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Therapy**

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Thrombus Permeability on Dynamic CTA Predicts Good Outcome after Reperfusion Therapy

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ABSTRACT

BACKGROUND AND PURPOSE: Thrombus permeability assessed on conventional CTA is associated with neurologic outcome in patients with acute ischemic stroke. We aimed to investigate whether dynamic CTA can improve the accuracy of thrombus permeability assessment and its predictive value for outcome.

MATERIALS AND METHODS: We reviewed consecutive patients with acute ischemic stroke who had occlusion of the M1 segment of the middle artery cerebral artery and underwent pretreatment perfusion CT. Thrombus permeability, determined by thrombus attenuation increase (TAI), was assessed on 26-phase dynamic CTA derived from perfusion CT. TAI_{max} was defined as the maximum TAI among phases; TAI_{peak} as TAI of peak arterial phase; TAI_{con} as TAI on phase 13. Good outcome was defined as a 3-month mRS score of ≤ 2 .

RESULTS: One hundred four patients were enrolled in the final analysis. The median TAI_{max} , TAI_{peak} , and TAI_{con} were 30.1 HU (interquartile range, 13.0–50.2 HU), 9.5 HU (interquartile range, –1.6–28.7 HU), and 6.6 HU (interquartile range, –5.1–24.4 HU), respectively. Multivariable regression analyses showed that TAI_{max} (OR = 1.027; 95% CI, 1.007–1.048; $P = .008$), TAI_{peak} (OR = 1.029; 95% CI, 1.005–1.054; $P = .020$), and TAI_{con} (OR = 1.026; 95% CI, 1.002–1.051; $P = .037$) were independently associated with good outcome. The areas under the ROC curve of TAI_{max} , TAI_{peak} , and TAI_{con} in predicting good outcome were 0.734, 0.701, and 0.658, respectively.

CONCLUSIONS: Thrombus permeability assessed on dynamic CTA could be a better predictor of outcome after reperfusion therapy than that assessed on conventional single-phase CTA.

ABBREVIATIONS: AIS = acute ischemic stroke; AUC = area under the curve; IQR = interquartile range; PH = parenchymal hemorrhage; ONT = onset to intravenous thrombolysis; ROC = receiver operating characteristic; TAI = thrombus attenuation increase; TAI_{con} = TAI on phase 13; TAI_{max} = the maximum TAI among phases; TAI_{peak} = TAI of peak arterial phase

Cerebral large-artery occlusion accounts for about one-third of acute ischemic strokes (AISs), which may cause severe disability and high mortality rates.^{1–6} Effort has been made on neuroimaging to predict the outcome of acute ischemic stroke be-

cause improved neurologic outcome is the goal for treatment. Thrombus characteristics on admission imaging, such as clot length, density, and location, may have the potential to predict the outcome of patients with AIS under different treatments.⁷

In patients with AIS, the thrombus is commonly regarded as a cork where the artery is completely occluded.⁸ The permeability of thrombi has been well-characterized in preclinical studies.^{9–11} It has been suggested that thrombus permeability might be related to the physical porosity of thrombus and might reflect the ability of soluble molecules to move within the gaps among adjacent platelets, fibrin filaments, and red blood cells.^{8,9,12,13} Preclinical studies have demonstrated that high permeability of the thrombus within the occluded artery allowed residual blood to flow through the thrombus,^{9,10} which may have a positive effect on neurologic outcome after acute ischemia due to the compensating oxygenation of brain tissue distal to the occluded artery. Recently, thrombus attenuation increase (TAI) was used to assess the thrombus permeability on conventional single-phase CT angiography and noncontrast CT. A pervious thrombus with a high TAI

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was found to be associated with better neurologic outcome after reperfusion therapy in patients with AIS.^{8,12}

The enhancement of arteries on conventional single-phase CTA is affected by the acquisition time because the contrast filling of the occlusion site is delayed compared with that in the normal condition.¹⁴ Therefore, the permeability of the thrombi may be underestimated if single-phase CTA is acquired before contrast completely penetrates the thrombus. Compared with single-phase CTA, dynamically acquired CTA provides a broad temporal coverage that spans from unenhanced through to the arterial and, subsequently, venous phases. In addition, previous studies have demonstrated that dynamic CTA can better characterize the intracranial thrombus burden than single-phase CTA.¹⁴

We thus hypothesized that dynamic CTA could overcome the timing limitation and improve the assessment accuracy of thrombus permeability. We then assessed thrombus permeability on 26-phase dynamic CTA derived from CT perfusion and aimed to investigate its predictive value for neurologic outcome in patients with AIS after reperfusion therapy.

MATERIALS AND METHODS

Patient Inclusion

We retrospectively reviewed our prospectively collected data base for consecutive patients with AIS who received intravenous thrombolysis with or without endovascular thrombectomy from May 2009 to February 2017. Then, we enrolled patients who fulfilled the following criteria: 1) They had a diagnosis of AIS confirmed by diffusion-weighted imaging or CT at 24 hours after symptom onset, 2) underwent CTP within 8 hours after stroke onset, 3) had occlusion of the M1 segment of the middle cerebral artery without involvement of the internal carotid artery, 4) underwent CTA or time-of-flight MR angiography at 24 hours after treatment, and 5) underwent follow-up NCCT or susceptibility-weighted imaging at 24 hours after treatment. We excluded patients who had poor image quality due to motion artifacts or incomplete consecutive acquisitions.

Ethics Statement

Ethical approval was obtained from the human ethics committee of our center. The clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Imaging Parameters

CTP was performed on a 64-slice CT scanner (Somatom Definition Flash; Siemens, Erlangen, Germany), including an NCCT scan (120 kV, 320 mA, contiguous 5-mm axial slices, 7-second acquisition time) and volume CTP (100 mm in the z-axis, 4-second delay after the start of contrast material bolus injection, 74.5-second total imaging duration, 80 kV, 120 mA, 1.5-mm slice thickness, 32×1.2 mm collimation). Volume CTP consisted of 26 consecutive spiral acquisitions of the brain. All 26 scans were divided into 4 parts: 1) two scans with 3-second cycle time, 2) fifteen scans with 1.5-second cycle time, 3) four scans with 3-second cycle time, and 4) five scans with 6-second cycle time. Axial slice coverage was 150 mm. A 60-mL bolus of contrast medium (iopamidol, Imeron; Bracco Sine, Shanghai, China) with a single

injection was used at a flow rate of 6 mL/s, followed by a 20-mL saline chaser at 6 mL/s.

Imaging Analysis

The Arterial Occlusive Lesion Scale was used to assess recanalization on 24-hour MRA or CTA (grade 0: complete occlusion of the target artery; grade 1: incomplete occlusion or partial local recanalization at the target artery with no distal flow; grade 2: incomplete occlusion or partial local recanalization at the target artery with any distal flow; grade 3: complete recanalization and restoration of the target artery with any distal flow).¹⁵ Recanalization and no recanalization were defined as arterial occlusive lesion grades 2–3 and 0–1, respectively. Hemorrhagic transformation was assessed on 24-hour SWI or NCCT according to the second European-Australasian Acute Stroke Study (ECASS II), including hemorrhagic infarction and parenchymal hemorrhage (PH).¹⁶ Previously validated thresholds were applied to measure the baseline hypoperfusion volume (time-to-maximum > 6 seconds)¹⁷ and infarct core volume (relative cerebral blood flow of <30%) on CTP.¹⁸

Thrombus Permeability Assessment

Thrombus permeability assessments were conducted on commercial software (MISTar; Apollo Medical Imaging Technology, Melbourne, Australia). The 26-phase dynamic CTA with 4.5-mm-thick maximum intensity projection was reconstructed from CTP source images. The proximal artery of the contralateral hemisphere was selected to generate the arterial input function curve. The measurements of TAI were performed as described previously.^{8,12,19} Three ROIs with a radius of 1 mm were placed on the thrombus by 2 experienced neuroradiologists blinded to the patients' information, with rater discrepancies settled by consensus discussion; the mean attenuation on each phase was calculated. The ROIs might partially overlap each other in case of a small thrombus. The mean attenuation of the thrombus on phase 1 was set as the reference value. The TAI of phase 2 to phase 26 was defined as the increase of the mean attenuation of the thrombus from phase 1 to each phase, respectively. Three parameters of TAI, including TAI_{max} , TAI_{peak} , and TAI_{con} , were used for the final analyses (Fig 1). TAI_{max} was defined as the maximal TAI among 25 phases (phases 2–26). TAI_{peak} was defined as the TAI of the arterial peak phase according to the arterial input function curve. The mean time between contrast injection and peak concentration on the normal side of the middle cerebral artery was 25 seconds (phase 13) in current study; thus, TAI_{con} was simulated as TAI on phase 13 of dynamic CTA.

Clinical Data

We reviewed demographic, clinical, and radiologic data, including age; sex; prior antiplatelet use; risk factors such as smoking, hypertension, diabetes mellitus, hyperlipidemia, smoking, and atrial fibrillation; time interval from stroke onset to intravenous thrombolysis (ONT); National Institutes of Health Stroke Scale score on admission; baseline hypoperfusion volume and infarct core volume on admission; hemorrhagic transformation and recanalization after intravenous thrombolysis; and modified Rankin Scale score after 3 months. Patients were dichotomized

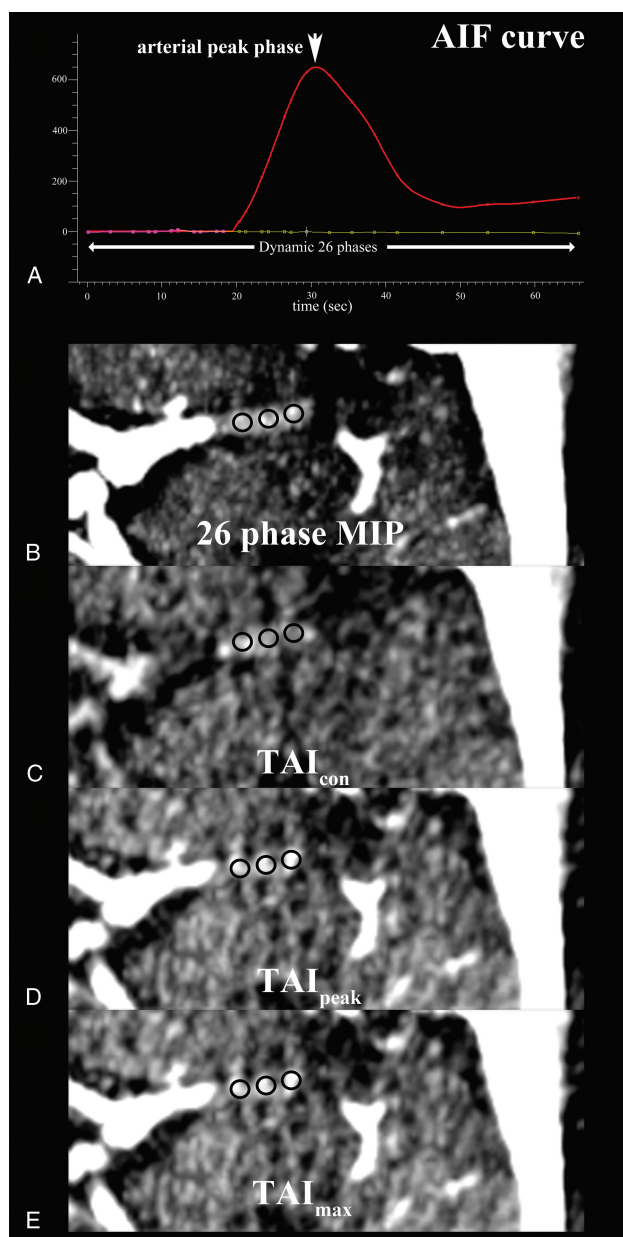


FIG 1. Illustration of thrombus attenuation increase assessment with 3 ROIs (black circles) measuring the average thrombus attenuations on a left M1 segment of the middle cerebral artery on motion-corrected dynamic CTA. The arterial input function (AIF) curve for all 26 phases was generated (A) and the thrombus permeability was assessed on the CTA images with maximum intensity projection (MIP) in all 26 phases (B), at the mean time delay following intravenous contrast injection in the current study (phase 13) (C), at the arterial peak phase (phase 18) (D), and at the phase with the maximum value (phase 22) (E) of the mean attenuation increase.

into good (mRS score of ≤ 2) and poor outcome (mRS score of > 2) at 90 days.

Statistical Analysis

Mean with SD, medians with interquartile range (IQR), and percentages were used to describe the distribution of continuous and categorical variables. The Fisher exact test was used to compare categorical variables among groups, whereas the independent-samples 2-tailed *t* test or the Mann-Whitney *U* test was used for the

continuous variables, as appropriate. The Spearman rank correlation test was used to test the association of TAI with clinical and imaging variables. The strength of these associations was compared using the area under the receiver operating characteristic (ROC) curve. The ROC-derived optimal cutoff was determined at the maximal Youden Index. Variables with a *P* value $< .1$ in univariate analyses were enrolled in the multivariable regression model. A *P* value $< .05$ was considered statistically significant. All statistical analyses were performed with SPSS, Version 22.0 (IBM, Armonk, New York).

RESULTS

Overall Characteristics

One hundred four patients with AIS with MCA-M1 were enrolled in the final analysis. The mean age was 68 ± 14 years, the mean NIHSS score was 14 ± 6 on admission, and 61 (58.7%) patients were male. The median ONT was 215 (IQR, 140–295) minutes. The median TAI_{max}, TAI_{peak}, and TAI_{con} were 30.1 HU (IQR, 13.0–50.2 HU), 9.5 HU (IQR, -1.6 –28.7 HU), and 6.6 HU (IQR, -5.1 –24.4 HU), respectively.

Association of TAI with Radiologic and Neurologic Outcome

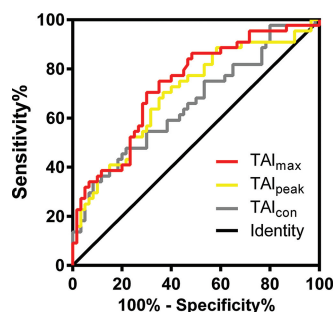
As shown in Table 1, 44 (42.3%) patients achieved good outcome. Patients with good outcome had higher TAI_{max}, TAI_{peak}, and TAI_{con} than those with poor outcome ($P < .001$, $P < .001$, and $P = .006$, respectively). Patients with good outcome were younger ($P = .005$) and had a lower baseline NIHSS score ($P < .001$), lower baseline infarct core volume ($P = .001$), lower baseline hypoperfusion volume ($P = .004$), and higher recanalization rates (84% versus 64%, $P = .023$) compared with those with poor outcome.

After we adjusted for age, baseline NIHSS score, atrial fibrillation, ONT, baseline infarct core volume, TAI_{max} (OR = 1.027; 95% CI, 1.007–1.048; $P = .008$), TAI_{peak} (OR = 1.029; 95% CI, 1.005–1.054; $P = .020$), and TAI_{con} (OR = 1.026; 95% CI, 1.002–1.051; $P = .037$) were independently associated with good outcome, respectively. Patients with PH had lower TAI_{max} and TAI_{peak} than those without PH, while TAI_{con} did not show a significant difference between patients with and without PH ($P = .308$).

The ROC curves of TAI_{max}, TAI_{peak}, and TAI_{con} in predicting good outcome are shown in Fig 2, and the areas under the curve (AUCs) were 0.734, 0.701, and 0.658, respectively. The AUCs of each single-phase CTA derived from CTP are shown in On-line Table. The optimal cutoffs were 30.9, 9.0, and 14.6 HU for TAI_{max}, TAI_{peak}, and TAI_{con}, respectively. Patients were then dichotomized into a pervious thrombus group and an impervious thrombus group according to the optimal cutoff values of TAI_{max}, TAI_{peak}, and TAI_{con}, respectively. After we adjusted for age, baseline NIHSS score, atrial fibrillation, ONT, and baseline infarct core volume, patients with a pervious thrombus had a higher rate of good outcome than those with an impervious thrombus when dichotomized by TAI_{max} (OR = 3.957; 95% CI, 1.463–10.705; $P = .007$) and TAI_{peak} (OR = 2.887; 95% CI, 1.075–7.754; $P = .035$) (Table 2). However, when dichotomized by TAI_{con}, patients with a pervious thrombus were not independently associated with

Table 1: Comparison of baseline characteristics according to clinical outcome

	Poor Outcome (mRS > 2) (n = 60)	Good Outcome (mRS ≤ 2) (n = 44)	P Value
Age (yr)	74 (65–81)	66 (58–76)	.005
Male (No.) (%)	33 (55.0%)	28 (63.6%)	.424
Baseline NIHSS (mean)	16 ± 5	11 ± 6	<.001
Onset-to-needle time (mean) (min)	230 (168–297)	207 (119–259)	.059
Endovascular thrombectomy (No.) (%)	22 (36.7%)	16 (36.4%)	1.000
Prior antiplatelet usage (No.) (%)	12 (20.0%)	9 (20.5%)	1.000
Risk factors			
Smoking (No.) (%)	18 (30.0%)	13 (29.5%)	1.000
Hypertension (No.) (%)	35 (58.3%)	22 (50.0%)	.431
Diabetes mellitus (No.) (%)	16 (26.7%)	6 (13.6%)	.146
Hyperlipidemia (No.) (%)	22 (36.7%)	21 (47.7%)	.315
History of stroke/TIA (No.) (%)	11 (18.3%)	5 (11.4%)	.415
Atrial fibrillation (No.) (%)	38 (63.3%)	20 (45.5%)	.076
Radiologic data			
Baseline infarct core volume (mean) (mL)	69.27 ± 49.51	40.72 ± 30.91	.001
Baseline hypoperfusion volume (mean) (mL)	134.28 ± 61.07	98.22 ± 60.43	.004
TAI _{max} (median) (IQR) (HU)	18.0 (10.0–38.7)	39.9 (26.1–73.3)	<.001
TAI _{peak} (median) (IQR) (HU)	4.6 (–4.2–17.5)	18.7 (5.9–43.0)	<.001
TAI _{con} (median) (IQR) (HU)	2.2 (–5.5–12.4)	10.4 (–2.0–36.7)	.006
Thrombus perviousness by dichotomized TAI _{max} (No.) (%)	18 (30.0%)	31 (70.5%)	<.001
Thrombus perviousness by dichotomized TAI _{peak} (No.) (%)	22 (36.7%)	31 (70.5%)	.001
Thrombus perviousness by dichotomized TAI _{con} (No.) (%)	13 (21.7%)	21 (47.7%)	.005

**FIG 2.** ROC curve of thrombus attenuation increase for TAI_{max}, TAI_{peak}, and TAI_{con}, respectively.

good outcome (OR = 2.323; 95% CI, 0.815–6.621; $P = .115$) (Table 2).

DISCUSSION

In the present study, we found that high thrombus permeability on dynamic CTA is an independent predictor of good outcome in patients with AIS. Most interesting, TAI_{max} and TAI_{peak} derived from CTP data are better imaging markers than TAI_{con} for predicting neurologic outcome.

Our finding that the permeable thrombus was strongly associated with good outcome is consistent with previous studies using conventional single-phase CTA.^{8,12} These studies also reported that the association between permeable thrombi and good outcome was independent of recanalization status.⁸ High thrombus permeability promotes anterograde filling of blood, and, therefore, less severely ischemic brain tissue.

Most important, our study revealed that the AUCs of TAI_{max} and TAI_{peak} for predicting good outcome (0.734 and 0.701) were higher than those of TAI_{con} (AUC = 0.658) and previously reported values (AUC = 0.67) using conventional single-phase CTA; these findings indicate that thrombus permeability assessed on dynamic CTA might be a better biomarker for predicting out-

Table 2: Multivariable regression for good outcome

	OR	95% CI	P Value
Model 1			
Age	0.966	0.926–1.008	.114
Baseline NIHSS	0.911	0.823–1.008	.071
Atrial fibrillation	0.872	0.298–2.555	.803
ONT	0.992	0.987–0.997	.004
Baseline infarct core volume	0.986	0.972–1.001	.061
Thrombus perviousness by dichotomized TAI _{max}	3.957	1.463–10.705	.007
Model 2			
Age	0.963	0.924–1.004	.074
Baseline NIHSS	0.912	0.826–1.006	.066
Atrial fibrillation	0.736	0.260–2.082	.564
ONT	0.992	0.987–0.997	.003
Baseline infarct core volume	0.988	0.974–1.002	.093
Thrombus perviousness by dichotomized TAI _{peak}	2.887	1.075–7.754	.035
Model 3			
Age	0.965	0.926–1.004	.080
Baseline NIHSS	0.917	0.827–1.016	.098
Atrial fibrillation	0.751	0.269–2.102	.586
ONT	0.992	0.987–0.997	.003
Baseline infarct core volume	0.986	0.972–1.000	.050
Thrombus perviousness by dichotomized TAI _{con}	2.323	0.815–6.621	.115

come. Usually, single-phase CTA is used to assess thrombus permeability by calculating the attenuation increase before and after contrast penetrating the thrombus. The thrombus permeability on single-phase CTA might be underestimated due to timing limitations, hemodynamic restriction, or even pseudo-occlusion.^{14,20} It was reported that delayed phases after the arterial peak phase on dynamic CTA could provide better thrombus depiction and prognostic information and thus might affect treatment decisions in the acute setting.^{14,21} A previous study using 3-phase CTA found that arterial phase CTA was superior to venous phase CTA (8 seconds after arterial phase CTA) or delayed-phase CTA

(16 seconds after arterial phase CTA) to assess the TAI.²² However, 3-phase CTA did not cover enough time points, and the optimal phase could be located between the arterial phase and venous phase. Thus, we believe dynamic CTA derived from CTP was better for evaluating clot perviousness. Moreover, the characteristics of the arterial input function curve were affected by cardiac function, vascular curvature, and vascular stenosis. Thus, parameters based on individual hemodynamic characteristics derived from CTP data can better represent thrombus permeability than conventional single-phase CTA. Furthermore, the evaluation of dynamic CTA has no additional x-ray exposure and contrast medium usage because it is based on CTP, which can also provide information about infarct core and penumbra.

To the best of our knowledge, we are the first to have found that low thrombus permeability was associated with a high rate of PH after reperfusion therapy. It has been shown that compensating oxygenation to ischemic brain tissue could reduce hemorrhagic transformation after thrombolysis.²³ Therefore, we postulate that permeable thrombi may enhance tissue oxygenation distal to the occlusion due to increased passage of blood, which reduces the rate of PH. Additionally, the negative correlation between TAI and baseline NIHSS score, infarct core volume, and hypoperfusion volume might imply less severity of ischemia in patients with pervious thrombi, which could be related to lower rates of PH.

We did not find a significant association between thrombus permeability and recanalization, inconsistent with previous studies,^{8,12} which may be due to the inclusion of patients who received endovascular thrombectomy because endovascular thrombectomy usually has higher recanalization with mechanical retrieval devices. Another reason may be due to the assessment of recanalization at 24 hours after stroke in our study, while previous studies underwent follow-up imaging at 3 days or even later.^{8,12} Besides, the sample size of the current study was relatively small, and all patients were from a single center. Thus, further investigations in larger and multicenter cohorts are needed.

This study has several limitations. First, this was a retrospective design and might have a potential risk of selection bias, though the data were prospectively collected using the same stroke registry and CTP protocol. Second, although the ROI placement was performed by 2 experts blinded to the patients' information with rater discrepancies settled by consensus discussion, variation still exists within a thrombus. Therefore, the mean attenuation of the 3 ROIs selected may not represent the entire thrombus. Third, the overlapping vessels, calcified clots, and vascular calcification might influence the attenuation measurements, though the ROIs were placed very carefully to avoid them. Fourth, further research about blood flow status on DSA is needed to explain the association between thrombus perviousness and good outcome. Finally, the sample size was modest, and all the samples were from a single center. Confirmation and extension of these findings in larger and multicenter cohorts are needed.

CONCLUSIONS

Our study suggests that thrombus permeability assessed on dynamic CTA could be a better predictor of outcome after reperfu-

sion therapy than that assessed on conventional single-phase CTA.

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