The Presence of a Right-to-Left Shunt Is Associated With Dramatic Improvement After Thrombolytic Therapy in Patients With Acute Ischemic Stroke

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Background and Purpose—The efficacy of pharmacological thrombolysis using tissue plasminogen activator depends on the relative fibrin content of the thrombus. We investigated whether patients with stroke with a right-to-left shunt (RLS), whose embolic source was associated with fibrin-rich thrombus formed in the venous system, were more likely to improve dramatically after thrombolytic therapy than those without RLS.

Methods—Patients with acute stroke treated with tissue plasminogen activator were assessed prospectively to determine the clinical factors associated with "dramatic improvement" after tissue plasminogen activator administration. "Dramatic improvement" was defined as a ≥10-point reduction in the total National Institutes of Health Stroke Scale score or a total National Institutes of Health Stroke Scale score of 0 or 1 at 7 days. The presence of an RLS was determined using contrast transcranial Doppler within 6 hours of stroke onset.

Results—Forty-four patients (26 males; mean age; 73.0±10.7 years; baseline National Institutes of Health Stroke Scale score,13.4±6.6) were enrolled. Twenty-one patients had dramatic improvement (D group). Contrast transcranial Doppler demonstrated an RLS in 17 (35.4%) patients. On multivariate logistic regression analysis using hyperlipidemia, atrial fibrillation, RLS, DWI-ASPECTS (>8), baseline National Institutes of Health Stroke Scale score (<10), and glucose (<120 mg/dL) as variables with a $P<0.1$ on univariate analysis, RLS (OR, 5.9; CI,1.3 to 27.3; $P=0.022$) was the only independent factor associated with dramatic improvement.

Conclusion—The presence of an RLS on contrast transcranial Doppler was an independent factor associated with dramatic improvement after tissue plasminogen activator administration. (***Stroke.* 2009;40:303-305.**)

Key Words: atrial fibrillation ■ outcome ■ right-to-left shunting ■ TCD ■ tissue plasminogen activator

Intravenous administration of tissue plasminogen activator (tPA) can improve clinical outcomes in patients with acute ischemic stroke.[1] However, the clinical markers associated with dramatic improvement after tPA therapy have not been identified.

One potential cause of embolic stroke is a right-to-left shunt such as a patent foramen ovale, which is termed paradoxical embolism.[2,3] In paradoxical embolism, most of the thrombus is produced in the deep venous system and is rich in fibrin.[4] The action of tPA is considered to be fibrin-dependent because of its favorable binding constant for fibrin-bound plasminogen and its activation of plasminogen in association with fibrin.[5,6] Therefore, we hypothesized that tPA thrombolysis was more effective in patients with stroke with a right-to-left shunt than in patients without a right-to-left shunt. Contrast transcranial Doppler (c-TCD) examination was performed to evaluate the presence of a right-to-left shunt within 6 hours of stroke onset. The association between dramatic recovery after tPA thrombolysis and the presence of a right-to-left shunt on c-TCD was investigated.

Subjects and Methods

Consecutive patients with acute anterior circulation stroke treated with tPA within 3 hours of stroke onset between October 2006 and January 2008 were studied.

The following clinical data were collected from all patients: (1) patient age and gender; (2) arterial blood pressure before tPA infusion; (3) National Institutes of Health Stroke Scale (NIHSS) score before and 7 days after tPA infusion; (4) vascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia; (5) presence of potential cardiac embolic sources; (6) presence of a right-to-left shunt on c-TCD; (7) stroke subtype using modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[7]; (8) laboratory parameters before tPA infusion; (9) administration of antithrombotic agents such as antiplatelet agents and warfarin; (10) baseline diffusion-weighted imaging findings before tPA infusion using DWI-ASPECTS[8] and M1 occlusion, M2 occlusion, and internal cerebral artery occlusion on initial MR angiography were identified; and (11) the presence of deep venous thrombosis by ultrasonography within 24 hours after tPA infusion. The inclusion and exclusion criteria for the use of intravenous tPA were in accordance with those of the Japan Alteplase Clinical Trial.[9]

Neurologists prospectively determined the patients' NIHSS scores before and 7 days after tPA infusion. Three measures of clinical recovery based on modified methods used in previous study were

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Table 1. Univariate Analysis: Factors Associated With Dramatic Recovery at 7 Days

	Total Patients (n=48)	Dramatic Recovery (n=21)	Nondramatic Recovery (n=27)	P
Age, years	73.0±10.7	70.2±12.6	75.1±8.6	0.423
Male	26 (54.2%)	13 (61.9%)	13 (48.1%)	0.343
Hypertension	25 (52.1%)	10 (47.6%)	15 (55.6%)	0.588
Diabetes mellitus	6 (12.5%)	2 (9.5%)	4 (14.8%)	0.683
Hyperlipidemia	8 (16.7%)	6 (28.6%)	2 (7.4%)	0.051
AF	24 (50.0%)	7 (33.3%)	17 (63.0%)	0.042
Previous myocardial infarction	4 (8.3%)	4 (19.2%)	0	0.146
Right-to-left shunt	17 (35.4%)	11 (52.4%)	6 (22.2%)	0.030
Deep venous thrombosis	0/27 (0%)	0/14 (0%)	0/13 (0%)	1.000
TOAST classification				
Cardioembolic	28 (58.3%)	10 (47.6%)	18 (66.7%)	0.184
Atherothrombotic	3 (6.3%)	2 (9.5%)	1 (3.7%)	0.581
Lacunar	3 (6.3%)	1 (4.8%)	2 (7.4%)	0.999
Undetermined/others	14 (29.2%)	8 (38.1%)	6 (22.2%)	0.230
Baseline DWI ASPECTS score	8.2±2.2	8.9±1.7	7.6±2.5	0.071
MR angiography				
Internal carotid artery occlusion	11 (22.9%)	3 (14.3%)	8 (29.6%)	0.304
M1 occlusion	20 (41.7%)	10 (47.6%)	10 (37.0%)	0.461
M2 occlusion	6 (12.5%)	1 (4.8%)	5 (18.5%)	0.212
No occlusion	11 (22.9%)	7 (33.3%)	4 (14.8%)	0.174
Use of antiplatelet therapy				
Warfarin or aspirin	16 (33.3%)	10 (45.5%)	8 (26.6%)	0.217
NIHSS score at baseline	13.4±6.6	11.6±6.7	14.7±6.3	0.085
Systolic blood pressure, mm Hg	161.3±23.7	160.0±24.8	162.3±23.2	0.633
Diastolic blood pressure, mm Hg	90.5±16.5	87.6±17.0	93.0±16.0	0.229
Time from symptom onset to treatment, minutes	143.0±27.8	138.4±27.6	146.6±27.9	0.262

used.[10] "Dramatic improvement" was defined as a ≥10-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. "Good improvement" was defined as a ≥4-point reduction in the total NIHSS score. "Worsening" was defined as a ≥4-point increase in the total NIHSS score. Patients were divided into 2 groups: patients who had dramatic improvement (D group) and patients who did not have dramatic improvement (non-D group).

The presence of a right-to-left shunt was determined using c-TCD within 6 hours of stroke onset. The middle cerebral artery or the right internal carotid artery was insonated from a temporal window or the orbital window with a 2-MHz handheld transducer (DWL MultiDop T, Lindau, Germany). A right-to-left shunt was diagnosed if at least one microbubble after injection of the agitated saline was recorded in one vessel within 30 seconds after injection.[11]

Statistical analysis was performed using StatView version 5 statistical software to establish which factors were associated with a good outcome. Significance of intergroup differences was assessed using Fisher exact test for categorical variables and the Mann–Whitney *U* test and Kruskal-Wallis *U* test for continuous variables. Multivariable logistic regression analysis was performed to determine factors that could be considered independent predictors of dramatic improvement after tPA therapy. Variables with a $P<0.1$ on univariate analysis were included in the multivariate model. Values of $P<0.05$ were considered statistically significant.

Results

A total of 65 consecutive patients with stroke were treated with tPA. One patient was excluded because he had a pacemaker. Thirteen patients had a posterior circulation stroke. Three patients were excluded because of insufficient transcranial Doppler studies. As a result, 48 patients (26 males, 22 females; mean age, 73.0±10.7 years) were enrolled. The times from symptom onset to the initial MRI study and tPA bolus were 95.6±30.5 minutes and 143.0±27.8 minutes, respectively.

Dramatic improvement, good improvement, and worsening at Day 7 were observed in 21, 9, and 8 patients, respectively. Therefore, the D group had 21 patients and the non-D group had 27 patients. One non-D group patient had a symptomatic cerebral hemorrhage. C-TCD demonstrated a right-to-left shunt in 17 (35.4%) patients. The initial MR angiogram demonstrated occluded brain arteries in 37 patients (77.1%) and no occlusive lesions in 11 patients (22.9%). Table 1 shows the characteristics of the D group and the non-D group. Atrial fibrillation (AF) was less common and a right-to-left shunt was more common in the D group than in the non-D group (33.3% versus 63.0%, $P=0.042$; and 52.4% versus 22.2%, $P=0.030$, respectively).

Table 2 shows the clinical characteristics of patients with and without a right-to-left shunt. Patients with a right-to-left shunt more frequently had dramatic improvement (64.7% versus 32.3%, $P=0.030$). On the other hand, internal cerebral artery occlusion was more frequently seen in patients without a right-to-left shunt than in patients with a right-to-left shunt (35.5% versus 0%, $P=0.004$).

Table 2. Characteristics of Patients With and Without a Right-to-Left Shunt

	Right-to-Left Shunting		
	Patients With (N=17)	Patients Without (N=31)	*P*
Neurological recovery			
Dramatic improvement	11 (64.7%)	10 (32.3%)	0.030
Good improvement	1 (5.9%)	8 (25.8%)	0.130
Worsening	4 (23.5%)	4 (12.9%)	0.429
MR angiography before tPA infusion			
Internal carotid artery occlusion	0	11 (35.5%)	0.004
M1 occlusion	10 (58.8%)	10 (32.3%)	0.074
M2 occlusion	2 (11.8%)	4 (12.9%)	0.909
No occlusion	5 (29.4%)	6 (19.4%)	0.428

On multivariate logistic regression analysis using hyperlipidemia, AF, a right-to-left shunt, DWI ASPECTS (>8), baseline NIHSS score (<10), and glucose (<120 mg/dL) as variables that had a $P<0.1$ on univariate analysis, a right-to-left shunt (OR, 5.9; CI, 1.3 to 27.3; $P=0.022$) was found to be the only independent factor associated with dramatic improvement (Table 3).

Discussion

In the present study, the presence of a right-to-left shunt, which was demonstrated in 35.4% of patients, was found to be associated with neurological dramatic improvement after tPA infusion.

It has been suggested that the efficacy of pharmacological thrombolysis is dependent on the relative fibrin content.[12,13] Therefore, fibrin-rich thrombi may be more resolved by tPA than platelet-rich thrombi. Thus, patients with acute stroke with a right-to-left shunt, whose embolic source is thought to be a fibrin-rich thrombus in the deep venous system, may more frequently have dramatic improvement after tPA thrombolysis. However, patients with AF having fibrin-rich clots did not frequently have dramatic recovery. Clot dissolution depends on clot size and age as well as thrombus composition.[14] Fresh and old clots have been shown to form in cardiac cavities, including the left atrium in cases with AF.[15] Furthermore, transesophageal echocardiography sometimes demonstrates large thrombi in the left atrium in patients with stroke with AF. Therefore, we believe that thrombus associated with AF sometimes contain old and large clot and may be resistant to tPA therapy.

The present study had several limitations. Because some patients with acute stroke with disturbed consciousness and aphasia could not perform the Valsalva maneuver, an adequate transcranial Doppler could not be performed in all patients. Thus, the frequency of a right-to-left shunt might have been underestimated. Second, of course, patients with a right-to-left shunt do not all always have paradoxical embolism. We could not find the deep venous thrombosis in any patients with a right-to-left shunt at all. The thrombus might be dissolved by tPA therapy. We may be able to find deep venous thrombosis before tPA infusion. Finally, the number of our patients was small. Therefore, we need a large sample study to confirm our results.

Table 3. Multivariate Analysis of Variables Associated With Dramatic Response to tPA

	OR	95% CI	*P*
Right-to-left shunt	5.93	1.289–27.293	0.022
Hyperlipidemia	4.98	0.499–49.601	0.171
AF	0.82	0.146–4.584	0.818
DWI ASPECTS >8	2.19	0.453–10.565	0.330
NIHSS score at baseline <10	2.27	0.393–13.085	0.360
Glucose <120 mg/dL	3.63	0.770–17.082	0.103

In conclusion, the presence of a right-to-left shunt detected by c-TCD was associated with neurological dramatic improvement after tPA treatment. C-TCD examination may be useful for predicting the outcome in patients with acute stroke treated with tPA.

Disclosures

None.

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Letters to the Editor

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Response to Letter by Sharma et al and Leibeskind

Response:

We would like to thank Dr Sharman et al and Dr Liebeskind for their interest in our recent publication in which presence of a right-to-left shunt was associated with dramatic improvement after thrombolytic therapy in acute ischemic stroke patients. We demonstrated that tissue plasminogen activator (t-PA) thrombolysis was more effective in stroke patients with a right-to-left shunt than in patients without a right-to-left shunt. We believed that the action of t-PA is considered to be fibrin-dependent because of its favorable binding constant for fibrin-bound plasminogen and its activation of plasminogen in association with fibrin.[1,2] Sharma et al proposed the possibility that high dose of t-PA through patent foramen ovale (PFO) could result in high rate of recanalization of occluded artery after t-PA infusion. They took interest in the relationship between size or function grading of PFO and dramatic clinical recovery. We were very interested in their suggestion and investigated size of PFO in our patients. Contrast transcranial Doppler demonstrated an right to left shunt in 17 (35.4%) patients. Of them, 13 patients were examined by transesophageal echocardiography to evaluate the PFO. The severity of shunt was assessed by transesophageal echocardiography using modified Lethen criteria, <10 (small), and >10 (large) microbubbles/3 seconds, respectively, with contrast echo.[3] Three of 5 (60%) patients with large PFO had dramatic recovery, and 7 of 8 (88%) patients with small PFO had one. Therefore, there was no difference in rate of dramatic recovery between large and small PFO. However, the sample size is small. We should need more samples to elucidate Sharman's hypothesis.

Liebeskind suggested that venous hemodaynamics enhanced collateral perfusion in patients with PFO, which induced the dramatic recovery after t-PA therapy. We read the comments with great interest. As Liebeskind mentioned, venous hemodaynamics might be affected by parallel cardiac preload. Therefore, we believe that patients with atrial fibrillation (AF) may have potential heart failure, and venous pressure is increased. In the present study, 24 patients with AF were enrolled. In fact, of them, 11 patients had brain natriuretic peptide >200 pg/mL, which indicates potential cardiac failure. However, patients with AF did not have more frequently dramatic recovery than those without AF (29.2% versus 58.3%; $P=0.0417$). Thus, we did not reach agreement that venous hemodaynamics enhanced collateral perfusion, which might induce the dramatic recovery after t-PA therapy. Off course, there is difference in venous hemodaynamics between patients with PFO and AF. Therefore, we should need a study to elucidate Liebeskind's hypothesis.

Disclosures

None.

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M1 Susceptibility Vessel Sign on T2* as a Strong Predictor for No Early Recanalization After IV-t-PA in Acute Ischemic Stroke

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Background and Purpose—In acute stroke patients treated with intravenous tissue plasminogen activator (t-PA), early recanalization of occluded arteries can improve the clinical outcome. The magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi can present as hypointense signals on T2*-weighted gradient echo imaging. We investigated whether the gradient echo imaging M1 susceptibility vessel sign (M1 SVS) can predict no early recanalization after t-PA infusion.

Methods—Patients with internal carotid artery and M1 occlusion were prospectively studied. MRI studies, including DWI, T2*, and MRA, were performed before and within 30 minutes and 24 hours after t-PA infusion. The NIHSS score was obtained before and 7 days after t-PA administration. The relationship between the presence of the M1 SVS and no early recanalization and patient outcome was examined.

Results—A total of 48 patients (29 men; mean age, 74.6±11.2 years) were enrolled. M1 SVS was present in 13 (27.1%) patients and absent in 35 (72.9%) patients. There were no significant differences in clinical characteristics between the 2 groups. Follow-up MRA within 30 minutes after t-PA infusion revealed that 20 (57.1%) of the 35 patients without the M1 SVS had early recanalization, but that none of the 13 patients with the M1 SVS had early recanalization (P=0.0002). Seven days after t-PA infusion, dramatic improvement was more frequently observed in patients without the M1 SVS (51.4%) than in those with the M1 SVS (0%, P=0.0007).

Conclusion—The M1 SVS on T2* appears to be a strong predictor for no early recanalization after t-PA therapy. (***Stroke.* 2009;40:3130-3132.**)

Key Words: T2* recanalization ■ tissue plasminogen activator ■ outcome

Intravenous administration of tissue plasminogen activator (IV-t-PA) can improve clinical outcomes in patients with acute ischemic stroke.[1] Early arterial recanalization has been recognized as a marker of good outcome after t-PA infusion.[2–4] However, about one-third of acute stroke patients treated with t-PA do not undergo recanalization.[5]

The magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi may result in hypointense signals on T2*-weighted gradient echo imaging (GRE). Cho et al[6] reported that red thrombi in occluded vessels were visualized as hypointense signals within vascular cisterns on T2*. They called such radiological findings the "GRE susceptibility vessel sign (GRE SVS)." The GRE SVS may reflect thrombus composition. Hemoglobin desaturation from oxyhemoglobin to deoxyhemoglobin occurs within a few hours. Thus, in hyperacute clot cases, the main component may still be oxyhemoglobin, and such emboli would not be identified as GRE SVS on T2*. In other words, the GRE SVS is present in older thrombi, which may be resistant to t-PA therapy.

We investigated whether acute stroke patients with the GRE SVS at the M1 portion of the middle cerebral artery (MCA), which we termed M1 SVS, had early recanalization after IV-t-PA, using serial magnetic resonance angiography (MRA) studies both before and immediately after t-PA administration. We also investigated the relationship between the M1 SVS and patient outcome.

Subjects and Methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 hours of stroke onset between October 2006 and October 2008 were studied prospectively. Of them, the patients with internal carotid artery (ICA) occlusion and proximal M1 occlusion on MRA before t-PA infusion were enrolled into the present study. Inclusion and exclusion criteria for intravenous t-PA were used in accordance with the Japan Alteplase Clinical Trial.[7]

Before t-PA infusion, all patients underwent MRI studies, including diffusion-weighted imaging (DWI), T2*, and MRA, to identify the occluded arteries. Next, follow-up MRA was performed within 30 minutes and 24 hours after the end of t-PA administration to identify the presence or absence of recanalization in the occluded

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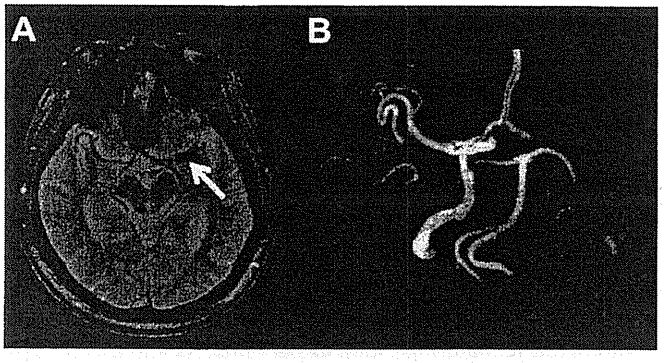

Figure. A 74-year-old male patient with atrial fibrillation presented with right hemiparesis and aphasia. His NIHSS score was 22. There are M1 SVS in the occluded vessel on T2* (A; arrow) and in the left ICA occlusion (B) on acute scans (65 minutes after onset). The patient was treated with IV t-PA. Follow-up MRA within 30 minutes after t-PA infusion did not show early recanalization. The patient died from brain herniation 5 days after t-PA therapy.

arteries. The M1 SVS was defined as a hypointense signal of the horizontal of the MCA on T2* within a vascular cistern in corresponding symptomatic occlusive vessels.[6] 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).

Recanalization was graded as complete, partial, or no recanalization, as follows: (1) complete recanalization, reappearance of entire occluded artery and distal branch of vessels; (2) partial recanalization, restoration of part of the distal vessel supplied by an occluded artery; and (3) no recanalization, persistent occlusion.

We used 3 measures of clinical recovery based on modifications of methods used in previous studies.[1] "Dramatic improvement" was defined as a reduction of ≥10 in the total NIHSS score or complete recovery. "Good improvement" was defined as a reduction in the total NIHSS score of ≥4. "Worsening" was defined as an increase in the total NIHSS score of ≥4 or death.

Statistical analysis was performed using StatView version 5 statistical software to establish associations among no recanalization, clinical recovery, and clinical factors. Significance of intergroup differences was assessed using Fisher 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.

Results

A total of 94 consecutive stroke patients were treated with t-PA. One patient was excluded because he had a pacemaker. Initial MRA demonstrated ICA occlusion in 22 patients and M1 occlusion in 26 patients. Thus, 48 patients (29 men, 19 women; mean age, 74.6±11.2 years) were enrolled into the present study.

The M1 SVS was present in 13 (27.1%) patients and absent in 35 (72.9%) patients. The Figure shows a patient with the M1 SVS. Table 1 shows the 2 groups' clinical characteristics. There were no significant differences in the clinical characteristics between the 2 groups.

Follow-up MRA within 30 minutes after t-PA infusion revealed recanalization in 20 patients (complete in 14 patients, partial in 6) and no recanalization in 28. Interestingly, all 13 patients with the M1 SVS had no recanalization (Table 2). However, 20 (57.1%) of the 35 patients without the M1 SVS had recanalization ($P=0.0002$). One patient with the M1 SVS did not have follow-up MRA 24 hours after t-PA infusion because of severe stroke. Of the remaining 12 patients with the M1 SVS, complete recanalization 24 hours after t-PA infusion was not observed in any patient, but partial recanalization was seen in 7 patients (58.3%). Of the 35 patients without the M1 SVS, 26 (72.3%) had recanalization (partial in 12 patients and complete in 14 patients; $P=0.4653$).

Table 1. Univariate Statistics for Patients With and Without M1 SVS on T2*

	M1 SVS on T2*		
	With n=13	Without n=35	*P*
Age	74.5±8.9	74.7±12.1	0.7019
Female	4 (30.8%)	15 (42.9%)	0.5218
Time from symptom onset to treatment, min	145.8±28.0	142.6±27.2	0.8528
Hypertension	5 (38.5%)	22 (62.9%)	0.1300
Diabetes mellitus	1 (7.7%)	5 (14.3%)	0.5393
Hyperlipidemia	1 (7.7%)	5 (14.3%)	0.5393
Right to left shunt (RLS)	2/12 (16.7%)	10 (29.4%)	0.4725
Atrial fibrillation (AF)	11 (84.6%)	22 (62.9%)	0.1819
Occluded artery			0.2104
ICA	8 (61.5%)	14 (40.0%)	
Complete ICA occlusion	7	10	
ICA top occlusion	1	4	
M1	5 (38.5%)	21 (60.0%)	
Use of antiplatelet therapy			
Warfarin	2 (15.4%)	6 (17.1%)	0.9999
Aspirin	2 (15.4%)	7 (20.0%)	0.9999
NIHSS score	19.2±3.5	16.9±6.8	0.2103
DWI-ASPECTS	5.8±2.9	7.5±2.2	0.0513
Systolic blood pressure, mm Hg	156.2±17.4	156.0±22.7	0.6933
Diastolic blood pressure, mm Hg	90.3±17.7	86.7±14.7	0.2899
Glucose, mg/dl	135.8±25.2	146.3±45.8	0.8255
Stroke Type			
Cardioembolic stroke	11 (84.6%)	26 (74.3%)	0.7021
Large artery diseases	0 (0.0%)	4 (11.4%)	0.5627
Undetermined stroke	2 (15.4%)	5 (14.3%)	0.9999

Table 2 shows the neurological recovery of patients with and without the M1 SVS on T2*. At 24 hours after t-PA infusion, dramatic improvement was more frequently observed in patients without the M1 SVS (34.2%) than in patients with the M1 SVS (0%, $P=0.021$). At 7 days after t-PA infusion, dramatic improvement was more frequently observed in patients without the M1 SVS (51.4%) than in patients with the M1 SVS (0%, $P=0.0007$). However, worsening was more frequently observed in patients with the M1 SVS (46.2%) than in patients without the M1 SVS (14.3%, $P=0.0475$).

Discussion

The present study demonstrated that no patient with the M1 SVS had early recanalization after t-PA therapy, and that such patients had poor outcomes. Thus, the M1 SVS on T2* appears to be a strong predictor for no early recanalization after t-PA therapy.

Table 2. Neurological Recovery of Patients With and Without M1 SVS on T2*

	M1 SVS on T2*		
	With n=13	Without n=35	P
Recanalization after t-PA infusion			
Within 1 hour	0	20 (51.7%)	0.0002
Partial	0	6	
Complete	0	14	
24 hours	7/12 (58.3%)	26 (74.3%)	0.4653
Partial	7/12	12	
Complete	0	14	
24 hours after t-PA infusion			
Dramatic recovery	0	12 (34.2%)	0.021
Good improvement	2 (15.4%)	11 (31.4%)	0.4662
Worsening	2 (15.4%)	1 (2.9%)	0.1744
7 days after t-PA infusion			
Dramatic recovery	0	18 (51.4%)	0.00007
Good improvement	3 (23.1%)	7 (20.0%)	0.9999
Worsening	6 (46.2%)	5 (14.3%)	0.0475

Clot dissolution depends on clot size, the site of occlusion, clot composition, surface area of the clot exposed to blood flow, and penetration of t-PA into the clot structure.[8] Old and large thrombi may be more resistant to thrombolysis than fresh and small thrombi. Blood goes though sequential stages of degradation from oxyhemoglobin to deoxyhemoglobin, methemoglobin, and then hemosiderin. Deoxyhemoglobin, methemoglobin, and hemosiderin can be detected as signal loss on T2*.[9] If the main component of hyperacute clots is oxyhemoglobin, T2* cannot demonstrate them as hypointense (the M1 SVS) on T2*. Patients without the M1 SVS had more fresh clots than those with the M1 SVS. Furthermore, the M1 SVS may be a sign of a more extensive thrombus. In fact, 8 of 13 patients with the M1 SVS had ICA occlusion. Therefore, t-PA therapy may be effective in patients without the M1 SVS compared with those with the M1 SVS.

Cho et al[6] reported that the GRE SVS might predict cardioembolic stroke. In the present study, 11 of 13 patients with the GRE SVS had cardioembolic stroke, which was compatible with Cho's results. Schellinger et al[10] reported that the GRE SVS did not predict the therapeutic effect of IV-t-PA therapy. They studied ICA (n=9), M1 (n=13), P1 (n=5), A1 (n=1), and branch (n=16) occlusion. However, we assessed the presence of the M1 SVS at the proximal M1 and ICA occlusion and excluded P1, A1, and branch occlusion from our study. They did not assess the recanalization rate in patients with the SVS of each artery, and the early recanalization rate in patients with the SVS of M1 and ICA occlusion was not mentioned. We believe that some of their patients with the SVS of P1, A1, and branch occlusion had early recanalization because the embolus size in such patients was small compared with ICA and M1 occlusion. This may have resulted in the apparent discrepancy between Schellinger's and our results.

The present study had several limitations. Our MRI parameters for DWI and T2* were a slice thickness of 5 mm and an interslice gap of 2 mm. An MRI protocol with a gap of 2 mm might be not the ideal protocol for the detection of vessel signs if the vessel was 2 to 3 mm thick. Secondly, the use of MRA is somewhat inaccurate for detecting vessel occlusion or stenosis.[11] Third, MRI cannot be performed in patients in whom metallic materials, such as pacemakers and metal clips, have been implanted. One such patient was excluded from our study. Finally, the rates of recanalization may have been lower because the dose of t-PA (0.6 mg/kg)[7] is lower in Japan than the internationally approved dosage of 0.9 mg/kg.

In conclusion, M1 SVS on T2* appears to be a strong predictor for no early recanalization after t-PA therapy.

Disclosures

None.

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Recanalization of the MCA should play an important role in dramatic recovery after t-PA therapy in patients with ICA occlusion

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ABSTRACT

Background and purpose: The intravenous t-PA thrombolysis is not thought to be effective in most patients with internal carotid artery (ICA) occlusion. However, we have sometimes observed dramatic recovery in patients with ICA occlusion after t-PA therapy. The aim of the present study was to investigate the mechanism of dramatic recovery in such patients.

Methods: Consecutive ICA occlusion patients treated with t-PA were prospectively studied. MRI, including MRA, was performed before and within 1 h and 24 h after t-PA thrombolysis. Patients were divided into 2 groups: dramatic recovery (D group) and non-dramatic recovery (ND group).

Results: The subjects consisted of 21 consecutive stroke patients (14 males; mean age, 76.5 ± 8.4 years). Six (28.6%) patients (D group) had dramatic improvement and 15 (71.4%) patients (ND group) did not. The frequency of partial or complete recanalization within 1 h and 24 h after t-PA infusion was 14.3% and 50.0% for the ICA, 9.5% and 40.0% for the MCA, and 23.8% and 65.0% for the ICA or MCA, respectively. There was no difference in the frequency of ICA recanalization 24 h after t-PA infusion between the 2 groups (66.7% for D group vs. 42.9% for ND group, $P=0.629$); however, MCA recanalization was more frequent in the D group than in the ND group (100.0% vs. 14.3%, $P=0.0004$).

Conclusion: Recanalization of the MCA, which provides collateral flow, appears to play an important role in dramatic recovery after t-PA therapy in patients with ICA occlusion.

1. Introduction

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcome in acute ischemic stroke patients [1,2]. However, several investigators reported that t-PA was not effective in patients with internal carotid artery (ICA) occlusion [3,4]. 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. However, we have sometimes observed dramatic recovery in patients with ICA occlusion after t-PA therapy. The aim of the present study was to investigate the frequency of dramatic recovery after t-PA infusion in patients with ICA occlusion and the mechanism in such patients using magnetic resonance imaging (MRI), including MR angiography (MRA).

2. Subjects and methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2005 and October 2008 were studied. Patients with ICA occlusion on MRA before t-PA infusion were enrolled in the present study. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded, since MRI is contraindicated in such patients. Furthermore, patients with recurrence within 7 days of t-PA infusion were also excluded. The inclusion and exclusion criteria for intravenous t-PA that were used were in accordance with the Japan Alteplase Clinical Trial [5].

The following clinical data were collected from all patients: 1) age and gender; 2) NIHSS scores before and 24 h and 7 days after t-PA infusion; 3) DWI-ASPECTS on initial DWI before t-PA infusion; 4) recanalization of the ICA occlusion within 1 h, 24 h, and 7 days after t-PA infusion; 5) vascular risk factors, including hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL); 6) presence of potential cardiac sources of emboli; and 7) modified Rankin scale (mRS) at 3 months after t-PA therapy.

A neurologist determined the NIHSS scores before and 24 h and 7 days after t-PA infusion. Three measures of clinical recovery based on modified methods used in previous studies were used [6]. "Dramatic improvement" was defined as a ≥10 point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. "Good improvement" was defined as a ≥4 point reduction in the total NIHSS score. "Worsening" was defined as a ≥4 point increase in the total NIHSS score. The patients were divided into 2 groups: patients who had dramatic improvement 7 days after t-PA therapy (D group) and patients who did not have dramatic improvement (ND group). "Poor outcome" was defined as an NIHSS score ≥20 7 days after t-PA therapy. Symptomatic cerebral hemorrhage was defined as a ≥4 point

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increase in the total NIHSS score. Favorable and poor outcomes at 3 months after t-PA therapy were defined as an mRS 0–3 and >3 or death, respectively.

Prior to t-PA infusion, MRI studies, including DWI and MRA, were done to measure DWI-ASPECTS [7] and to identify the presence of arterial occlusion. ICA occlusion was defined as follows: MRA showed no delineation of the ICA (complete ICA occlusion) or partial delineation of the ICA without delineation of the top of the ICA (ICA top occlusion). Furthermore, the status of the MCA was also investigated and classified as complete MCA occlusion, partial MCA occlusion, or patent MCA. Subsequently, follow-up MRA was performed within 1 h and 24 h after t-PA administration to determine the presence or absence of recanalization of the ICA occlusion and the MCA occlusion. Recanalization was graded as complete, partial, or no recanalization, as follows: 1) complete recanalization, reappearance of the entire occluded artery and the distal vessel branches; 2) partial recanalization, from complete occlusion to partial occlusion, and restoration of part of the distal vessels supplied by the occluded artery; and 3) no recanalization, persistent complete and partial occlusion.

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). DWI-ASPECTS was used to evaluate the affected middle cerebral artery territory. The experienced researcher (K.K.) who evaluated the MRA findings was blinded to patient clinical background and the initial presence of an occluded artery.

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 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 and absence of a source of cardiac embolism and >50% arterial stenosis. Undetermined stroke was used when no etiological source of emboli could be identified.

The clinical characteristics of the 2 groups were compared. Statistical analysis was performed using StatView version 5 statistical software. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann–Whitney *U* test and the Kruskal–Wallis *U* test for continuous variables. Values of $P<0.05$ were considered statistically significant. All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients.

3. Results

Ninety-two consecutive stroke patients received t-PA treatment. The initial MRA demonstrated ICA occlusion in 22 patients, but 1 patient was excluded because of a recurrent stroke 24 h after t-PA infusion. Therefore, 21 patients with ICA occlusion (14 males, 7 females; mean age, 76.5 ± 8.4 years) were enrolled in the present study. The time from symptom onset to the initial MRI study was 93.5 ± 27.1 min, and the time from symptom onset to the t-PA bolus was 145.9 ± 25.7 min. Mean baseline NIHSS score was 19.5 ± 5.0 (9–27).

3.1. Initial MRA findings

Of 21 patients with ICA occlusion, 10 patients had complete ICA and MCA occlusion. One patient had complete ICA occlusion with partial MCA occlusion. Eight patients had ICA top occlusion with complete MCA occlusion. Two patients had ICA top occlusion with partial MCA occlusion.

3.2. Follow-up MRA 1 h after t-PA infusion

Overall, 16 patients had no recanalization, 4 patients had partial recanalization (3 patients in the ICA, 1 in the MCA), and 1 patient had complete recanalization of the MCA but persistent complete ICA occlusion.

3.3. Follow-up MRA 24 h after t-PA infusion

One patient who died due to brain herniation 4 days after t-PA therapy did not undergo MRA. Thus, follow-up MRA was performed in 20 patients. Two patients had complete recanalization of both the ICA and the MCA, 11 had partial recanalization (5 patients in the ICA, 3 in the MCA, and 3 in both the ICA and the MCA), and 7 patients had no recanalization. Of the 11 patients who had partial recanalization, 2 had partial recanalization of the ICA with complete MCA recanalization, 3 had partial recanalization of the ICA but persistent MCA occlusion, 2 patients had complete ICA recanalization but persistent MCA occlusion, and 1 had complete ICA recanalization with partial MCA recanalization. Thus, the frequency of partial recanalization was 25.0% for the ICA, 15.0% for the MCA, and 0.0% for both the ICA and the MCA. On the other hand, the frequency of complete recanalization was 25.0% for the ICA, 25.0% for the MCA, and 10.0% for both the ICA and the MCA. Therefore, the frequency of partial or complete recanalization was 50.0% for the ICA, 40.0% for the MCA, and 65.0% for the ICA and the MCA.

3.4. Patient outcome 7 days and 3 months after t-PA therapy

Dramatic improvement, good improvement, and worsening at day 7 were observed in 6, 5, and 4 patients, respectively. Therefore, the D group had 6 patients, and the ND group had 15 patients. No patients had symptomatic cerebral hemorrhages. Table 1 shows the characteristics of the 2 groups. The initial NIHSS score, blood pressure, and glucose were lower in patients with dramatic improvement than in patients with no dramatic improvement. Seven days after t-PA therapy, 66.7% of patients with no dramatic improvement had an

Table 1
Univariate analysis: factors associated with dramatic recovery at 7 days.

	Dramatic recovery	Non-dramatic recovery	*P*
	N=6	*N*=15	
Age (years)	79.2 ± 8.1	75.5 ± 8.6	0.3115
Male	6 (100.0%)	8 (53.3%)	0.0609
Hypertension	4 (66.7%)	7 (46.7%)	0.6351
Diabetes mellitus	1 (16.7%)	3 (20.0%)	0.9999
Hyperlipidemia	1 (16.7%)	2 (13.3%)	0.9999
Atrial fibrillation (AF)	2 (33.3%)	11 (73.3%)	0.1462
TOAST classification			
Cardioembolic	1 (16.7%)	11 (73.3%)	0.0464
Atherothrombotic	3 (50.0%)	1 (6.7%)	0.0526
Undetermined/others	2 (33.3%)	3 (20.0%)	0.5975
Baseline DWI-ASPECTS score	7.7 ± 2.4	6.1 ± 2.7	0.1990
MRA			
ICA top occlusion	3 (50.0%)	7 (46.7%)	0.9999
Complete ICA occlusion	3 (50.0%)	8 (53.3%)	0.9999
Partial MCA occlusion	0 (0.0%)	3 (30.0%)	0.5263
Complete MCA occlusion	6 (100.0%)	12 (80.0%)	0.5263
NIHSS score at baseline	15.3 ± 5.9	21.1 ± 3.7	0.0391
24 h after t-PA infusion	6.8 ± 7.7	19.3.3 ± 4.8	0.0391
7 days after t-PA infusion	3.0 ± 3.5	21.9 ± 9.5	0.0005
NIHSS score ≥20 at 7 days	0 (0.0%)	10 (66.7%)	0.0057
Systolic blood pressure (mmHg)	143.3 ± 11.3	164.3 ± 15.6	0.0081
Diastolic blood pressure (mmHg)	72.8 ± 9.3	94.3 ± 16.8	0.0045
Time from symptom onset to treatment, min	139.3 ± 26.3	149.0 ± 26.5	0.1328
Glucose (mg/dl)	131.2 ± 30.2	151.7 ± 22.1	0.0199

NIHSS score≥20, but no patients with dramatic recovery had an NIHSS score≥20. At 3 months after t-PA therapy, four patients had favorable outcome (2; mRS 0, and 2; mRS 3), and 17 patients (5; mRS 4, 7; mRS 5 and 5; death) had poor outcome.

3.5. Relation between recanalization of the ICA and the MCA and patient outcome 7 days after t-PA therapy

3.5.1. Within 1 h after t-PA infusion

There was no difference in the frequency of ICA recanalization between the 2 groups. However, the patients with dramatic improvement more frequently had MCA recanalization than those without dramatic improvement, but the difference was not statistically significant (33.3% vs. 0.0%, $P=0.07$, Table 2).

3.5.2. 24 h after t-PA infusion

There was no difference in the frequency of ICA recanalization between the 2 groups. However, all patients with dramatic recovery had MCA recanalization, but only 14.3% of patients without dramatic recovery had MCA recanalization (100.0% vs. 14.3%, $P=0.0004$, Table 2). Fig. 1 shows a patient with dramatic recovery due to MCA recanalization without ICA recanalization. There was no difference in the frequency of an NIHSS score≥20 between those with ICA recanalization and those with no recanalization (40% vs. 50%, 0.9999). However, fewer patients with MCA recanalization had an NIHSS score≥20 than those with no MCA recanalization (11.1% vs. 63.6%, $P=0.0281$).

3.6. Relation between recanalization of the ICA and the MCA and patient outcome 3 months after t-PA therapy

In four patients with favorable outcome, no patients had ICA recanalization and 1 (25.0%) had MCA recanalization within 1 h after t-PA infusion. On the other hand, 3 (17.6%) patients out of 17 patients with poor outcome had ICA recanalization and 1 (5.9%) had MCA recanalization. At 24 h after t-PA infusion, all four patients with favorable outcome had MCA recanalization and 2 (50%) patients had ICA recanalization. On the other hand, 4 (25.0%) out of 16 patients with poor outcome had MCA recanalization and 8 (50.0%) patients had ICA recanalization. Thus, the patients with favorable outcome more frequently had MCA recanalization at 24 h after t-PA infusion than those with poor outcome (100% vs. 25.0%, $P=0.0144$), but there

Table 2
Relation between recanalization rate of ICA and MCA occlusion and patient outcome 7 days after t-PA therapy.

	Dramatic recovery	No dramatic recovery	*P*
	N=6	*N*=15	
Within 1 h after t-PA infusion			
Recanalization of ICA	1 (16.7%)	2 (13.3%)	0.99999
Partial	1	2	
Complete	0	0	
Recanalization of MCA	2 (33.3%)	0 (0.0%)	0.0714
Partial	1	0	
Complete	1	0	
	N=6	*N*=14	
24 h after t-PA infusion			
Recanalization of ICA	4 (66.7%)	6 (42.9%)	0.6285
Partial	2	3	
Complete	2	3	
Recanalization of MCA	6 (100%)	2 (14.3%)	0.0004
Partial	2	1	
Complete	4	1	

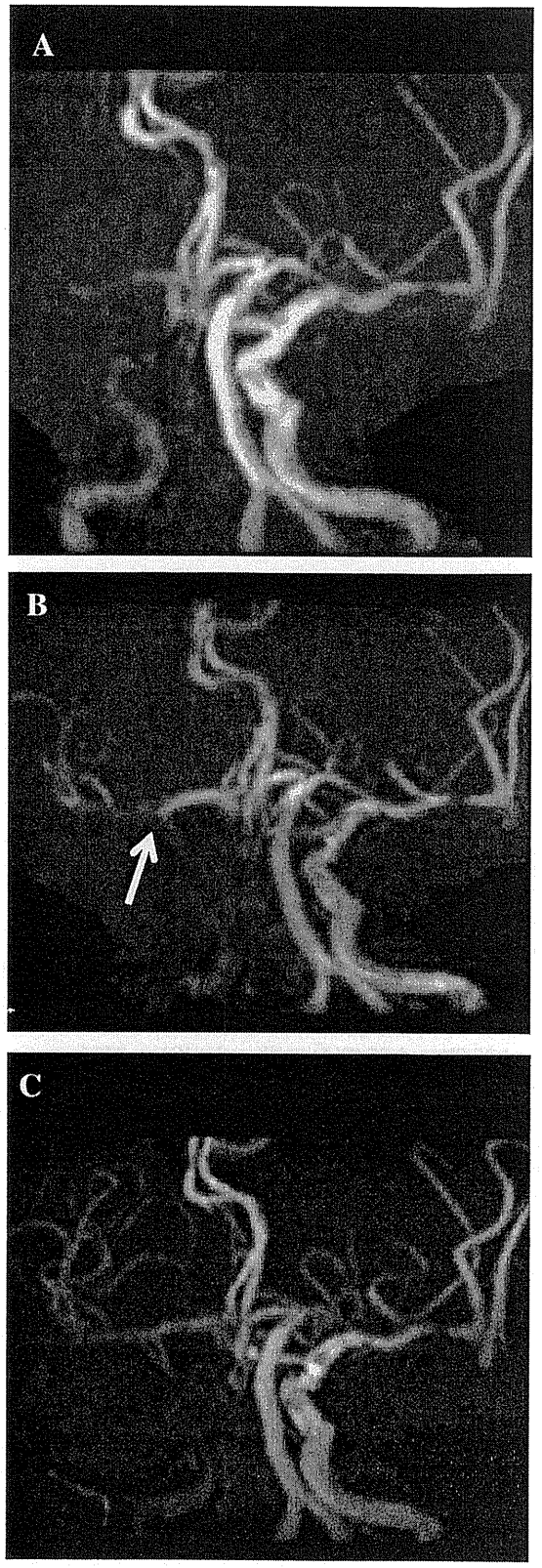

Fig. 1. A 93-year-old man with an NIHSS score of 11 before t-PA infusion. A shows the initial MRA before t-PA infusion, which shows ICA top occlusion and MCA occlusion. B shows the follow-up MRA within 1 h after t-PA infusion, which shows recanalization (arrow) of the MCA, but no recanalization of the ICA. The NIHSS score changed from 11 to 4. C demonstrates the follow-up MRA 24 h after t-PA; it shows persistent MCA recanalization, but no recanalization of the ICA. The NIHSS score decreased to 1, and the patient had dramatic recovery after t-PA therapy.

Table 3
Relation between recanalization rate of ICA and MCA occlusion of favorable and poor patient outcome 3 months after t-PA therapy.

	Favorable outcome	Poor outcome	P
	N=4	N=17	
Within 1 h after t-PA infusion			
Recanalization of ICA	0 (0.0%)	3 (17.6%)	0.9999
Partial	0	3	
Complete	0	0	
Recanalization of MCA	1 (25.5%)	1 (5.9%)	0.3524
Partial	0	1	
Complete	1	0	
	N=4	N=16	
24 h after t-PA infusion			
Recanalization of ICA	2 (50.0%)	8 (50.0%)	0.9999
Partial	1	4	
Complete	1	4	
Recanalization of MCA	4 (100.0%)	4 (25.0%)	0.0144
Partial	2	1	
Complete	2	3	

was no difference in frequency of ICA recanalization between the two groups (50% vs. 50%, $P=09999$) (Table 3).

4. Discussion

In the present study, dramatic recovery was observed in 28.7% of patients, and recanalization of the MCA but not the ICA was strongly associated with dramatic recovery.

Previous reports using TCD showed that the recanalization rate of MCA occlusion was approximately 60% within 1 h after t-PA administration [8–12]. However, the recanalization of ICA occlusion after t-PA infusion was lower, resulting in poor patient outcome [3,4]. The reason for failure of recanalization was that the embolus responsible for ICA occlusion was larger and, therefore, likely to be resistant to t-PA therapy. In the present study, the frequency of partial and complete recanalization within 1 h and 24 h after t-PA infusion was 14.3% and 50.0% for the ICA and 9.5% and 40.0% for the MCA, and 23.8% and 65.0% for either the ICA or MCA, respectively. Therefore, the recanalization rate within 1 h after t-PA infusion was lower, but the recanalization rate 24 h after t-PA was relatively higher than we expected.

Interestingly, recanalization of the MCA but not the ICA was strongly associated with dramatic recovery, and no MCA recanalization was related to poor outcome. Considering the possible mechanism, this appears reasonable. Even if the ICA occlusion did not recanalize, recanalization of the occluded MCA should supply blood as collateral flow to the penumbral area of the MCA territory. Therefore, recanalization of the MCA but not the ICA after t-PA infusion should play an important role in dramatic recovery.

Recently, during t-PA infusion, TCD was shown to enhance recanalization of the occluded MCA [11]. According to our data, even in patients with ICA occlusion, TCD, which might help MCA recanalization, should be a useful tool to potentially improve patient outcome after t-PA therapy.

In the present study, 6 (28.6%) of the 21 patients with ICA occlusion treated with t-PA therapy had dramatic recovery. Estimates of the natural history of ICA occlusion suggest that only 2%–12% will go on to have a good recovery, 40%–69% will be left with a severe deficit, and 16%–55% will die as a result of their infarct [13]. Therefore, t-PA therapy may be effective in patients with ICA occlusion, but its effectiveness may be low. Flint [14] reported that mechanical thrombectomy of acute intracranial ICA occlusion using the Merci Retriever device had a high rate of successful vessel recanalization. The recanalization rate was 53% using the Merci Retriever alone and 63% using the Merci Retriever plus adjunctive endovascular treatment. Therefore, when we see acute stroke patients with ICA occlusion, we may consider the Merci Retriever rather than t-PA thrombolysis.

The present study had several limitations. Firstly, 1 patient who died did not have follow-up MRI studies. Secondly, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis [15]. Finally, the dose of t-PA (0.6 mg/kg, the approved dose in Japan) [5] used was lower than the internationally approved dosage of 0.9 mg/kg.

In conclusion, the present study demonstrated that dramatic recovery was observed in 28.6% of patients, and recanalization of the ICA and MCA within 1 h and 24 h after t-PA infusion was 0% and 23.1%, and 65.0% and 10.0%, respectively. Recanalization of the MCA but not the ICA was strongly associated with dramatic recovery. Recanalization of the MCA, which provides collateral flow in ICA occlusion patients, appears to play an important role in dramatic recovery after t-PA therapy.

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Early Recanalization Rate of Major Occluded Brain Arteries after Intravenous Tissue Plasminogen Activator Therapy Using Serial Magnetic Resonance Angiography Studies

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Key Words
Tissue plasminogen activator · Magnetic resonance angiography · Acute stroke · Recanalization thrombolysis

Abstract
Purpose: The present study investigated early recanalization rate of major occluded arteries after tissue plasminogen activator (t-PA) infusion using serial magnetic resonance angiography (MRA) studies. ***Methods:*** Consecutive stroke patients treated with t-PA within 3 h of onset were prospectively studied. Four serial MRA studies were conducted: before, immediately, 24 h and 5–7 days after t-PA infusion. ***Results:*** Initial MRA demonstrated occluded brain arteries in 64 patients: M1 occlusion, 30 patients; M2, 12, and internal carotid artery (ICA), 22. Combining M1 and M2 occlusion, the recanalization rates (complete and partial) were 52.3% (19.0 and 33.3%) within 1 h, 80.9% (47.6 and 33.3%) at 24 h and 87.8% (73.2 and 14.6%) 7 days after t-PA infusion. However, the recanalization rate of ICA occlusion was 31.8% (4.5 and 27.3%) within 1 h, 51.1% (14.3 and 47.6%) at 24 h and 66.7% (38.9 and 27.8%) 7 days after t-PA infusion. Complete recanalization rate at 24 h and 7 days was lower in ICA occlusion than M1 and M2 occlusion ($p = 0.014$ and $p = 0.016$). ***Conclusion:*** Within 1 h after t-PA infusion, approximately half the patients with major arteries occlusion had early recanalization. ICA occlusion is resistant to intravenous t-PA therapy compared with middle cerebral artery occlusion.

The intravenous (IV) administration of tissue plasminogen activator (t-PA) can improve clinical outcome in acute ischemic stroke patients [1, 2]. IV thrombolysis using t-PA achieves arterial recanalization in approximately 50% of stroke cases [3–10]. In those studies, the recanalization rate during and after t-PA therapy was evaluated using transcranial Doppler (TCD). However, TCD sometimes cannot diagnose internal carotid artery (ICA) and M2 occlusion for methodology. Therefore, the early recanalization rate of ICA and M2 occlusion seems to be unclear. On the other hand, magnetic resonance angiography (MRA) can more correctly diagnose ICA and M2 occlusion than TCD [11]. The aim of the study was to assess the early recanalization rate of ICA, M1 and M2 occlusion after IV t-PA therapy using serial MRA.

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Methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2006 and April 2007 were prospectively studied. Only patients thought to have anterior-circulation ischemia were included in the present study. The following clinical data were collected from all patients: (1) patient age and gender; (2) arterial blood pressure before t-PA infusion; (3) NIHSS score before, 1 h after and 24 h after t-PA infusion; (4) presence of arterial occlusion on MRA before t-PA infusion; (5) presence or absence of recanalization of occluded arteries within 30 min, 24 h and 5–7 days after t-PA administration; (6) DWI-ASPECTS [12]; (7) vascular risk factors, including hypertension, diabetes mellitus and hyperlipidemia; (8) presence of potential cardiac sources of emboli; (9) stroke subtype [13], and (10) laboratory parameters before t-PA infusion. Inclusion and exclusion criteria for IV t-PA were in accordance with the Japan Alteplase Clinical Trial [14]. The dose of t-PA was 0.6 mg/kg.

Before t-PA infusion, magnetic resonance imaging (MRI) studies, including MRA, were performed to identify the occluded arteries. Next, follow-up MRA was performed within 1 h, 24 h and 7 days after the end of t-PA administration to identify the presence or absence of recanalization in the occluded arteries. Patients with heart valve replacements, pacemakers or clipping of cranial arteries were excluded because MRI is contraindicated in such patients.

All patients underwent MRI/MRA including diffusion-weighted imaging. MRI was performed using a commercially available echo planar instrument on a 1.5-T unit (Signa EXCITE XL version 11.0; GE Healthcare, Milwaukee, Wisc., USA). The presence of large artery occlusion was assessed by MRA. Occluded arteries on the initial MRA were identified as follows: M1, M2 and ICA occlusion. According to our previous criteria [15], recanalization was graded as complete, partial or no recanalization as follows: (1) complete recanalization, reappearance of the entire occluded artery and the distal branches; (2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery, and (3) no recanalization, persistent occlusion. Experienced researchers who evaluated the MRA findings were blinded to patient clinical background and initial presence of an occluded artery.

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography (ECG), 24-hour ECG monitoring and transthoracic echocardiography. Transesophageal echocardiography was also performed when appropriate. The following potential emboligenic cardiac diseases were considered: atrial fibrillation; acute and previous myocardial infarction; mitral valve disease; 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 that corresponded to the neurological deficits.

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

NIHSS scores were obtained before as well as 1 and 7 days after t-PA infusion by a neurologist. Three measures of clinical recovery based on modified methods used in previous studies were used [16]. 'Dramatic improvement' was defined as a reduction of ≥10 in the total NIHSS score or complete recovery, 'good improvement' was defined as a reduction in the total NIHSS score of ≥4 and 'worsening' was defined as an increase in the total NIHSS score of ≥4. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of ≥4 when the intracerebral hemorrhage was likely to be the cause of the clinical deterioration.

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 to determine stroke subtype. Large-vessel disease was defined as >50% arterial stenosis or occlusion corresponding to the neurological deficits in the absence of a source of cardiac embolism. A cardioembolic stroke was defined as the presence of potential cardiac sources of emboli. Lacunar stroke was defined as the presence of infarction <15 mm, the absence of a 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. Significance of intergroup differences was assessed using Fisher's exact test for categorical variables. Values of $p < 0.05$ were considered statistically significant. All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients. The design of the study was approved by the Ethics Committee of the Kawasaki Medical School.

Results

A total of 102 consecutive stroke patients received t-PA treatment. One patient was excluded because he had a pacemaker. One patient did not have MRI before t-PA infusion because there was no time for the MRI study. Twenty patients had a posterior circulation stroke. As a result, 80 patients (47 males, 33 females; mean age 74.1 ± 10.4 years) were enrolled in the present study. The duration between symptom onset and the initial MRI study and t-PA bolus were 94 ± 30 and 141 ± 29 min, respectively. Symptomatic cerebral hemorrhage within 7 days after t-PA infusion was observed in 1 patient with a baseline NIHSS score of 7.

MRA Results

Of the 80 patients with anterior circulation stroke, the initial MRA demonstrated occluded brain arteries in 64 patients (80.0%) and no occlusive lesions in 16 patients (20.0%). M1 was occluded in 30 patients, M2 in 12 and ICA in 22. Table 1 shows the clinical characteristics of the 64 patients with an occluded artery on the initial MRA. The outcome at 7 days after t-PA therapy of 16 patients without occlusive lesions was dramatic improve-

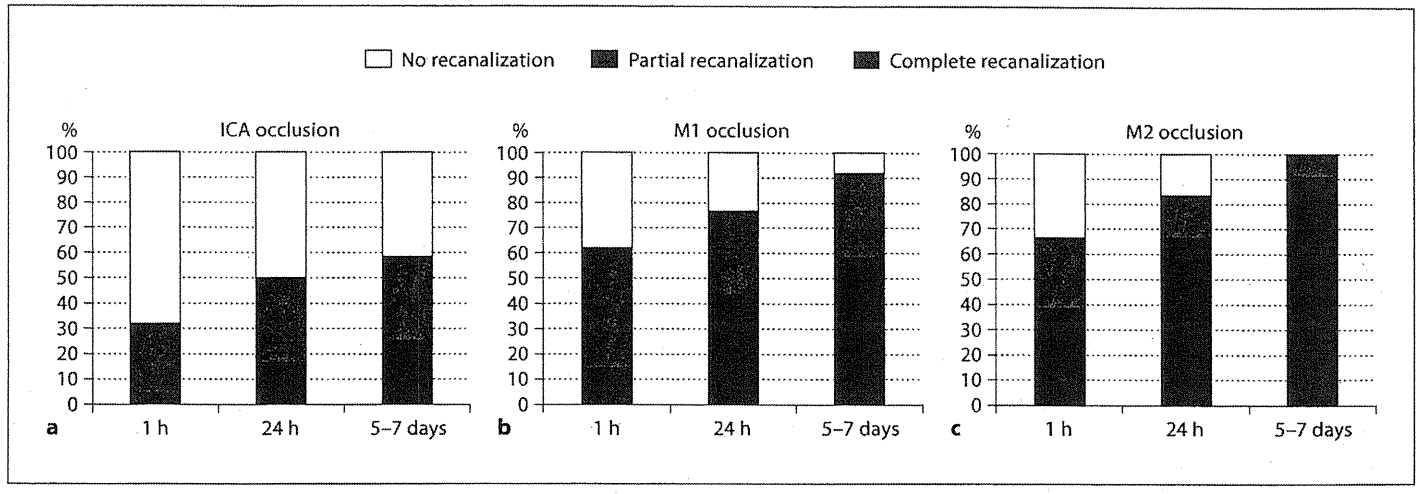

Fig. 1. Time course of the recanalization rate after IV thrombolysis in patients with ICA (**a**), M1 (**b**) and M2 occlusion (**c**).

ment in 11 patients, good improvement in 1 and worsening in 1.

Of the 64 occluded arteries, follow-up MRA after t-PA infusion showed recanalization in 29 patients (45.4%; complete in 9, partial in 20) within 1 h. One patient with ICA occlusion did not have follow-up MRI 24 h after t-PA infusion because of a severe stroke. Therefore, 63 patients underwent follow-up MRI 24 h after t-PA infusion. Of 63 patients, follow-up MRI showed recanalization in 47 patients (74.6%; complete in 23, partial in 24) 24 h after t-PA infusion. Four patients with ICA occlusion and 1 patient with M2 occlusion died because of brain herniation due to a severe stroke. Therefore, 59 patients underwent follow-up MRI 7 days after t-PA infusion. Of 59 patients, follow-up MRI showed recanalization in 48 patients (81.4%; complete in 37, partial in 11) 7 days after t-PA infusion. As a result, the recanalization rate (complete and partial) was 45.3% (14.1 and 31.2%) within 1 h, 74.6% (36.5 and 38.1%) at 24 h and 81.5% (62.8 and 18.7%) 7 days after t-PA infusion.

With respect to the site of the occluded artery, the recanalization rate (complete and partial) in patients with ICA occlusion was 31.8% (4.5 and 27.3%) within 1 h, 51.9% (14.3 and 47.6%) at 24 h and 66.7% (38.9 and 27.8%) 7 days after t-PA infusion (fig. 1a). In patients with M1 occlusion, the recanalization rate was 50.0% (16.7 and 33.3%) within 1 h, 77.6% (43.3 and 33.3%) at 24 h and 83.4% (66.7 and 16.7%) 7 days after t-PA infusion (fig. 1b). In patients with M2 occlusion, the recanalization rate was 58.3% (25.0 and 33.3%) within 1 h, 91.6% (58.3 and

Table 1. Patients' clinical characteristics (n = 64)

Age, years	75.1 ± 10.5
Male	38 (59.4)
Hypertension	39 (61.0)
Diabetes mellitus	11 (17.2)
Hyperlipidemia	10 (15.6)
Atrial fibrillation	43 (67.2)
TOAST classification	
Cardioembolic	45 (70.3)
Atherothrombotic	4 (6.3)
Lacunar	NA
Undetermined/others	15 (23.4)
DWI-ASPECTS	7.3 ± 2.4
MRA	
ICA occlusion	22 (34.4)
M1 occlusion	30 (46.9)
M2 occlusion	12 (18.8)
NIHSS score at baseline	16.4 ± 6.6
NIHSS score at 7 days	11.0 ± 9.3
Systolic blood pressure, mm Hg	155.7 ± 21.7
Diastolic blood pressure, mm Hg	85.7 ± 15.9
Time from symptom onset to treatment, min	138.5 ± 30.2
Laboratory data	
$HbA1_C$, %	5.6 ± 0.6
Leukocytes, /μl	6,460.0 ± 2,402.6
Erythrocytes, × 10,000/μl	422.8 ± 58.9
Platelets, × 10,000/μl	19.3 ± 5.0
Creatinine, mg/dl	0.9 ± 0.7
Glucose, mg/dl	143.9 ± 42.7
PT-INR	1.1 ± 0.2
D-dimer	2.8 ± 5.9

Figures in parentheses are percentages. NA = Not available.

Table 2. Recanalization rate after t-PA therapy in previous studies and the present study

Study	Patients	Occluded artery	Modality	t-PA dose mg/kg	Time after t-PA bolus	Total %	Complete, %	Partial %
Ribo et al. [9]	179	MCA	TCD	0.9	1 h	45	17	28
Labiche et al. [6]	54	MCA	TCD	0.9	1 h	67	33	33
Christou et al. [4]	40	MCA ICA	TCD	0.9 or 0.6	1 h	70	30	40
Alexandrov et al. [3]	63	MCA	TCD	0.9	1 h	NA	13	NA
Saqqur et al. [10]	39	ICA	TCD	0.9 or 0.6	2 h	18	NA	NA
Saqqur et al. [10]	276	MCA	TCD	0.9 or 0.6	2 h	36	NA	NA
Ribo et al. [9]	179	MCA	TCD	0.9	2 h	53	31	22
Labiche et al. [7]	75	MCA	TCD	0.9	2 h	64	33	31
Alexandrov et al. [3]	63	MCA	TCD	0.9	2 h	NA	13	NA
Present study	42	MCA	MRA	0.6	2 h	52	19	33
Demchuk et al. [5]	71	MCA ICA	TCD	0.9 or 0.6	several hours	68	NA	NA
Ribo et al. [9]	179	MCA	TCD	0.9	6 h	59	42	17
Present study	42	MCA	MRA	0.6	24 h	81	48	33
Linfante et al. [8]	17	ICA	MRA CTA TCD	0.9	1–3 days	31	NA	NA
Linfante et al. [8]	16	MCA	MRA CTA TCD	0.9	1–3 days	88	NA	NA
Neumann-Haefelin et al. [11]	82	MCA	MRA	NA	1 day	60	12	48
Present study	42	MCA	MRA	0.6	7 days	88	73	15

CTA = Computed tomographic angiography; NA = not available.

33.3%) at 24 h and 100.0% (90.9 and 9.1%) 7 days after t-PA infusion (fig. 1c). Combining M1 and M2 occlusion, the recanalization rate was 52.3% (19.0 and 33.3%) within 1 h, 80.9% (47.6 and 33.3%) at 24 h and 87.8% (73.2 and 14.6%) 7 days after t-PA infusion. The complete recanalization rate within 1 h after t-PA infusion was not different among M1, M2 and ICA occlusion ($p = 0.270$). However, complete recanalization rate at 24 h and 7 days was lowest in ICA occlusion among 3 categories ($p = 0.014$ and $p = 0.016$).

Patient Outcome and Early Recanalization

Dramatic improvement, good improvement and worsening 7 days after t-PA infusion were observed in 25, 14 and 13 patients, respectively. Dramatic improvement was more common in patients with complete early recanalization within 1 h after t-PA infusion (7 of 9 patients) than in patients without recanalization (7 of 35; $p = 0.0022$). On the other hand, worsening was less common in patients with complete early recanalization (1 of 9 patients) than in patients without recanalization (10 of 35; $p = 0.4108$), but the difference was not statistically significant.

Discussion

MRA demonstrated that the recanalization rate (complete and partial) was 45.3% (14.1 and 31.2%) within 1 h, 74.6% (36.5 and 38.1%) at 24 h and 81.5% (62.8 and 18.7%) 7 days after t-PA infusion. With respect to the patients with middle cerebral artery (MCA) occlusion, including M1 and M2 occlusion, the recanalization rate (complete and partial) was 52.3% (19.0 and 33.3%) within 1 h, 80.9% (47.6 and 33.3%) at 24 h and 87.8% (73.2 and 14.6%) 7 days after t-PA infusion. Table 2 shows the recanalization rates reported in previous studies after t-PA therapy using 0.9 mg/kg [3–11]. In 7 previous studies using TCD, the mean recanalization rate of MCA occlusion within 2 h after t-PA infusion was 50.6% (95% CI 36.0–65.2). Therefore, the early recanalization rate (52%) of the present study using 0.9 mg/kg was similar to that of previous studies using TCD. Therefore, the dose of t-PA using 0.6 mg/kg may be effective like 0.9 mg/kg for thrombolysis therapy in Japanese acute stroke patients.

In the present study, MRA rather than TCD was used to evaluate the presence of recanalization of occluded arteries, because several cases of elderly female and/or Asian patients with an insufficient temporal bone window have been described [17]. Furthermore, there may be

a difference between MRA and TCD in their ability to identify the presence of recanalization. MRA can identify the presence of ICA, M1 and M2 occlusion. However, TCD cannot always diagnose the presence of ICA occlusion accurately and cannot identify the M2 occlusion. Furthermore, TCD cannot evaluate the number of M2 branches that are occluded, while MRA can accurately detect occluded M2 branches. Therefore, MRA should be more sensitive than TCD for the assessment of partial M2 occlusion and recanalization of M2 occlusion. In fact, our study had a slight difference in early recanalization rate between M1 and M2 occlusion.

In the present study, MCA occlusions had a higher recanalization rate than ICA occlusions. These results are compatible with the report by Linfante et al. [8]. The reason was that the recanalization rate was strongly associated with the size of the embolus. The larger size of the embolus is likely to be resident to t-PA. In other words, the embolus of ICA occlusion should be larger compared with that of MCA occlusion. Therefore, the early recanalization rate of ICA occlusion was lower compared with that of MCA occlusion.

In patients with ICA occlusion, the recanalization rate was only 31.8% within 1 h after t-PA infusion. Therefore, we should need a new strategy instead of IV t-PA therapy. 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 t-PA [18]. Of these 80 patients, 53% had successful ICA recanalization with the Merci Retriever alone and 63% had ICA recanalization with the use of the Merci Retriever plus adjunctive endovascular treatment. Therefore, a combination of IV/intraarterial or mechanical thrombolysis may be needed to achieve early recanalization of ICA occlusion.

The present study has several limitations. Occlusion in the distal portions of the MCA may be difficult to evaluate using MRA, but serial changes in MRA findings should facilitate the evaluation of distal arterial recanalization. Secondly, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis [19]. Finally, MRI cannot be performed in patients who have had artificial metallic materials, such as pacemakers and metal clips, implanted. In fact, one such patient was excluded from the present study.

In conclusion, within 1 h after the end of t-PA infusion, approximately half of the patients with major arteries occlusion had early recanalization. ICA occlusion is resistant to IV t-PA therapy compared with MCA occlusion.

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4．急性脳血管症候群のMRA・CTA

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なかがわらじょうじ ふもと けんたろう かみやま けんじ

- 急性脳血管症候群（acute cerebrovascular syndrome：ACVS）は，従来のTIAまたはminor stroke（発症後7日以内にmRSが0または1となる）からなる．
- 従来のTIAは，DWI-陰性TIA：TIA（−），DWI-陽性TIA：TIA（＋）に分類される．
- TIA（−）とTIA（＋）は，脳梗塞巣の有無を除けば，神経症状の持続時間が1時間以内の症例の頻度，責任脳血管病変の出現の頻度などが類似しており，背景にある脳虚血病態の構成が同一と考えられた．
- TIA（−）およびTIA（＋）を含む従来のTIAでは，神経症状の持続時間が比較的短いこと，脳主幹動脈のアテローム血栓の関与が大きいこと，脳血管の閉塞機序として動脈原性塞栓が関与すること，などがあらためて確認された．
- ACVSの急性期管理ではDWIによる脳梗塞巣の評価に加えて，MRA・CTAによる責任脳血管病変（頸動脈病変，頭蓋内主幹動脈病変）の評価がきわめて重要と考えられる．

Key Words：急性脳血管症候群（ACVS），一過性脳虚血発作（TIA），拡散強調画像（DWI），磁気共鳴血管造影（MRA），コンピュータ断層血管造影（CTA）

急性脳血管症候群（acute cerebrovascular syndrome：ACVS）は，脳血管の閉塞性病変を原因とする急性脳虚血を共通の背景病態として発症する一連の神経脱落症候を包括する新たな診断名として提唱され，その診断対象は従来の一過性脳虚血発作（transient ischemic attack：TIA，神経症状の持続時間は24時間以内）から軽症脳梗塞（minor stroke）までを含む．このような臨床病態診断が必要となる背景として，第一に，MRI拡散強調画像（DWI）などの画像診断の進歩により，TIAとminor strokeの境界（神経症状の持続時間なのか，脳組織障害の有無なのか）が曖昧になったこと，第二に，TIAが脳梗塞の切迫発作であるとする観点からTIAに対して早期の治療介入が必要であるとの認識が広がったこと，などが挙げられる．いずれにしてもACVSは，早期の治療介入により転帰の改善が得られる臨床病態診断として重要である．2009年に発表されたTIAの定義と評価に関する科学的声明（AHA/ASA Scientific statement）によれば，TIAの新たな定義は「急性梗塞を伴わず，脳や脊髄，網膜の限局性虚血によって引き起こされた神経障害の一過性エピソード」となり，従来の時間をベースとした基準とは異なり，脳組織をベースとした基準が示された[1]．そして，2011年に発表されたAHA/ASAの脳梗塞およびTIAの二次予防に関するガイドラインでの推奨事項は，TIAに関してどちらの定義が用いられようとも脳梗塞とTIAの両者に適応されるとされ[2]，その区別の重要性は低下している．

周知のようにTIAの脳虚血病態は脳梗塞と同様で，その脳虚血病態の構成も脳梗塞と同様と考えられる．これまでTIAの脳虚血病態については，歴史的に脳主幹動脈のアテローム血栓を原因とする動脈原性塞栓が重要視されてきたが，心原性脳塞栓[3]やラクナ梗塞[4]もその脳虚血病態として想定する必要がある．このことは，ACVSの脳虚血病態を考慮する場合も同様である．

ACVSに対する早期の治療介入に際しては，その脳虚血病態を早期に鑑別するために，DWIによる脳梗塞巣の確認と，磁気共鳴血管造影（MRA）やコンピュータ断層血管造影（CTA）

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表1　ACVS 60 症例の分類と神経症状の持続時間，責任脳血管病変，脳梗塞出現例の病型分類

分類：n	神経症状の持続時間			責任脳血管病変（MRA）				脳梗塞の臨床分類		
	<1 hr	1～24 hr	24 hr<	(−)	ICA	MCA	VBS	LA	AT	CE
TIA（−） 10	8	2	—	7	1	2	0	—	—	—
TIA（+） 25	18	7	—	15	2	6	2	9	11	5
minor stroke 25	—	—	25	21	0	3	1	17	5	3
60	26	9	25	43	3	11	3	26	16	8

TIA（−）：DWI-陰性 TIA，TIA（+）：DWI-陽性 TIA，ICA：内頸動脈，MCA：中大脳動脈，VBS：椎骨脳底動脈系，LA：ラクナ梗塞型，AT：アテローム血栓性脳梗塞型，CE：心原性脳塞栓型

を用いた責任脳血管病変の評価を行う必要があり，鑑別された脳虚血病態に応じた適切な対応が重要と考えられる．そこで，本稿では，ACVS 症例の脳虚血病態の特徴と早期の MRA・CTA の意義について解説する．

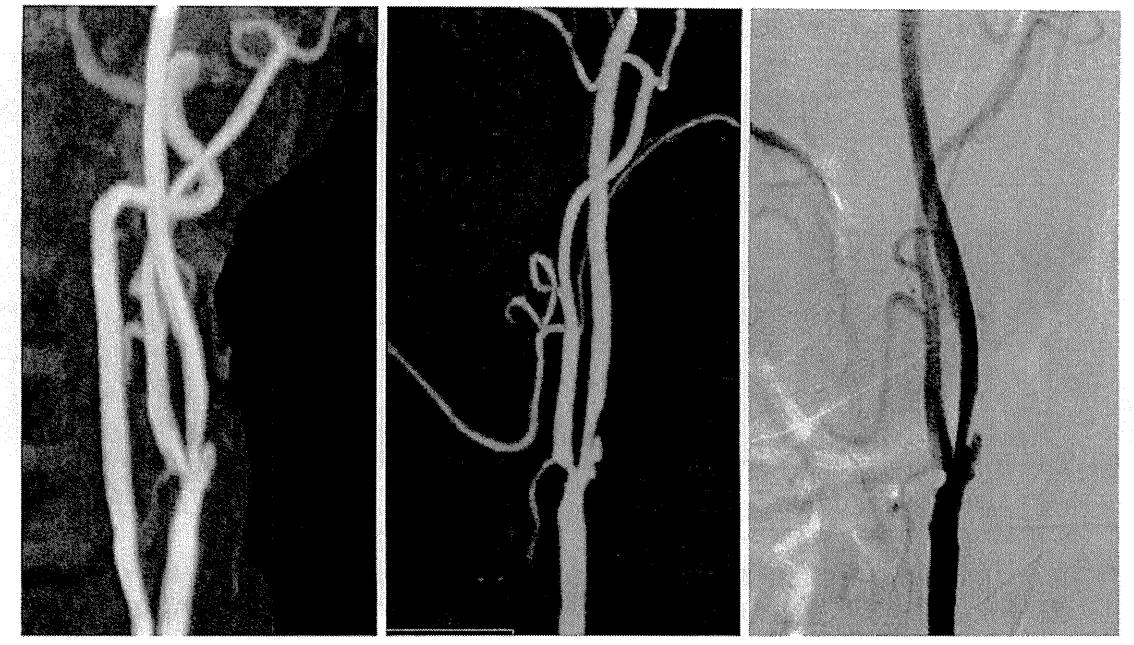
□ 対象と方法

平成 22 年 5 月から平成 23 年 1 月の 9ヵ月間の当院に入院となり，国際多施設非介入共同研究による前向き観察研究[5]に登録された ACVS 患者 60 症例（発症後 7 日以内の TIA または minor stroke，平均年齢 64.9±11.5 歳）を対象として，ACVS の脳虚血病態の特徴を検討した．対象の性別は，男性 39 例（平均年齢 61.3±11.4 歳），女性 21 例（平均年齢 70.1±10.2 歳）であった．TIA の定義は，発症 24 時間以内に消失する脳虚血発作としたが，このうち DWI にて脳梗塞巣を伴わない TIA 症例を DWI-陰性 TIA：TIA（−），脳梗塞巣を伴う TIA 症例を DWI-陽性 TIA：TIA（+）と分類して検討した．また，minor stroke の定義は，神経症状が 24 時間以上持続し，発症後 7 日以内に modefied Rankin Scale（mRS）が 0 または 1 となる軽症脳梗塞とした．対象症例は，発症後 24 時間以内に入院となり，入院時に初回 MRI（T2WI，T2* WI，DWI，Flair）および MRA 検査が施行された．初回の DWI にて脳梗塞巣が確認されなかった症例に対しては，入院翌日に 2 回目の DWI が施行され，脳梗塞の有無が確認された．頸動脈病変，頭蓋内主幹動脈病変は入院時の MRA・CTA にて診断されたが，詳細な診断が必要な場合には，入院翌日以降に DSA が追加された．

今回の検討では，各症例の神経症状の持続時間（1 時間以内，1～24 時間，24 時間以上に分類），責任脳血管病変（なし，内頸動脈：ICA，中大脳動脈：MCA，椎骨脳底動脈系：VBS に分類），脳梗塞出現例の病型分類（ラクナ梗塞型：LA，アテローム血栓性脳梗塞型：AT，心原性脳塞栓型：CE に分類）などが調査集計された．

□ 結　果（表 1）

ACVS 60 症例は，TIA（−）：10 例，TIA（+）：25 例，minor stroke：25 例に分類され，TIA（−）と TIA（+）が全体の 58%を占め，従来の TIA の範疇では 35 例中 25 例 71%に脳梗塞巣が確認された．神経症状の持続時間は，TIA（−）では 1 時間以内：8 例（80%），1～24 時間：2 例（20%），TIA（+）では 1 時間以内：18 例（72%），1～24 時間：7 例（28%）となり，1 時間以内の頻度は両者とも 70%以上で同等であった．責任脳血管病変は，TIA（−）では 10 例中 3 例（30%，ICA：1 例，MCA：2 例），TIA（+）では 25 例中 10 例（40%，ICA：2 例，MCA：6 例，VBS：2 例），minor stroke では 25 例中 4 例（16%，MCA：3 例，VBS：1 例）に確認され，TIA（−）と TIA（+）では 30～40%に責任脳血管病変が認められ，minor stroke の 2～3 倍であった．脳梗塞出現例の病型分類は，



MRA　　CTA　　DSA

図1　TIA（−）の代表例（72歳，男性）

X月X日午後0時30分ごろ，突然数秒間，右片麻痺，構音障害が出現した．1時間後，独歩にて来院．DWIでは異常所見はなかったが，頸部MRAで左頸動脈に潰瘍を伴う狭窄病変が認められ，精査のため入院となった．入院後，頸部CTAおよびDSAを行ったところ，左頸動脈の狭窄度や狭窄病変の描出については，MRAよりもCTAおよびDSAが優れていた．血圧は，正常範囲であったが，LDL-Choが高値であったことより，抗血小板剤とスタチンの内服を開始した．入院後TIAの再発なく，4日後に退院となった．

TIA（+）ではLA：9例（36%），AT：11例（44%），CE：5例（20%），minor strokeではLA：17例（68%），AT：5例（20%），CE：3例（12%）となり，TIA（+）ではATの頻度が44%と高く，minor strokeにおけるATの頻度の約2倍であった．一方，minor strokeではLAの頻度が高く，TIA（+）におけるLAの頻度の約2倍であった．

ACVSに該当する症例では，発症後早期の画像診断による病型診断を行うことにより，早期に適切な治療介入が可能となった．入院後早期に施行されたMRA・CTAが脳虚血病態の確定と治療介入に有用であったTIA（−）の代表症例を**図1**に，TIA（+）の代表症例を**図2，3**に提示する．

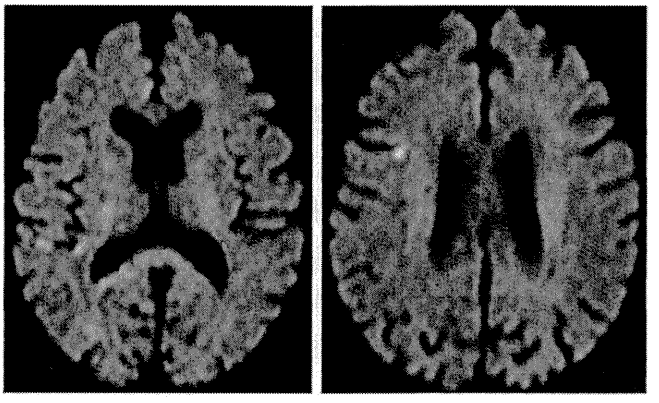


図2　TIA（+）の代表症例（80歳，女性）のDWI

4日前から毎日，いずれも1〜2分間の左半身（顔面含まず）の脱力発作が出現し，他医を受診．TIAと診断され，当院に紹介となった．高血圧症，2型糖尿病，脂質異常症などの基礎疾患はなし．DWIでは，右大脳半球に複数の高信号spot（動脈原性塞栓が関与）を認めた．

□ 考　察

発症後7日以内のTIA（−），TIA（+）またはminor stroke（発症後7日以内にmRSが0または1となる）からなるACVSの脳虚血病態の特徴を明らかにするために，当院に入院となった60例のACVS症例を対象として，神経症状の持続時間，責任脳血管病変，脳梗塞出現例の病型分類などについて比較検討した．