlusive disease and differences between measures of various PET parameters/ICG-VA parameters in patients with and without postoperative HPS. The Wilcoxon signed ranks test was used to identify differences between measures of various ICG-VA parameters before and after the bypass procedures. Area under the receiver operating characteristic curve (AUC) was also used to evaluate diagnostic accuracy. Correlations between measured values of ICG-VA parameters and of PET parameters were determined by Pearson's correlation coefficient. The degree of agreement between measured values of ICG-VA and PET parameters was estimated by the Bland–Altman graphical procedure.[2] Statistical significance was set at the $P < 0.05$ level.

RESULTS

Both the ICG-VA protocol and the PET protocol were successfully conducted. During injection of the ICG, systolic arterial blood pressure was maintained between 100 and 120 mmHg, without significant differences before and after the bypass procedure. The mean temporary recipient vessel occlusion time was 25.1 ± 7.9 (range, 15.9–45.5) min. The patency of bypass graft was evaluated during surgery by ICG-VA. Postoperative MRA also confirmed the patency of bypass graft in all cases, and MRI showed that symptomatic cerebral infarction did not occur after surgery in any patient. Three patients were diagnosed with HPS during the week after surgery, based on findings from SPECT and typical symptoms (paresis and dysarthria; aphasia; headache and seizure, respectively). After the diagnosis, systolic arterial blood pressure was more strictly controlled below 120 mmHg. Symptoms were transient and resolved completely in all cases. Average values and ratio of ipsilateral to contralateral side for each PET parameter were not significantly different when comparing patients with and without postoperative HPS [Table 2]. Any of the other patients did not present asymptomatic hyperperfusion by the postoperative routine SPECT examination.

Comparison of patients with and without major cerebral artery occlusive disease

The results for the entire data set are summarized in Table 3. The average values from six ROIs were examined. I_{MAX} did not differentiate ($P = 0.29$, AUC = 0.64) between patients with occlusive disease (302.8 ± 112.9 AIs) and control subjects (369.6 ± 127.4 AIs). CBFi did not differentiate ($P = 0.082$, AUC = 0.73) between impaired

Table 2: Average values and ratio of ipsilateral to contralateral side of each positron emission tomography parameter in patients with *vs*. without postoperative hyperperfusion syndrome

PET parameters	HPS		*P* value
	Yes (*n*=3)	No (*n*=7)	
CBF	32.1±2.8	33.9±6.3	0.91
CBF ratio	0.73±0.05	0.84±0.13	0.31
CBV	5.08±0.55	4.40±0.65	0.21
CBV ratio	1.29±0.22	1.14±0.12	0.43
MTT	9.6±1.7	8.0±1.8	0.31
MTT ratio	1.78±0.40	1.39±0.28	0.14
OEF	51.3±8.0	50.0±2.8	0.43
OEF ratio	1.26±0.24	1.10±0.08	0.21

PET: Positron emission tomography, HPS: Hyperperfusion syndrome, CBF: Cerebral blood flow, CBV: Cerebral blood volume, MTT: Mean transit time, OEF: Oxygen extraction fraction

perfusion (31.7 ± 17.6 AIs/s) and normal perfusion (46.4 ± 22.6 AIs/s). In contrast, RT discriminated between impaired (8.4 ± 2.3 s) and normal cerebral perfusion (6.7 ± 0.8 s) with moderate accuracy (P = 0.034, AUC = 0.78). TTP was found to most successfully discriminate between impaired (14.9 ± 3.1 s) and normal cerebral perfusion (11.7 ± 1.6 s) with moderate to high accuracy (P = 0.013, AUC = 0.83).

Correlation between hemodynamic parameters of the icg-va and pet protocol

Associations between measures of ICG-VA parameters and of PET parameters were examined using Pearson's correlation coefficient in patients with major cerebral artery occlusive disease [Figure 2]. CBFi showed significant but weak correlations with CBF ($|r|$ = 0.535, $P < 0.01$) and CBF ratio ($|r|$ = 0.315, $P < 0.05$). There were significant and moderate correlations between RT and MTT ($|r|$ = 0.534, $P < 0.01$) and between TTP and MTT ($|r|$ = 0.628, $P < 0.01$), as measured from the PET study. Furthermore, RT ($|r|$ = 0.774, $P < 0.01$) and TTP ($|r|$ = 0.807, $P < 0.01$) were significantly and strongly correlated with MTT ratio.

However, because correlation coefficients are measures of the association between two methods but not of the agreement between them, the degree of agreement between RT and MTT and between TTP and MTT were assessed using the Bland–Altman graphical technique.[2] Figure 3a shows a Bland–Altman plot depicting the difference between RT and MTT (Y-axis) against their means (X-axis) for all ROIs. There was no systematic bias (fixed bias, proportional bias). The mean difference between the two measurements was −0.2 s (95% confidence interval: −0.8 s, 0.4 s) with 95% limit of agreement (−4.6 s, 4.2 s). Figure 3b shows a Bland–Altman plot depicting the difference between TTP and MTT against their means for all ROIs. The mean difference between the two measurements was 6.3 s (95% confidence interval: 5.6 s, 6.9 s) with 95% limit of agreement (1.4 s, 11.2 s). As shown in the regression line of the difference versus mean of the two methods, there was fixed bias and proportional bias.

Changes in icg-va parameters before and after bypass procedures

Figure 4 shows the changes in each parameter before and after bypass procedures in each of the 10 patients with major cerebral artery occlusive disease. I_{MAX} significantly increased from 302.6 ± 122.9 to 366.9 ± 106.7 AIs after bypass (P = 0.047). CBFi significantly increased from 31.7 ± 17.6 to 49.2 ± 17.3 AIs/s (P = 0.0093). RT was significantly shortened from 8.4 ± 2.3 to 6.3 ± 1.5 s (P = 0.0051). TTP was also significantly shortened from 14.9 ± 3.1 to 11.6 ± 2.3 s (P = 0.0093). There was no significant difference in any ICG-VA parameter when comparing postbypass patients and control subjects (I_{MAX}: P = 0.71, CBFi: P = 0.55, RT: P = 0.23, TTP: P = 0.88).

Table 4 summarizes ICG-VA parameters in patients with postoperative HPS and in patients without postoperative HPS. RT before bypass procedures was significantly longer in patients with postoperative HPS than in patients without postoperative HPS: 11.8 ± 2.1 and 7.8 ± 1.1 s, respectively (P = 0.017). TTP before bypass procedures was not significant different when comparing patients with postoperative HPS and patients without postoperative HPS: 17.6 ± 3.9 and 13.9 ± 2.0 s, respectively (P = 0.053). I_{MAX} and CBFi before bypass procedures and all ICG-VA parameters after bypass procedures were not significantly different when comparing patients with postoperative HPS and patients without postoperative HPS. Statistical analysis revealed no significant differences in the ratio of I_{MAX} and CBFi before and after bypass procedures when comparing

Table 3: Average values of parameters measured by the intraoperative near-infrared indocyanine green videoangiography protocol just after craniotomy in patients with *vs*. without major cerebral artery occlusive disease

ICG-VA parameters	(*n*=10)		*P* value	AUC
	Impaired perfusion	Normal perfusion		
I_{MAX}	302.8±112.9	369.6±127.4	0.29	0.64
CBFi	31.7±17.6	46.4±22.6	0.082	0.73
RT	8.4±2.3	6.7±0.8	0.034	0.78
TTP	14.9±3.1	11.7±1.6	0.013	0.83

ICG-VA: Intraoperative near-infrared indocyanine green videoangiography, I_{MAX}: Maximum intensity, CBFi: Cerebral blood flow index, RT: Rise time, TTP: Time to peak, AUC: Area under the receiver operating characteristic curve

Table 4: Average values and ratio of each parameters measured by the intraoperative near-infrared indocyanine green videoangiography protocol before and after bypass procedures in patients with *vs*. without postoperative hyperperfusion syndrome

ICG-VA parameters	HPS		*P* value
	Yes (*n*=3)	No (*n*=7)	
CBFi			
Pre	23.8±9.5	33.1±17.6	0.57
Post	52.0±30.5	48.0±11.5	0.73
Post/pre	2.1±0.52	1.8±1.0	0.21
RT			
Pre	11.8±2.1	7.8±1.1	0.017
Post	6.3±2.2	6.2±0.8	0.73
Post/pre	0.60±0.032	0.80±0.056	0.017
TTP			
Pre	17.6±3.9	13.9±2.0	0.053
Post	11.4±4.0	11.8±1.7	0.73
Post/pre	0.64±0.081	0.85±0.095	0.017

ICG-VA: Intraoperative near-infrared indocyanine green videoangiography, HPS: Hyperperfusion syndrome, CBFi: Cerebral blood flow index, RT: Rise time, TTP: Time to peak

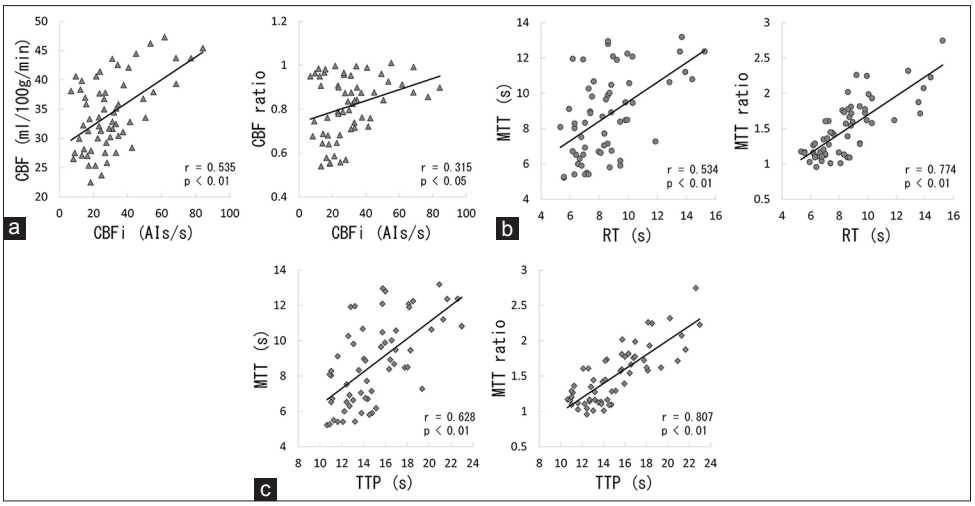

Figure 2: (a) Correlations between CBFi measured by the ICG-VA protocol and CBF and between CBFi and CBF ratio in 60 regions of interest among 10 patients. (b) Correlations between RT measured by the ICG-VA protocol and MTT, and between RT and MTT ratio, in 60 regions of interest among 10 patients. (c) Correlations between TTP measured by the ICG-VA protocol and MTT and between TTP and MTT ratio in 60 regions of interest among 10 patients. The black line shows the best fit linear regression for eye guide. The Pearson correlation coefficient (r) and p value are shown in each graph

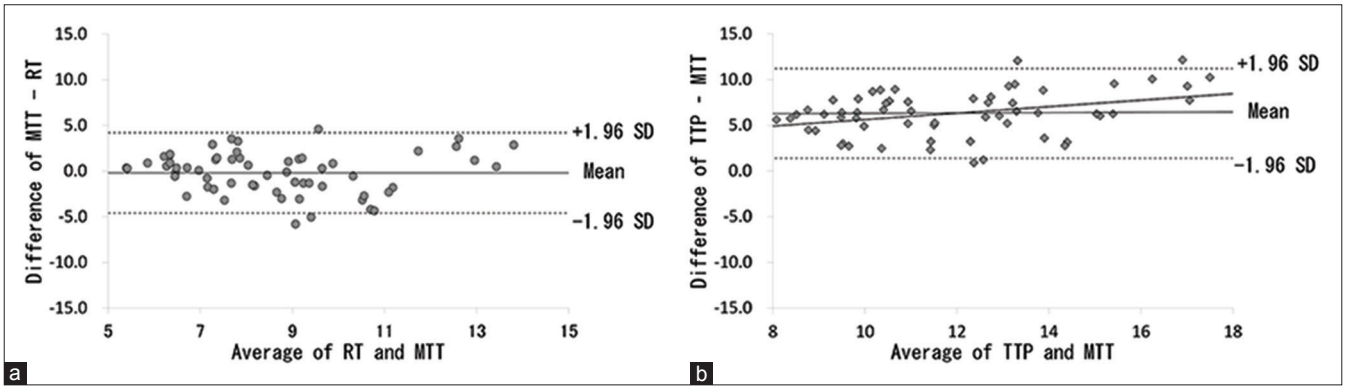

Figure 3: (a) Bland–Altman plot of the means of RT and MTT versus the difference between RT and MTT. Each circle represents one region of interest. Mean bias −0.2 s (solid line) with 95% limits of agreement from −0.8 to 0.4 s (dotted line) are shown. (b) Bland–Altman plot of the means of TTP and MTT versus the difference between TTP and MTT. Each diamond represents one region of interest. Mean bias 6.3 s (solid line) with 95% limits of agreement from 1.4 to 11.2 s (dotted line) are shown. The fine black line shows the best fit linear regression

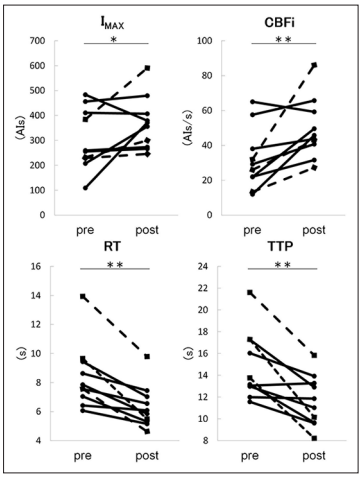

Figure 4: Line graphs showing the changes of four parameters before and after STA-MCA anastomosis in 10 patients. Dot lines represent patients with hyperperfusion syndrome. **P<0.01 and *P<0.05

patients with postoperative HPS and patients without postoperative HPS. However, the ratio of RT before and after bypass procedures was significantly lower in patients with postoperative HPS than in patients without postoperative HPS: 0.60 ± 0.032 and 0.80 ± 0.056, respectively (P = 0.017). Similarly, the ratio of TTP was also significantly lower in patients with postoperative HPS than in patients without postoperative HPS: 0.64 ± 0.081 and 0.85 ± 0.095, respectively (P = 0.017).

DISCUSSION

This study showed that cerebral perfusion in the hemodynamically compromised brain was delayed and that time-dependent parameters of the ICG transit curve (RT and TTP) quantitatively correlated with measures obtained by radio-nuclear examination. On the

other hand, I_{MAX} and CBFi, which are volume-dependent parameters, were less reliable for quantitative assessment when compared with time-dependent parameters.

I_{MAX} is easily affected by variables associated with ICG transit curve imaging, such as the focal distance between the microscope and the surface of the brain. It is also affected by light volume in the operating room. As a logical consequence, CBFi is also partially affected by these factors. This may explain why CBFi was not able to discriminate between normal and impaired cerebral perfusion with high accuracy and why it did not strongly correlate CBF/CBF ratio measured from PET. Although CBFi is useful for qualitative evaluation within a single imaging, use of CBFi for quantitative evaluation may be difficult.

RT and TTP were able to discriminate between impaired cerebral perfusion and normal cerebral perfusion with moderate accuracy and strongly correlated with MTT. Bland–Altman analysis showed a wide limit of agreement between RT and MTT (-4.6 s to 4.2 s), and between TTP and MTT (1.4–11.2 s). In addition, between TTP and MTT there was fixed bias and proportional bias. These findings suggest that RT and TTP are not necessarily consistent with MTT (because of random error) and that TTP may overestimate poor perfusion (because of proportional bias). However, even PET, which is the gold standard for quantitative cerebral perfusion analysis, potentially includes random error depending on the individual and the imaging conditions. In fact, the correlation between RT/TTP and MTT ratio was stronger than that between RT/TTP and MTT. These observations suggest that RT and TTP accurately reflect the true MTT. In fact, RT appeared to be the most reliable quantitative parameter among all the ICG-VG parameters examined in this study.

These correlations and degrees of confidence are interesting and noteworthy results to help validate microscope-integrated analysis of intraoperative ICG fluorescence angiography. This study may promote further clinical study on cerebral blood flow and metabolism using ICG-VA. In clinical practice, these time-dependent parameters from the ICG transit curve may help to make better intraoperative decision based on quantitative cerebral circulation time, such as the number of anastomoses, selection of recipient vessels, and so on. Then additional studies are required for understanding the threshold and for assessment how the decision-making improve clinical outcome. In this study, we also assessed whether these parameters predict postoperative HPS. As will be described in next paragraph, the result is interesting in cerebral blood flow and metabolism and be useful in clinical practice.

In a small number of cases, PET parameters were not significantly different when comparing patients with postoperative HPS and those without postoperative HPS. However, CBV/CBV ratio, MTT/MTT ratio, and OEF/OEF ratio were larger and CBF/CBF ratio was smaller in patients with postoperative HPS than in patients without postoperative HPS, all of which is consistent with findings from previous reports. In this case series, 3 of 10 patients developed postoperative HPS, which is a higher rate than that reported recently.[31] This might be related to the fact that the cerebral hemodynamic state of most of the patients was sufficiently impaired to result in elevation in the OEF. Alternatively, the surgical procedure (double anastomosis of STA to MCA in order to ensure sufficient blood flow) may contribute to the occurrence of postoperative HPS. However, restoration of sufficient blood flow by this surgical procedure might lead to avoidance of symptomatic cerebral infarction during the acute postoperative phase. Further, none of the patients in this study had recurrence of stroke during the postoperative follow-up period (median, 18 months; range, 12-31 months). In addition to the number of anastomoses, other factors related to the bypass procedure, such as selection of recipient vessel, diameter of donor graft, and occlusion time of recipient vessel, may also affect the risk of development of postoperative HPS. Therefore, intraoperative factors that can predict the onset of postoperative HPS likely reflect the state of cerebral perfusion before and after the bypass procedures. Using intraoperative ICG-VA, Woizik *et al*. assessed cortical perfusion in patients who underwent decompressive craniotomy for severe cerebral infarction.[30] They concluded that the CBFi value calculated in the cortical surface of the ischemic area was lower than that of penumbral area. Recently, Uchino *et al*. reported that the ratio of CBFi before and after bypass procedures was significantly higher in five patients with postoperative asymptomatic hyperperfusion than in two patients without postoperative hyperperfusion.[28] These reports did not investigate the quantitative accuracy of the ICG-VA parameter. The findings regarding the occurrence of postoperative hyperperfusion in our study are generally consistent with those in the latter report, but our precise examination of ICG-VA parameters showed that the use of time-dependent parameters, such as RT and TTP, is more reliable than volume-dependent parameters, such as I_{MAX} and CBFi, for quantitative assessment between different scans. Further, it should be emphasized that our study focused on symptomatic postoperative hyperperfusion rather than asymptomatic postoperative hyperperfusion.

The present findings should be viewed in the context of several methodological limitations. First, the number of patients in our study was small, and complete blinding was not done. Additional subjects are required to establish a solid conclusion. Second, the study and control subjects were not perfectly matched in terms of potentially confounding factors. Physiological parameters

were also different when comparing the PET study and the intraoperative period in the study subjects. Third, patients with occlusive cerebrovascular disease did not reach stage II brain perfusion and were excluded as candidates for extracranial to intracranial bypass; therefore, these patients were not included in this analysis.

This is the significant study to demonstrate that cerebral circulation time can be quantitatively assessed using microscope-integrated analysis of intraoperative ICG fluorescence angiography. In addition, the conclusions of this study were strengthened by the fact that data assessment by PET (i.e. the gold standard of quantitative assessment for cerebral perfusion and metabolism) was used for comparison purposes.

CONCLUSION

This study showed that cerebral perfusion in the hemodynamically compromised brain was delayed and that some time-dependent parameters of the ICG transit curve (RT and TTP) assessed by microscope-integrated dynamic ICG fluorescence analysis during surgery quantitatively correlated with measures obtained by radio-nuclear examination. Further, analysis of ICG-VA parameters may provide useful information regarding the development of HPS after STA-MCA anastomosis in patients with severe hemodynamic compromise and may contribute to the reduction of serious and persistent complications due to postoperative hyperperfusion.

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