



Original Article

Computed tomography perfusion imaging after aneurysmal subarachnoid hemorrhage can detect cerebral vasospasm and predict delayed cerebral ischemia after endovascular treatment

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ABSTRACT

Background: Endovascular treatment (ET) can improve angiographic cerebral vasospasm (CV) after aneurysmal subarachnoid hemorrhage, but was unrelated to clinical outcomes in previous analyses. Appropriate detection of CV and precise indications for ET are required. This study investigated whether changes in computed tomography perfusion (CTP) parameter can determine indications for ET in CV and predict its effectiveness.

Methods: Participants comprised 140 patients who underwent neck clipping or coil embolization. CTP was performed a week after aneurysmal treatment or when clinical deterioration had occurred. Patients were divided into ET and non-ET groups by propensity score matching. In addition, the ET group was divided into subgroups with and without new cerebral infarction (CI). All CTP images in the three groups were retrospectively investigated qualitatively and quantitatively. CI was diagnosed from CT at 3 months postoperatively.

Results: Of the 121 patients examined, 15 patients (11%) needed ET. In qualitative analysis, all ET group patients displayed extension of time-to-peak (TTP) at the region of vasospastic change, regardless of the presence of CI. Quantitative analysis showed significant decreases in cerebral blood volume ($P < 0.01$), cerebral blood flow (CBF) ($P < 0.001$), and extension in TTP ($P < 0.01$) in the ET group compared with the non-ET group. A significant decrease in CBF ($P < 0.001$) and extension in mean transit time ($P < 0.001$) was seen in the ET with CI subgroup compared with the ET without CI subgroup.

Conclusion: CTP in the vasospastic period may be an indication for ET and predict the effectiveness of ET for CV to improve clinical outcomes.

Keywords: Aneurysmal SAH, Cerebral vasospasm, CT perfusion, Endovascular fasudil injection

INTRODUCTION

Delayed cerebral ischemia (DCI) -induced by cerebral vasospasm (CV) after aneurysmal subarachnoid hemorrhage (aSAH) is an important factor associated with poor prognosis.^[2,8,11] Precise detection of CV and appropriate treatment is required to prevent DCI. Digital subtraction angiography (DSA) is considered a gold-standard method for detecting CV, but the ideal diagnostic modality would be noninvasive, quick, and repeatable for detecting CV and DCI. A previous meta-analysis of the

application of computed tomography perfusion (CTP) in the time window for DCI after aSAH concluded that CTP can be used in the diagnosis of DCI.^[3] However, those reports only evaluated the relationship between clinical outcome and timing of DCI, and not between clinical outcome and endovascular treatment (ET) for CV. The current standard of treatment for DCI is based on nutrition, precautions against hypovolemia and hyponatremia, and intravenous administration of nimodipine.^[1] When CV develops, hemodynamic augmentation therapies with crystalloids, colloids, and inotropic agents are considered. ET is considered one treatment option for DCI.^[4,17,21] One analysis of the efficacy of ET for CV after aSAH indicated the effectiveness of ET for achieving angiographic improvement of CV, despite limited clinical outcomes.^[23] Appropriate patient selection and adaptation of ET may thus lead to improved clinical outcomes. Recently, CTP imaging has allowed visualization of brain perfusion and ensured the establishment of ET treatment algorithms for both detection and estimation of therapeutic values in acute ischemic stroke.^[15] CTP is capable of judging and adapting the utility of ET in ischemic regions. Since the extent to which the region affected by vasospasm progresses to cerebral infarction (CI) depends on local cerebral hemodynamic status, CTP images may allow visualization of the precise adaptation of ET and prediction of the

efficacy in avoiding infarct growth after ET treatment. However, no studies have investigated whether CTP can predict indications for ET and clinical outcomes. The present study investigated whether CTP parameter changes seen a week after aSAH onset can predict the effectiveness of ET for CV.

MATERIALS AND METHODS

Patient population

From January 2014 to September 2017, a total of 140 consecutive patients who underwent neck clipping or coil embolization of ruptured aneurysm within 48 h after the onset of aSAH were enrolled. Diagnostic CT angiography (CTA) was performed during the first 12 h after admission for detection of the aneurysm site. The main factors for selecting endovascular coil embolization were the difficulty of clip application and an aneurysm located in the posterior circulation. Patients with any of the following conditions were excluded: Hunt and Kosnik (H-K) Grade V; head trauma; renal disease; or congestive heart failure. In total, 121 patients were included in the present study [Figure 1].

Patients were divided into a group in which ET was performed for CV (ET group) and a group in which no CV

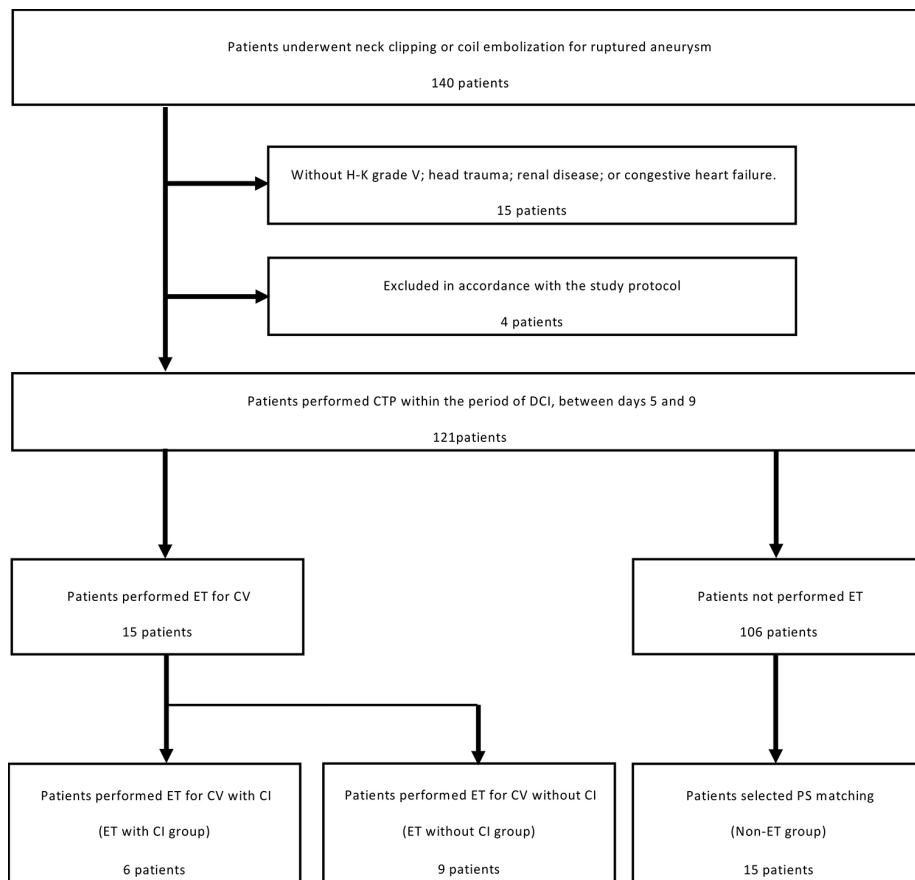


Figure 1: Flowchart of patient selection.

suitable for ET was identified (non-ET group). Patients in the non-ET group were selected by applying propensity score (PS) matching using SPSS version 25 software (IBM, Tokyo, Japan) adjusted for age, sex, aneurysm location, and clinical SAH data (H-K grade and Fisher grade) as a control group in contrast to the ET group. CI due to CV was diagnosed from CT at performed 3 months postoperatively, and the ET group was then divided into subgroups with and without CI.

Perioperative management and ET

All patients remained normovolemic and normotensive after SAH. The protocol to prevent CV in our institute was described previously.^[13,14] We used transcranial Doppler ultrasonography (TCD) to screen for the presence of CV. Diagnostic confirmation of CV was emergently performed when clinical symptoms deteriorated and angiography revealed elevated mean flow velocity on TCD. Regardless of the existence of CV, routine DSA was typically performed in all cases within postoperative days 5–9 for detecting asymptomatic CV that may incur DCI. When CV was detected, hemodynamic augmentation therapy was initiated with crystalloid, colloid, and inotropic agents (dopamine or dobutamine).^[13,14] Furthermore, intra-arterial injection of fasudil hydrochloride hydrate (IAFC) or percutaneous angioplasty (PTA) for ET was performed consecutive to diagnostic DSA. The indication for ET is defined as a focal narrowing of vessel diameter by $\geq 50\%$ on DSA compared with the same segment in the initial CTA at the time of SAH. IAFC was performed using the internal carotid artery or vertebral artery through the same catheter used for angiography, with the tip positioned in the proximal internal carotid artery or vertebral artery. Thirty milligrams of fasudil hydrochloride were injected over 10–20 min [Figure 2a and b]. IAFC or PTA was finished after improving the narrowing of vessel diameter to $< 50\%$ on DSA. When CV recurred, transarterial injection or PTA was performed again until DCI was ended.

CTP protocol

CTP was performed for all cases during the typical time period for DCI, between postoperative days 5 and 9, in asymptomatic patients and on the same day that clinical deterioration or change in TCD occurred in symptomatic patients to screen for CV. If CV was recognized, CTA was performed and DSA was performed consecutively, as mentioned above. A standard scanning protocol for CTP is applied at our institution using a 64-slice multidetector-row CT scanner (SOMATOM Definition Flash; Siemens Healthineers, Tokyo, Japan). CTP data were acquired with a periodic spiral approach (adaptive 4-dimensional spiral mode) of 30 periodic spiral mode scans of the brain with cranial-caudal coverage of 100 mm in z-axis (sampling time per volume, 1.5 s). We intravenously administered 35 mL of iodine contrast medium (Iopamiron

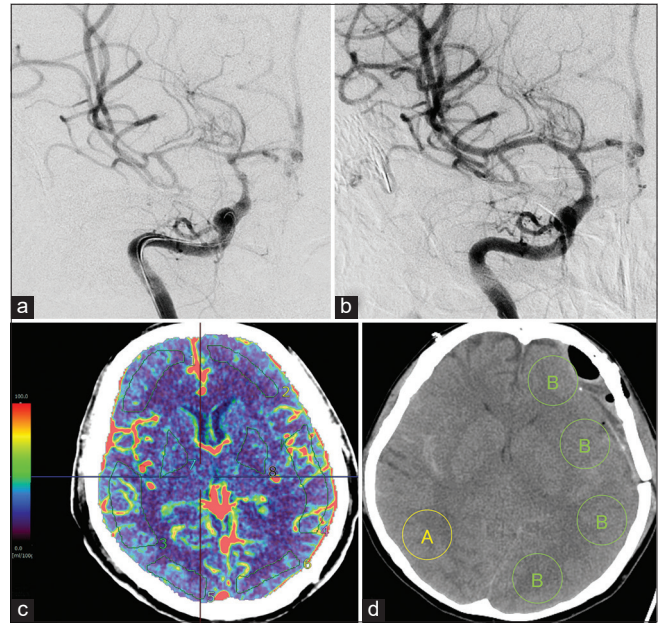


Figure 2: (a) Digital subtraction angiography (DSA) shows vasospastic change in the right middle cerebral artery (MCA) (black arrowhead). (b) Vasospastic change in the right MCA is improved after intra-arterial injection of fasudil hydrochloride (IAFC) (black arrowhead). (c) Computed tomography perfusion (CTP) is acquired with a Synapse Vincent 4D perfusion image. Eight regions of interest (ROIs) are measured quantitatively in each patient with aSAH within days 5–9 postictus. (d) An ROI showing vasospastic change on DSA is categorized as a vasospastic region (A), and the ROI contralateral to the side of the ischemic region is categorized as a non-vasospastic region (B). In the non-vasospastic region, four values are obtained from the ROI and averaged to reduce bias. The ratio A/B is then calculated.

370; Bayer Schering Pharma, Berlin, Germany) at a flow rate of 5 mL/s followed by a 25-mL saline push at the same rate. The CTP scan (80 kV; 140 mAs; rotation time, 0.28 s; collimation, 32×1.2 mm; scan time, 1.5 s; cycle time, 1.5 s) was started after an individual delay time adjusted with a test bolus. Delay time was calculated as a rise in the time-density curve -3 s with injection of 10 mL of iodine contrast medium at a flow rate of 5 mL/s added to 20 mL of saline at the same flow rate as the test bolus.

Image and data analysis

All CT perfusion images and DS angiograms were interpreted by an experienced senior neurosurgeon (I.N.). CT perfusion images were analyzed qualitatively using rainbow color scale maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time-to-peak (TTP). Next, postprocessing of the acquired images into CBF, CBV, and MTT maps was performed quantitatively using Synapse VINCENT 4D perfusion (Fujifilm, Tokyo, Japan). This software

uses a deconvolution method, which is considered the most accurate for low-contrast injection rates. The postprocessing protocol was selected for all patients according to recommended guidelines (ASIST-Japan 2006).^[24] From the acquired CTP imaging, we determined the following region of interest (ROI): bilateral sides of the cerebral cortex in the frontal lobe, temporal lobe, occipital lobe, and parietal lobe [Figure 2c]. CBF, CBV, MTT, and TTP were measured in each ROI. Another neurosurgeon (K.O.) identified whether vasospastic change was present on DSA. Any ROI that showed vasospastic change on DSA was categorized as a vasospastic region (A), and the contralateral ROI was then categorized as a non-vasospastic region (B). In the non-vasospastic region, four values were obtained from the ROI and averaged to reduce bias. For each ROI, A and B were installed, as shown in [Figure 2d]. If a vasospastic change was not observed (non-ET group), mean ROI of the ruptured side was established as A, and mean ROI of the contralateral side as B. In the case of anterior communicating artery aneurysms, A was established as the mean of the lower ROI and B as the contralateral side to A. The ratio A/B was then calculated. We compared the three groups of non-ET, ET with CI, and ET without CI, as described above. Neurosurgeons who examined CT perfusion images were not aware of the results of cerebral angiograms at the time of interpretation. Reports on CT perfusion images and cerebral angiograms were examined retrospectively, and the presence or absence of CV as reported was recorded in a database.

Study outcomes

The primary outcome was CTP parameter changes to determine indications for ET of CV and predict its effectiveness in the populations of non-ET, ET with CI, and ET without CI. Qualitative and quantitative evaluations in CTP were thus performed for three groups (non-ET, ET with CI, and ET without CI). Exclusion criteria were CTP performed after ET or >9 days after ictus and CI already confirmed on CTP. CI was diagnosed from CT performed 3 months postoperatively.

Statistical analysis

Statistical comparisons among groups were conducted using one-way analysis of variance. Where indicated, individual comparisons were performed using Student’s t test. Statistical significance was ascribed to the data for values of *P* < 0.05.

RESULTS

Study population characteristics

A total of 121 patients (83 women and 38 men) were examined and CTP parameters after aSAH were measured.

The mean age of patients was 67 years (range, 28–84 years). Fifteen patients (12%) showed ET and received IAFC for CV and none received PTA. Fifteen patients from the non-ET group as controls were selected by PS matching, as mentioned in [Figure 1]. After 1:1 PS matching of subjects, respective group demographics were similar (age: 65.7 ± 17.8 vs. 65.4 ± 10.7 years, *P* = 0.48; female sex: 67% vs. 80%, *P* = 0.68; aneurysm location in anterior circulation: 87% vs. 87%, *P* = 1.00; H&K grade 3–5: 60% vs. 67%, *P* = 1.00; Fisher group 3–4: 87% vs. 93%, *P* = 1.00). All aneurysms in these groups were treated by clipping and demographic characteristics of the study population are shown in Table 1. All patients in the ET group showed vasospastic changes on DSA. In the ET group, six patients presented with delayed CI on final CT (40%), while no patients in the control group presented with

Table 1: Clinical and demographic characteristics of each group with aSAH*.

Characteristic	Value	
	ET group	Non-ET group
Number of patients	15	15
Mean age in yrs	65.7±17.8	65.4±10.7
Sex (female)	10 (67%)	12 (80%)
Hunt and Kosnik Grade		
I–II	5 (33.3)	5 (33.3)
III–IV	8 (53.3)	10 (66.6)
V	1 (6.6)	N.A
others [†]	1 (6.6)	N.A
Fisher grade		
I–II	2 (13.3)	1 (6.6)
III–IV	13 (86.6)	14 (93.3)
Aneurysm site, n [‡]		
Acom	3 (20)	6 (40)
MCA	4 (26.7)	2 (13.3)
ICA	5 (33.3)	5 (33.3)
(IC-PcoA/IC-AchoA)		
VA-BA	3 (20)	2 (13.3)
Treatment		
Clipping	15 (100)	15 (100)
Spasm		
Spasmatic change in DSA	15 (100)	0 (0)
symptomatic [§]	10 (66.6)	0 (0)
LDA in final CT	6 (40)	0 (0)
Outcome (mRS)		
0–2	8 (53.3)	12 (80)
3–5	7 (46.7)	3 (20)
6	0	0

*Values are expressed as the number (%). [†]Others represent idiopathic case in the course of coil embolization for unruptured aneurysm, [‡]ACoA = Anterior communicating artery; MCA = Middle cerebral artery; ICA = Internal carotid artery; PCoA = Posterior communicating artery; AChoA = Anterior choroidal artery; BA = Basilar artery; VA = Vertebral artery. mRS; modified Rankin Score, [§]the definition of symptomatic: The presence of neurological worsening including focal deficit, decline in level of consciousness, and motor paresis

delayed CI. Consequently, clinical outcomes were better in the non-ET group than in the ET group because of DCI.

Qualitative analysis and quantitative analysis of CTP parameters

On qualitative analysis, all patients in the ET group showed extension of TTP in the region of vasospastic change on DSA, regardless of the presence of CI [Figure 3]. Quantitative analysis of CTP parameters showed significant decreases in CBV ($P < 0.01$), CBF ($P < 0.001$), and extension in TTP ($P < 0.01$) in the ET group compared with the non-ET group. Furthermore, significant decreases in CBF ($P < 0.001$) and extension in MTT ($P < 0.001$) were evident in the ET with CI subgroup compared with the ET without CI subgroup [Figure 4].

DISCUSSION

Strength of this study was its position as the first study to investigate indications and prediction of effectiveness for ET using CTP within the temporal window for DCI. Significant decreases in CBV and CBF and extension in TTP were seen in the ET group compared with the non-ET group in

quantitative CTP parameter analysis. The results indicate that changes in these parameters influence the efficacy of ET. In addition, significant decreases in CBF and extension in MTT were found in the ET with CI group compared with the ET without CI group. The result indicates that further deterioration of these parameters would lead to poor outcomes irrespective of ET. In short, these results indicate that detection of CV using CTP in the vasospastic period can be useful for comprehending hemodynamic conditions under CV and may predict the effectiveness of ET for CV to improve clinical outcomes.

Can CTP on days 5–9 raise awareness of DCI?

Suitable and timely comprehension of CV after aSAH improves outcomes in terms of DCI, but assessment of neurological findings and identification of impending DCI is difficult in cases of severe aSAH. DCI mostly occurs 4–14 days after hemorrhage.^[9,12,22] A previous meta-analysis reported that CTP on admission cannot be used to reliably predict DCI, but CTP within the temporal window for DCI might be helpful in determining the cause of clinical deterioration.^[3] The timing of CTP performed within the temporal window

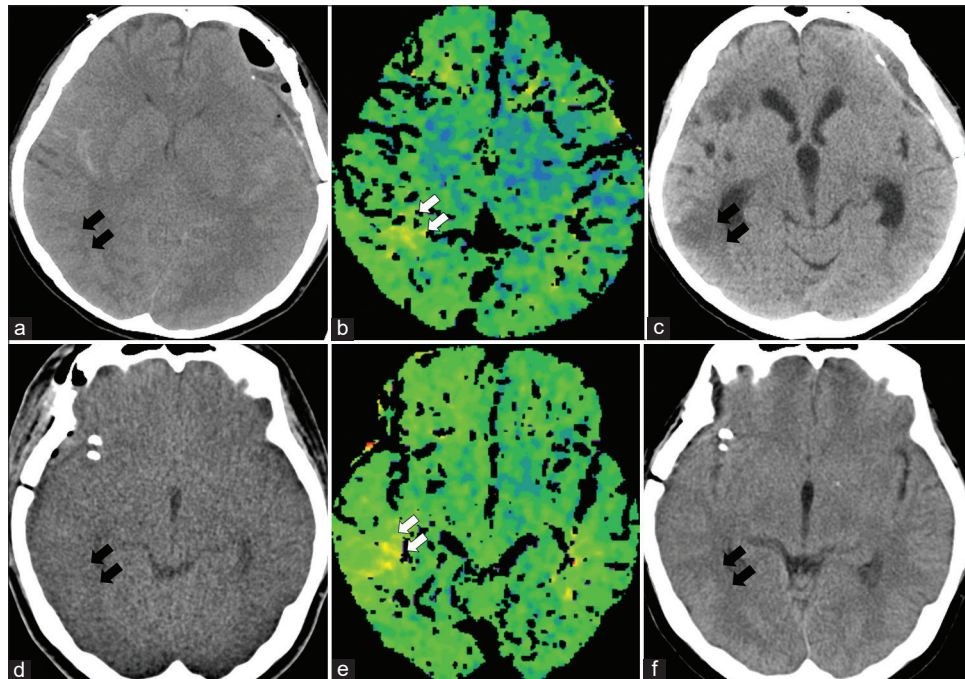


Figure 3: Clinical progression in illustrative cases from the ET with cerebral infarction (CI) subgroup (a-c) and the ET without CI subgroup (d-f) using CT after operation and after 1 month and TTP image within days 5–9. All data for TTP in the ET group show qualitative extension. (a) A patient in the ET with CI subgroup shows no apparent infarction on CT at 1 day postoperatively. (b) TTP from the same patient indicates extension of TTP in the region of vasospastic change on DSA (white arrow). (c) Despite perioperative management including IAFC, the region showing extension of TTP finally develops cerebral infarction with CT after 1 month (black arrow). (d) A patient from the ET with no CI subgroup shows slight low-density changes in the right temporal lobe on CT the day after the operation (black arrow). (e) The image from TTP in this patient indicates extension of TTP in the region of vasospastic change on DSA (white arrow). (f) Under perioperative management including IAFC, the region showing extension of TTP still shows no cerebral infarction on CT after 1 month (black arrow).

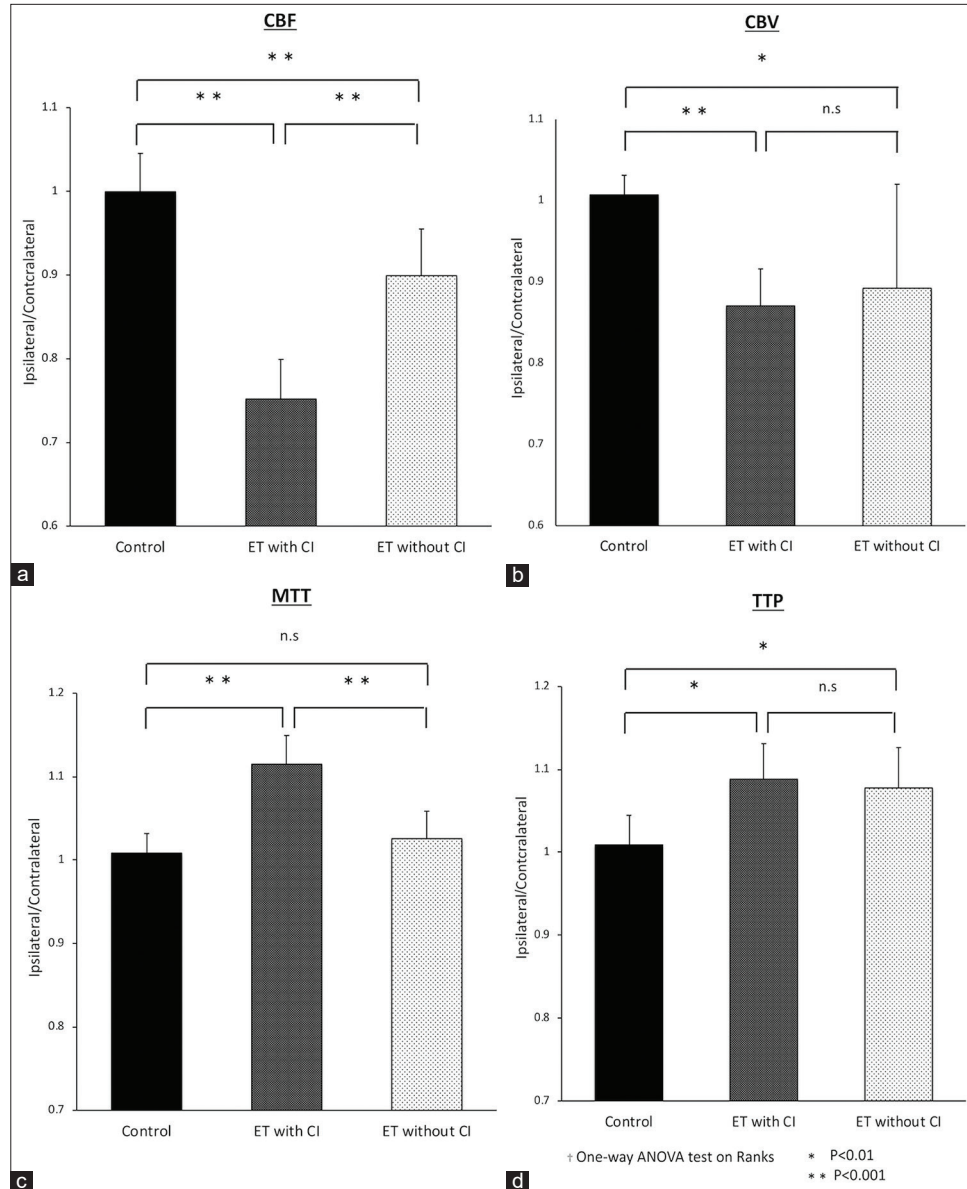


Figure 4: The ratio of A and B from ROIs calculated from Synapse Vincent 4D perfusion images as quantitative analysis is shown for three groups, a Non-ET group as control, an ET with CI group and an ET without CI group. The non-ET group was selected by PS matching. Comparison of CBF (a), CBV (b), MTT (c), and TTP (d) between the non-ET group and the ET w/o CI group indicates significant decreases in CBV ($P < 0.01$) and CBF ($P < 0.001$) and extension in TTP ($P < 0.01$). Comparison between the ET with CI group and the ET without CI group shows significant decreases in CBF ($P < 0.001$) and extension in MTT ($P < 0.001$).

for DCI in most studies was mostly days 6–8 postictus.^[10,18,25] Indeed, the purpose of previous studies was to predict and detect CV, not treatment. The timing of CTP in DCI could be lengthened to days 6–8 postictus as physicians examine whether to perform ET for CV. TCD is an established monitoring tool for identifying CV after aSAH. A rapid increase in blood flow velocity in TCD was related to severe CV.^[16] However, the increase of blood flow velocity in TCD is not equivalent to cerebral hypoperfusion and is unsuitable for comprehending hemodynamic status. Concerning

detection of tissues at risk, CTP should be an essential part of the diagnostic workup in addition to daily clinical assessment and daily measurement by TCD. In our series, the group with ET included 10 patients with symptomatic CV, of whom six patients eventually experienced CI, although none of the five asymptomatic patients with ET developed CI. The result of no CI among patients with asymptomatic CV may suggest the effectiveness of ET. In that respect, the timing of CTP between days 5 and 9 after hemorrhage would be appropriate before CI occurred.

Can ET improve CV and outcomes?

The efficacy of ET for the treatment of CV following aSAH remains debatable. A meta-analysis showed that intra-arterial injection of vasodilators enabled angiographic response in 89% of patients and clinical improvement in 63%. That study indicated that IAFC leads to robust angiographic response and fair rates of neurological response and good clinical outcomes. However, a previous study reported that IAFC or the combination of IAFC and PTA did not improve clinical outcomes.^[23] Hosmann *et al.* reported that a key factor contributing to the discrepancy between angiographic improvement and outcome is delayed diagnosis of impending ischemia, and considered the ideal timing of endovascular procedures needed to prevent CI.^[7] We therefore speculated that previous reports were unable to prove good clinical outcomes after ET for CV despite angiographic improvement. In the present study, the indication of ET was adopted for symptomatic cases and asymptomatic cases with vessel narrowing $\geq 50\%$ compared to initial CTA based on previous studies.^[19,21] The difference compared with previous reports was that this study performed CTP before ET for evaluation of cerebral perfusion and thus to more fully comprehend cerebral ischemic status.

Can CTP judge indications for ET and predict effectiveness?

Kunze *et al.* performed a retrospective ROI-based CTP study of 53 patients with aSAH who underwent CTP 3 times on day 3 or 4, day 6 or 7, and day 9 or 10 and additionally at any other time point when CV was suspected. TTP was the parameter showing the highest sensitivity for detection of CV.^[12] In a prospective study conducted by Hickmann *et al.* under a similar protocol, TTP offered the most sensitive and most specific predictor of clinically relevant vasospasm.^[6] Sanelli *et al.* performed a retrospective ROI-based CTP study between days 6 and 8 after aSAH. Quantitative CTP revealed significantly reduced CBF and prolonged MTT as risk factors for clinically relevant to DCI, permanent neurologic deficits, and infarction.^[18] All of these studies were focused on the possibility of detecting DCI or predicting clinical outcome, unrelated to indications for ET or prediction of the effect of ET as in the present study. In previous studies about ET for CV in aSAH patients, the decision-making process for treatment has mostly involved angiographic observation and clinical deterioration, indicative of DCI, not evaluation of cerebral perfusion.^[7,20] Many studies did not consider cerebral perfusion. To improve outcomes, selection of patients based on cerebral perfusion may be needed for CV after SAH. Appropriate timing of CTP is important to judge the necessity for ET in terms of indications and prediction of

effectiveness. A further study of more effective approaches to ET using CTP is required.

Limitations of the study

We have to acknowledge several limitations in the present study. First, quantitative analysis in this investigation yielded significant results, but the number of clinical samples was small. Second, the study was a retrospective analysis with PS matching, not a prospective study. Third, the existence of CI was judged from CT, not MRI. Detection of CI due to CV was related to the size of the infarction, which would also have led to neurological deterioration related to final outcome. Fourth, the CTP protocol and ROIs introduced potential sources of bias. CTP was affected by the CT device and CTP protocol used in each institution. Results from previous ROI-based quantitative analyses are thus not necessarily more widely applicable to other hospitals. To reduce bias, our study calculated the ratio of the vasospastic region to of non-vasospastic region. This value may prove helpful for comparisons with other studies. CTP parameters of symptomatic vasospastic region could be underestimated by asymptomatic vasospasm in symmetrical contralateral regions. Systemic hemodynamic changes parallel to development of CV could affect CTP parameters even in contralateral asymptomatic side. SAH is known to lead to spontaneous and progressive elevations in mean arterial blood pressure, which could affect CTP parameters.^[5] Furthermore, changes in systemic hemodynamics may not be adequately compensated for by cerebral autoregulation impairment by focal vasospasm at the contralateral side.^[20] That is why four values were obtained from the ROI and averaged as the contralateral non-vasospastic region for reduction of these biases in the present study. Verification of whether ROI averages are suitable for measuring non-spastic regions is needed in the future. The 8 ROIs used did not include the cerebellum. This study thus provided limited brain coverage. A fifth limitation was that the definition of DCI in asymptomatic patients with CV was inexact. However, asymptomatic patients may have DCI. The purposes of this study were the adaptation and prediction of effectiveness in ET. For the purposes of our study, we included asymptomatic patients although the ET and non-ET groups already showed bias in terms of hemodynamic severity. In our series, six of 10 patients in the ET group subsequently developed CI, and earlier ET could have reduced CI. Further study is required to clarify whether earlier timing of CTP and ET will reduce CI caused by CV after aSAH.

CONCLUSION

CTP in the vasospastic period after aSAH was effective for comprehending the condition of dramatic changes in CV. Decreases in CBV and CBF and extension of TTP may provide indications for ET to improve clinical outcomes.

Statement of ethics

All study patients signed a written authorization allowing access to their medical records for research purposes, and our institutional review board approved the research protocol (No. 2035).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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