digital subtraction angiography (DSA) [9, 10], magnetic resonance imaging (MRI) [11], magnetic resonance angiography (MRA) [12, 13], computed tomography angiography (CTA) [14–16] and conventional transsurface carotid ultrasonography (TSCU) [17–20], TSCU is handy and safe. However, ICA dissection typically occurs at least 2 cm distal to the bifurcation, at the level of the second and third cervical vertebrae, and extends over a variable distance [3]. The distal extracranial ICA cannot be examined by TSCU as it lies behind bones and cannot be imaged in B-mode. Doppler on TSCU can provide information about the distal ICA only if there is a flow-limiting stenosis or occlusion that results in abnormal waveforms. Thus, the lesion may be underdiagnosed by routine TSCU examination.

Transoral carotid ultrasonography (TOCU), a new ultrasound technique that was developed in our institute [21], can identify the distal extracranial ICA that is invisible on TSCU [21]. We and others have reported the utility of TOCU in evaluating various ICA pathologies, including distal extracranial ICA stenosis, occlusion, pseudo-occlusion, moya moya disease and dissection [22–28]. In particular, TOCU seems to be superior to TSCU in detecting ICA dissection during acute stroke because of its ability to visualize the high portion of the extracranial ICA. We previously reported some cases with ICA dissection proven by TOCU [26–28]. However, the utility of TOCU should be assessed not only in isolated cases. In this study, the utility of TOCU in evaluating consecutive patients with ICA dissection as the final diagnosis was examined based on comparison with other imaging modalities, such as DSA, MRI and TSCU.

Subjects and Methods

Patients with stroke or transient ischemic attack (TIA) caused by extracranial ICA dissection confirmed by DSA from our database of 6,026 patients with ischemic stroke or TIA who were admitted to our hospital between 1999 and 2010 were reviewed.

Basically, all patients in our database underwent intracranial MRI/MRA and TSCU unless MRI was contraindicated. When ICA stenosis or occlusion was detected on these regular examinations or when dissection was suspected as a cause of ICA lesions based on typical histories and symptoms, including sports activities and cephalocervical pain, or absence of other obvious causes for the lesions, DSA was performed after obtaining the patient's informed consent. Three-dimensional (3D) rotational angiography with a standard Integris BV5000 biplane system (Philips Medical System, Best, The Netherlands) was also performed if needed. The system provides contrast angiographic vascular luminal rotational X-ray image acquisition in multiple planes with reconstruction on a 3D work station [10]. The diagnosis of ICA dissection was made by DSA based on the review by Provenzale [11] and the criteria of the Spontaneous Cervicocephalic Arterial Dissections Study [29]. Briefly, the presence of an intimal flap with a double lumen was a direct finding for identifying ICA dissection. The pearl-and-string sign, string sign, pearl sign, retention of contrast, total occlusion with proximal distension, and tapered occlusion on DSA needed further evidence, such as morphological change on DSA or intramural hematoma on T_1 MRI. The level of the dissection was established based on DSA findings. The findings of TSCU, TOCU and MRI/MRA were compared using DSA as the gold standard. Patients' clinical backgrounds, stroke types, stroke risk factors, and prognoses were reviewed as well.

TSCU and TOCU Examinations

TSCU and TOCU examinations were performed using an ATL Ultramark 9 HDI (Advanced Technology Laboratories, Bothell, Wash., USA) with a 5- to 10-MHz linear probe and a 5- to 9-MHz micro convex probe, respectively, or an Aplio™ XU (Toshiba Co. Ltd, Tokyo, Japan) with a 7.5-MHz linear probe and a 6-MHz micro convex probe, respectively. For TSCU examination, the standard approach using B mode, color flow imaging, and pulsed Doppler was performed in the decubitus position. The probes for TOCU examination were originally designed for transrectal use. We performed TOCU in patients with ICA territory stroke who were suspected to have pathological lesions at the extracranial distal ICA based on TSCU or intracranial MRI/MRA findings; evaluation of the extracranial distal ICA was mandatory. We used a protocol for identifying patients who needed to undergo further evaluations for ICA dissection, notably patients with ICA territory ischemia or retinal ischemia of unknown etiology based on standard evaluations including head computed tomography, head MRI and MRA, TSCU, electrocardiogram monitoring and blood test. Those with concomitant symptoms or signs, such as headache, neck pain, face pain, ipsilateral Horner's syndrome, pulsatile tinnitus or lower cranial nerve palsy, were especially suspected of having ICA dissection. For such patients, DSA or cervical MRI/MRA was preferentially performed and TOCU was added if needed prior to mid-2008. After mid-2008, TOCU was preferentially performed. TOCU was repeated to evaluate morphological changes every 1–3 days during hospitalization when ICA dissection was detected on initial examination. The details of the TOCU examination procedure have been reported previously [21]. Briefly, the probe was covered with a disposable probe cover made of sterile thin gum after covering the tip of the probe with echo jelly. Then, the probe was inserted transorally and touched the pharyngeal posterolateral wall. Basically, we did not use local anesthesia because the pharyngeal reflex rarely occurs. For patients with severe pharyngeal reflex, one or two pushes of 8% xylocaine spray to the pharyngeal posterolateral wall were used. The display was in the vertical plane to longitudinally detect and assess extracranial ICA, and in the axial plane for horizontal assessment. The ICA was identified by delineation of a vessel running linearly from the lower to the upper pharynx and by confirming that flow was proceeding upward to the skull base and that branching was absent using B-mode and color flow imaging. The ICA was usually identified at the level of the second and third cervical vertebrae, based on our unpublished data, which show the spatial relationship between the TOCU probe and the cervical vertebrae on the X-ray. B-mode was used

Table 1. Clinical characteristics

	Case 1 [26]	Case 2 [28]	Case 3	Case 4 [27]	Case 5	Case 6	Case 7	Case 8
Sex	male	male	female	male	male	male	male	male
Age, years	37	52	62	69	51	57	42	48
Type of stroke	IS	TIA	IS	IS	IS	IS	IS	IS
Prior history of stroke	absent	absent	absent	absent	absent	absent	absent	absent
Risk factors	dyslipidemia, smoking, drinking	hypertension	none	none	none	none	hypertension	none
Affected side	right	right	right	left	right	left	right	left
Cephalocervical pain	headache	absent	absent	orbital pain	absent	absent	headache	headache
Neurological findings	hoarseness, hemiparesis	hemiparesis	dysarthria, hemiparesis	hyperesthesia, visual field blurring	USN, dysarthria, hemiparesis, hypoesthesia	aphasia	USN, dysarthria, hemiparesis, hypoesthesia	aphasia, hemiparesis

IS = Ischemic stroke; USN = unilateral spatial neglect.

to measure the distal ICA diameter from the near to the far adventitial edge. Pulsed Doppler was used to measure the flow velocity of the distal ICA with an angle correction within 60° between the blood flow direction and the Doppler interrogation. Color Doppler was used to identify flow signals in true and false lumens. The lumen which tapered from the ICA was defined as a true lumen and the other was defined as a false lumen [17]. When flow signals were absent in false lumens, the lumens were considered to be thrombosed. An intimal flap with a double lumen was a definite finding for identifying ICA dissection by both TSCU and TOCU. Furthermore, the maximum diameter of the dilated extracranial ICA was measured from the near to the far adventitial edges and compared with the diameter of the contralateral ICA at almost the same distance from the carotid bifurcation. The probe was carefully horizontally swept in the vertical plane to detect the maximum diameter of the vessel's center to avoid overmeasurement in case the vessel is tortuous or turning.

MR Examinations

MRI of the cervical ICA was performed on a 1.5-tesla scanner (Magnetom Vision or MAGNETOM Sonata, Siemens Medical Systems, Erlangen, Germany) with standard neck array coils. The MRI protocol was composed of T_1-weighted images and 3D-time of flight MRA. MRA was performed on both intracranial and extracranial vessels. Intracranial MRA was performed on admission and extracranial MRA was performed during hospitalization. Gadolinium-enhanced MRA was not performed routinely. Intramural hematoma and luminal diameter on both sides were assessed by T_1 MRI while intimal flap with double lumen, stenosis and dilatation, and pseudoaneurysm were evaluated by MRA by an experienced radiologist. Patients who did not tolerate MRI because of claustrophobia or because they had pacemakers were diagnosed based on brain CT and DSA.

Data Evaluation

Continuous variables were compared with the Wilcoxon signed rank test. A value of $p < 0.05$ was considered statistically significant.

Results

Eight patients (7 men, age 37–69 years) with extracranial ICA dissection were identified from the database. Seven patients developed ischemic stroke and 1 developed TIA ipsilaterally to the affected ICA. The initial TOCU examination was performed after confirmation of dissection by DSA in 5 patients and prior to DSA in the other 3 (cases 5, 6, 8), whose clinical history strongly suggested ICA dissection. The detailed clinical presentations of 3 of these 8 patients have been previously reported [26–28]. Table 1 summarizes the patients' clinical characteristics, and table 2 shows the results of the DSA, TSCU, TOCU and MRI/MRA examinations. The basis of the diagnosis by DSA was the double-lumen sign with an intimal flap in 2, dilatation and stenosis in 3, and tapered occlusion in 4. On DSA, the dissection site was restricted to the level between the first and third cervical vertebrae in 4 patients, and the dissection extended from the third cervical vertebra to the intracranial ICA in the remaining 4 patients. Four patients showed morphological changes of dissection on follow-up DSA. In case 2, who initially had an intimal flap with a double lumen on day 1, a saccular type pseudoaneurysm was detected on day 16. In case 4, who initially had severe stenosis on day 1, an intimal flap with a double lumen with a fusiform-type pseudoaneurysm appeared on day 7. In case 5, who initially had proximal dilatation and stenosis, and a distal saccular-type aneurysm on day 3, the stenotic lesion became wider and an additional aneurysm was detected on day 19. In case 8, who initially had an ICA tapering occlusion on day 1, the ICA was recanalized on day 17. Figures 1 and

Table 2. Imaging findings

Modality	Findings	Case 1 [26]	Case 2 [28]	Case 3	Case 4 [27]	Case 5	Case 6	Case 7	Case 8
CT/MRI	location of ischemia	ant-choroid, PCA	corona radiata	MCA cortex	MCA central gyrus	MCA cortex and deep area	MCA cortex	MCA cortex	MCA cortex
DSA	location of dissection	C3-siphon	C1–C2	C1–C2	C1–C2	C1–C3	C3-distal IC	C3-distal IC	C3-distal IC
	location of carotid artery bifurcation	between C3 and C4	C3	between C3 and C4	C3	between C3 and C4	C4	C4	between C3 and C4
	intimal flap with double lumen[1]	–	–	present	present	–	–	–	–
	dilatation and stenosis	–	present	–	present	present	–	–	–
	tapering occlusion	present	–	–	–	–	present	present	present
	pseudoaneurysm	–	saccular	fusiform	fusiform	saccular	–	–	–
	morphological change	–	present	–	present	present	–	–	present
TOCU	intimal flap/double lumen[1]	present	present	present	present	present	present	present	present
	false lumen	thrombosed	thrombosed	not thrombosed	thrombosed[2]	thrombosed	thrombosed	thrombosed	thrombosed[2]
	stenosis	–	present	–	present	present	–	–	–
	occlusion	–	–	–	–	–	–	–	–
	dissected arterial diameter, mm	7.1	7.3	6.3	7.0	7.9	6.5	7.7	6.5
	contralateral arterial diameter, mm	5.0	4.0	5.6	5.6	4.4	4.9	4.2	4.9
	pseudoaneurysm	–	undetectable	fusiform	fusiform	saccular	–	–	–
	morphological change	–	present	–	present	present	–	–	present
	initial Doppler flow abnormality	present[3]	present[4]	–	present[3]	–	present[3]	present[3]	present[3]
	sequential flow pattern change	–	present[2]	–	present[4]	present[4]	–	–	present[5]
TSCU	intimal flap/double lumen[1]	–	–	–	–	–	–	–	–
	arterial narrowing	present	–	–	–	present	–	–	present
	dissected arterial diameter, mm	8.8	9.9	4.3	6.7	5.8	4.5	4.8	8.5
	contralateral arterial diameter, mm	7.3	5.9	4.0	5.3	6.0	4.8	4.3	5.4
	arterial dilatation	–	present	–	–	–	–	–	–
	morphological change	–	–	–	–	present	–	–	present
	initial Doppler flow abnormality	present[3]	–	–	present[3]	–	present[3]	present[3]	present[3]
	sequential flow pattern change	–	–	–	present[5]	present[4]	–	–	present[5]
Cervical MRI and MRA	intimal flap with double lumen	–	–	present	present	–	–	–	–
	intramural hematoma	present	present	–	–	present	present	present	present
	ICA stenosis	–	present	–	–	present	–	–	present
	occlusion	present	–	–	–	–	present	present	present
	pseudoaneurysm	–	present	–	–	present	–	–	–

ant-choroid = Anterior choroidal artery; C1 = first cervical vertebra level; C2 = second cervical vertebra level; C3 = third cervical vertebra level; CT = computed tomography; MCA = middle cerebral artery; PCA = posterior cerebral artery; siphon, carotid siphon; USN = unilateral spatial neglect; C1–3 = cervical vertebra levels; siphon, carotid siphon.

[1] Direct findings of arterial dissection.

[2] Normalized peak flow velocity.

[3] Absence of end diastolic velocity indicating distal occlusion.

[4] High peak flow velocity (>200 cm/s) indicating stenosis.

[5] Normalized end-diastolic flow velocity.

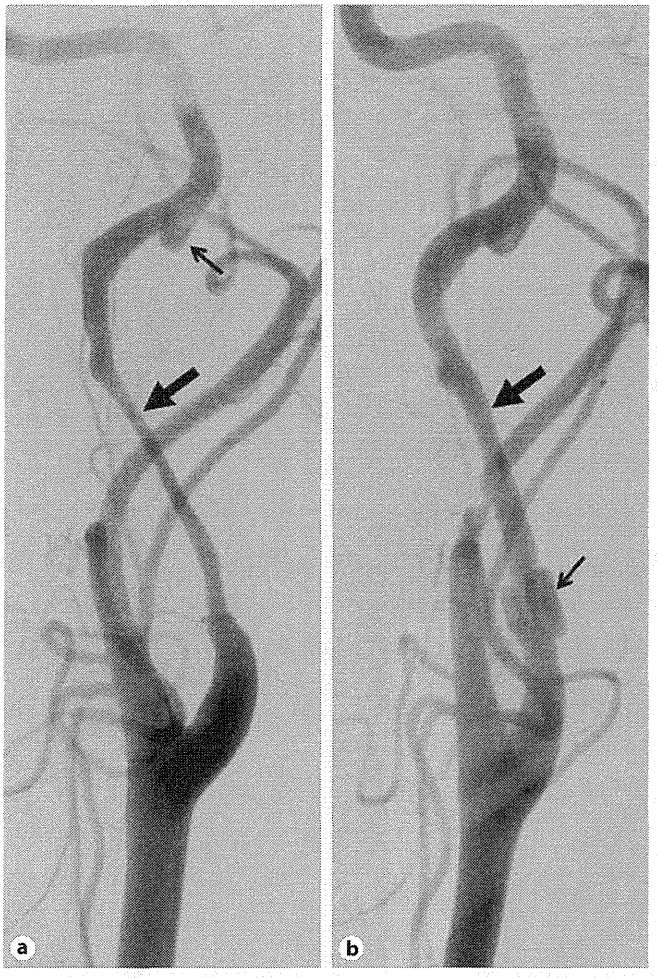

Fig. 1. Dissection of the extracranial ICA on a common carotid DSA image in case 5. **a** Right anterior oblique view on day 3. Dilatation and stenosis in the proximal ICA (thick arrow) and an aneurysm in the distal extracranial ICA (thin arrow) are shown. **b** Right anterior oblique view on day 19. The stenotic lesion becomes wider (thick arrow). A new aneurysm appears in the proximal ICA (thin arrow).

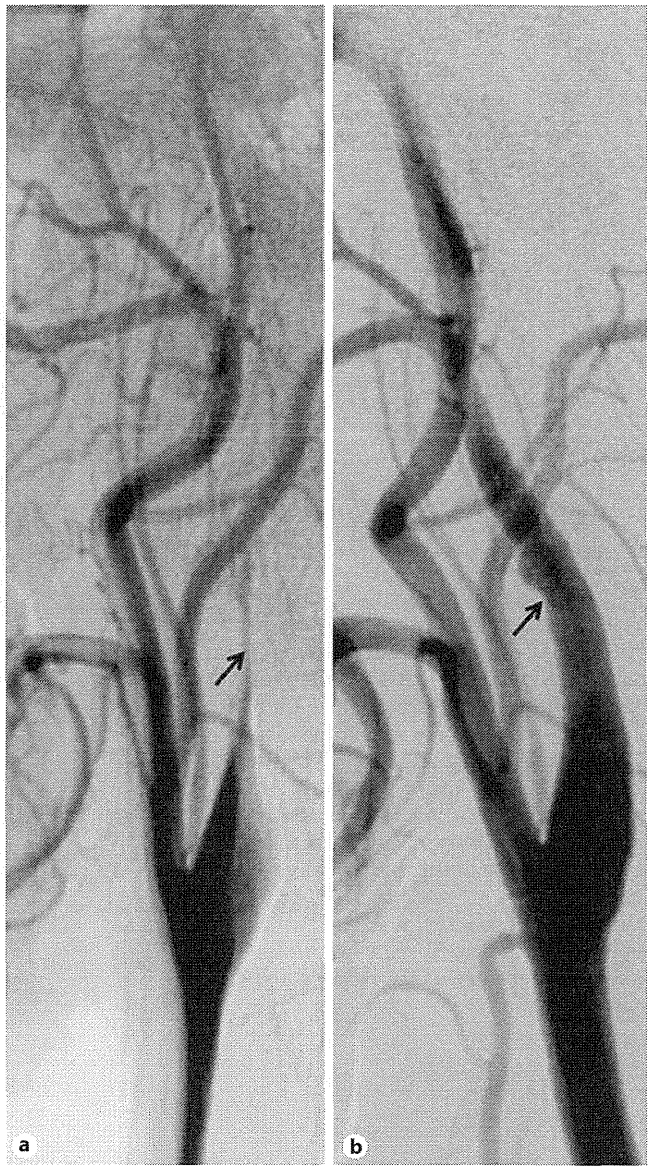

Fig. 2. Dissected ICA on a common carotid DSA image in case 8. **a** Lateral view on day 1, showing tapering ICA occlusion (arrow). **b** Recanalized dissected ICA (arrow) on day 17.

2 show sequential DSA images in cases 5 and 8, respectively.

By TOCU, a double lumen with an intimal flap was identified in all 8 patients. Color signals were absent in false lumens of 7 patients on the initial TOCU, indicating a thrombosed lumen; on the 2nd follow-up TOCU, little forward blood flow was present in the false lumen and in the course of time the flow volume increased gradually, indicating disappearance of the intraluminal thrombi in 1 patient (case 4) [27]. The luminal diameter at the height of the second cervical vertebra was 7.3 ± 0.7 mm in the dissected ICA and 4.9 ± 0.6 mm in the contralateral ICA in all patients ($p = 0.008$). No patient had a tortuous or turning vessel at the measurement point. On the initial Doppler examination, 5 patients displayed absence of end-diastolic velocity, indicating distal ICA occlusion, and 1 patient had ICA stenosis. As all the occluded arte-

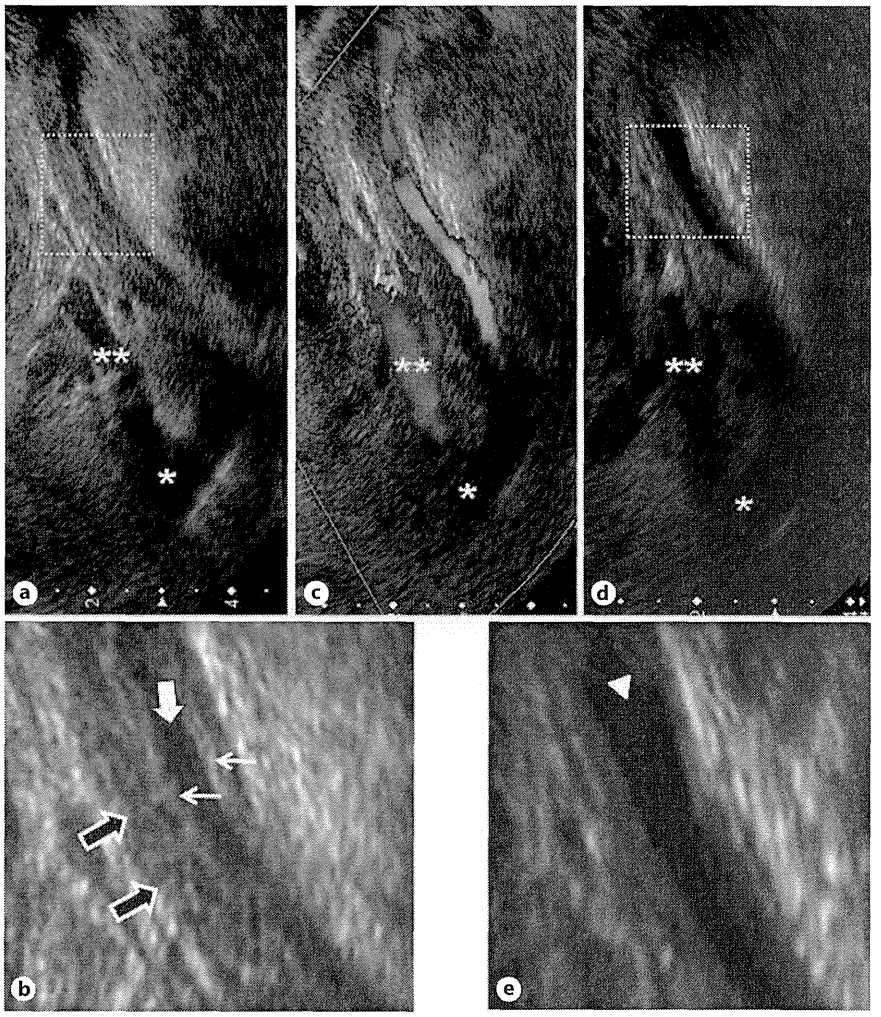

Fig. 3. Dissected ICA on TOCU images in case 5. **a**, **b** Longitudinal B-mode image of the right ICA on day 3. Narrowing of the true lumen (thick arrow), thrombosed false lumens (open arrows), and intimal flaps (thin arrows) are shown more than 2 cm distal to the carotid bifurcation. **c** Color Doppler image on day 3. Antegrade blood flow in the true lumen is observed. **d**, **e** Follow-up B-mode images on day 26. The true lumen turns wider (arrowhead). * and ** indicate the carotid bifurcation and external carotid artery, respectively. **b**, **e** Magnified images of lesions surrounded by dotted frames in **a** and **d**, respectively.

rial sites were at the level of the intracranial ICA, direct findings of ICA occlusion were not made by TOCU. On follow-up TOCU, dynamic changes of the dissected artery were detected in 4 patients (cases 2, 4, 5, 8). Narrowing of the true lumen and increased flow velocity, indicating a stenotic change in the ICA, improved on sequential follow-up TOCU (cases 2, 4, 5). In case 8, reperfusion with antegrade blood flow of the true lumen was detected. A pseudoaneurysm was detected in 3 patients (cases 3–5), and a pseudoaneurysm was missed in case 2, probably due to its high position. Figures 3 and 4 show sequential TOCU images in cases 5 and 8, respectively.

In contrast, definite findings specific to dissections, including a double lumen with an intimal flap, could not be made by TSCU in any patients. Six patients (cases 1, 4–8) showed nonspecific findings indicative of arterial stenosis or occlusion; 3 had mild arterial narrowing (<50%) with presumably a thin, echogenic intravascular structure which probably represents an intimal flap was found at a short distance above the bifurcation on B-mode images [17], 5 (cases 1, 4, 6, 7, 8) had absent end-diastolic flow of the ICA, suggesting distal ICA occlusion, and 1 (case 5) had increased peak systolic flow velocity exceeding 200 cm/s (203 cm/s), suggesting ICA stenosis.

Arterial dilatation of the proximal carotid ICA was visualized in only 2 patients by TSCU whereas TOCU identified arterial dilatation of the dissected extracranial ICA using in all patients.

Cervical MRI/MRA was performed in all patients from 6 days to 1 month after stroke onset. Gadolinium-

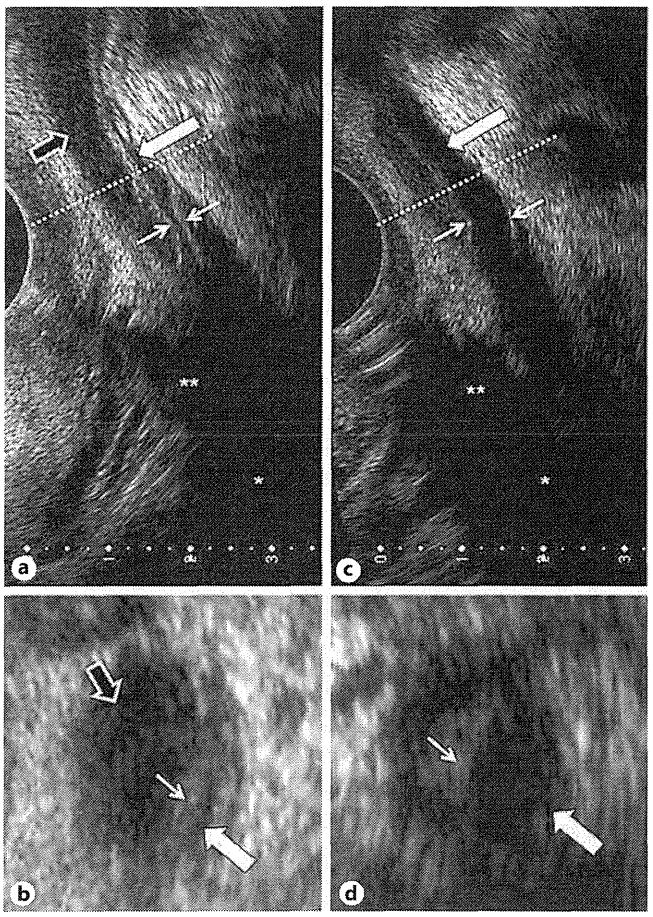

Fig. 4. Dissected ICA on TOCU images in case 8. **a**, **b** Longitudinal (**a**) and axial (**b**) B-mode TOCU images on day 8, showing narrowing of the true lumen (filled arrows), thrombosed false lumens (open arrows), and intimal flaps (thin arrows). **c**, **d** Follow-up B-mode images on day 32. The wider true lumen (filled arrows) and intimal flaps (thin arrows) are shown. * and ** indicate the carotid bifurcation and external carotid artery, respectively. Dotted lines in **a** and **c** indicate the levels of axial B-mode in **b** and **d**, respectively.

enhanced MRA was performed in 3 patients (cases 2, 5, 6). Cervical MRA images revealed an intimal flap with a double lumen in 2 patients, ICA stenosis and a pseudoaneurysm in another 2 patients, and ICA tapering occlusion and a thrombosed false lumen in 4 patients. On the axial view of T_1-weighted MRI, 6 patients had intramural hematomas, with high signals between the first and third cervical vertebrae in 2 and from the third vertebra to the intracranial ICA in 4. The luminal diameter on T_1-weighted images was 7.7 ± 0.9 mm in the dissected ICA and 5.6 ± 0.8 mm in the contralateral ICA ($p = 0.008$).

Discussion

The utility of TOCU in the diagnosis of ICA dissection has only been reported in isolated case reports, all from our institute [26–28]. This is the first report on the identification of ICA dissection using TOCU in consecutive stroke patients with ICA dissection as the final diagnosis. The first major finding of this study is that TOCU provided results comparable with those made by DSA and MRA for the diagnosis of dissection based on the presence of an intimal flap with a double lumen in all patients. Although Benninger et al. [30] reported that TSCU plus transcranial ultrasound was highly accurate in the diagnosis of ICA dissection, their definition of the diagnosis was mainly based on indirect findings, such as changes in the ICA blood flow pattern. It seems to be difficult to identify direct findings such as intimal flap and double lumens by TSCU. In addition, several unique signs, such as arterial stenosis, patency and thrombotic changes in true and false lumens, were also easily detectable using TOCU. The second major finding is that sequential changes in morphology and color flow signals, which are other important findings indicative of dissection, were identified in half of the present patients on follow-up TOCU. Third, a larger luminal diameter of the dissected ICA as compared with the contralateral ICA was measurable by TOCU. These results show the advantages of TOCU over TSCU in the diagnosis of dissection. Since the carotid artery bifurcation is generally higher in Asian patients (at the lower part of the third cervical vertebra) than in Western patients (approximately the fourth cervical vertebra) [31, 32], TOCU seems to be especially useful in Asian patients.

The utility of TOCU in the diagnosis of ICA dissections has changed over the last 12 years. In 5 of 8 patients in whom ICA dissections had already been proven by DSA, TOCU was simply used to confirm the diagnosis and to follow up changes over time. In 3 recent patients, we used TOCU before DSA in those with suspected ICA dissection whereas we preferred cervical MRI/MRA evaluations for suspected lesions of the extracranial distal ICA.

Since TOCU was not done in all of the patients of our database, the specificity of the diagnosis of ICA dissection using TOCU cannot be assessed. Thus, we cannot conclude that TOCU represents a gold standard for diagnosing dissections. At least, one can say that TOCU is useful for identifying false lumens and obtaining information as to their blood flow. For example, changes in the color flow signals in the false lumen indicate growth or

decrease of intramural clots. In contrast, DSA often delineates false lumens as nonspecific arterial stenosis or occlusion and requires a 3D rotational technique for detailed identification. T_1-weighted MRI of an intramural hematoma is better or more convincing, especially in cases of ICA occlusion identified by DSA. TOCU is superior to MRI and MRA for the documentation of real-time blood flow visualization and flow velocity measurement; such information reflects changes in arterial diameter and arterial reopening. In patients with only flap and/or aneurysmal dilatation TOCU might provide complementary information to that provided by DSA and MRI/MRA. In addition, TOCU is noninvasive, does not augment the dissection, and is easily repeatable at the bedside. Thus, TOCU is available both as a screening and as a frequent follow-up method of uncommon strokes. For example, a patient with developing arterial dilatation or aneurysmal change on follow-up within a short interval is a candidate for emergent surgery or intra-arterial catheter treatment.

The tip of the probe is about 2 cm across in diameter. The pharyngeal reflex rarely occurs because the probe just touches the posterolateral wall and the examination usually takes only a few minutes. Based on our unpublished data, ICA was visible without local anesthesia in more than 95% of the patients and no patients had aspiration pneumonia related to TOCU.

This study has some limitations. The first limitation is the small patient number, which partly results from the ethnic peculiarity; a nationwide survey in Japan indicates that only 2.4% of all patients with cervicocephalic dissection had extracranial ICA dissection whereas 63% had intracranial vertebral artery dissection [29]. Second, some patients having ICA dissection might have been misdiagnosed and might have missed the opportunity to undergo TOCU. DSA is not routine for all stroke inpatients and the lack of universally established criteria for dissection might prevent accurate diagnosis even by DSA. Third, TOCU was performed after DSA in the initial 5 patients; this caused sample selection bias. Finally, the imaging quality of TOCU has greatly improved during the 10-year study period; e.g. a newer Aplio™ XU with a 6-MHz micro convex probe provides a wider view of the ICA (up to 6–7 cm from the bifurcation) than the ATL Ultramark 9 HDI with a 5- to 9-MHz micro convex probe (approximately up to 3 cm) [21].

In conclusion, TOCU enabled definite diagnoses of extracranial ICA dissection and was superior to conventional TSCU. TOCU is a promising diagnostic tool in patients with extracranial ICA dissection.

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Disclosure Statement

None.

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Common Carotid Artery Dissection Caused by a Frontal Thrust in Kendo (Japanese Swordsmanship)

Rieko Suzuki, MD; Masato Osaki, MD; Kaoru Endo, MD; Tatsuo Amano, MD; Kazuo Minematsu, MD, PhD; Kazunori Toyoda, MD, PhD

A 66-year-old right-handed man suddenly developed left hemiplegia after an opponent thrust at his neck with a bamboo sword during a practice game of Kendo (Japanese swordsmanship; Figure 1). Fifty minutes later, he visited our emergency service. His blood pressure was 77/55 mm Hg in the left arm but could not be measured in the right arm; his right radial artery was initially pulseless but became palpable 1 hour later. He was somnolent and had left unilateral spatial neglect, left complete hemiplegia, and left-sided sensory disturbance. Enhanced computed tomography (CT) showed an occlusion 15 mm distal to the origin of the right common carotid artery (CCA) without any abnormal findings at the aorta and innominate and right subclavian arteries. On emergent carotid ultrasonography, an intraluminal filling defect occupied the right CCA and swung back and forth with pulsation. He was diagnosed as having ischemic stroke, possibly caused by traumatic CCA dissection, although an infarct was not identified on brain CT.

On the second day, fresh infarcts were identified in the right hemisphere on diffusion-weighted MRI, and the right internal carotid, middle cerebral, and posterior cerebral arteries were poorly demonstrated on magnetic resonance angiography (Figure 2). On the fourth day, the right CCA was recanalized, and the intimal flap was identified on ultrasonography (Figure 3 and Movie I in the online-only Data Supplement). A mobile thrombus was identified within the true lumen, but its shape changed on the follow-up ultrasonography 9 hours later. The false lumen diminished, and the thrombus disappeared with a mild aneurysmal change after day 30. The patient was diagnosed as having a definite dissection of the CCA. These dynamic changes were also identified on CT angiography (Figure 4). The right distal CCA was severely stenotic on the fourth day. The stenosis became milder with aneurysmal change on day 10. The intimal flap and double lumens in the right CCA were detected on axial CT scans. The small false lumen was also identified in the distal

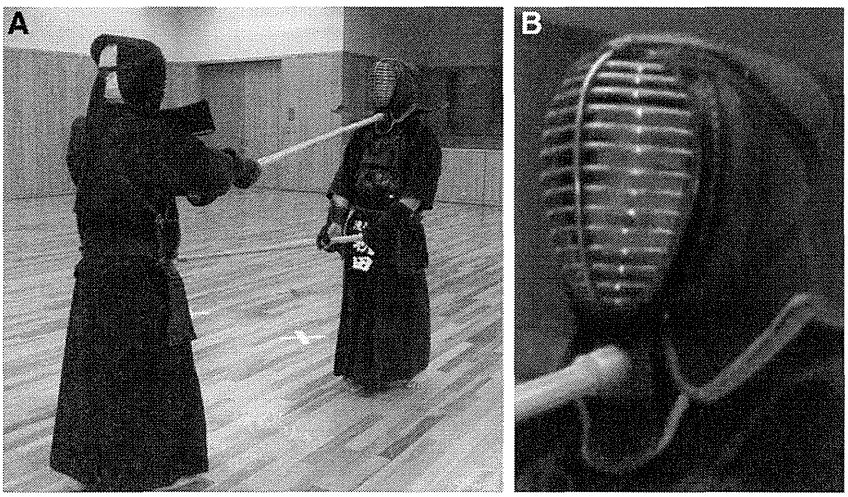

Figure 1. A, A performance of tsuki in Kendo. **B**, A bamboo sword is thrust at the partner's throat armor.

From the Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan.

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Correspondence to Rieko Suzuki, MD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita,Osaka, Japan. E-mail rsuzuki@hsp.ncvc.go.jp

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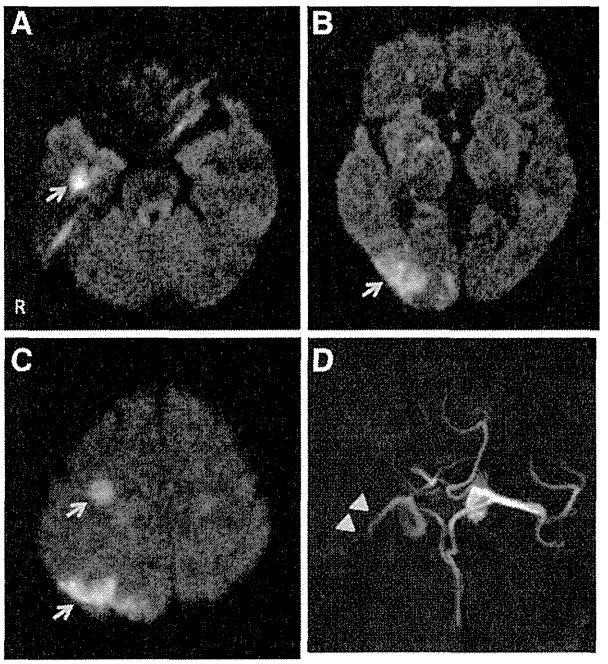

Figure 2. Brain magnetic resonance (MR) images on day 2. **A** through **C**, Diffusion-weighted MR imaging studies demonstrating fresh and scattered infarcts in the right middle and posterior cerebral artery areas (arrows). **D**, MR angiography demonstrating poor visualization of the right internal carotid, middle cerebral (arrowhead), and posterior cerebral arteries.

innominate artery, indicating the existence of the reversible innominate dissection that had caused pulselessness at the time of the initial examination. At hospital discharge on day 49, the patient still had severe hemiplegia. He did not develop recurrent stroke.

A frontal thrust of Kendo can cause cervical artery dissection and stroke,[1] although it has rarely been reported.[2] The strength of this report is that dynamic changes in the morphology of the dissected CCA were clarified through the use of both ultrasonography and CT angiography examinations.

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Disclosures

None.

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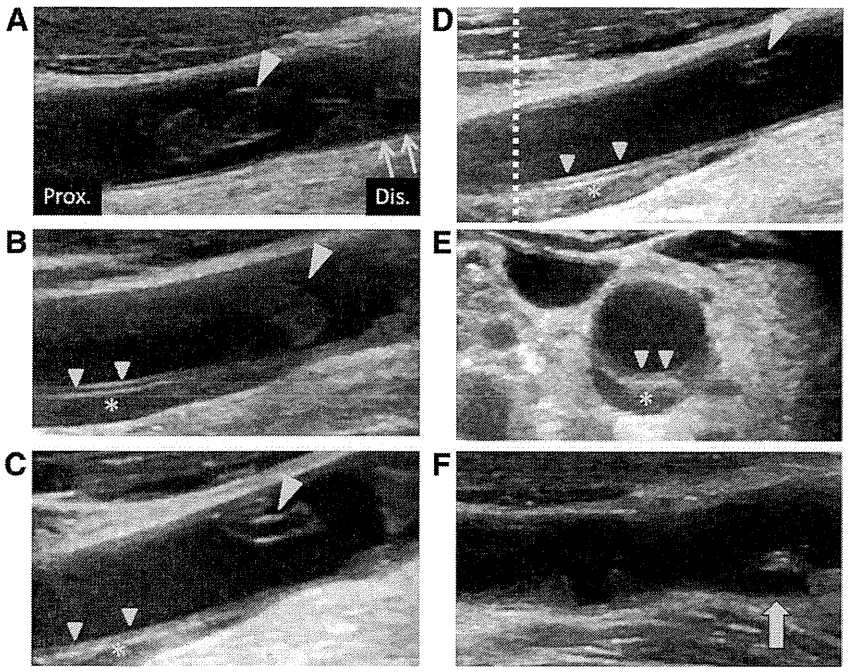

Figure 3. Changes in a B-mode image of the right common carotid artery (CCA). **A**, On day 2, the distal CCA is occluded with a thrombosed false lumen (arrows). A mobile thrombus is identified proximal (Prox.) to the occlusion site (arrowhead). **B** through **E**, Longitudinal (**B–D**) and axial (**E**) B-mode images on day 4 at 10 AM (**B**), 7 PM (**C**), and 9 PM (**D** and **E**). **E**, Axial image of a dotted line on **D**. The distal (Dis.) CCA is recanalized. The mobile thrombus gradually changes in shape (arrowhead). An intimal flap (small arrowhead) and a thrombosed false lumen (asterisk) are seen at the proximal CCA. **F**, On day 48, the mobile thrombus and the thrombosed false lumen disappear completely. Aneurysmal formation is seen (filled arrow).

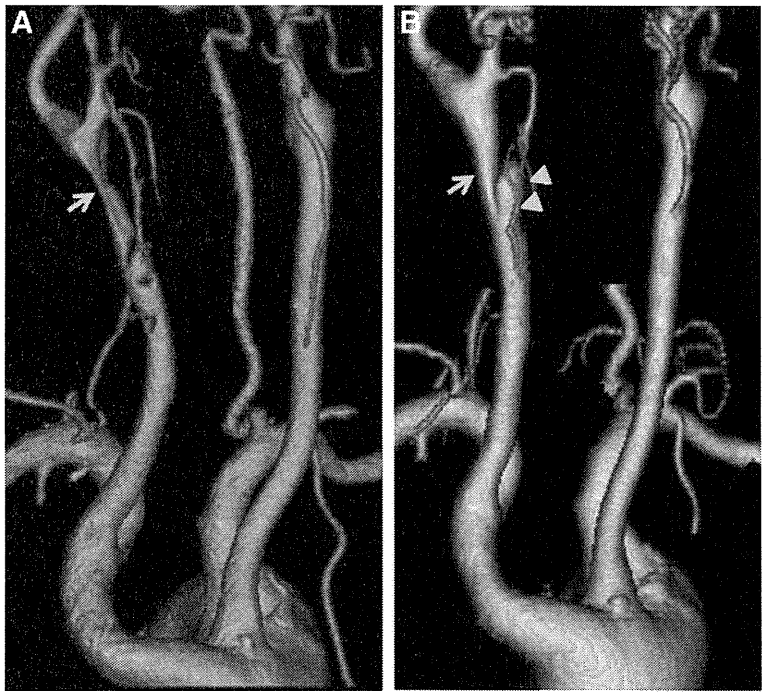

Figure 4. Cervical computed tomography angiography. **A**, On day 4, the right distal common carotid artery (CCA) is stenotic (arrow). **B**, On day 23, the stenotic CCA becomes wider (arrow), and aneurysmal formation is evident (arrowhead).

「脳梗塞 t-PA 研究会」第 5 回研究集会

＜短　報＞

rt-PA 投与後の早期再発，進行および症候性頭蓋内出血による早期神経症候増悪の検討

福田　真弓[1)]　古賀　政利[1)]　森　真由美[1)]　大崎　正登[1)]
長束　一行[2)]　峰松　一夫[1)]　豊田　一則[1)]

要旨：【目的・方法】脳梗塞発症早期の神経症候増悪（END）は予後不良と関連する．当院で rt-PA を施行した連続 200 例［女性 65 例（33％），74 ± 11 歳］について rt-PA 投与 24 時間以内の END の頻度，原因，関連因子および転帰を調べた．【結果】END を 30 例（15.0％）に認め，内訳は脳梗塞早期再発が 3 例（1.5％），脳梗塞の進行が 21 例（10.5％），頭蓋内出血が 6 例（3.0）であった．脳梗塞早期再発は高齢で入院時 D-dimer が高値であった．頭蓋内出血でワルファリン，脳梗塞の進行で抗血小板薬の内服が多かった．END は END なしに比べ，退院時 NIHSS と 3 カ月後 mRS が高値であった．【結語】rt-PA 投与後の END は 1 割以上に出現し，転帰不良と関連していた．END の原因ごとに関連因子が異なっていた．

Key words: rt-PA, acute stroke, early neurological deterioration, recurrence, progressive stroke
（脳卒中 34: 47–50, 2012）

はじめに

脳梗塞発症早期の神経症候増悪（early neurological deterioration; END）は，転帰不良と関連する[1)]．rt-PA 静注療法後の END の原因としては，脳梗塞の早期再発（early recurrence of ischemic stroke; ERIS），症候性頭蓋内出血（symptomatic intracranial hemorrhage; SICH），脳梗塞の進行（progressive stroke; PS）が挙げられる．本検討では，rt-PA 投与後の END の頻度，原因，関連因子，転帰を明らかにする．

対象と方法

2005 年から 2010 年に当センターで rt-PA 療法を施行した急性期脳梗塞患者連続 200 例を対象とした．END は rt-PA 投与開始後 24 時間以内に NIHSS が 4 点以上増悪したものと定義した．ERIS を，rt-PA 投与後に発症した投与前と異なる血管領域での新規梗塞とし，SICH を，増悪後の CT で増悪症状に関連する頭蓋内出血を検出したものと定義した．PS を，ERIS および SICH がない増悪とした．入院診療録を用いて，性別，年齢，既往歴，発症前内服薬，rt-PA 投与前後の治療内容，END の有無とその原因，脳梗塞病型を調べた．早期虚血巣の拡がりは，来院時に撮像した CT より Alberta Stroke Program Early CT score（ASPECTS）を算出した．退院時 National Institute of Health Stroke Scale（NIHSS）および 3 カ月後の modified Rankin Scale（mRS）を調査した．

結　果

rt-PA を投与された 200 例中，END を 30 例（15％）に認めた．内訳は，ERIS が 3 例（1.5％），SICH が 6 例（3.0％），PS が 21 例（10.5％）であった．ERIS の 3 例中，rt-PA 施行中の再発が 2 例であった．Table 1 に END 群と非 END 群との比較を示す．2 群間では，既往症，入院時 NIHSS や rt-PA 投与開始までの時間，治療前の ASPECTS，脳梗塞病型，閉塞血管部位，投与後の抗血栓療法および降圧薬の使用，脂質，血糖値を含む検査所見に差はなかった．脳梗塞発症前の

[1)]国立循環器病研究センター脳血管内科
[2)]同　脳神経内科
（2011 年 12 月 5 日受付，2011 年 12 月 7 日受理）

Table 1　END 群と非 END 群の比較

	全例	END	非 END	p value
n	200 (100)	30 (15)	170 (85)	
年齢	74 ± 11	76 ± 9	73 ± 11	0.22
男性	135 (68)	19 (63)	116 (68)	0.59
高血圧	133 (67)	20 (67)	113 (67)	0.82
糖尿病	34 (17)	6 (20)	28 (16)	0.63
脂質異常症	58 (29)	6 (20)	52 (31)	0.24
虚血性心疾患	26 (14)	4 (15)	22 (14)	0.85
心房細動	100 (52)	18 (60)	82 (49)	0.1
脳梗塞	39 (20)	8 (27)	31 (18)	0.29
肝機能異常	8 (4)	0 (0)	8 (4.7)	0.23
腎機能障害	17 (8.5)	2 (6.7)	15 (8.8)	0.7
アスピリン内服歴	50 (25)	12 (40)	38 (22)	0.039
ワルファリン内服歴	25 (13)	4 (13)	21 (12)	0.88
入院時 NIHSS*	12 (7, 17)	11 (7, 17)	12 (7, 17)	0.44
発症－治療開始時間 (min)**	133 ± 28	129 ± 29	133 ± 28	0.4
投与直前収縮期血圧 (mmHg)**	150 ± 21	151 ± 21	150 ± 22	0.68
ASPECTS*	9 (8, 10)	9 (8, 10)	9 (7, 10)	0.52
rt-PA 投与中の降圧薬使用	27 (14)	4 (13)	23 (14)	0.95
24 時間以内の抗血栓療法	6 (3)	2 (6.7)	4 (2.4)	0.2
脳梗塞病型				
心原性塞栓	142 (71)	20 (67)	122 (61)	
アテローム血栓性梗塞	28 (14)	4 (13)	24 (14)	n.s.
その他	30 (15)	6 (20)	24 (14)	
閉塞血管				
ICA	28 (16)	7 (23)	21 (12)	
M1	68 (39)	6 (20)	62 (36)	
M2	30 (17)	9 (30)	21 (12)	n.s.
BA	3 (1.7)	1 (3.3)	2 (1.1)	
36 時間以内の頭蓋内出血	47 (24)	13 (43)	34 (20)	0.006
MRA 上の閉塞血管再開通 +	76 (68)	9 (47)	67 (72)	0.03
退院時 NIHSS*	3 (1, 11)	13 (5, 23)	2 (1, 10)	<0.001
退院時 mRS*	3 (1, 4)	4 (3, 5)	2 (1, 4)	<0.001
3 カ月後 mRS*	3 (1, 4)	4 (3, 5)	2 (1, 4)	0.001

n (%), *Median (IQR), **mean ± SD

n.s.: not significant
+: modified Mori Grade ≥ 3
NIHSS: National Institute of Health Stroke Scale
ASPECTS: Alberta Stroke Program Early CT score
mRS: modified Rankin Scale
ICA: 内頸動脈, M1: 中大脳動脈水平部, M2: 中大脳動脈島部, BA: 脳底動脈

Table 2　増悪原因別の検討

	非 END (n=170)	END 全体(n=30)	PS (n=21)	SICH (n=6)	ERIS (n=3)
年齢	73 ± 11	76 ± 9	75 ± 10	75 ± 5	87 ± 6*
悪性腫瘍	9 (5.2)	2 (6.7)	1 (4.8)	0 (0)	1 (33)*
心房細動	82 (49)	18 (60)	12 (57)	4 (67)	2 (67)
アスピリン内服	38 (22)	12 (40)	10 (48)*	2 (33)	0
ワルファリン内服	21 (12)	4 (13)	1 (4.8)	3 (50.0)*	0
D-dimer, μg/ml	2.7 ± 4.1	2.6 ± 3.1	2.2 ± 1.7	1.3 ± 0.8	8.3 ± 6.9*
退院時 mRS**	2 (1, 4)	4 (3, 5)	4 (4, 5)	3.5 (3, 4)	2 (0, 5)
3 カ月後 mRS**	2 (1, 4)	4 (3, 5)	5 (4, 5)*	3 (1, 4)	1 (0, 4)

* vs 非 END; $p<0.05$　　n(%), **Median (IQR)
END: early neurological deterioration (早期神経症状増悪)
PS: progressive stroke (梗塞巣の進行)
SICH: symptomatic intracranial hemorrhage (症候性頭蓋内出血)
ERIS: early recurrence of ischemic stroke (脳梗塞早期再発)
mRS: modified Rankin Scale

アスピリン内服率，36 時間以内の頭蓋内出血が，END 群で有意に多く，入院中の任意の時間に施行したフォローアップ MRA での閉塞血管再開通が，非 END 群で有意に多かった．退院時 NIHSS，退院時 mRS，3 カ月後 mRS はいずれも END 群で不良であった．

Table 2 に END 原因別の関連因子を示す．ERIS は，非 END と比較して有意に高齢で，悪性腫瘍の合併が多く，発症時の D-dimer が有意に高値であった．抗血小板薬の内服は PS で，ワルファリンの内服は SICH で有意に多かった．

考　察

本研究における rt-PA 後早期の神経症候増悪の頻度は 15%で，既報告とほぼ類似する結果であった[1-3]．rt-PA 投与後に血管再開通を認めないことが，神経症候増悪と長期予後不良に関連すると報告されているが[3]，今回の検討も同様の結果であった．本検討では，24 時間以内の再発が 1.5%にみられ，rt-PA 施行中の再発が 1.0%であった．ERIS についての過去の報告では，再発頻度は 24 時間以内に 0.59%[4]，72 時間以内に 2.6%[5]とされるが，後者の文献で投与開始 1 時間以内の再発に限った場合の再発は 1.3%であり，頻度については本研究とほぼ同程度と考えられた．ERIS のメカニズムに関しては，心筋梗塞に対する血栓溶解療法において血栓溶解薬の投与により心腔内に存在した血栓が分解し，全身の塞栓症を来したとする報告がある[6]．また脳梗塞に対する急性期血栓溶解療法後の脳梗塞再発に関する症例報告もある[7]．Awadh ら[5]は，心房細動が ERIS に関連すると報告しているが，本研究では心房細動との関連は見られなかった．本検討では ERIS で D-dimer が有意に高値を示した．rt-PA 非施行の急性期脳梗塞の検討では，D-dimer 高値は脳梗塞の進行と再発に関連し[8]，D-dimer の高値は体内での凝固・線溶系の活動度を反映し，早期再発を予測するマーカーになる可能性がある．

発症前抗血栓療法と SICH との関連については，ワルファリン内服例で SICH の発症が 10 倍多く[9]，抗血小板薬投与群で頭蓋内出血が有意に多く，2 剤併用になると高率に頭蓋内出血を合併する[10]ことが報告されている．本検討において発症前のアスピリン内服が PS に関連したが，アスピリンの内服例は動脈硬化疾患が併存している可能性が高く，高度な動脈硬化合併に伴う梗塞進行を反映しているのかもしれない．

なお，本研究の限界として，単一施設連続例での検討であり，特に ERIS の症例数が少ないことがあげられ，今後の症例蓄積が必要と考えられる．

結　論

rt-PA 投与後の早期増悪は全体の 15%にみられ，転帰不良と関連した．早期再発例は高齢で凝固線溶亢進状態を示していた．症候性頭蓋内出血を起こした

患者に発症前のワルファリン内服例が多く，早期に脳梗塞が進行した患者に発症前の抗血症板薬の内服例が多かった．

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Abstract

Early neurological deterioration in acute stroke patients following intravenous rt-PA

Mayumi Fukuda, M.D.,[1] Masatoshi Koga, M.D.,[1] Mayumi Mori, M.D.,[1] Masato Osaki, M.D.,[1] Kazuyuki Nagatsuka, M.D.,[2] Kazuo Minematsu, M.D.,[1] and Kazunori Toyoda, M.D.[1]

[1] Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center

[2] Department of Neurology, National Cerebral and Cardiovascular Center

Early recurrence of ischemic stroke (ERIS), as well as symptomatic intracranial hemorrhage (SICH) and progressive stroke (PS), causes early neurological deterioration (END) after thrombolysis. This study's goal was to investigate the incidence, characteristics, and mechanisms of END within 24 h after rt-PA infusion. Of 200 patients (65 women, 74±11 years) who were treated with intravenous rt-PA, 15.0% developed END: 1.5% with ERIS, 3.0% with SICH, and 10.5% with PS. As compared to patients without END, those with ERIS were older and had a higher D-dimer level on admission. Patients with SICH and those with PS more frequently took oral warfarin and antiplatelets, respectively, prior to stroke onset. mRS at 3 months were higher in patients with END than those without.

Key words: rt-PA, acute stroke, early neurological deterioration, recurrence, progressive stroke

(Jpn J Stroke 34: 47–50, 2012)

特集Ⅰ　脳を救え！—急性期脳梗塞の最新治療事情—

脳を救え：静注血栓溶解と超音波血栓溶解*

古賀政利**

Key Words：alteplase, acute ischemic stroke, symptomatic intracerebral hemorrhage, therapeutic time window within 4.5 hours of stroke onset, sonothrombolysis

はじめに

虚血性脳血管障害急性期における治療の核となったアルテプラーゼ静注による血栓溶解療法〔遺伝子組み換えプラスミノゲン・アクティベーター(rt-PA)静注療法〕は，わが国では米国から9年遅れて2005年10月に保険承認され，6年以上が経過した．SAMURAI rt-PA registry[1]や市販後全例登録調査(J-MARS)[2]から，諸外国よりも低用量である本療法の安全性と有効性が確認されてきた．2008年には本療法の発症4.5時間以内の有効性が示され[3]，諸外国が治療時間を発症4.5時間まで延長している．新規血管内治療装置が登場してきたが，rt-PA静注療法のエビデンスレベルが最も高い．また，rt-PA静注療法における血管再開通を促進する超音波血栓溶解療法が注目されている．ここでは，わが国における静注血栓溶解療法承認までの経緯，その安全性と有効性，諸外国における発症4.5時間以内への治療適応拡大の現状を概説し，そして，超音波血栓溶解療法についても触れる．

静注血栓溶解療法

1995年に米国のNational Institute of Neurological Disorders and Stroke(NINDS)試験[4]により，発症3時間以内の虚血性脳血管障害に対するrt-PAであるアルテプラーゼ(0.9mg/kg)によるrt-PA静注療法の有効性が示され，1996年に米国食品医薬局(Food and Drug Administration：FDA)が急性期脳梗塞の治療薬として本療法を認可した．その後，多くの国々で承認され医療体制の整備が行われてきた．わが国では，1992年に世界に先駆けてMoriらが発症6時間以内の脳塞栓症を対象にした二重鎖のrt-PAであるデュテプラーゼによる偽薬対照群間比較試験の結果を報告し，デュテプラーゼの有効性を示した[5]．また，Yamaguchiらは，デュテプラーゼ2,000万単位と偽薬との多施設共同二重盲検群間比較試験を行い同様の結果を得た[6]．しかしながら，特許権を巡る訴訟によりデュテプラーゼの製造販売は中止となり，脳梗塞への適応拡大申請も幻となった．

わが国で，2002年から2003年にかけアルテプラーゼによるrt-PA静注療法の第3相治験であるJapan Alteplase Clinical Trial(J-ACT)[7]が実施された．この結果と，海外でのこれまでの本薬に関する大規模ランダム化比較試験(RCT)や市販後臨床試験成績などを総合して，わが国における保険適応が承認された．この治験はアルテプラーゼの単一用量オープン試験であった．対象選択基準と方法はNINDS試験にほぼ準拠したが，用量はNINDS試験の3分の2(0.6mg/kg)であっ

* Intravenous rt-PA therapy and sonothrombolysis.

** Masatoshi KOGA, M.D., Ph.D.: 国立循環器病研究センター脳卒中集中治療科〔〒565-8565 大阪府吹田市藤白台5-7-1〕; Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Osaka 565-8565, JAPAN

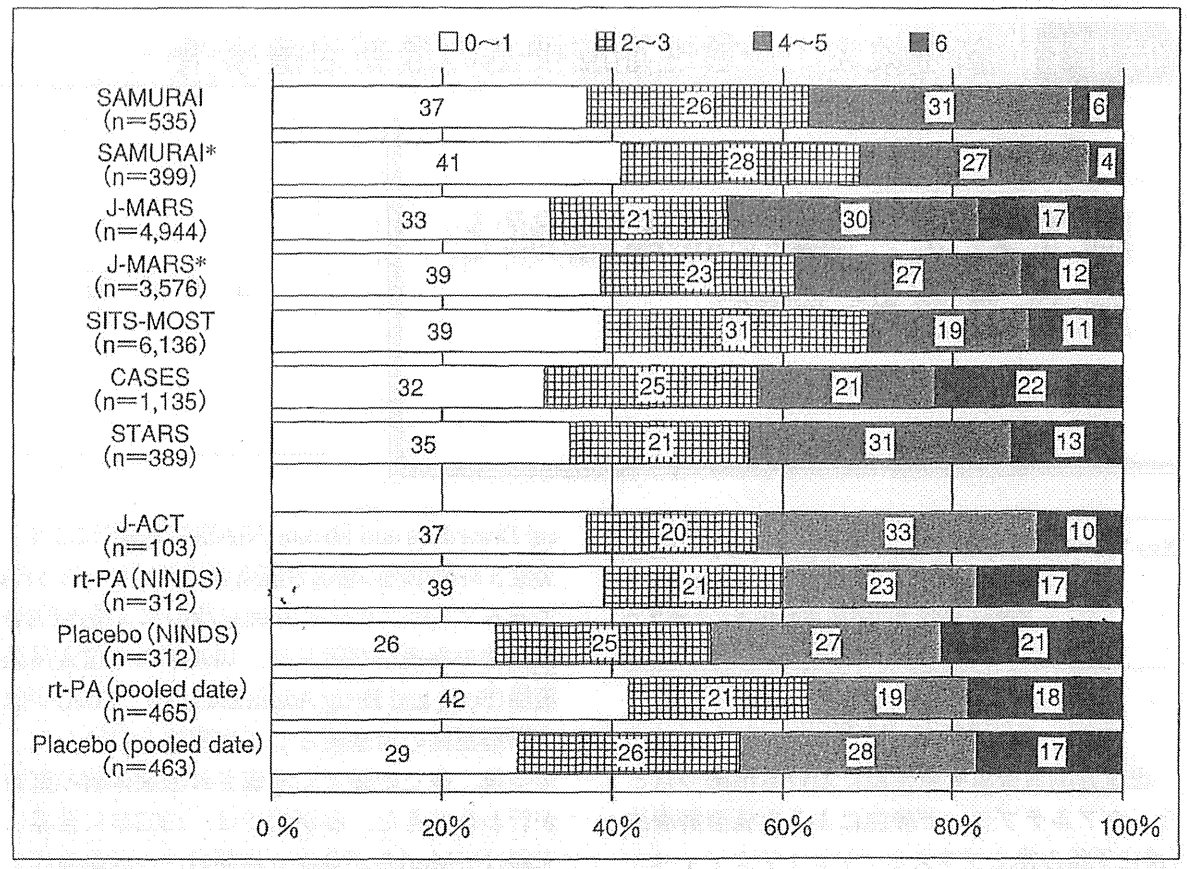

図1　発症3時間以内の国内外の承認後調査・臨床試験における発症90日後modified Rankin Scale
＊欧州適応基準(80歳以下かつNIHSSスコア25未満)を満たす．

た．その結果，発症3か月目の転帰良好〔modified Rankin Scale(mRS) 0～1〕は37％で，NINDS試験の実薬群の39％とほぼ同じであり，死亡率は9.7％対17％とJ-ACTでより低かった(図1，表1)．早期の症候性頭蓋内出血は5.8％で，NINDS試験の6.4％とほぼ同じであった(表1)．よって，本療法が欧米で報告されているアルテプラーゼ0.9mg/kgの静注療法と同程度の臨床的有効性ならびに安全性を有すると結論され，2005年10月に虚血性脳血管障害急性期に対して保険承認された．

本療法の実施には，日本脳卒中学会による「rt-PA(アルテプラーゼ)静注療法適正治療指針」[8]を遵守し適正に使用しなければならない．この指針は本療法の承認にあわせて発表され，rt-PA静注療法のエビデンス，施設基準，チェックリスト，本療法に必要な知識，本療法の実際が示されている．実際の臨床現場では，この中で示されたチェックリストを使用して，適応例，慎重投与，禁忌例を検討することになる．慎重投与例とは，投与を考慮してもよいが，副作用その他が出現しやすく，かつ良好な予後も期待できない場合を意味する．また，投与後の管理では，神経症候，血圧の厳格な観察および対処が求められている．神経症候増悪時には迅速な診断を行い，必要があれば可及的速やかに開頭血腫除去術などの脳外科的処置を実施する．本指針は発表から6年が経過しており，本年中にも発症4.5時間までの治療適応拡大(後述)や市販後調査から浮かび上がってきた諸問題に関する改訂が予定されている．

市販後研究や調査により確認されたわが国におけるrt-PA静注療法の安全性と有効性

rt-PA静注療法は，その有効性に対する期待が高い一方で，頭蓋内出血などの重篤な副作用の心配もあり，市販後登録研究や調査が行われた．

表1 発症3時間以内の国内外の臨床試験・承認後調査における安全性の比較

	%(95%信頼区間)	
	症候性頭蓋内出血*	3か月後までの死亡**
臨床試験		
J-ACT(日本，n=103)	5.8	9.7
NINDS(米国，n=312)	6.4	17
無作為割付試験(NINDS, ECASS I-II, ATLANTIS)の実薬群(n=463)	8.6(6.3～11.6)	17.3(14.1～21.1)
各国の承認後調査(研究)		
SAMURAI rt-PA registry(日本，n=600)	3.8	7.2
J-MARS(日本，n=7,492)	3.5(3.1～3.9)	13.1(12.4～13.9)
SITS-MOST(EU，n=6,483)	7.3(6.7～7.9)	11.3(10.5～12.1)
CASES(カナダ，n=1,135)	4.6(3.4～6)	22.3(20～25)
STARS(米国，n=389)	3.3(1.8～5.6)	13#

*「症候性頭蓋内出血」は発症24～36時間後の頭蓋内出血で，NIHSSスコアが1点以上(J-ACTは原則4点以上)の増悪を伴うものを指す．**「3か月後までの死亡」のうち#STARSのみは1か月後までの死亡を示す．

厚生労働科学研究費補助金による「わが国における脳卒中再発予防のための急性期内科治療戦略の確立に関する研究」(SAMURAI研究，主任研究者・豊田一則)の一環として，研究班員が所属している国内10施設共同で2005年10月から2008年7月までにrt-PA静注療法を受けた600例を登録した(SAMURAI rt-PA registry)[1]．この研究では，画像上の頭蓋内出血は19.8%，36時間以内の症候性頭蓋内出血は3.8%であった．3か月間に7.2%が死亡し(表1)，原疾患による直接死が15例，肺炎が6例，心不全が5例，心破裂が1例，感染性心内膜炎が1例を占めた．発症前mRS≧2であった65例を除外すると発症3か月後に37.2%が完全自立(mRS≦1)した．欧州の市販後調査(SITS-MOST)[9]と同様の解析(80歳を超える高齢者や投与前NIHSSスコア25以上の重症例を除外)を行うと，40.6%が3か月後に完全自立であった(図1)．多数の脳卒中患者を治療する国内基幹施設における良好な治療成績が明らかとなった．

Japan post-Marketing Alteplase Registration Study(J-MARS)[2]は，承認後2年間にその安全性と有効性を検討するために行われた市販後使用成績調査(全例調査)である[4]．推定使用症例数8,313例中7,692例が登録され，うち有効な調査票を回収した7,492例(97.4%)が解析された．62%が男性で，年齢の中央値は72歳であった．臨床病型では心原性脳塞栓症が60%と最多であった．副作用報告は2,412件(32.2%)で，治療後36時間以内の頭蓋内出血は16.2%，症候性頭蓋内出血は3.5%，3か月以内の死亡は13.1%(表1)，頭蓋内出血を死因とする死亡は0.9%であった．施設あたりの治療症例数が多いほど症候性頭蓋内出血発生率が低下することがわかった．発症前に完全自立(mRS≦1)であり，かつ3か月後のmRSを評価しえた4,944例の検討では，3か月後の完全自立はJ-MARS 33%で，死亡はJ-MARS 17%であった(図1)．この理由として，80歳を超える高齢者や重症例がJ-MARSに多く含まれていたことが考えられた．SITS-MOST[9]，Canadian Alteplase for Stroke Effectiveness Study(CASES)[10]，Standard Treatment with Alteplase to Reverse Stroke(STARS)試験[11]はそれぞれ欧州諸国，カナダ，米国での市販後調査成績である(図1，表1)．特に，SITS-MOSTは6,483例を登録した過去最大規模の調査で，国内成績と比較検討するうえでも大いに参考になる．SITS-MOSTでは，80歳を超える高齢者や投与前NIHSS 25以上の重症例は検討対象から除外しているが，J-MARSに登録された症例から同様の症例を除外した3,576例では完全自立39%，死亡12%となり，諸外国と同様の結果であった．

発症4.5時間までの治療適応拡大

2008年にEuropean Cooperative Acute Stroke Study(ECASS)III[3]の結果が報告され，発症3～4.5時間までの虚血性脳血管障害に対するアルテプラーゼを用いたrt-PA静注療法の有効性と安全

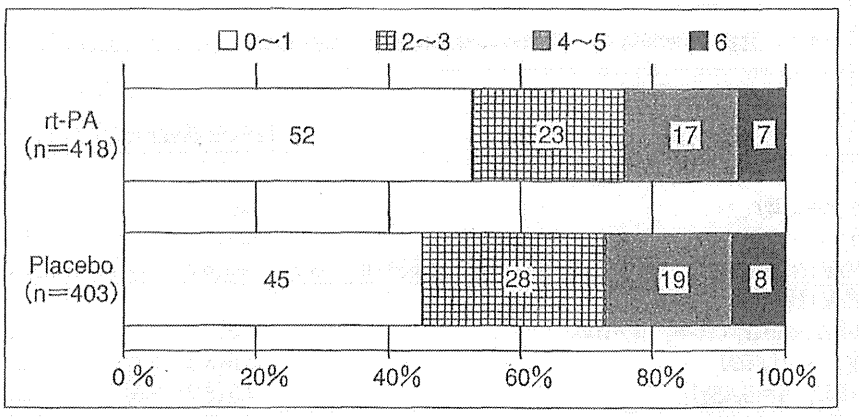

図2　発症3～4.5時間の臨床試験(ECASS III)における発症90日後modified Rankin Scale　(文献[3]より引用改変)

表2　発症3～4.5時間の臨床試験(ECASS III)における安全性評価項目

	n(%)		オッズ比(95%信頼区間)	P
	アルテプラーゼ群(n=418)	偽薬群(n=403)		
すべての頭蓋内出血	113(27.0)	71(17.6)	1.73(1.24～2.42)	0.001
症候性頭蓋内出血				
ECASS III定義*	10(2.4)	1(0.2)	9.85(1.26～77.32)	0.008
ECASS II 定義**	22(5.3)	9(2.2)	2.43(1.11～5.35)	0.02
SITS-MOST定義#	8(1.9)	1(0.2)	7.84(0.98～63.00)	0.02
NINDS定義†	33(7.9)	14(3.5)	2.38(1.25～4.52)	0.006
致死的頭蓋内出血	3(0.7)	0	—	—
死亡	32(7.7)	34(8.4)	0.90(0.54～1.49)	0.68

*発症7日以内のNIHSSスコアが4点以上増悪，もしくは死因となった頭蓋内出血で，神経学的増悪の主因である場合．**発症7日以内のNIHSSスコアが4点以上増悪，もしくは死因となった頭蓋内出血．#治療開始22～36時間にparenchymal hematoma type2で24時間以内のNIHSSスコアが4点以上増悪，もしくは死因となった頭蓋内出血．†治療開始36時間以内のNIHSSスコアが1点以上増悪した頭蓋内出血．
(文献[3]より引用改変)

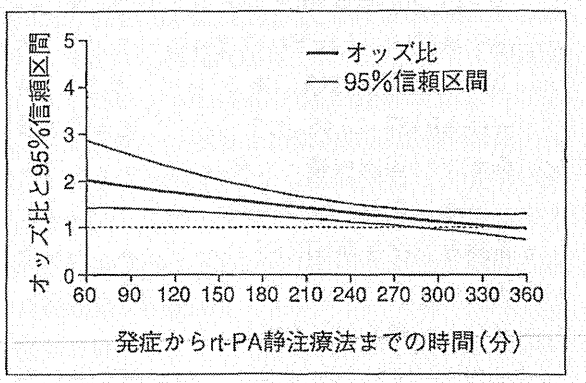

図3　発症ー治療時間と発症90日後完全自立の関係　(文献[12]より引用改変)

性が示された．この研究では，418例がアルテプラーゼ，403例が偽薬に無作為に割り付けられた．主要評価項目として発症3か月後転帰良好(mRS 0～1)が比較され，実薬群52%，偽薬群45%(P=0.04)であった(図2)．症候性頭蓋内出血はアルテプラーゼ群2.4%と偽薬群0.2%(P=0.008)(表2)であったが，死亡はそれぞれ7.7%と8.4%(P=0.68)で差はなかった(図2)．2010年にはすべての主要なアルテプラーゼを使用した虚血性脳血管障害の無作為割付試験に登録された3,670例の統合解析結果[12]が報告された．rt-PA静注療法を受けた患者では完全自立(mRS≦1)の補正オッズ比が発症ー治療1.5時間以内で2.55(95%信頼区間1.44～4.52)，1.5～3時間で1.64(1.12～2.40)，3～4.5時間で1.34(1.06～1.68)，4.5～6時間で1.22(0.92～1.61)で，4.5時間まではrt-PA群で完全自立が有意に多く，4.5～6時間では差が消失した(図3)．死亡は4.5時間以降に増加する傾向があった．症候性頭蓋内出血と発症ー治療時間に有意な関連はなかった．この解析でも発症4.5時間までのア

表3 CLOTBUST試験における治療開始2時間の閉塞血管再開通，神経学的症候改善と再開通血管再閉塞および発症3か月後転帰

	n(%)		P
	モニター群(n=63)	非モニター群(n=63)	
治療開始2時間までの評価項目			
複合評価項目*	31(49)	19(30)	0.03
治療開始2時間以内の完全再開通	29(46)	11(18)	<0.001
治療開始2時間以内の神経学的改善	18(29)	13(21)	0.4
NIHSSスコア3点以下への改善	9(14)	5(8)	
NIHSSスコア10点以上の減少	9(14)	8(13)	
治療開始2時間以内の完全再開通もしくは神経学的改善	16(25)	5(8)	0.02
治療開始2時間以内の再閉塞	11(18)	14(22)	0.7
治療開始2時間での完全再開通継続	24(38)	8(13)	0.002
発症3か月後転帰	(n=53)	(n=49)	
完全自立(mRS≦1)	22(42)	14(29)	0.2
死亡(mRS 6)	8(15)	9(18)	0.4

*事前に設定された複合評価項目で，治療開始2時間以内の閉塞血管の完全再開通もしくは治療開始2時間以内の神経学的改善(NIHSSスコア3点以下への改善もしくはNIHSSスコア10点以上の減少)．

(文献[16]より引用改変)

ルテプラーゼの有効性と安全性が示された．これらの結果に基づき，欧州では2009年にガイドラインを改定して発症4.5時間以内に対する本療法が推奨され，2011年11月に欧州15か国の相互認証方式で発症4.5時間まで適応が拡大された．米国・カナダも2009年に，豪州も2010年にガイドラインを同様に改訂した．豪州では2010年に発症3～4.5時間の患者にアルテプラーゼの投与が承認された．わが国では発症3時間以内が治療対象となっているが，脳卒中学会で適正治療指針の改訂作業中であり，治療適応時間の見直しを含めた改訂が本年中にも予定されている．たとえ，治療可能時間が4.5時間までに延長されたとしてもrt-PA静注療法の効果を最大限にするために，発症－治療時間を短縮するための努力を忘れてはならない．

超音波血栓溶解療法

超音波による血栓溶解促進作用に関する研究は，最初にわが国から発表された．1981年にin vitroで人工血栓にウロキナーゼ添加と超音波照射を併用すると，その溶解率がウロキナーゼ添加単独よりも向上することが示された[13]．1989年にはイヌの両側股動脈の塞栓モデルで，rt-PA静注下で超音波に曝露することにより，再開通時間の短縮とrt-PA投与量を減らしうることが報告された[14]．この血栓溶解促進のメカニズムは，超音波が血栓を形成するフィブリン塊の約数ミクロンのメッシュ状の隙間へのrt-PAの浸潤を加速すると同時に，血栓を構成するフィブリン/フィブリノーゲン分解産物(fibrin/fibrinogen degradation products：FDP)を血栓外に除去し，rt-PAを効率よく血栓に浸透させる作用と考えられている[15]．この効果は，超音波のきわめて微弱なエネルギーの効果で，いわゆるキャビテーションや温熱作用などとは異なる．

2004年Alexandrovら[16]は，CLOTBUST試験で臨床応用されている2 MHz探触子を備えた経頭蓋ドプラ(transcranial Doppler：TCD)を用いて，中大脳動脈閉塞による虚血性脳血管障害126例を無作為にrt-PA静注療法開始から60分間モニターする群としない群に割り付けると，主要評価項目(治療開始2時間以内の完全再開通，もしくは神経学的改善)はモニター群で高率であることを報告した(49%対30%，P=0.03)(表3)．症候性頭蓋内出血は両群とも3例(4.8%)で，3か月後の転帰良好(mRS≦1)はモニター群42%，非モニター群29%であった(P=0.2)(表3)．この報告によって超音波血栓溶解療法が世界的に注目を集めることとなった．Cerevast Therapeutics社はハンズフリー(検査者の技術を必要としない)で頭蓋血管に超音波を照射できるTCD装置(Clotbust