Original Paper

Initial 'TTP Map-Defect' of Computed Tomography Perfusion as a Predictor of Hemorrhagic Transformation of Acute Ischemic Stroke

Mizuya Shinoyama[a, c]   Jyoji Nakagawara[a]   Hiroshi Yoneda[c]
Michiyasu Suzuki[c]   Hidetoshi Ono[b]   Ichiro Kunitsugu[d]
Kenji Kamiyama[a]   Toshiaki Osato[a]   Hirohiko Nakamura[a]

Departments of [a]Neurosurgery and [b]Radiology, Nakamura Memorial Hospital, Sapporo, and Departments of [c]Neurosurgery and [d]Public Health, Yamaguchi University School of Medicine, Yamaguchi, Japan

Key Words

Hemorrhagic transformation · Computed tomography perfusion · Time to peak · Ischemic stroke

Abstract

Background: Hemorrhagic transformation (HT) following acute ischemic stroke is a major problem, especially for the indication of reperfusion therapy including intravenous administration of recombinant tissue plasminogen activator (IV rt-PA). The specific predictive factors of HT have not yet been established. The present study evaluated the findings of computed tomography perfusion (CTP) images as predictors of subsequent HT to identify patients with low HT risk for reperfusion therapy such as IV rt-PA. **Methods:** We retrospectively reviewed 68 consecutive stroke patients (41 males; mean age 72.9 years) with steno-occlusive lesions in the major trunk, including 10 patients who underwent IV rt-PA. Each HT was detected on a follow-up T2*-weighted magnetic resonance image until 2 weeks after stroke onset and categorized into four groups [hemorrhagic infarction (HI) type 1 and 2, and parenchymal hematoma (PH) type 1 and 2] according to the European Cooperative Acute Stroke Study (ECASS) classification. We assessed clinical features and radiological findings between the HT and non-HT groups or the PH2 and non-PH2 groups. The efficacy of initial time to peak (TTP) mapping of CTP for predicting HT or PH2 was evaluated. **Results:** Thirty-four patients (50%) developed subsequent HT: 18 (52.9%) had HI and 16 (47.1%) had PH, including 9 PH2 patients (13.2%). IV rt-PA was not signifi-

Michiyasu Suzuki, MD

Department of Neurosurgery, Clinical Neuroscience
Higher Biointegration, Yamaguchi University Graduate School of Medicine
1-1-1 Minami Kogushi, Ube, Yamaguchi 755-8505 (Japan)
E-Mail michi@yamaguchi-u.ac.jp

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cantly associated with HT or PH2 occurrence. Forty of the 68 patients (59%) revealed defect areas on the initial TTP mapping (TTP map-defect), and 34 of these 40 patients (85%) developed secondary HT and 9 patients (22.5%) developed PH2. Initial 'TTP map-defect' was significantly associated with the occurrence of HT ($p < 0.0001$) and PH2 ($p = 0.0070$). Thirty of the 34 patients (88.2%) in the HT group experienced delayed recanalization of the occluded vessels, in contrast to only 8 of the 34 patients (23.6%) in the non-HT group. All patients of the PH2 group showed recanalization ($p = 0.0042$). In 40 'TTP map-defect'-positive patients, delayed recanalization was associated with the occurrence of HT ($p < 0.0001$) and PH2 ($p = 0.0491$). All 28 patients without 'TTP map-defect' did not develop HT, including 8 patients (28.6%) with delayed recanalization. *Conclusions:* Initial 'TTP map-defect' of CTP could accurately predict HT risk including PH2 risk and identify low-risk patients even in the delayed period.

Introduction

Hemorrhagic transformation (HT) in acute ischemic stroke occurs either spontaneously [1] or after thrombolytic therapy [2–4]. Thrombolytic therapy consisting of intravenous administration of recombinant tissue plasminogen activator (IV rt-PA) reduces ischemic brain injury in some patients but causes symptomatic HT in 6–10% of treated patients, resulting in a mortality rate of 45–61% [2–4]. Therefore, thrombolytic therapy is considered to be a double-edged sword. Partly because of the risk of hemorrhagic complication, only 3.4–5.2% of all transferred ischemic stroke patients could undergo IV rt-PA in the USA in 2009 [5]. Therefore, pre-treatment selection to identify patients with low risk of HT could increase the opportunity for reperfusion therapy. The estimation of the individual HT risk is more important because of the widened therapeutic time window for IV rt-PA beyond 4.5 h [6].

Various clinical factors such as etiologies or underlying medical histories have been proposed as indicators for HT, but the specific predictors have not yet been established [7–12]. Initial radiological findings of extensive early ischemic lesions or poor collateral flow on conventional computed tomography (CT) or magnetic resonance image (MRI) could be predictors of HT; however, they have not yet been shown to predict accurate patients' risk of HT.

Recently, perfusion imaging has become important in the diagnosis of acute ischemic stroke. Bolus-chase CT perfusion (CTP) or MR perfusion (MRP) uses dynamic contrast-enhanced data to produce parametric color overlay maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). These parameters have already been proved to accurately indicate focal brain perfusion and applied to clinical use in acute cerebral infarction [13–16]. Perfusion images have been reported to predict the patient's hemorrhagic outcome by assessing parameters such as permeability of contrast [17], CBV [18] or relative MTT [19]. However, their results are not suitable to anticipate the therapeutic time window of IV rt-PA.

Among the parameters, in particular, TTP mapping shows focal hypoperfusion at higher sensitivity [20–24]. Moreover, TTP mapping has advantages in short data processing time without complex calculations such as deconvolution, so it has been widely applied in the clinical setting. However, the predictive value of TTP mapping for estimating the risk of HT in patients with acute ischemic stroke has not been evaluated.

The present study evaluated the efficacy of initial TTP mapping on admission as a predictor of subsequent HT to identify patients with low HT risk [25] for reperfusion therapy.

Methods

Inclusion Criteria

We retrospectively reviewed the radiological findings of all patients with ischemic stroke who were admitted to the stroke service of the Nakamura Memorial Hospital from January to September 2010. We evaluated patients with a steno-occlusive lesion in the intra- or extra-cranial major cerebral vessels who underwent both CTP and MRI as initial imaging assessments within the first 24 h of stroke onset.

The criteria for the study were as follows: initial CT and MRI showed no intracranial hemorrhage and a follow-up MRI was performed at least twice, the first on the day after stroke onset (day 2) and the second within 2 weeks. Both MRIs included diffusion-weighted imaging, T2*-weighted imaging, and magnetic resonance angiography (MRA).

rt-PA was administered according to the Japanese guidelines [26, 27]. Patients who died of extra-cranial causes within the first 2 weeks were excluded.

Imaging Procedure

All CTP studies were performed using a 128-slice CT scanner (SOMATOM Definition AS+; Siemens, Forchheim, Germany) with adaptive 4D-spiral mode. The technique is based on a constant periodic bidirectional table movement. The imaging parameters were 80 kV and 180 mAs, 20 spiral images with an image volume of 96 mm on the z-axis, and a travel time of 1.5 s per spiral. Reconstructed images of 5 mm were obtained for every 1 mm of the total imaging volume.

A bolus of 40 ml of the non-ionic contrast material Iohexol 350 (Omnipaque 350; Dai-ichi-Sankyo, Tokyo, Japan) was injected through a 20-gauge cannula placed in the cubital vein at a flow rate of 5 ml/s followed by 20 ml of saline chaser.

MRI was performed with a 1.5-T clinical whole-body unit (Magnetom Avanto; Siemens, Erlangen, Germany). The parameters of T2*-weighted gradient-echo imaging were repetition time (TR) 650 ms, echo time (TE) 24.5 ms, 20-degree flip angle, 256 × 168 matrix, 230-mm field of view, 5-mm-thick sections with 1-mm interslice gaps, and number of excitations 1 (acquisition time = 1:31). The parameters of multi-shot diffusion-weighted echo planar imaging were TR 3,500 ms, TE 94 ms, 128 × 96 matrix, 230-mm field of view, 5-mm-thick sections with 1-mm interslice gaps, number of excitations 2, PAT factor 2, b values of 0, and 1,500 s/mm^2 (acquisition time = 0:40).

Data Processing and Analysis

Data were evaluated with commercially available 3D perfusion software (Syngo Volume Perfusion CT Neuro; Siemens, Forchheim, Germany). The signal-to-noise ratio was improved using spatiotemporal filtering for all data (adaptive 4D noise reduction). Vessels were automatically detected on the time maximum intensity projection images (fig. 1a). All voxels along the vasculature above a configured percentage of maximum enhancements were excluded from the calculation.

CBF, CBV, and MTT were determined with a deconvolution-based algorithm (fig. 1b–d) [28]. TTP was determined as the time lag indicated by the time attenuation curve (TAC) (fig. 1f R1–R3) between the injection of the contrast medium and the local bolus peak in the brain tissue. For example, TAC in the contralateral hemisphere, considered to indicate normal perfusion, showed a time interval of 17 s (fig. 1f R3), but R1 in the ischemic hemisphere showed a delayed time interval of 27 s. According to the time lag, the color map was constructed as in figure 1e. However, in the most seriously ischemic part, TAC did not show any local bolus peak as in figure 1f R2, which was interpreted as showing that the contrast medium did not sufficiently penetrate into the brain tissue because of extreme hypoperfusion.

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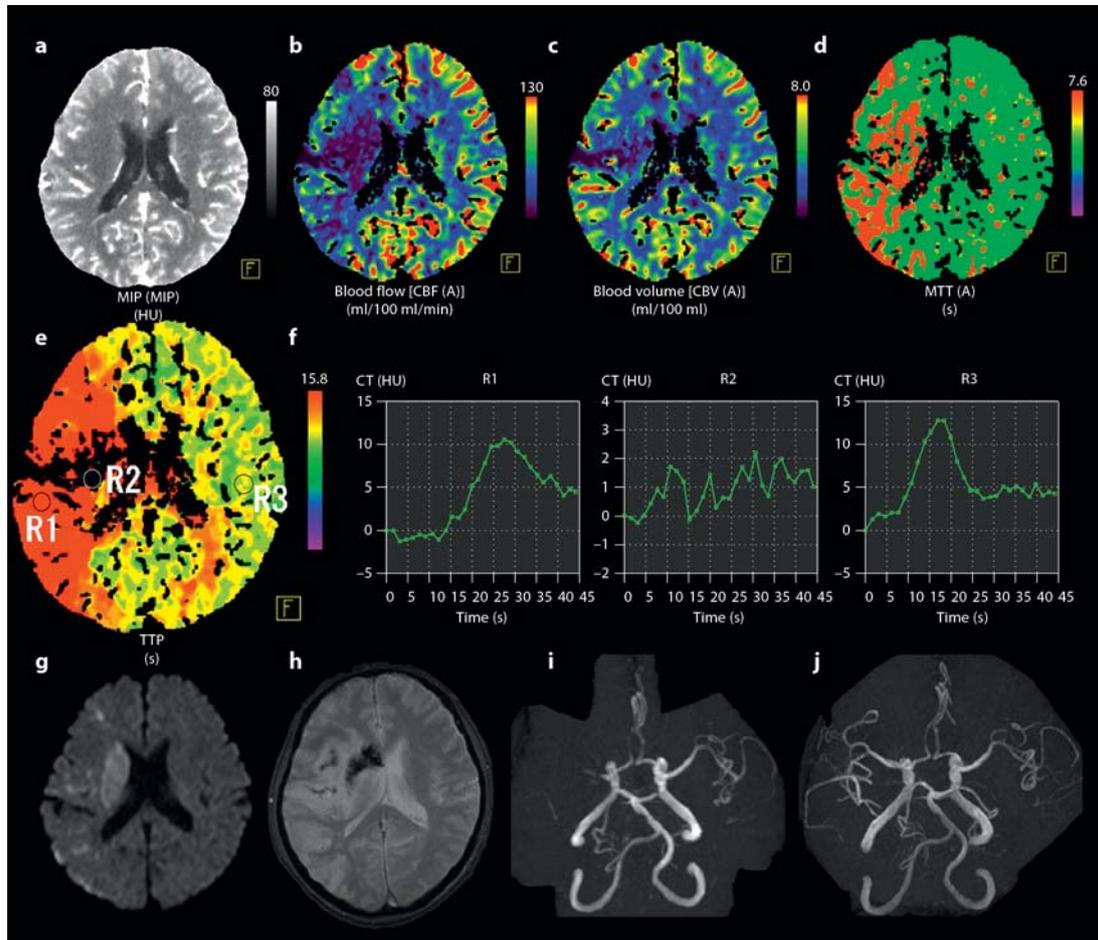
Fig. 1. A 70-year-old man with right middle cerebral artery (M1) occlusion who achieved spontaneous recanalization and developed PH. **a** Maximum intensity projection (MIP) image showing no apparent enhanced lesion. **b** CBF map showing hypoperfusion. **c** CBV map showing low blood volume, and **d** MTT map showing delayed transit time in a large part of the right middle cerebral artery territory, but the area intended to develop HT was not visible in these images. **e** TTP map demonstrating the 'defect' area surrounded by areas with delayed time interval in the same region. **f** Analysis of TAC showing a normal curve (R3), delayed curve (R1), and undetectable local bolus peak (R2). x-axis: time interval from injection, y-axis: Hounsfield unit (HU). **g** Initial diffusion-weighted image showing vague high intensity indicating acute cerebral infarction. **h** T2*-weighted imaging on day 10 demonstrating secondary HT in the same area as the initial 'TTP map-defect'. Initial MRA showing the right M1 occlusion (**i**) and follow-up MRA on day 10 showing complete recanalization (modified Mori scale grade 3) (**j**).

In this situation, we could not transfer areas with any delayed time interval onto the TTP map. Therefore, we defined these defect areas on the initial TTP map as 'TTP map-defect', which was clearly distinguishable from the surrounding area of moderate hypoperfusion (fig. 1e).

Image Analysis

The presence of HT was assessed on initial and follow-up T2*-weighted images using the standard MRI criteria for hemorrhage, and HT was also assessed on any unscheduled CT scans obtained at the occasion of any clinical deterioration. T2*-weighted imaging showed hemorrhagic infection (HI) as low-intensity signal within the ischemic area, within four cat-

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egories according to the European Cooperative Acute Stroke Study (ECASS) classification [2]: (1) HI1 (hemorrhagic infarction 1) defined as small petechiae along the margins of the infarct; (2) HI2 (hemorrhagic infarction 2) defined as confluent petechiae within the infarcted area but no space-occupying effect; (3) PH1 (parenchymal hemorrhage 1) defined as blood clots within 30% of the infarcted area with some slight space-occupying effect, and (4) PH2 (parenchymal hemorrhage 2) defined as blood clots in over 30% of the infarcted area with a substantial space-occupying effect (fig. 1h).

Symptomatic intracerebral hemorrhage (sICH) was defined as clinical deterioration with an increase of more than four points in the National Institutes of Health Stroke Scale (NIHSS) score, if the hemorrhage was likely to be the cause of the clinical deterioration [1]. Recanalization of occluded major trunks was also assessed on follow-up MRA according to the modified Mori grade [29]: grade 0, no reperfusion; grade 1, movement of the thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in less than 50% of the branches in the occluded arterial territory, and grade 3, nearly complete recanalization with reperfusion in more than 50% of the branches in the occluded arterial territory (fig. 1). In this study, grades 2 and 3 were defined as significant recanalization. All images were assessed by two reviewers, one expert neurosurgeon (M. Shinoyama) and one expert neuroradiologist (H. Ono) unaware of the clinical information except for the affected side.

Review of Clinical Data

Patients underwent clinical assessment with the NIHSS on admission and discharge, and with the modified Rankin Scale on discharge. We reviewed the patients' clinical data: baseline neurological deficits as assessed by the NIHSS score; history of hypertension, cardioembolic stroke risk factors such as atrial fibrillation, and diabetes; and current smoking or alcohol intake. In addition, laboratory data such as platelet count, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), and serum glucose level were also assessed.

Statistical Analysis

Categorical data were analyzed with the two-tailed χ^2 test. Continuous variables were analyzed with the unpaired Student t test or, in case of abnormally distributed data, with the Mann-Whitney U test. Statistical analysis was performed with commercially available software (SPSS v17). A p value of less than 0.05 was considered to indicate a significant difference.

Results

Patient Characteristics

A total of 68 patients, 41 males and 27 females aged 72.9 ± 11.7 years (mean ± SD) fulfilling the study criteria, were admitted to the stroke service of the Nakamura Memorial Hospital between January and September 2010. The overall median NIHSS score was 7 (range 0–30, mean 8.8).

Ten of the 68 patients (14.7%) were treated with IV rt-PA (0.6 mg/kg) within 3 h of stroke onset according to the Japanese guidelines for rt-PA use. Twenty-eight patients (41%) had been transferred within 3 h from stroke onset, but 18 were excluded from receiving IV rt-PA according to the Japanese guidelines.

The clinical characteristics of the patients with or without HT are shown in table 1. Secondary HT developed within 2 weeks of follow-up MRI (HT group) in 34 of the 68 patients (50%), including 18 HI patients (52.9%: HI1 n = 6, 17.6%; HI2 n = 12, 35.3%) and 16 PH pa-

Table 1. Patient characteristics

	Non-HT group (n = 34)	HT group (n = 34)	p
Mean age ± SD, years	72.3 ± 12.6	73.7 ± 11.2	0.6611
Age >65 years, n (%)	25 (73.5)	27 (79.4)	0.5675
Male gender, n (%)	24 (70.6)	17 (50)	0.0828
Type of infarction, n (%)			
Cardioembolic	14 (41.2)	29 (85.3)	0.0002
Atherothrombotic	18 (52.9)	5 (14.7)	0.0003
Undetermined	2 (5.9)	0 (0)	0.1512
Site of thrombus, n (%)			
ICA	9 (26.5)	6 (17.6)	0.3803
ACA A1	3 (8.8)	1 (2.9)	0.3026
MCA M1	9 (26.5)	16 (47.1)	0.0783
MCA M2	8 (23.5)	8 (23.5)	1
PCA P2	2 (5.9)	3 (8.8)	0.6422
VA-BA system	3 (8.8)	0 (0)	0.0765
Medical history, n (%)			
Diabetes mellitus	8 (23.5)	11 (32.4)	0.4175
Hypertension	23 (67.7)	21 (61.8)	0.6118
Hypercholesterolemia	8 (23.5)	10 (29.4)	0.5825
Atrial fibrillation	7 (20.6)	22 (64.7)	0.0001
Stroke	6 (17.7)	5 (14.7)	0.7419
Current smoking, n (%)	9 (26.5)	8 (23.5)	0.7794
Current alcohol use, n (%)	5 (14.7)	6 (17.7)	0.7419
Pre-stroke drug, n (%)			
Antiplatelet	5 (14.7)	7 (20.6)	0.3549
Anticoagulant	3 (8.8)	7 (20.6)	0.0996
Radiological findings, n (%)			
TTP map-defect	6 (17.6)	34 (100)	0.0001
Recanalization	8 (23.6)	30 (88.2)	0.0001
Medication			
IV rt-PA	5 (14.7)	5 (14.7)	1
On admission			
Mean NIHSS score ± SD	5.1 ± 5.6	12.5 ± 7.2	0.0001
NIHSS score >6, n (%)	11 (32.4)	29 (85.3)	0.0001
On discharge			
Mean NIHSS score ± SD	2.4 ± 3.9	8.0 ± 7.0	0.0001
NIHSS score >6, n (%)	6 (17.6)	18 (52.9)	0.0023
mRS score 0–1, n (%)	20 (58.8)	7 (20.6)	0.0013
mRS score 0–2, n (%)	23 (67.7)	11 (32.5)	0.0036

ICA = Internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; VA-BA = vertebrobasilar; mRS = modified Rankin Scale.

tients (47.1%: PH1 n = 7, 20.6%; PH2 n = 9, 26.5%), but not in the other 34 patients (non-HT group). There was no significant difference in the incidence of HT between patients treated and not treated with IV rt-PA. Four of the 34 HT patients (11.8%) had sICH, all of ECASS category PH2. One of these 4 patients with sICH underwent IV rt-PA. Fifteen of the 34 patients (44.1%) with HT revealed a hemorrhagic lesion on day 2 on the first follow-up MRI, and the other 19 patients on the second follow-up MRI.

Significantly more patients had a cardioembolic etiology in the HT group, whereas significantly fewer patients had an atherothrombotic etiology. Analysis of the patients' medical history showed that only atrial fibrillation was significantly more frequent in the

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Table 2. Patient characteristics

	Non-PH2 group (n = 59)	PH2 group (n = 9)	p
Mean age ± SD, years	72.9 ± 12.0	73.6 ± 9.2	0.8511
Age >65 years, n (%)	45 (76.3)	7 (77.8)	0.9209
Male gender, n (%)	36 (61.0)	5 (55.6)	0.7551
Type of infarction, n (%)			
Cardioembolic	34 (57.6)	9 (100)	0.0141
Atherothrombotic	23 (39.0)	0 (0)	0.0213
Undetermined	2 (3.4)	0 (0)	0.5750
Site of thrombus, n (%)			
ICA	14 (23.7)	1 (11.1)	0.3951
ACA A1	4 (6.8)	0 (0)	0.4207
MCA M1	21 (35.6)	4 (44.4)	0.6080
MCA M2	14 (23.7)	2 (22.2)	0.4250
PCA P2	3 (5.1)	2 (22.2)	0.0665
VA-BA system	3 (5.1)	0 (0)	0.4890
Medical history, n (%)			
Diabetes mellitus	14 (23.7)	1 (11.1)	0.3951
Hypertension	41 (69.5)	4 (44.4)	0.1390
Hypercholesterolemia	15 (25.4)	3 (33.3)	0.6164
Atrial fibrillation	26 (44.1)	4 (44.4)	0.9831
Stroke	11 (18.6)	0 (0)	0.1571
Current smoking, n (%)	15 (25.4)	2 (22.2)	0.8363
Current alcohol use, n (%)	9 (15.3)	2 (22.2)	0.5970
Pre-stroke drug, n (%)			
Antiplatelet	12 (20.3)	3 (33.3)	0.3812
Anticoagulant	10 (16.9)	1 (11.1)	0.6577
Radiological findings, n (%)			
TTP map-defect	31 (52.5)	9 (100)	0.0070
Recanalization	29 (49.2)	9 (100)	0.0042
Medication			
IV rt-PA	7 (11.9)	3 (33.3)	0.0903
On admission			
Mean NIHSS score ± SD	8.6 ± 7.5	10.2 ± 6.9	0.5302
NIHSS score >6, n (%)	33 (55.9)	7 (77.8)	0.2148
On discharge			
Mean NIHSS score ± SD	4.9 ± 6.3	6.2 ± 6.0	0.5489
NIHSS score >6, n (%)	19 (32.2)	5 (55.6)	0.1721
mRS score 0–1, n (%)	24 (40.7)	2 (22.2)	0.2886
mRS score 0–2, n (%)	30 (50.8)	4 (44.4)	0.7205

ICA = Internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; VA-BA = vertebrobasilar; mRS = modified Rankin Scale.

HT group. Neurological findings and clinical outcomes showed significant differences between the HT and non-HT groups. The mean NIHSS score of the HT patients was significantly higher than that of the non-HT patients. Severe deficits (NIHSS score >6) on admission were also significantly associated with HT. Both the NIHSS and the modified Rankin Scale scores were significantly worse in the HT group at discharge. Administration of pre-stroke antiplatelet and anticoagulant agents tended to be more common in the HT group, but not significantly. Atrial fibrillation was significantly more common in the HT group, but only 7 patients (20.6%) had undergone anticoagulant administration before stroke onset.

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Table 3. Recanalization of patients with 'TTP map-defect'

| | Recanalization | | p |
	yes	no	
Non-HT group vs. HT group			<0.0001
Non-HT	0 (0)	6 (15.0)	
HT	30 (75.0)	4 (10.0)	
Non-PH2 group vs. PH2 group			0.0491
Non-PH2	21 (52.5)	10 (25.0)	
PH2	9 (22.5)	0 (0)	

The mean PT-INR on admission showed no differences between the groups (non-HT group vs. HT group: 1.15 ± 0.24 vs. 1.16 ± 0.24, mean $\pm$ SD, p = 0.939). In addition, laboratory examination on admission showed no significant differences in serum glucose level (non-HT group vs. HT group: 134.3 ± 52.5 vs. 125.2 ± 38.2 mg/dl, p = 0.416) and other coagulation parameters such as APTT (non-HT group vs. HT group: 29.9 ± 3.7 vs. 31.1 ± 5.8 s, p = 0.327) and platelet count (non-HT group vs. HT group: 16.8 ± 4.6 vs. $18.5 \pm 5.2 \times 10^4/\mu l$, p = 0.146). No differences were found in age, sex, location of occluded site, history of diabetes, hypertension, hypercholesterolemia, and stroke, as well as current smoking or alcohol intake.

The clinical characteristics of the patients with or without PH2 are shown in table 2. Significantly more patients had a cardioembolic etiology in the PH2 group, whereas significantly fewer patients had an atherothrombotic etiology. There were no significant differences in the underlying medical histories and patients' clinical severity in contrast to the results of the HT versus non-HT group analysis. Mean PT-INR of the non-PH2 group was significantly higher than that of the PH2 group (1.16 ± 0.25 vs. 1.08 ± 0.06, p = 0.029). Moreover, serum glucose level of the non-PH2 group was lower than that of the PH2 group (127.1 ± 47.8 vs. 147.0 ± 17.5 mg/dl, p = 0.032). In contrast, coagulation parameters such as APTT (non-PH2 group vs. PH2 group: 30.8 ± 5.0 vs. 28.2 ± 2.8 s, p = 0.062) and platelet count (non-PH2 group vs. PH2 group: 18.0 ± 4.7 vs. $15.4 \pm 5.6 \times 10^4/\mu l$, p = 0.238) showed no significant differences.

Imaging Findings

The radiological findings are also shown in tables 1 and 2. Forty patients revealed 'TTP map-defect' on the initial CTP map, and 34 of these 40 patients (85%) developed HT (table 1). Of these 40 patients, 9 patients (22.5%) showed PH2 (table 2). In the HT group, 30 of 34 patients (88.2%) experienced delayed recanalization of the occluded vessels on follow-up MRA until 1 week after onset in contrast to only 8 of 34 patients (23.6%) in the non-HT group (table 1). In the PH2 group, all patients showed delayed recanalization.

Table 3 shows the association between recanalization and following hemorrhagic outcome (HT or PH2) of 40 patients with initial 'TTP map-defect'. In these positive patients, recanalization caused significant HT or PH2. During the analysis for HT, 30 patients (75%) with recanalization developed HT. In the other 10 patients without recanalization, 6 patients (15%) did not develop HT and 4 patients (10%) showed HI, but no PH (HI1 n = 1, HI2 n = 3). Patients with both 'TTP map-defect' and delayed recanalization subsequently developed HT without exception, and the areas of HT were consistent with the 'TTP map-defect' on the initial CTP map (fig. 1). Nine patients (22.5%) with recanalization developed PH2 (table 3). There were no patients with 'TTP map-defect' and without delayed recana-

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lization, resulting in PH2. All 28 patients without 'TTP map-defect' did not develop HT, including 8 patients (28.6%) with delayed recanalization (data not shown).

Neurological Findings and Prognosis

There were significant differences in patients' neurological severity on admission or discharge between the positive and negative 'TTP map-defect' groups. The initial mean NIHSS score of the patients with 'TTP map-defect' was significantly higher than that of the patients without defect (positive vs. negative 'TTP map-defect' group: 12.2 ± 7.2 vs. 4.0 ± 4.6, $p < 0.001$). Severe deficits (NIHSS score >6) on admission were also significantly associated with 'TTP map-defect' (positive vs. negative group: 32 vs. 6, $p < 0.001$). The functional outcomes of the 'TTP map-defect'-positive group were severer than those of the negative group (positive vs. negative group: modified Rankin Scale 0–1, 8 vs. 18, $p < 0.001$; modified Rankin Scale 0–2, 12 vs. 22, $p < 0.001$).

Discussion

This is the first study demonstrating that initial TTP mapping on admission could identify patients at risk of HT following acute ischemic stroke. All patients with HT had shown 'TTP map-defect' on the initial CTP map, whereas patients without 'TTP map-defect' did not develop any HT irrespective of vessel recanalization. These findings suggest that stroke without 'TTP map-defect' might involve the non-stagnant vasculature, which could be due to the rich collateral flow, with certain tolerance against reperfusion even if delayed. The present findings indicate the diagnostic efficacy of TTP mapping for the estimation of the HT risk after acute ischemic stroke.

Several radiological parameters have been evaluated to predict HT [7], based on various aspects such as CBF, tissue perfusion, blood-brain barrier, brain edema, and others. Single-photon emission CT indicating low CBF has been reported to predict the risk of HT [30–32]. A significant relationship was first identified between qualitative CBF analyzed by ^{99m}Tc-labeled hexamethylpropyleneamine oxime single-photon emission CT and subsequent HT [30]. Residual CBF of less than 35% in the ipsilateral cerebellum also showed high risk of HT using the same modality in a series of patients with intra-arterial thrombolysis [31, 32]. Furthermore, in studies using perfusion imaging, the volume of a low CBV lesion may be closely correlated with HT risk [14]. Prolonged relative MTT was also reported as independent predictor of secondary HT [15]. Our results were encouraged by these previous studies showing correlations between local hypoperfusion and high HT risk.

The present study showed that 'TTP map-defect' could clearly classify patients into a high-HT risk group (85% HT risk, 22.5% PH2 risk) and a low-HT risk group (0% HT risk). The sensitivity of 'TTP map-defect' for the occurrence of HT or PH2 was 100%, and the specificity was 82.4 and 47.5%, respectively. These findings are consistent with previous animal studies, which showed that extreme hypoperfusion resulted in damage to the blood-brain barrier integrity, especially endothelial tight junction disruption, and the development of HT [33, 34].

Findings of TTP mapping may alter the indication of thrombolytic therapy. The therapeutic time window of IV rt-PA is supposed to be 3–4.5 h from the onset [35], but it might depend on both the recanalization rate of reperfusion treatment and the local ischemic threshold. For instance, a much wider time window has been proposed in patients with arterial thrombolysis [36] or posterior circular lesion [37]. In this context, we emphasize that TTP mapping could differentiate low-HT risk patients from high-HT risk patients within the therapeutic time window frame to achieve safe reperfusion treatment. Moreover, TTP map-

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ping may identify patients with low HT risk, even if they have a delayed arrival time beyond 4.5 h.

On the other hand, findings of TTP mapping may also alter post-thrombolytic management. Previous reports have shown that elevation or variability of blood pressure correlated to HT development in patients with or without IV rt-PA [38–40]. We propose that the blood pressure level of patients with 'TTP map-defect' should be controlled strictly and be more stable and lower than that of patients without 'TTP map-defect'. Although knowledge on HT risk could be useful, further prospective and large-size examinations are needed for confirming the efficacy of TTP mapping in the management of pre- or post-thrombolytic therapy.

Perfusion imaging, such as CTP and MRP, is superior to other modalities in terms of fewer limitations of time, place, drug supply, or duration of examination. In particular, CTP by multi-detector row CT can provide efficient spatial resolution of whole-brain imaging. For instance, even HT risk caused by small lesions associated with distal branch occlusion, such as downstream of M2, could be clearly detected by CTP, but not by conventional CT or MRI [7]. In the future, the presence or absence of a 'TTP map-defect' should be confirmed using MRP to avoid the exposure to radiation required by CTP. Additionally, MRP can be obtained with various parameters including CBV, permeability, and apparent diffusion coefficient value at the same time and in the same plane, thus allowing a multi-imaging assessment for reperfusion treatment.

The present study has several limitations. One major limitation is the small sample size and retrospective nature, with potential bias. Previously identified clinical predictors were not correlated with HT in this series, which is probably attributable to the small sample size. Moreover, we could not assess the association between symptomatic and asymptomatic ICH because of the small number of sICH cases (n = 4). Further, the small sample size also restricted analysis of the variables including 'TTP-map defect' using multivariate analysis. While our results are suggestive, a prospective trial with more patients is required to reinforce this preliminary finding of 'TTP map-defect' as a predictor of HT. The second limitation is the assessment procedure. We did not evaluate patient variables such as imaging, neurology, and outcome in a blind procedure. The third limitation is that our procedure could not be applied to patients with renal failure because of the toxicity of the contrast medium.

In conclusion, our study shows that the initial 'TTP-map defect' of CTP is able to predict HT following acute ischemic stroke. TTP mapping can differentiate low-HT risk patients within the therapeutic time window frame or with unknown onset from patients with high HT risk and allows safe administration of reperfusion treatment.

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