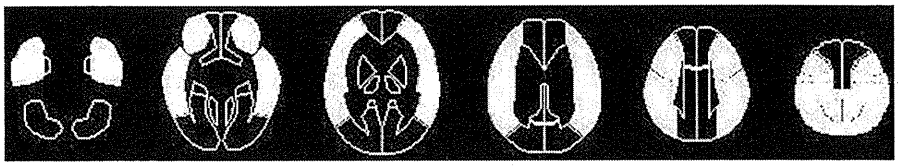

Fig 2. Diagrams showing the ROIs of a 3D stereotaxic ROI template. The white ROIs (precentral, central, parietal, angular, and temporal segments) indicate territories perfused by the bilateral MCAs.

Concordance rates in interobserver and intraobserver agreements of MRA grading in 108 cerebral hemispheres with lesions

First Review by First Observer		Second Review by First Observer			First Review by Second Observer		
MRA Grade	Number of Hemispheres	MRA Grades	Number of Hemispheres	Concordance Rate in Intraobserver Agreement	MRA Grade	Number of Hemispheres	Concordance Rate in Interobserver Agreement
A	59	A	59	1.00	A	59	1.00
		B	0		B	0	
		C	0		C	0	
		D	0		D	0	
B	26	A	0	0.85	A	0	0.85
		B	22		B	22	
		C	4		C	4	
		D	0		D	0	
C	16	A	0	0.94	A	0	0.88
		B	1		B	1	
		C	15		C	14	
		D	0		D	1	
D	7	A	0	1.00	A	0	0.71
		B	0		B	0	
		C	0		C	2	
		D	7		D	5	

Note:—MRA indicates MR angiography.

proportion of concordant assessments was calculated as the number of concordant assessments divided by the total number of assessments. The κ values obtained were interpreted relative to the criteria of Fleiss: values 0.40 or less represent poor agreement, values between 0.40 and 0.75 represent fair to good agreement, and values more than 0.75 represent excellent agreement.[28]

Descriptive data were expressed as the mean ± SD. The first MRA grading assessments by the first observer were used for all of the following analyses. We examined differences of CVR to acetazolamide among the 4 MRA grades using 1-way analysis of variance followed by Scheffé multiple comparisons. Differences were deemed statistically significance if P was less than .05. We evaluated the incidences of reduced CVR to acetazolamide among the 4 MRA grades using the χ^2 test followed by Bonferroni inequality correction. Differences between each MRA grade were deemed statistically significant if P was less than .05/6 = 0.0083. In addition, the grading accuracy of MRA to detect reduced CVR to acetazolamide was assessed with the receiver operating characteristic curve.

Results

The first observer at the first review assessed 108 cerebral hemispheres with lesions among 87 patients as MRA grades of A, (59) B, (26) C (16), and D (7). Interobserver [concordant rate = 0.93, κ = 0.88 (95% CI, 0.76–0.99)] and intraobserver [concordant rate = 0.95, κ = 0.93 (95% CI, 0.80–0.99)] agreements in MRA grading were excellent. Although the concordance rate of cerebral hemispheres with MRA grade A was 1.00 for both the interobserver and intraobserver agreements, the rates for the other MRA grades were less than 0.90, except for the intraobserver agreement in MRA grades C and D (Table). However, none of cerebral hemispheres with MRA grade B, C, or D was subsequently graded as A in any review by either observer. All 66 cerebral hemispheres without lesions among 87 patients were assessed as MRA grades of A in all reviews.

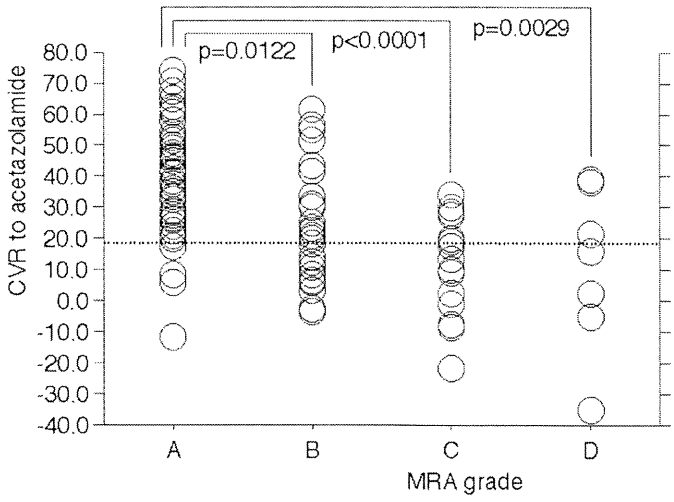

Fig 3. Comparison of CVR to acetazolamide among the 4 MRA grades in cerebral hemispheres with lesions.

Figure 3 shows CVR to acetazolamide according to each MRA grade in 108 cerebral hemispheres with lesions. CVR was significantly lower in cerebral hemispheres with MRA grade B (24.4 ± 19.0%), C (11.5 ± 15.6%), or D (11.2 ± 26.3%) than in those with MRA grade A (38.4 ± 16.3%). However, there was no difference in hemispheric CVR to acetazolamide when comparing MRA grades B, C, and D. The incidences of reduced CVR to acetazolamide in cerebral hemispheres accord-

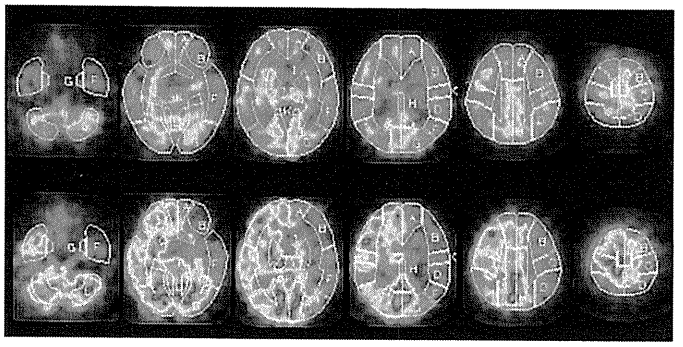

Fig 4. A 70-year-old man with symptomatic left ICA stenosis (90%) exhibiting MRA grade C (Fig 1). Single-photon emission CT scan shows reduction of resting cerebral blood flow (*upper images*) and poor acetazolamide-induced increases in perfusion (*lower images*) in the left MCA territory.

ing to MRA grade were 6.8% (4/59) for A, 42.3% (11/26) for B, 62.5% (10/16) for C, and 57.1% (4/7) for D. Although the incidence was significantly higher in cerebral hemispheres with MRA grade B ($P < .0001$), C ($P < .0001$), or D ($P = .003$) than in those with MRA grade A, there was no difference when comparing MRA grades B, C, and D. None of the 66 cerebral hemispheres without lesions exhibited reduced CVR to acetazolamide.

Sensitivity and specificity in the cutoff point lying closest to the left upper corner of the receiver operating characteristic curve in the detection of reduced CVR to acetazolamide in cerebral hemispheres with lesions were 86.2% and 69.6%, respectively, when the cutoff point was set between MRA grades A and B (grade A vs grade B, C, and D). Positive predictive values and negative predictive values were 51.0% and 93.2%, respectively. Figure 4 shows SPECT images in a patient with MRA grade C.

Discussion

Our study demonstrates that a simple MRA method can assess hemodynamic impairment with a high negative predictive value. Although the signal intensity of the MCA in the MRA was visually graded with use of a subjective process, the interobserver and intraobserver agreements of these measurements were excellent.

The ^{123}I-IMP-autoradiography method with SPECT used in our study accurately quantifies CVR and can adequately define subgroups of patients with reduced CVR.[24] Furthermore, recent prospective studies have demonstrated that reduced CVR to acetazolamide measured by quantitative brain perfusion SPECT (defined by values less than the mean −2 SD of the CVR or 95% confidence limits obtained in control subjects) can predict the risk for stroke recurrence in patients with symptomatic ICA occlusive disease[7,8] and the risk for cerebral hyperperfusion after carotid endarterectomy.[11] The same definition of reduced CVR was used in this study.

While single-slab 3D TOF MRA used in our study is less appropriate than multiple overlapping thin-slab acquisition to show intracranial vessels,[21] the signal intensity of the arteries displayed by the former method correlates with blood flow velocity.[22] As a result, CVR to acetazolamide was significantly lower in cerebral hemispheres with reduced MCA signal intensity than in those with normal MCA signal intensity. Furthermore, the incidence of reduced CVR to acetazolamide was significantly higher in cerebral hemispheres with reduced MCA signal intensity than in those with normal MCA signal intensity.

Our study also determined the threshold of MRA grading required to detect hemispheres with reduced CVR. Assuming the SPECT-CVR as the true determinant of hemodynamic impairment, MRA grading was associated with a 93.2% negative predictive value for the detection of reduced CVR in cerebral hemispheres with lesions. The interobserver and intraobserver variability for MRA grading had a concordance rate of 1.00 in cerebral hemispheres with normal MCA signal intensity, and none of the cerebral hemispheres determined as having reduced MCA signal intensity were subsequently graded as having normal MCA signal intensity at any other time. In addition, all cerebral hemispheres without lesions and without reduced CVR to acetazolamide were assessed as MRA grades of A in all reviews. These properties support the usefulness of this MRA method as a screening test for hemispheric hemodynamic impairment.

Our study possessed several limitations. When the ICA is chronically occluded, the collateral blood flows via the anterior or posterior communicating arteries, or the leptomeningeal anastomosis often perfuses the occluded area, thereby maintaining normal hemodynamics. By contrast, longer paths of collateral blood flow result in higher saturation of inflowing spins. As a result, collateral blood flow signals are lost, and the affected MCA is not displayed in single-slab 3D TOF MRA. In addition, when 1 or more MCA branches are not visualized in the MRA, they may simply be occluded, and the degree of the visualization may not reflect the velocity of inflowing blood relevant to ICA steno-occlusive diseases. These phenomena may account for the low positive predictive value for the detection of reduced hemispheric CVR with use of the present method.

In our study, we used axial single-slab 3D TOF MRA of the intracranial arteries that was parallel to the anterior/posterior commissure line. Although the MRA sequence and method are unique, they are easily reproducible on most clinical 1.5T MR imagers. Thus, the present MRA methods may not be limited to particular institutions.

In contrast to the 3T MR imaging model used in our study, most institutions commonly use a 1.5T MR imager. Although use of a 1.5T MR imager for 3D TOF MRA results in inferior depiction of intracranial arteries because of lower spatial resolution and lower signal-to-noise ratio with decreased T1 relaxation time,[29,30] MRA imaging is more sensitive and specific for decreased velocity of inflowing blood with a 1.5T MR imager than with a 3T MR imager. Thus, the use of a 1.5T MR imager may be suitable for the detection of hemodynamic impairment in conjunction with this method.

Although SPECT with an acetazolamide challenge is a reliable method to identify patients with hemodynamic impairment,[7,8,10,11,24] the clinical use of SPECT is precluded by its high cost and limited availability. In addition, acetazolamide is associated with a variety of frequent adverse effects, including metabolic acidosis, hypokalemia, numbness of the extremities, headache, tinnitus, gastrointestinal tract disturbances, and Stevens-Johnson syndrome.[31,32] Recent studies have demonstrated that the perfusion-weighted MR imaging-cerebral blood volume method also can identify patients with hemodynamic impairment.[33,34] However, gadolinium-based

contrast agents may be associated with the development of nephrogenic systemic fibrosis in the setting of renal insufficiency.[35] By contrast, the present MRA method does not require administration of radioisotope or contrast agents, and its short scanning time is well suited for clinical screening tests.

Conclusions

Our study demonstrates that a simple MRA method can assess hemodynamic impairment with a high negative predictive value. When patients are diagnosed with hemodynamic impairment in the affected cerebral hemisphere by the present method, results should be confirmed with the use of positron-emission tomography, SPECT with an acetazolamide challenge, or perfusion-weighted MR imaging. Regardless, use of the present method as a screening test will eliminate the need for follow-up studies in nearly half of patients (45% in our study). However, the present method also failed to detect hemodynamic impairment in 7% of patients. Additional investigation regarding the relationship between the MRA grading system and the risk for stroke recurrence in patients with symptomatic ICA occlusive disease or the risk for cerebral hyperperfusion after carotid endarterectomy will be beneficial to determine the effect of false-negative results in the clinical setting.

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Does ICA Occlusion Frequently Have Intracerebral Hemorrhage after IV Tissue Plasminogen Activator Therapy for Ischemic Stroke?

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Key Words
Hemorrhage · ICA occlusion · Intracerebral hemorrhage · Tissue plasminogen activator therapy · Ischemic stroke

Abstract
Background/Aims: The main predictors of intracerebral hemorrhage (ICH) are clinical stroke severity and large ischemic lesions. Therefore, ICA occlusion as severe stroke is thought to frequently have ICH after tissue plasminogen activator (t-PA) therapy. The aim of this study was to investigate whether ICA occlusion more frequently had ICH after t-PA therapy compared with other occluded arteries. ***Subjects and Methods:*** We prospectively studied consecutive stroke patients treated with t-PA within 3 h of onset. We investigated the frequency of ICH after t-PA therapy for each occluded artery. ***Results:*** 165 patients were enrolled. Initial MRA demonstrated ICA occlusion in 38 patients, M1 in 48, M2 in 28, and BA and PCA in 12. At 24 h after t-PA infusion, 113 (68.5%) patients (non-HT group) did not have hemorrhagic transformation, 37 (22.4%; HI group) had hemorrhagic cerebral infarction and 15 (9.1%; ICH group) had ICH. The ICH group most frequently had M2 occlusion, NIHSS ≥15, and ≥1/3 of the MCA territory among the three groups. The frequency of ICH was 2.6% in no occlusion, 10.5% in ICA occlusion, 6.3% in M1, 21.4% in M2, and 8.3% in PCA and BA (p = 0.1016). ***Conclusion:*** Patients with ICA occlusion did not have ICH more frequently after t-PA therapy in comparison to other occluded arteries.

Introduction

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke [1]. The most important complication of t-PA therapy is symptomatic intracerebral hemorrhage (ICH). According to the NINDS classification [2], hemorrhagic transformation (HT) is classified as hemorrhagic cerebral infarction (HI) and ICH according to appearance on computed tomography (CT). ICH is associated with early neurological deterioration and poor outcome. The main predictors of clinically significant ICH are clinical stroke severity, and early changes identified on CT [3–8]. Therefore, ICA occlusion as severe stroke is thought to frequently have ICH after t-PA therapy compared with other occluded arteries. The aim of this study was to investigate whether ICA occlusion more frequently had ICH after t-PA therapy compared with other occluded arteries.

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Subjects and Methods

We prospectively studied consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2005 and June 2010. Patients with heart valve replacements, pacemakers or clipping of cranial arteries were excluded due to contraindications for MRI. The following clinical data were collected from all patients: patient age and gender; NIHSS score before and at 24 h and 7 days after t-PA infusion; presence of arterial occlusion on MRA before t-PA infusion; vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia and smoking; presence of potential cardiac sources of emboli; laboratory parameters before t-PA infusion; administration of antithrombotic agents such as antiplatelet agents and warfarin; and the presence or absence of an early recanalized occluded artery on MRA 24 h after t-PA infusion. Inclusion and exclusion criteria for intravenous t-PA were used in accordance with the Japan Alteplase Clinical Trial [9]. The dose of t-PA used was 0.6 mg/kg.

Before t-PA infusion, we performed MRI studies, including diffusion-weighted imaging, MRA and T2*-weighted gradient-echo imaging (T2*) to assess the area of the ischemic lesion and to identify the occluded arteries and the presence of microbleeds. The area of ischemic lesion on diffusion-weighted imaging was divided into two groups: <1/3 and ≥1/3 of the MCA territory. Next, follow-up MRI was performed at 24 h after t-PA to assess the presence of HT on T2* at 24 h. MRI was performed using a commercially available echo planner instrument operation on a 1.5-T unit (Signa EXCITE XL version 11.0; GE Healthcare, Milwaukee, Wisc., USA). The imaging protocol consisted of a T2*-weighted gradient echo (repetition time: 600 ms; echo time: 17 ms; flip angle: 30°), diffusion-weighted echo planar (repetition time: 8,000 ms; echo time: 70 ms) imaging series, and intra- and extracranial MRA.

The presence of a large artery occlusion was assessed by MRA. Occluded arteries on initial MRA were identified as follows: ICA occlusion, M1 occlusion, M2 occlusion, BA occlusion and PCA occlusion.

HT on T2* at 24 h after t-PA infusion was defined as the new appearance of low-intensity lesions on follow-up T2* compared with initial T2*. HTs were classified according to the modified NINDS classification [2]. HI was defined as small petechiae or confluent petechiae within the infracted area, but with no space-occupying effect. ICH was defined as a typical homogeneous hypodense lesion with a sharp border with or without edema or mass effect within the brain. This hypodense lesion could arise at a site remote from the vascular territory of the ischemic stroke or within, but not necessarily limited to, the territory of the presenting cerebral infarction. Microbleeds were defined as small silent foci of signal loss on T2* other than the principal lesions responsible for stroke episodes. The experienced researcher (K.K.) who evaluated MRI findings was blinded to the patient clinical background data.

Symptomatic cerebral hemorrhage was defined as an increase in total NIHSS score of ≥4 if the ICH was likely to be the cause of clinical deterioration.

MRA was performed 24 h after the end of t-PA administration to identify the presence or absence of early recanalization of the occluded arteries. Recanalization was graded as follows: (1) complete recanalization, reappearance of entire occluded artery and distal vessel branches; (2) partial recanalization, restoration of part of the distal vessel supplied by an occluded artery; or (3) no recanalization, persistent occlusion. The positive group for recanalization showed partial or complete recanalization 24 h after t-PA infusion, while the negative recanalization group showed no recanalization.

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography, 24-hour electrocardiography monitoring and transthoracic echocardiography. Transesophageal echocardiography was also performed if the condition of the patient was suitable. The following potential emboligenic cardiac diseases were considered: atrial fibrillation, previous acute myocardial infarction, mitral valve disease and dilated cardiomyopathy.

We divided the patients into three groups: non-HT, HI and ICH. The clinical characteristics were compared among the three groups and the frequency of ICH after t-PA therapy for each occluded artery was examined. The significance of intergroup differences was assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test and Kruskal-Wallis U test for continuous variables. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using StatView version 5 statistical software. All study protocols followed the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all patients.

Results

A total of 168 consecutive stroke patients were treated with t-PA. Three patients were excluded due to the presence of a pacemaker. As a result, 165 patients (89 men, 76 women; mean and median age: 75.4 ± 11.0 and 76 years) were enrolled into the present study. Time between symptom onset and initial MRI study and t-PA bolus were 102.6 ± 40.6 min (median: 100) and 144.1 ± 30.1 min (median: 150), respectively.

Initial MRA demonstrated occluded brain arteries in 126 patients (76.4%) and no occlusive lesions in 39 patients (23.7%). The ICA was occluded in 38 patients, M1 in 48, M2 in 28, PCA in 3 and BA in 9. At 24 h after t-PA infusion, 52 patients (31.5%) showed HT on T2*, with HI in 37 patients (22.4%) and ICH in 15 patients (9.1%). Symptomatic ICH was observed in 6 patients (3.6%) within 24 h of t-PA infusion. Five patients had M2 occlusion and 1 patient did not have an occluded artery. The baseline characteristics of the patients are shown in table 1. The ICH group most frequently had an M2 occlusion, NIHSS ≥15, and ≥1/3 of the MCA territory among the three groups. Regarding the site of occlusion, the frequency of ICH was 2.6% in no occlusion, 10.5% in ICA occlusion, 6.3% in M1, 21.4% in M2, and 8.3% in PCA and BA ($p = 0.1016$; fig. 1 and table 2). Therefore, ICA occlusion was not frequently associated with occurrence of ICH after t-PA therapy.

Table 1. Baseline clinical data of patients in the non-HT, HI and ICH groups

	Non-HT (n = 113)	HI (n = 37)	ICH (n = 15)	p
Median age, years	77	76	74	0.901
Female	53 (46.9)	17 (45.9)	6 (40.0)	0.881
Median time from symptom onset to MRI imaging, min	101	98	90	0.729
Median time from symptom onset to treatment, min	150	146	149	0.998
Median systolic blood pressure, mm Hg	151	150	162	0.054
Hypertension	67 (59.3)	26 (70.3)	11 (73.3)	0.334
Diabetes mellitus	29 (25.7)	6 (16.2)	3 (20.0)	0.475
Hyperlipidemia	34 (30.1)	3 (8.1)	3 (20.0)	0.024
Smoking	48 (42.5)	10 (27.0)	4 (26.7)	0.159
Atrial fibrillation	53 (46.9)	23 (62.2)	11 (73.3)	0.067
Median glucose, mg/dl	132	146	139	0.230
>150	37 (32.7)	17 (45.9)	7 (46.7)	0.253
Use of antithrombotic agents	36 (31.9)	15 (40.5)	5 (33.3)	0.625
Warfarin	8 (7.1)	4 (10.8)	2 (13.3)	0.607
Aspirin	29 (25.7)	10 (27.0)	3 (20.0)	0.887
MRA findings				
Occluded artery	78	34	14	
ICA	25 (22.1)	9 (24.3)	4 (26.7)	0.905
M1	28 (24.8)	17 (45.9)	3 (20.0)	0.027
M2	14 (12.4)	8 (21.6)	6 (40.0)	0.019
BA	9 (8.0)	0 (0)	0 (0)	0.112
PCA	2 (1.8)	0 (0)	1 (6.7)	0.264
No occlusion	35 (31.0)	3 (8.1)	1 (6.7)	0.005
≥1/3 MCA	28 (24.8)	17 (45.9)	10 (66.7)	0.001
Microbleeds	23 (20.5)	8 (21.6)	5 (33.3)	0.531
Recanalization 24 h after t-PA infusion	46 (40.7)	29 (78.4)	10 (66.7)	0.0002
NIHSS score				
Median at baseline	13	17	16	0.114
≥15	48 (42.5)	23 (62.2)	10 (66.7)	0.042
Median at 24 h after t-PA infusion	6	11	19	0.000
Median at 7 days after t-PA infusion	7	7	17	0.011

Values in parentheses represent percentages.

Table 2. Baseline clinical data of patients with no occlusion and ICA, M1, M2, BA and PCA occlusion

	ICA (n = 38)	M1 (n = 48)	M2 (n = 28)	BA (n = 9)	PCA (n = 3)	No occlusion (n = 39)
Non-HT	25 (65.8)	28 (58.3)	14 (50.0)	9 (100)	2 (66.7)	35 (89.7)
HI	9 (23.7)	17 (35.4)	8 (28.6)	0 (0)	0 (0)	3 (7.7)
ICH	4 (10.5)	3 (6.3)	6 (21.4)	0 (0)	1 (33.3)	1 (2.6)
Atrial fibrillation	23 (60.5)	33 (68.8)	18 (64.3)	4 (44.4)	2 (66.7)	7 (18.0)
Median glucose, mg/dl	137	140	131	137	122	139
>150	22 (57.9)	32 (66.7)	18 (64.3)	6 (66.7)	3 (100)	23 (59.0)
NIHSS score						
Median at baseline	19	16.5	10	19	5	7
≥15	30 (78.9)	28 (58.3)	10 (35.7)	7 (77.8)	0 (0)	6 (15.4)
Ischemic lesion on DWI ≥1/3 MCA	20 (52.6)	22 (45.8)	13 (46.3)	0 (0)	0 (0)	0 (0)
Recanalization 24 h after t-PA infusion	20 (52.6)	38 (79.2)	20 (71.4)	5 (55.6)	2 (66.7)	NA

Figures in parentheses represent percentages. DWI = Diffusion-weighted imaging.

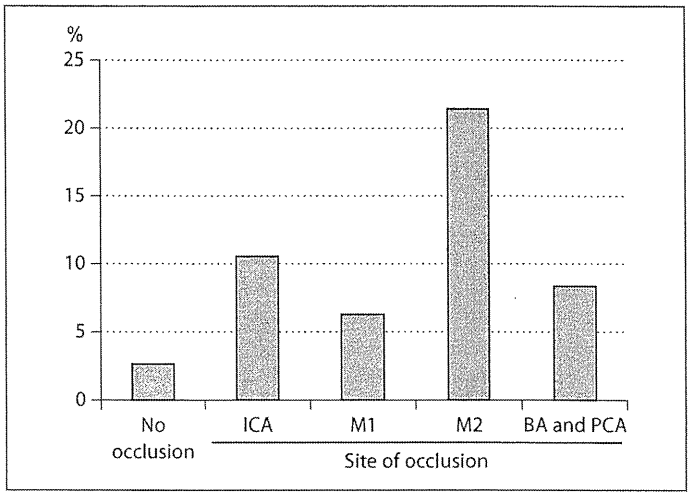

Fig. 1. Frequency of ICH for each occluded artery.

Follow-up MRA 24 h after t-PA infusion revealed that recanalization of the occluded artery occurred least in the non-HT group among the three groups (42.5% for the non-HT group, 78.4% for the HI group and 66.7% for the ICH group; $p = 0.0002$). Among patients with ICA, M1 and M2 occlusions, the recanalization rate was lowest in ICA occlusion (52.6% for ICA occlusion, 79.2% for M1 occlusion and 71.4% for M2 occlusion; $p = 0.0292$).

Discussion

We demonstrated that patients with ICA occlusion did not have ICH more frequently after t-PA therapy compared with other occluded arteries and that ICA occlusion was not statistically associated with the occurrence of ICH after t-PA therapy.

HT can happen spontaneously. Blood extravasation towards the brain tissue requires an alteration of the blood-brain barrier, which occurs immediately or with some delay after the ischemic event [10]. HI is a secondary phenomenon related to the severity of the ischemic lesion, a result of ischemic damage to the microvasculature, possibly related to reperfusion, but unrelated to t-PA treatment [11–13]. Conversely, ICH have been associated with t-PA treatment, presumably involving the biological effects of t-PA [5, 14]. Therefore, when t-PA is administered, it is important to avoid the occurrence of ICH after t-PA therapy. The main predictors of clinically significant ICH are age, clinical stroke severity, high blood pressure, hyperglycemia and early changes identified on CT [3–7, 15–18]. Therefore, ICA occlusion as a severe stroke is thought to be associated with the occurrence of ICH. However, in the present study, ICA occlusion did not frequently have ICH after t-PA therapy. Lansberg et al. [19] reported that early reperfusion was strongly associated with symptomatic ICH in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evaluation (DEFUSE) study. In our study, the recanalization rate of ICA occlusion was lower than M1 and M2 occlusions. Several investigators reported that t-PA was not effective in patients with ICA occlusion [20, 21]. The reason for this was that the embolus responsible for ICA occlusion was larger than that responsible for other arterial occlusions, and such an embolus was likely to be resistant to t-PA. Therefore, the patients with ICA occlusion did not frequently have ICH after t-PA therapy compared with other occluded arteries.

In the present study, M2 occlusion most frequently had ICH and was associated with ICH. Why did patients with M2 occlusion display the highest frequency of ICH? Patients with ICH most frequently had ischemic lesions $\geq 1/3$ of the MCA territory among the non-HT, HI and ICH groups. Therefore, occurrence of ICH after t-PA therapy is associated with the area of ischemic lesions. On the other hand, in the present study, the frequency of an ischemic lesion $>1/3$ of the MCA territory was not different among ICA, M1 and M2 occlusions. The patients with MCA branch (M2) occlusion experience a greater load of t-PA to the damaged ischemic lesion compared to patients with occlusion involving a main artery such as M1 or ICA. ICH is more likely to occur due to the biological effects of t-PA. We therefore believe that patients with M2 occlusion will more frequently show ICH as a side effect of t-PA than patients with M1 or ICA occlusion.

The present study displays several limitations. MRI is unable to be performed in patients who have implantations containing metallic materials, such as pacemakers and metal clips. In fact, 3 patients were excluded from our study for this reason. Second, the use of MRA is somewhat inaccurate for detecting vessel occlusion or stenosis [22]. Finally, the sample size was relatively small. A larger study is needed to confirm our hypothesis.

In conclusion, patients with ICA occlusion did not have ICH after t-PA therapy more frequently in comparison to other occluded arteries.

Disclosure Statement

There are no conflicts of interest to disclose.

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Clinical and MRI Scale to Predict Very Poor Outcome in Tissue Plasminogen Activator Patients

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Key Words
Tissue plasminogen activator · Patient outcome · MRI scale

Abstract
Background and Purpose: The present study aimed to devise a simple scale to predict very poor outcome after tissue plasminogen activator (t-PA) therapy using clinical and MRI factors. ***Methods:*** Consecutive stroke patients treated with t-PA within 3 h of onset were studied prospectively. Clinical factors and MRI findings independently associated with very poor outcome (modified Rankin Scale score 4–6) at 3 months after t-PA therapy were assessed. ***Results:*** The subjects were 117 patients. Multivariate logistic regression analysis revealed the following independent factors associated with very poor outcome: time from stroke onset to treatment ≥140 min (OR 2.790, 95% CI 1.082–7.193; p = 0.0337), baseline National Institutes of Health Stroke Scale score ≥20 (OR 3.794, 95% CI 1.199–12.009; p = 0.0233), glucose ≥180 mg/dl (OR 3.288, 95% CI 1.126–9.600; p = 0.0295), internal carotid artery occlusion (OR 6.187, 95% CI 5.090–18.354; p = 0.0129) and M1 susceptibility vessel sign (OR 6.379, 95% CI 1.194–34.074; p = 0.030). Those 5 variables were selected in the scale, with each factor as 1 point. Frequencies of patients with a very poor outcome for each score were as follows: score 0, 26.3%; score 1, 30.6%; score 2, 70.0%, and score 3–5, 100%. ***Conclusion:*** A clinical scale using clinical and MRI factors can predict very poor outcome in t-PA patients.

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke [1]. However, the frequency of a modified Rankin Scale (mRS) score 4–5 and death (score 6) at 3 months after t-PA therapy is approximately 40–50% [1–4]. Patients with an mRS score 4–5 have more than moderate disability and always need assistance for a physical demand and walking [5]. Therefore, the outcome of patients with an mRS score 4–6 should be very poor. The following factors are reportedly associated with poor outcomes: older age, delayed t-PA infusion, neurological severity, hyperglycemia, no early recanalization of the occluded artery, and large ischemic lesions [6–8]. Compared with CT, MRI before t-PA infusion can provide more information, such as site of arterial occlusion, size of ischemic lesions and the susceptibility vessel sign, which has been associated with patient outcome after t-PA therapy [9, 10]. Therefore, using MRI findings in addition to clinical factors should result in a more accurate scale to predict poor outcomes. We aimed to devise a simple scale for predicting very poor outcomes using clinical and MRI factors.

Subjects and Methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2006 and August 2010 were studied prospectively. Patients with an mRS score >3 before stroke onset were excluded from the study.

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The following clinical data were collected from all patients: (1) patient age and sex; (2) time from symptom onset to treatment; (3) arterial blood pressure before t-PA infusion; (4) National Institutes of Health Stroke Scale (NIHSS) score before t-PA infusion; (5) diffusion-weighted imaging Alberta Stroke Program Early CT Score (DWI-ASPECTS) and presence of M1 susceptibility vessel sign (M1 SVS) on T2* [10] before t-PA infusion; (6) presence of arterial occlusion on magnetic resonance angiography (MRA) before t-PA infusion; (7) vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia and smoking; (8) stroke subtype; (9) laboratory parameters including glucose level before t-PA infusion, and (10) mRS score at 3 months after t-PA therapy. Inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial [11].

Before t-PA infusion, all patients underwent MRI studies, including diffusion-weighted imaging, T2* and MRA, to identify the occluded arteries and the presence of M1 SVS on T2*. The main occluded arteries were identified as follows: M1 occlusion, M2 occlusion and internal carotid artery (ICA) occlusion. The M1 SVS was defined as a hypointense signal of the horizontal portion of the middle cerebral artery on T2* within a vascular cistern corresponding to symptomatic occlusive vessels [10].

One expert neurologist (K.K.), blind to all clinical information, assessed MRI. MRI was performed using a commercially available echo planar instrument operating on a 1.5-Tesla unit (Signa Excite XL version 11.0; GE Healthcare, Milwaukee, Wisc., USA). The neuroimaging protocol for acute stroke in our hospital included DWI trace sequence (TR/TE 6,000 ms/78 ms; b values 0 and 1,000 s/mm^2; field of view 24 cm; acquisition matrix 128 × 192 matrix, and 6.0 mm with a 1.0-mm intersection gap), and a time-of-flight MRA covering the circle of Willis (TR/TE 25 ms/6.9 ms; 20° flip angle).

Using clinical, radiological, cardiac and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment criteria [12] to determine the stroke subtype. Large-vessel disease was defined as >50% arterial stenosis or occlusion corresponding to neurological deficits in the absence of a source of cardiac embolism. Cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Lacunar stroke was defined as the presence of infarction <15 mm, with no source of cardiac embolism and >50% arterial stenosis. Undetermined stroke was used when no etiological source of emboli could be identified.

Very poor outcomes at 3 months after t-PA therapy were defined as mRS scores 4–6. Multivariate logistic regression analysis was performed to determine factors independently associated with very poor outcome using variables identified on univariate analysis at a level of $p < 0.1$. Cutoff values for continuous variables were determined using the sensitivity and specificity cure analysis. Firstly, we analyzed the data using only clinical variables excluding MRI factors. Next, to assess utility of MRI factors before t-PA infusion, we analyzed the data using MRI findings in addition to clinical factors. We chose independent variables on multivariate logistic regression analysis and devised the very poor outcome scale score.

Statistical analysis was performed using StatView version 5 statistical software to establish associations among clinical factors and patient outcomes at 3 months after t-PA therapy. The significance of intergroup differences was assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test and Kruskal-Wallis U test for continuous variables. All data were unadjusted, and values of $p < 0.05$ were considered significant.

All study protocols followed the principles outlined in the Declaration of Helsinki and were approved by the local ethics review committee at Kawasaki Medical School. Written informed consent was obtained from all patients.

Results

A total of 172 consecutive stroke patients were treated with t-PA. Overall, 25 patients had a posterior circulation stroke. Two patients were excluded because they had a pacemaker. One patient did not undergo MRI before t-PA infusion due to lack of time for the MRI study. A total of 27 patients had mRS scores >3 before t-PA therapy. As a result, 117 patients (61 men, 56 women, mean age 75.8 ± 9.8 years, median 76) were enrolled in the present study. The duration between symptom onset and the t-PA bolus was 142.1 ± 29.8 min.

At 3 months after t-PA therapy, 21 patients had an mRS score 0, 15 an mRS score 1, 5 an mRS score 2, 16 an mRS score 3, 16 an mRS score 4, 31 an mRS score 5, and 13 an mRS score 6. Therefore, 60 patients had a very poor outcome (mRS score 4–6). Table 1 shows the clinical characteristics of patients with mRS scores 0–3 and 4–6.

Patients with an mRS score 4–6 were older than those with an mRS score 0–3 (77.9 ± 9.3 vs. 73.6 ± 9.9 years; $p = 0.0217$). Time from stroke onset to treatment tended to be longer in those with an mRS score 4–6 than in those with an mRS score 0–3 (146.8 ± 28.6 vs. 137.2 ± 30.4 min; $p = 0.0719$). The baseline NIHSS score was lower in patients with an mRS score 0–3 than in those with an mRS score 4–6 [median (interquartile range, IQR): 10 (5–15) vs. 18 (14–22); $p < 0.0001$]. ICA occlusion and M1 SVS were more frequently observed in patients with an mRS score 4–6 than in those with an mRS score 0–3 (36.7 vs. 8.8%, $p = 0.0003$; and 30.0 vs. 5.3%, $p = 0.0005$). No occlusion on MRA before t-PA infusion was more frequent in patients with an mRS 0–3 than in those with an mRS score 4–6 (26.3 vs.15.0%; $p = 0.0026$). The glucose concentration before t-PA infusion was higher in patients with an mRS score 4–6 than in those with an mRS score 0–3 (156.0 ± 44.6 vs. 141.1 ± 39.3 mg/dl; $p = 0.0372$). Baseline DWI-ASPECTS was higher in patients with an mRS score 0–3 than in those with an mRS score 4–6 [median (IQR): 9 (7–110) vs. 7 (5–9); $p = 0.0014$]. The sensitivity and specificity cure analysis yielded cutoff levels predicting an mRS score 4–6 with high sensitivity and high specificity as follows: time from stroke onset to treatment ≥140 min (sensitivity 61.7% and specificity 56.1%), age

Table 1. Clinical characteristics of patients

	mRS score 0–3 (n = 57)	mRS score 4–6 (n = 60)	p
Age, years	73.6 ± 9.9	77.9 ± 9.3	0.0217
Patients ≥75 years old	28 (43.1)	40 (66.7)	0.0545
Female	27 (47.4)	29 (48.3)	0.9999
Hypertension	41 (71.9)	36 (60.0)	0.1739
Diabetes mellitus	12 (21.1)	12 (20.0)	0.9999
Hyperlipidemia	13 (22.8)	10 (16.7)	0.4035
Smoking	18 (52.9)	30 (42.3)	0.3636
Atrial fibrillation	28 (49.1)	36 (60.0)	0.2374
Onset to treatment, min	137.2 ± 30.4	146.8 ± 28.6	0.0719
Onset to treatment ≥140 min	26 (45.6)	38 (63.3)	0.0543
Median baseline NIHSS score	10 [5–15]	18 [14–22]	<0.0001
Baseline NIHSS score ≥20	8 (14.0)	25 (41.7)	0.0009
Systolic blood pressure, mm Hg	154.0 ± 21.3	151.5 ± 22.7	0.6627
Diastolic blood pressure, mm Hg	82.7 ± 14.9	82.7 ± 16.8	0.9710
Glucose, mg/dl	141.1 ± 39.3	156.0 ± 44.6	0.0372
Glucose ≥180 mg/dl	9 (15.8)	17 (28.3)	0.1028
Hemoglobin A1C, %	5.6 ± 0.7	5.7 ± 0.8	0.1982
Leukocytes/μl	6,831.2 ± 2,681.9	6,917.3 ± 2,354.5	0.6236
Erythrocytes, × 10,000/μl	428.8 ± 54.5	416.8 ± 82.4	0.3539
Platelets, × 10,000/μl	19.5 ± 4.3	19.6 ± 5.5	0.7230
Creatinine, mg/dl	0.66 ± 1.60	0.56 ± 1.39	0.7435
Stroke type			
Cardioembolic stroke	28 (49.1)	39 (65.0)	0.0827
Large artery diseases	5 (8.8)	4 (6.7)	0.6693
Lacunar stroke	3 (5.3)	0	0.1125
Undetermined stroke	21 (36.8)	17 (28.3)	0.3786
MRI findings			
Median baseline DWI-ASPECTS	9 [7–10]	7 [5–9]	0.0014
DWI-ASPECTS <5	2 (3.6)	12 (20.0)	0.0066
Site of occlusion on MRA before t-PA infusion			
ICA	5 (8.8)	22 (36.7)	0.0003
M1	23 (40.4)	19 (31.7)	0.3277
M2	14 (24.6)	10 (16.7)	0.2905
No occlusion	15 (26.3)	9 (15.0)	0.0026
M1 SVS on T2*	3 (5.3)	18 (30.0)	0.0005

Figures in parentheses are percentages; figures in brackets are IQRs.

≥75 years (58.8 and 59.2%); NIHSS ≥20 (75.8 and 58.3%); glucose ≥180 mg/dl (65.4 and 52.7%), and DWI-ASPECTS <5 (85.7 and 52.9%).

Firstly, we selected 5 variables excluding MRI factors that were identified on univariate analysis at $p < 0.1$. Multivariate logistic regression analysis revealed that baseline NIHSS ≥20 [odds ratio (OR) 4.227, 95% confidence interval (CI) 1.543–11.581; p = 0.0051] was the only independent factor associated with an mRS score 4–6. Other remaining factors were not significantly associated with very poor outcome: ≥75 years (OR 1.716, 95% CI 0.757–3.890; p = 0.1963), time from stroke onset to treatment ≥140 min (OR 2.001, 95% CI 0.889–4.501; p = 0.0936), cardioembolic stroke (OR 1.176, 95% CI 0.495–2.793; p = 0.7137) and glucose ≥180 mg/dl (OR 2.551, 95% CI 0.953–6.827; p = 0.0621).

Next, we selected 9 variables, including MRI information before t-PA infusion, identified on univariate analysis at $p < 0.1$. Multivariate logistic regression analysis revealed independent factors associated with an mRS score 4–6 as follows: time from stroke onset to treatment ≥140 min (OR 2.790, 95% CI 1.082–7.193; p = 0.0337), baseline NIHSS ≥20 (OR 3.794, 95% CI 1.199–12.009; p = 0.0233); glucose ≥180 mg/dl (OR 3.288, 95% CI 1.126–9.600; p =

Table 2. Multivariate logistic regression analysis for factors associated with an mRS score >3

	OR	95% CI	p
Age ≥75 years	1.994	0.783–5.074	0.1477
Time from stroke onset to treatment ≥140 min	2.790	1.082–7.193	0.0337
Baseline NIHSS score ≥20	3.794	1.199–12.009	0.0233
Glucose ≥180 mg/dl	3.288	1.126–9.600	0.0295
DWI-ASPECTS <5	1.639	0.236–11.367	0.6171
ICA occlusion before t-PA infusion	5.090	1.412–18.354	0.0129
No occlusion before t-PA infusion	1.511	0.457–5.003	0.4989
M1 SVS	6.379	1.194–34.074	0.3020
Cardioembolic stroke	1.257	0.434–3.640	0.6727

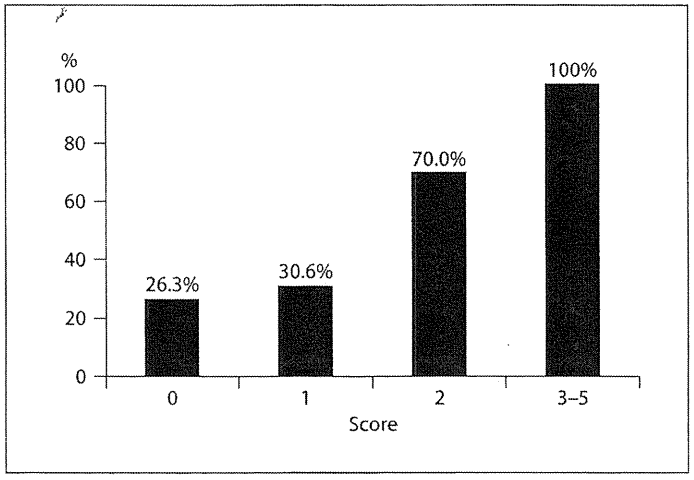

Fig. 1. Relationship between score and frequency of very poor outcome (mRS score 4–6) at 3 months after t-PA therapy.

0.0295), ICA occlusion (OR 6.187, 95% CI 5.090–18.354; p = 0.0129) and M1 SVS (OR 6.379, 95% CI 1.194–34.074; p = 0.030) (table 2).

We chose these 5 variables for use in the very poor outcome scale score. One point each was assigned for M1 SVS, time from stroke onset to treatment ≥140 min, baseline NIHSS ≥20, glucose ≥180 mg/dl and ICA occlusion, for a possible total of 5 points (table 3). The relationship between the very poor outcome scale score and frequency of patients with an mRS score 4–6 is shown in figure 1. Frequencies of patients with very poor outcomes for each score were as follows: 5 (26.3%) of 19 patients with a scale score of 0, 15 (30.6%) of 49 patients with score 1, 21 (70.0%) of 30 patients with score 2, 13 (100%) of 13 patients with score 3, 5 (100%) of 5 patients with score 4, and 1 (100%) of 1 patient with score 5 (fig. 1).

Table 3. Components of the poor outcome scale

Baseline NIHSS score ≥20	yes = 1 no = 0
Time from stroke onset to treatment ≥140 mm	yes = 1 no = 0
ICA occlusion	yes = 1 no = 0
M1 SVS	yes = 1 no = 0
Glucose ≥180 mg/dl	yes = 1 no = 0
Total	5 points

Discussion

The present study demonstrated that the time from stroke onset to treatment ≥140 min, baseline NIHSS ≥20, glucose ≥180 mg/dl, M1 SVS on T2* and ICA occlusion were factors independently associated with very poor outcome 3 months after t-PA therapy on multivariate logistic regression analysis. Using these factors, a simple scale to predict very poor outcome was devised.

Previous studies have reported that poor outcome was associated with hyperglycemia, high acute blood pressure, lower ASPECTS on CT or MRI, severe neurological deficits and ICA occlusion before t-PA infusion [1, 4, 7–9, 11, 13, 14]. The present results, except for high blood pressure, were compatible with previous findings. The effect of emergent intravenous antihypertensive agents on stroke outcome is a matter of contention. Martin-Schild et al. [15] reported that lowering blood pressure before intravenous t-PA therapy was not associated with poor outcomes.

The unique feature of our scale was that MRI findings were added to clinical factors. Excluding MRI factors, multivariate logistic regression analysis revealed only one factor, baseline NIHSS score ≥20, associated with poor outcome; this was why factors strongly associated with very poor outcome were missing. MRI including T2* and

MRA can assess the site of the occluded artery and SVS, which cannot be evaluated by conventional nonenhanced CT. We recently reported that M1 SVS on T2* was a strong predictor for no early recanalization after t-PA therapy [10]. Therefore, M1 SVS on T2*, as well as ICA occlusion, was thought to be strongly associated with very poor outcome. MRI findings were included as factors of a score to predict very poor outcome, which should result in a more accurate scale.

In the present study, 5 independent factors were found to be associated with very poor outcome 3 months after t-PA therapy. Of 5 factors, all patients (score ≥3) with more than 2 factors had a poor outcome 3 months after t-PA therapy. Intracranial mechanical thrombectomy is a therapeutic option for acute ischemic stroke patients failing tPA [16]. Therefore, we should consider combination therapy (t-PA therapy plus endovascular treatment) for such patients before t-PA therapy.

The present study had several limitations. First, the use of MRA is somewhat inaccurate for detecting vessel occlusion or stenosis [17]. Second, MRI cannot be performed in patients in whom metallic materials, such as pacemakers and metal clips, have been implanted. Two such patients were excluded from the present study.

In conclusion, time from stroke onset to treatment ≥140 min, baseline NIHSS ≥20, glucose ≥180 mg/dl, M1 SVS on T2* and ICA occlusion were independent factors associated with very poor outcome 3 months after t-PA therapy. We devised a simple score that can be used to predict very poor outcome in t-PA patients using these factors. In particular, all patients with a score ≥3 had very poor outcomes.

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Admission hyperglycemia and serial infarct volume after t-PA therapy in patients with and without early recanalization ☆

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ABSTRACT

Background and purpose: The present study examined the effects of admission hyperglycemia and early recanalization (ER) after t-PA administration on infarct volume and patient outcome.
Methods: Acute ischemic stroke patients with major artery occlusion treated with t-PA within 3 h of onset were studied prospectively. Hyperglycemia was identified as admitting blood glucose value ≥ 130 mg/dl. We compared serial infarct volume and patient outcome between normoglycemic and hyperglycemic groups, and assessed correlation between admitting blood glucose value and Δinfarct volume (7 days—baseline) between patients with and without ER.
Results: 97 patients (ICA occlusion in 30, M1 in 44, and M2 in 23 patients) were enrolled in the present study; 52 had hyperglycemia, and 40 had ER. The initial infarct volume did not differ between the normoglycemic and hyperglycemic groups. However, infarct volume at 7 days was larger in the hyperglycemic group than in the normoglycemic group (156.2 ± 157.1 cm^3, vs. 85.4 ± 140.7 cm^3, $P = 0.0061$) and the baseline admitting blood glucose value was correlated with Δinfarct volume (7 days—baseline) ($r = 0.340$, $P = 0.0014$). Regarding ER, Δinfarct volume (7 days—baseline) in patients without ER was correlated with admitting blood glucose value($r = 0.372$, $P = 0.0078$). However, in patients with ER, Δinfarct volume was not associated with admitting blood glucose value ($r = 0.225$, $P = 0.1173$). Good outcome (mRS 0–2) at 3 months was more frequent in normoglycemic patients than hyperglycemic patients (43.2% vs. 22.2%, $P = 0.0418$).
Conclusion: Admission hyperglycemia was associated with infarct volume expansion and patient outcome in t-PA patients. However, if ER occurs, hyperglycemia should not adversely affect infarct volume.

1. Introduction

Hyperglycemia is common in the early phase of stroke. Baird TA et al. [1] reported that hyperglycemia was an independent determinant of infarct expansion after stroke onset. Hyperglycemia is thought to be associated with increased mortality and poor recovery [2–5].

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke [6]. Early arterial recanalization is a marker of good outcome after t-PA infusion [7–9]. The frequency of good outcome as reflected by a modified Rankin Scale (mRS) score of 0–2 at 3 months after t-PA therapy is approximately 50% [6,10–12]. Poor outcomes are associated with hyperglycemia, older age, high acute blood pressure, neurological severity, activated protein C, no early recanalization of the occluded artery, large ischemic lesions on CT or magnetic resonance imaging (MRI) before t-PA infusion, and internal carotid artery (ICA) occlusion [6,11,13–22].

Parsons [3] reported that, in patients with acute perfusion–diffusion mismatch, hyperglycemia was correlated with greater final infarct size and worse functional outcome. On the other hand, hyperglycemia in patients without acute perfusion–diffusion mismatch did not correlate with poor outcome. Therefore, we hypothesized that early recanalization that is recanalization occurring within 1 h after t-PA administration, will not adversely affect the infarct volume and patient outcome even if patients had hyperglycemia. The present study examined associations between admission blood glucose levels before t-PA infusion and infarct volume and patient outcomes by early recanalization.

2. Subjects and methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2006 and June 2010 were studied prospectively. Patients who had major artery occlusion on initial MRA before t-PA infusion were enrolled. The following clinical data were collected from all patients: 1) patient age and sex; 2) time from

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symptom onset to treatment; 3) arterial blood pressure before t-PA infusion; 4) NIHSS score before, 1 h, 24 h and 7 days after t-PA infusion; 5) DWI before, 1 h, and 24 h after t-PA infusion; 6) FLAIR 7 days after t-PA infusion; 7) presence of arterial occlusion on MRA before t-PA infusion; 8) presence or absence of recanalization of occluded arteries within 60 min after t-PA administration; 9) occurrence of hemorrhagic transformation on T2* 24 h after t-PA infusion; 10) vascular risk factors, including hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), and smoking; 10) stroke subtype [23]; 12) laboratory parameters, including glucose level before t-PA infusion; and 13) mRS score after t-PA therapy. The inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial [19].

The patients were divided into two groups according to their admission blood glucose level: normoglycemic group <130 mg/dl and hyperglycemic group ≥ 130 mg/dl. The blood glucose threshold of 130 mg/dl was used according to Williams' [4] definition.

Before t-PA infusion, all patients underwent MRI studies, including diffusion-weighted imaging (DWI) and MRA, to identify the occluded arteries. Next, follow-up DWI was performed within 60 min and 24 h after the end of t-PA administration to measure the change in infarct volume. To identify the final infarct volume, FLAIR was performed 7 days after t-PA therapy. One neurologist (Y.S.), blind to all clinical information, assessed MRI and measured IIV using NIH image software. First, the perimeter of the area of abnormal signal intensity was traced on each DWI and FLAIR, and then NIH image calculated the total volume using the thickness and the traced area on the slice. The window level and window width were chosen to obtain the best contrast between the lesion and the normal surrounding tissue. The average workstation time of this study was 20 min for each sequence. The Δinfarct volume at 1 h, 24 h, and 7 days was defined as the infarct volume 1 h, 24 h, and 7 days after t-PA infusion minus the initial infarct volume prior to t-PA thrombolysis.

MRA was performed within 60 min after the end of t-PA administration to identify the presence or absence of early recanalization of the occluded arteries. Recanalization was graded as follows: 1) complete recanalization, reappearance of entire occluded artery and distal vessel branches; 2) partial recanalization, restoration of part of the distal vessel supplied by an occluded artery; or 3) no recanalization, persistent occlusion. [24]The positive group for recanalization showed partial or complete recanalization within 60 min after t-PA infusion, while the negative recanalization group showed no recanalization.

MRI was performed using a commercially available echo planar instrument operating on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). The neuroimaging protocol for acute stroke in our hospital included a fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE, 8002 ms/109 ms; TI, 2000 ms; field-of-view, 24 cm; acquisition matrix, 256×224; and section thickness, 6.0 mm with a 1.0-mm intersection gap), diffusion-weighted (DWI) trace sequence (TR/TE, 6000 ms/78 ms; b values, 0 and 1000 s/mm^2; field-of-view, 24 cm; acquisition matrix, 128×192 matrix, and 6.0 mm with a 1.0 mm intersection gap), T2* gradient echo sequence (TR/TE, 700 ms/20 ms; field-of-view, 24 cm; acquisition matrix, 256×192; and section thickness, 6.0 mm with a 1.0 mm intersection gap), and a time-of-flight MRA covering the circle of Willis (TR/TE, 25 ms/6.9 ms; 20 flip angle).

A neurologist determined the NIHSS scores before, immediately after, 24 h after, and 7 days after t-PA infusion. Three measures of clinical recovery based on methods modified from those of previous studies were used [25]. "Dramatic improvement" was defined as a $\geq$10-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. "Good improvement" was defined as a $\geq$4-point reduction in the total NIHSS score. "Worsening" was defined as a $\geq$4-point increase in the total NIHSS score. Good and poor outcomes at 3 months after t-PA therapy were defined as an mRS score of 0–2 and >3 or death, respectively.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [23] to determine stroke subtype. Large vessel disease (LVD) was defined as >50% arterial stenosis or occlusion corresponding to neurological deficits in the absence of a source of cardiac embolism. Cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Lacunar stroke was defined as the presence of infarction <15 mm, without source of cardiac embolism and >50% arterial stenosis. Undetermined stroke was used when no etiological source of emboli could be identified.

Statistical analysis was performed using StatView version 5 statistical software. Spearman's rank correlation coefficients were used to test the association between admission blood glucose levels and change in infarct volume between initial and 1 h, 24 h, and 7 days. Next, the clinical characteristics, infarct volume before, 1 h, 24 h, and 7 days after t-PA administration, and patient outcomes at 3 months after t-PA therapy were compared between the normoglycemic and hyperglycemic groups. Furthermore, the patients were divided into four subgroups according to the presence and absence of early recanalization, and hyperglycemia and normoglycemia. Patient outcomes and infarct volumes were compared among the four subgroups. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann–Whitney U test and Kruskal–Wallis U test for continuous variables. All data were unadjusted, and values of $P<0.05$ were considered significant.

All study protocols followed the principles outlined in the Declaration of Helsinki, and were approved by the local ethical review committee at Kawasaki Medical School and written informed consent was obtained from all patients.

3. Results

A total of 166 consecutive stroke patients were treated with t-PA. Two patients were excluded because they had a pacemaker. One patient did not undergo MRI before t-PA infusion due to a lack of time for the MRI study. Initial MRA demonstrated ICA occlusion in 30 patients, M1 occlusion in 44 patients, and M2 occlusion in 23 patients. Thus, 97 patients (48 men, 49 women; mean age, 76.3 ± 10.3 years) were enrolled into the present study. The duration between symptom onset and t-PA bolus was 137.0 ± 30.8 min.

The admission blood glucose was 144 ± 40.4 mg/dl; 52 patients had hyperglycemia and 45 patients had normoglycemia. The hyperglycemic group more frequently had DM than the normoglycemic group (23.1% vs. 6.7%, $P=0.0258$). HbA1c was higher in the hyperglycemic group than in the normoglycemic group (5.7 ± 0.6 vs. 5.4 ± 0.4, $P=0.0013$). Stroke type, site of occlusion, occurrence of hemorrhagic transformation and early recanalization rate did not differ between the two groups (Table 1).

Four patients did not have follow-up MRI studies at 24 h and 7 days, and 4 patients did not have follow-up MRI studies at 7 days because of death or severe stroke. The infarct volumes before and 1 h, 24 h, and 7 days after t-PA infusion were 28.2 ± 59.4 (median 8.0) cm^3, 45.4 ± 69.8 (16.7) cm^3, 93.9 ± 123.5 (44.1) cm^3, and 122.0 ± 152.7 (50.0) cm^3, respectively. The initial admitting blood glucose value was not correlated with the initial infarct volume ($r=0.050$, $P=0.6249$), however, it was correlated with Δinfarct volume (1 h–baseline) ($r=0.255$, $P=0.0126$), Δinfarct volume (24 h–baseline) ($r=0.280$, $P=0.0073$), and Δinfarct volume (7 days–baseline) ($r=0.340$, $P=0.0014$). Three patients (ICA occlusion($n=1$), M1 occlusion ($n=1$) and M2 occlusion($n=1$)) did not have large degree of infarct volume expansion in the first 24 h of stroke onset(<2; ratio of infarct volume at 24 h/initial infarct volume), but had large degree of delayed infarct volume expansion (>2; ratio of infarct volume at 7 days/infarct volume at 24 h). Of them, two patients had hyperglycemia.

The initial infarct volume did not differ between the normoglycemic and hyperglycemic groups (27.4 ± 72.1 cm^3 vs. 28.9 ± 46.5 cm^3, $P=0.6228$). However, infarct volumes at 1 h, 24 h, and 7 days were

Table 1
Clinical characteristics of patients.

	Admission blood glucose		P
	<130 mg/dl	≥130 mg/dl	
	No = 45	No = 52	
Age (years)	76.5 ± 11.6	76.2 ± 9.1	0.487
Female	18 (40.0%)	31 (59.6%)	0.054
Time from symptom onset to treatment, min	135.0 ± 31.9	138.7 ± 29.9	0.587
Risk factors			
Hypertension	30 (48.4%)	32 (51.6%)	0.600
Diabetes mellitus	3 (6.7%)	12 (23.1%)	0.026
Hyperlipidemia	8 (17.8)	7 (13.5%)	0.558
Atrial fibrillation (AF)	27 (60.0%)	36 (69.2%)	0.342
Smoking	17 (37.8%)	13 (25.0%)	0.175
Systolic blood pressure (mm Hg)	154.3 ± 20.5	153.6 ± 19.4	0.548
Diastolic blood pressure (mm Hg)	84.9 ± 14.9	83.8 ± 15.7	0.676
Laboratory data			
Leucocytes (/μl)	6284.7 ± 2395.6	7421.7 ± 2631.4	0.006
Platelets (×10,000/μl)	18.2 ± 4.5	20.1 ± 5.5	0.096
Glucose (mg/dl)	113.4 ± 9.8	171.3 ± 37.4	<0.0001
HbA1C	5.4 ± 0.4	5.7 ± 0.6	0.001
CRP(mg/dl)	0.6 ± 1.2	0.6 ± 1.4	0.118
Stroke type			
Cardioembolic stroke	27 (60.0%)	37 (71.2%)	0.248
Large vessel diseases	3 (6.7%)	4 (7.7%)	0.846
Undetermined stroke	15 (33.3%)	11 (21.2%)	0.177
MRI findings			
Occluded artery			
ICA	12 (26.7%)	18 (34.6%)	0.398
M1	20 (44.4%)	24 (46.2%)	0.866
M2	13 (28.9%)	10 (19.2%)	0.265
Recanalization 1 h after t-PA			
Present	19 (42.2%)	21 (40.4%)	1.000
Complete	7 (15.6%)	5 (9.6%)	0.376
Partial	12 (26.7%)	16 (30.8%)	0.657
Hemorrhagic transformation on T2[a] at 24 hours	17 (37.8%)	25 (48.1%)	0.307
NIHSS score at baseline	13.8 ± 6.1	17.1 ± 6.3	0.013
1 h after onset			
Dramatic recovery	7 (15.6%)	4 (7.7%)	0.337
Good recovery	8 (17.8%)	16 (30.8%)	0.139
Worsening	2 (4.4%)	2 (3.8%)	1.000
24 h after onset			
Dramatic recovery	16 (35.6%)	13 (25.0%)	0.257
Good recovery	12 (26.7%)	13 (25.0%)	0.852
Worsening	3 (6.7%)	7 (13.5%)	0.331
7 days after onset			
Dramatic recovery	25 (55.6%)	19 (36.5%)	0.061
Good recovery	8 (17.8%)	9 (17.3%)	0.952
Worsening	5 (11.1%)	12 (23.1%)	0.122
mRS 0–2 at 3 months[a]	16/37	10/45	0.042
Infarct volume (cm^3)			
Baseline	27.4 ± 72.1	28.9 ± 46.5	0.623
1 h	34.9 ± 73.2	54.4 ± 66.1	0.020
24 h	69.9 ± 120.2	115.6 ± 123.6	0.010
7 day	85.4 ± 140.7	156.2 ± 157.1	0.006

[a] 15 patients with initial mRS≥2 were excluded.

larger in the hyperglycemic group than in the normoglycemic group (54.4 ± 66.1 cm^3 vs. 34.9 ± 73.2 cm^3, P = 0.02 for 1 h; 115.6 ± 123.6 cm^3, vs. 69.9 ± 120.2 cm^3, P = 0.0102 for 24 h; and 156.2 ± 157.1 cm^3, vs. 85.4 ± 140.7 cm^3, P = 0.0061 for 7 days; Fig. 1).

Follow-up MRA 1 h after t-PA administration showed early recanalization in 40 patients. Infarct volume at baseline and 1 h after t-PA infusion was not different between patients with and without early recanalization (18.6 ± 21.9 cm^3 vs. 35.0 ± 74.8 cm^3, P = 0.3832; and 26.6 ± 33.2 cm^3 vs. 58.6 ± 84.6 cm^3, P = 0.0792). However, infarct volumes at 24 h and 7 days were smaller in patients

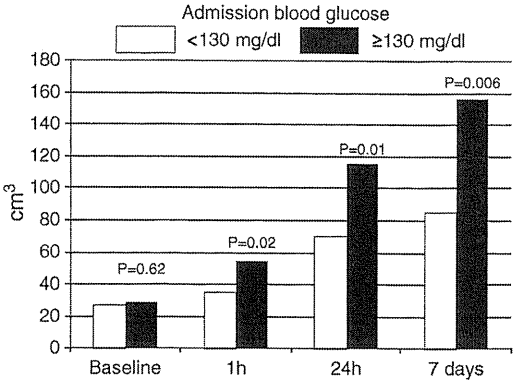

Fig. 1. Serial infarct volumes at baseline, 1 h, 24 h, and 7 days after t-PA therapy in normoglycemic and hyperglycemic patients.

with early recanalization than in those without early recanalization (49.0 ± 64.9 cm^3 vs. 127.8 ± 145.2 cm^3, P = 0.0074; and 49.6 ± 52.3 cm^3 vs. 173.5 ± 1178.3 cm^3, P = 0.0002).

We assessed correlation between admitting blood glucose value and Δinfarct volume between patients with and without early recanalization. In 40 patients with early recanalization, infarct volumes at baseline, 1 h, 24 h, and 7 days were not different between normoglycemic and hyperglycemic patients (22.3 ± 23.4 cm^3 vs.15.4 ± 19.8 cm^3, P = 0.2847, 19.7 ± 21.9 cm^3 vs.32.8 ± 40.4 cm^3, P = 0.4564, 35.6 ± 37.6 cm^3 vs. 61.2 ± 81.4 cm^3, P = 0.3098 and 39.6 ± 45.9 cm^3, vs. 60.1 ± 57.8 cm^3, P = 0.3602) (Table 2). Δinfarct volume (7 days—baseline) was not associated with admitting blood glucose value (Fig. 2A r = 0.225, P = 0.1173). On the other hand, in patients without early recanalization, baseline infarct volume was not different between normoglycemic and hyperglycemic patients (31.2 ± 93.2 cm^3 vs.38.1 ± 56.6 cm^3, P = 0.1145). However, infarct volumes at 1 h, 24, and 7 days were less in normoglycemic than in hyperglycemic patients (46.1 ± 93.6 cm^3 vs.69.1 ± 76.2 cm^3, P = 0.0249; 95.9 ± 152.2 cm^3 vs.156.3 ± 135.0 cm^3, P = 0.0120; and 121.7 ± 177.2 cm^3 vs. 217.9 ± 170.0 cm^3 P = 0.0066) (Table 2). Δinfarct volume (7 days—baseline) was correlated with admitting blood glucose value (Fig. 2B, r = 0.372, P = 0.0078).

Table shows the initial NIHSS scores and patient recovery at 1 h, 24 h and 7 days after t-PA administration and mRS scores 0–2 at 3 months for the 4 subgroups. Dramatic recovery was more frequent and worsening 7 days after t-PA administration was less common in normoglycemic than in hyperglycemic patients, but the differences were not significant (55.6% vs. 36.5%, P = 0.0606, and 11.1% vs. 23.5%, P = 0.1117). With respect to the presence and absence of early recanalization, dramatic recovery was more frequent and worsening 7 days after t-PA administration was less common in patients with early recanalization than in those without (68.2% vs. 31.8%, P < 0.0001; and 5.1% vs. 26.3%, P = 0.0072). Next, with respect to the presence of early recanalization and hyperglycemia and normoglycemia, among the 4 groups, dramatic recovery at 24 h and at 7 days after t-PA administration was most frequent in patients with early recanalization and normoglycemia (P < 0.0001). On the other hand, worsening at 24 h and at 7 days was most frequent in patients without early recanalization and with hyperglycemia (P = 0.0215).

Fifteen patients with mRS scores of ≥2 before t-PA therapy were excluded from outcome analysis. Of the 78 patients, 26 (31.7%) patients had a good outcome (mRS 0–2) 3 months after t-PA infusion. A good outcome was more frequent in normoglycemic than in hyperglycemic patients (43.2% vs. 22.2%, P = 0.0418). In patients with early recanalization, the frequency of good outcome was not different between normoglycemic and hyperglycemic patients (62.5% vs. 42.1%, P = 0.2291). On the other hand, in patients without early recanalization, a good outcome was more frequent in normoglycemic than in

Table 2
Serial infarct volume, patient outcome and admission blood glucose level in patients with and without early recanalization.

	Early recanalization		P	Non-early recanalization		P
	Admission blood glucose			Admission blood glucose		
	<130 mg/dl	≥130 mg/dl		<130 mg/dl	≥130 mg/dl	
	No = 19	No = 21		No = 26	No = 31	
Infarct volume						
Baseline	22.2 ± 24.1	15.4 ± 19.8	0.2847	31.2 ± 93.2	38.1 ± 56.6	0.1145
1 h	19.7 ± 21.9	32.8 ± 40.4	0.4564	46.1 ± 93.6	69.1 ± 76.2	0.0249
24 h	35.6 ± 37.6	61.2 ± 81.4	0.3098	95.9 ± 152.2	156.3 ± 135.0	0.0120
7 days	39.6 ± 45.9	60.1 ± 57.8	0.3620	121.7 ± 177.2	217.9 ± 170.0	0.0066
NIHSS score at baseline	14.8 ± 6.2	15.5 ± 6.7	0.7349	13.1 ± 6.1	18.1 ± 5.9	0.0040
1 h after onset						
Dramatic recovery	6 (31.6%)	3 (14.3%)	0.2647	1 (3.8%)	1 (3.2%)	0.9999
Good recovery	5 (26.3%)	8 (28.1%)	0.5106	3 (11.5%)	8 (25.8%)	0.1740
Worsening	0 (0%)	0 (0%)	0.9999	2 (7.7%)	2 (6.5%)	0.9999
24 h after onset						
Dramatic recovery	11 (57.9%)	8 (38.1%)	0.3422	5 (19.2%)	5 (16.1%)	0.7591
Good recovery	6 (31.6%)	8 (38.1%)	0.6661	6 (23.1%)	5 (16.1%)	0.5079
Worsening	0 (0%)	0 (0%)	0.9999	3 (11.5%)	7 (22.6%)	0.2750
7 days after onset						
Dramatic recovery	17 (89.5%)	13 (61.9%)	0.0692	8 (31.8%)	6 (19.4%)	0.3187
Good recovery	2 (10.5%)	2 (9.5%)	0.9999	6 (23.1%)	7 (22.6%)	0.9645
Worsening	0 (0%)	2 (9.5%)	0.4872	5 (19.2%)	10 (32.3%)	0.2659
mRS 0–2 at 3 months[a]	10/16 (62.5%)	8/19 (42.1%)	0.3561	6/21 (28.6%)	2/26 (7.7%)	0.0686

[a] 15 patients with initial mRS ≥ 2 were excluded.

hyperglycemic patients, but the difference was not significant (28.6% vs. 7.7%, P = 0.1152). Among the 4 groups, a good outcome at 3 months was less common in patients without early recanalization and with hyperglycemia (P = 0.0007) (Table 2).

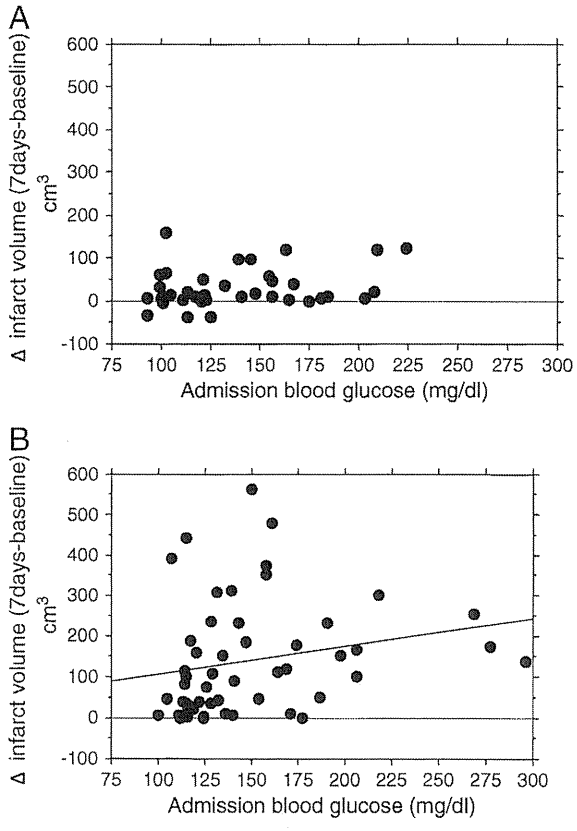

Fig. 2. Relationship between baseline admitting blood glucose value and Δinfarct volume (7 days–baseline) in patients with early recanalization (panel A, r = 0.225, P = 0.1173) and without early recanalization (panel B, r = 0.372, P = 0.0078).

4. Discussion

The present study demonstrated that admission hyperglycemia before t-PA administration was associated with infarct expansion and poor outcome. However, in patients who had early recanalization (within 1 h) after t-PA infusion, hyperglycemia did not appear to adversely affect infarct volume and patient outcome.

In the present study, a good outcome was less frequent in the hyperglycemic group than in the normoglycemic group. Hyperglycemia on admission is reportedly associated with a poor recanalization rate for the occluded artery and increased risks of death, symptomatic intracranial hemorrhage, and poor functional status [17,18]. However, in the present study, the hyperglycemic group did not show less frequent recanalization of the occluded artery than the normoglycemic group. Asymptomatic intracranial hemorrhage on T2* at 24 h after t-PA infusion tended to be more frequent in hyperglycemic than in normoglycemic patients, but this difference was not significant.

We also demonstrated that hyperglycemia appeared to contribute to poor outcomes in stroke patients. Hyperglycemia should worsen both cortical intracellular brain acidosis and mitochondrial function in the ischemic penumbra, which causes direct neuronal toxicity [26]. Furthermore, hyperglycemia-mediated increase in matrix metalloproteinase-9 can cause neuronal damage by an increase in cerebral edema [5]. Interestingly, hyperglycemic group had leucocytosis. The reason may contribute to inflammatory and oxidative stress. Moreover, hyperglycemia may be responsible for a procoagulant state that can further compromise blood supply to penumbral areas in acute ischemic stroke [5,26]. However, the underlying mechanisms remain unclear.

In the present study, the infarct volume expanded more in hyperglycemic than in normoglycemic patients, which was compatible with Baird's report [1]. Furthermore, we demonstrated that early recanalization (within 1 h) after t-PA administration did not adversely affect the final infarct volume and patient outcome even in patients with hyperglycemia. Early arterial recanalization is a marker of good outcome after t-PA infusion [7–9]. Els [27] reported that hyperglycemia was associated with infarct volume expansion as well as poor outcome despite t-PA induced recanalization. Els examined early recanalization using TCD on days 3 and 7 [27]. Therefore, there was considerable difference in the time of early recanalization between Els and the present study. Therefore, early recanalization after t-PA

administration should rescue the ischemic penumbra, and hyperglycemia did not adversely affect infarct volume and patient outcome. However, some patients without early recanalization after t-PA administration might have delayed recanalization. The ECASS III [28] subgroup analysis showed that delayed recanalization up to 4.5 h after the onset of stroke symptoms was also effective [29]. In the present study, although we did not investigate association between hyperglycemia and patient outcome in patients with delayed recanalization, delayed recanalization should rescue the ischemic penumbra, and hyperglycemia might not so adversely affect infarct volume and patient outcome compared with patients without delayed recanalization.

Surprisingly, three cases had large degree of delayed infarct expansion between 24 h and 7 days, but not in the first 24 h after stroke onset. All of them did not have early recanalization, and two had hyperglycemia. We suspected that collateral blood flow might be damaged after 24 h of t-PA infusion in such patients. The one of causes may be hyperglycemia, but it is unclear.

The present study had several limitations. First, the use of MRA is somewhat inaccurate for detecting vessel occlusion or stenosis [30]. Second, rates of recanalization may have been lower because the dose of t-PA (0.6 mg/kg) [19] is lower in Japan than the internationally approved dosage of 0.9 mg/kg. However, recently, Mori et al. [31] reported the dosage efficacy of 0.6 mg/kg, including the potential for early recanalization of occluded cerebral arteries, compared with the internationally approved dosage of 0.9 mg/kg in acute ischemic stroke. Thirdly, early recanalization is not the same as reperfusion. Reperfusion may be better than early recanalization to assess infarct volume expansion. Perfusion-weighted MRI (PWI) can detect hypoperfused tissue. However, in order to not delay the start of t-PA treatment, we did not include PWI examinations in the present study. Finally, the number of our patients was small, so, we need a large sample to prove our hypnosis.

In conclusion, admission hyperglycemia before t-PA administration was associated with infarct volume expansion and poor outcome. However, if early recanalization (within 1 h) after t-PA infusion occurs, the effect of hyperglycemia should not adversely affect infarct volume and patient outcome.

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Clinical and MRI Predictors of No Early Recanalization Within 1 Hour After Tissue-Type Plasminogen Activator Administration

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Background and Purpose—The aim of the present study was to investigate independent clinical and MRI factors associated with no early recanalization within 1 hour after tissue-type plasminogen activator (tPA) administration.

Methods—Patients with acute stroke within 3 hours of onset who were treated with tPA were studied prospectively. Patients with internal carotid artery, M1, and M2 occlusion were enrolled, and independent clinical and MRI factors associated with no early recanalization within 1 hour after tPA administration were examined using multivariate logistic regression analysis.

Results—One hundred thirty-two patients (63 men; mean age, 76.4±10.2 years; internal carotid artery occlusion in 37 patients, M1 occlusion in 58, and M2 occlusion in 37) were enrolled. Follow-up MR angiography within 60 minutes after tPA infusion revealed early recanalization in 49 (37.1%) patients (complete in 16 patients, partial in 33) and no recanalization in 83 (62.9%). Using 8 variables (atrial fibrillation, time from stroke onset to treatment ≥140 minutes, use of warfarin, glucose ≥135 mg/dL, large artery diseases, internal carotid artery occlusion, M1 occlusion, and M1 susceptibility vessel sign on T2*) identified on univariate analysis at $P<0.2$, multivariate logistic regression analysis revealed that M1 susceptibility vessel sign was the only independent factor associated with no early recanalization (OR, 7.157; 95% CI, 1.756 to 29.172; $P=0.006$). The sensitivity, specificity, positive predictive value, and negative predictive value of M1 susceptibility vessel sign for predicting no early recanalization were 31.3%, 93.9%, 89.7%, and 44.7%, respectively.

Conclusions—Of clinical and MRI factors before tPA infusion, M1 susceptibility vessel sign on T* is the only independent factor associated with no early recanalization within 1 hour after tPA administration. (***Stroke*. 2011;42:3150-3155.)**

Key Words: MRA, T2* ■ recanalization ■ susceptibility vessel sign ■ tissue-type plasminogen activator

Intravenous administration of tissue-type plasminogen activator (tPA) can improve clinical outcomes in patients with acute ischemic stroke.[1] Early arterial recanalization has been recognized as a marker of good outcome after tPA infusion.[2–7] Alexandrov et al[8] reported that, during tPA infusion, recanalization was complete in 30% and partial in 40% of patients on transcranial Doppler. Thus, approximately one third of patients with acute stroke treated with tPA do not undergo early recanalization. Therefore, intravenous tPA therapy has some limitation.

Lewandowski et al[9] reported that combined intravenous and local intra-arterial tPA therapy in patients with stroke within 3 hours of onset was feasible and provides better recanalization. Recently, the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial reported the efficacy of the Merci Retriever for opening intracranial vessels in patients ineligible for tPA.[10] Furthermore, Multi MERCI investigators reported that mechanical thrombectomy is efficacious in opening intracranial vessels in patients with acute ischemic stroke who have failed intravenous tPA.[11] Failed tPA patients may benefit from thrombectomy within 6 hours of stroke onset. Therefore, to add endovascular therapy to intravenous tPA in failed tPA patients, predicting no early recanalization before tPA infusion would be important.

Diabetes, delayed time from onset to treatment, noncardioembolic stroke, and atrial fibrillation have been reported to be associated with no early recanalization after tPA therapy.[12–15] MRI but not CT can accurately assess the ischemic infarct volume on diffusion-weighted imaging, the occluded artery on MR angiography (MRA), and the susceptibility vessel sign (SVS) on T2* in the superacute phase of stroke.[16] Internal carotid artery (ICA) occlusion and M1 SVS on T2* were also reported to be associated with failed tPA.[2,17,18] Therefore, we added MRI findings to clinical factors and investigated independent clinical and MRI factors associated with no early recanalization within 1 hour after tPA administration using multivariate logistic regression analysis.

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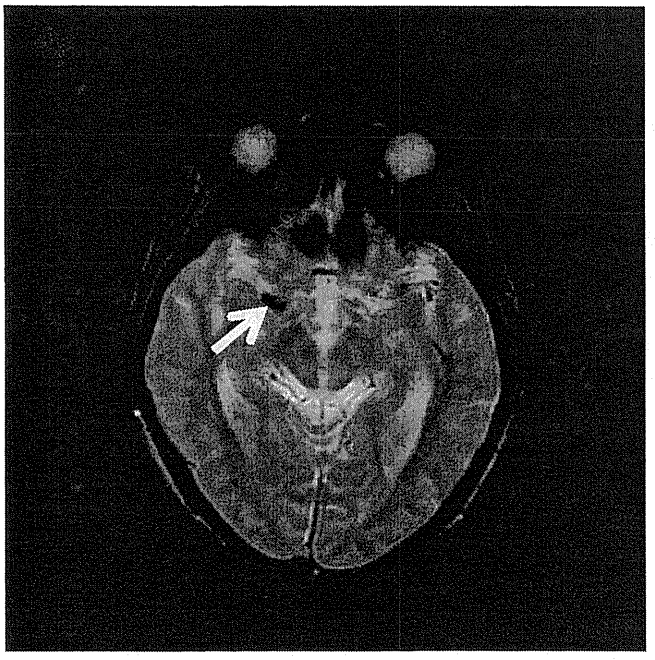

Figure 1. Arrow shows M 1 SVS on T2*. SVS indicates susceptibility vessel sign.

Subjects and Methods

Consecutive patients with acute anterior circulation ischemic stroke treated with tPA within 3 hours of stroke onset between October 2006 and March 2011 were prospectively studied. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded due to contraindications for MRI. Patients with M1, M2, and ICA occlusion on MRA before tPA infusion were studied. The following clinical data were collected from all patients: (1) patient age and sex; (2) arterial blood pressure before tPA infusion; (3) National Institutes of Health Stroke Scale score before tPA infusion; (4) presence of arterial occlusion on MRA before tPA infusion; (5) presence or absence of early recanalization of occluded arteries within 60 minutes after tPA administration; (6) M1 SVS on T2* before tPA infusion; (7) ischemic volume on diffusion-weighted imaging before tPA infusion; (8) vascular risk factors including hypertension, diabetes mellitus, and hyperlipidemia; (9) presence of potential cardiac sources of emboli; (10) stroke subtype; (11) laboratory parameters before tPA infusion; and (12) administration of antithrombotic agents such as antiplatelet agents and warfarin. Inclusion and exclusion criteria for intravenous tPA were in accordance with the Japan Alteplase Clinical Trial.[19]

Before tPA infusion, MRI studies including diffusion-weighted imaging, MRA, and T2* were performed to measure ischemic volume using National Institutes of Health Image software and to identify and assess the occluded arteries and M1 SVS. Follow-up MRA was performed within 60 minutes after the end of tPA administration to identify the presence or absence of recanalization in the occluded arteries. MRI was performed using a commercially available echoplanar instrument operating on a 1.5-T unit (Signa EXCITE XL Version 11.0; GE Healthcare, Milwaukee, WI).

The presence of large artery occlusion was assessed by MRA. Occluded arteries on initial MRA were identified as follows: M1 occlusion, M2 occlusion, and ICA occlusion. Recanalization was graded as complete, partial, or no recanalization as follows: (1) complete recanalization, reappearance of the entire occluded artery and distal branch of vessels; (2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery; and (3) no recanalization, persistent occlusion. Early recanalization was defined as complete or partial recanalization, and no early recanalization was defined as persistent occlusion 60 minutes after tPA infusion. The M1 SVS was defined as a hypointense signal of the proximal middle cerebral artery on T2* within a vascular cistern in corresponding symptomatic occlusive vessels (Figure 1).[17] An experienced researcher (K.K.) who evaluated the MRA findings was blinded to patient clinical background.

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography, 24-hour electrocardiographic monitoring, and transthoracic echocardiography. The following potential emboligenic cardiac diseases were considered: atrial fibrillation; acute and previous myocardial infarction; mitral valve disease; and dilated cardiomyopathy. All patients underwent color-flow duplex carotid ultrasonography on the day of admission. Significant arterial stenosis was identified if stenosis >50% or ulcerated plaque was found in the affected artery corresponding to the neurological deficits.

All patients had baseline blood samples drawn in the emergency room before MRI. Main hemostatic variables (leukocyte count, erythrocyte count, and platelet count), $HbA1_C$, C-reactive protein, creatinine, glucose, and D-dimer levels were determined.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment criteria[20] to determine stroke subtype. Large vessel disease was defined as >50% arterial stenosis or occlusion corresponding to neurological deficits in the absence of a source of cardiac embolism. Cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Undetermined stroke was used when no etiologic source of emboli could be identified.

Statistical analysis was performed using StatView Version 5 statistical software to establish associations between no early recanalization and clinical factors. Significance of intergroup differences was assessed using Fisher exact test for categorical variables and the Mann–Whitney U test and the Kruskal-Wallis U test for continuous variables. Multivariate logistic regression analysis was performed to determine factors independently associated with no early recanalization using variables with $P<0.2$ on univariate analysis, which were considered to be potential factors associated with no early recanalization. Cutoff values for continuous variables were determined using the areas under receiver operating characteristic curves. Values of $P<0.05$ were considered significant. All study protocols were approved by the ethics committee of Kawasaki Medical School.

Results

A total of 193 consecutive patients with stroke was treated with tPA. Four patients were excluded because they had a pacemaker, and 29 patients had vertebral–basilar stroke. Of the remaining 160 patients, initial MRA demonstrated ICA occlusion in 37 patients, M1 occlusion in 58 patients, M2 occlusion in 37 patients, and no occlusion in 28 patients. Thus, 132 patients (63 men, 69 women; mean age, 76.4±10.2 years) were enrolled in the present study.

Follow-up MRA within 60 minutes after tPA infusion revealed recanalization in 49 (37.1%) patients (complete in 16 patients, partial in 33) and no recanalization in 83 (62.9%). There were no differences in clinical characteristics between patients with complete recanalization and partial recanalization (Table 1). Then, we divided patients into 2 groups: early recanalization group (n=49) and no early recanalization group (n=83). Table 2 shows the 2 groups' clinical characteristics. The glucose level was higher in the no early recanalization group than in the early recanalization group (158.6±63.0 mg/dL versus 137.1±34.2 mg/dL, $P=0.0400$). ICA occlusion was more frequently observed in the no early recanalization group than in the early recanalization group (34.9% versus 16.3%, $P=0.0214$). M1 SVS was observed in 29 patients (22.0%, ICA occlusion in 19 and M1 occlusion in 10). Regarding site of occlusion, 19 (51.4%) of 37 patients with ICA occlusion had M1 SVS, and 10 (17.2%) of 58 patients with M1 occlusion had 1.