Impaired kidney function was associated with CMBs in this study, which was in agreement with the finding that a low GFR is associated with CMBs.[25] We postulated that endothelial dysfunction might have a key role in impaired kidney function and in the development of CMBs. The kidneys and the brain are early targets for damage by elevated blood pressure.[26] Blood pressure is the major determinant of arteriosclerosis and endothelial dysfunction in patients with chronic kidney disease,[27] and endothelial dysfunction within capillaries appears to contribute to the development of CMBs.[28] Recent studies have shown that endothelial dysfunction is an important mechanism of cerebrovascular damage in patients with lacunar infarction[29] that is correlated with an increased risk of acute ischemic stroke.[30] However, the exact mechanism remains unclear.

The present study has several limitations. First, measurements of the CAVI might not be accurate in patients with severe aortic stenosis, peripheral arterial disease or atrial fibrillation.[22] Second, antihypertensive agents influence arteriosclerosis, and it cannot be excluded that the CAVI was affected in patients taking such drugs.[31] Finally, we could not find any significant factors, including the CAVI, that distinguish between the patients with single CMBs and those with multiple CMBs. The number of patients in our study was relatively small. Further studies are needed to evaluate the association of the CAVI with systemic atherosclerosis and CMBs.

In conclusion, we found that CMBs are independently associated with a high CAVI. We also found that stroke patients with CMBs more frequently exhibit arteriolosclerosis and systemic atherosclerosis than those without CMBs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients — A preliminary study

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ABSTRACT

Background and purpose: The aim of the present study was to investigate whether administration of edaravone during t-PA infusion can enhance early recanalization in acute stroke patients.
Methods: This trial was undertaken as a multicenter, single blind, randomized, open-labeled study. Acute stroke patients with M1 or M2 occlusion within 3 h of onset were studied prospectively. The subjects were randomly allocated to edaravone (Edaravone group: when t-PA was intravenously infused, intravenous edaravone (30 mg) was started at the same time) and no edaravone (Non-Edaravone group). Early recanalization within 1 h after t-PA infusion and neurological recovery 24 h after t-PA infusion were compared between the two groups.
Results: 40 patients (23 men, 17 women; mean age, 76.4 ± 8.2 years, median 79 years) were enrolled; 23 patients were assigned to the Edaravone group and 17 to the Non-Edaravone group. Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072). Eight patients who underwent endovascular therapy immediately after t-PA infusion were excluded, and neurological recovery was analyzed. Remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (80.1% vs. 45.5%, P = 0.0396).
Conclusion: Early recanalization and good neurological recovery were more frequently observed in the Edaravone group than in the Non-Edaravone group. These results demonstrate that administration of edaravone during t-PA infusion should enhance early recanalization in acute stroke patients.

1. Introduction

As a treatment intervention for acute stroke patients, it has been proven that intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes [1]; t-PA-related early arterial recanalization has been recognized as a marker of a good outcome after t-PA infusion [2–7].

Edaravone, a free radical scavenger and neuroprotectant, was approved by the Japanese Ministry of Health, Labour and Welfare in 2001 for the treatment of ischemic stroke within 24 h of onset to improve the neurological symptoms, disorders of activities of daily living, and functional outcomes. [8] The Japanese Guidelines for the management of stroke 2009 suggest edaravone for acute stroke as a grade B recommendation. Therefore, edaravone is now widely used for acute stroke in Japan.

In healthy individuals, the vascular endothelium activates an acute thromboprotective response if intravascular clotting occurs. A pivotal part of this response is a massive release of the key fibrinolytic enzyme t-PA. [9] Once embolus occludes a major artery, endothelial cells are impaired, and sufficient t-PA may not be released from damaged endothelial cells. Therefore, endothelial cell damage should be avoided when intravascular clotting occurs.

Free radicals are generated soon after vessel occlusion and damage the neurovascular unit, including endothelial cells. [10] Edaravone exerts an antioxidant action that suppresses free radicals and inhibits vascular endothelial cell injury. [10,11] Therefore, we hypothesized that administration of edaravone during t-PA infusion in acute stroke patients could inhibit the endothelial cell injury at the occluded artery, and release of t-PA from endothelial cells could be maintained, which could enhance early recanalization. Thus, a multicenter study to investigate whether administration of edaravone during t-PA infusion can enhance the early recanalization in t-PA patients was conducted.

2. Subjects and methods

2.1. Study designs

This trial was undertaken as a multicenter, single blind, randomized, open-labeled study, which was approved by the ethics committee of

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Kawasaki Medical School. The subjects were randomly allocated to edaravone (Edaravone group) and no edaravone (Non-Edaravone group) by the envelope method. That is, papers representing assignments of Edaravone group or Non-Edaravone group were in envelope, and the physician randomly pulled one paper from the envelope and made treatment decision according to assignments on the paper. The frequency of early recanalization and neurological recovery was compared between the two groups (Fig. 1).

2.2. Subjects

This trial was conducted in two departments (Kawasaki Medical School and Red Cross Okayama Hospital) from November, 2009 to March, 2011. The subjects were selected according to the following selection criteria. The inclusion criteria were: 1) patients who met the criteria of the Japan Alteplase Clinical Trial [12]; and 2) patients with M1 or M2 occlusion on MRA before t-PA infusion. The major exclusion criteria were: 1) patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded due to contraindications for MRI; and 2) patients with renal impairment whose serum creatinine exceeded 1.5 g/dl.

2.3. Treatment regimen

2.3.1. Edaravone group

When t-PA was intravenously infused, edaravone (30 mg) was started by intravenous drip infusion over 30 min at the same time. From the next day, edaravone was given in the morning and evening for 7 days.

2.3.2. Non-Edaravone group

Edaravone was not used during t-PA infusion. Edaravone was given after follow-up MRI study, which was performed within 1 h of the end of t-PA infusion. From the next day, edaravone was given in the morning and evening for 7 days.

2.4. Evaluation

The following clinical data were collected from all patients: 1) patient age and sex; 2) arterial blood pressure before t-PA infusion; 3) NIHSS score before and 24 h after t-PA infusion; 4) DWI-ASPECTS [13] on DWI before t-PA infusion; 5) presence or absence of early recanalization of occluded arteries within 60 min after t-PA administration; 6) vascular risk factors including hypertension (HT), Diabetes mellitus (DM), hyperlipidemia (HL), and smoking; 7) stroke subtype; 8) laboratory parameters before t-PA infusion; 9) M1 susceptibility vessel sign(SVS) on T2* before t-PA infusion [14], and 10) hemorrhagic transformation on T2* at 24 h after t-PA infusion.

Before t-PA infusion, MRI studies including DWI, T2*, and MRA to assess DWI-ASPECTS and to identify the occluded arteries were performed. The M1 SVS was defined as a hypointense signal of the proximal MCA on T2* within a vascular cistern in corresponding symptomatic occlusive vessels. [14] Follow-up MRA was performed within 60 min after the end of t-PA administration to identify the presence or absence of early recanalization in the occluded arteries. Recanalization was graded as complete, partial, or no recanalization

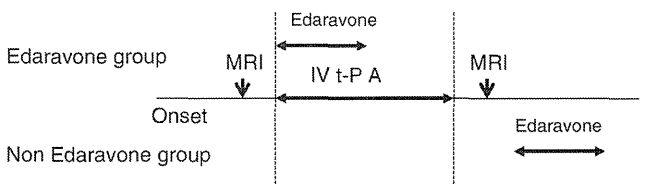

Fig. 1. Schematic of study protocol with IV t-PA treatment phases.

based on our previous report [14], as follows: 1) complete recanalization, reappearance of the entire occluded artery and the distal branches of vessels; 2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery; and 3) no recanalization, persistent occlusion. The presence and absence of recanalization were defined as complete or partial recanalization, and persistent occlusion 60 min after t-PA infusion, respectively. Next, to determine whether hemorrhagic transformation was present, follow-up T2* was performed 24 h after t-PA therapy. Hemorrhagic transformation was defined as the new appearance of low intensity lesions on the follow-up T2* compared to the initial T2*. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of ≥4 when the cerebral hemorrhage was likely to be the cause of clinical deterioration. The experienced researchers (KK and KK) who evaluated the MRI findings were blinded to patient clinical background data.

MRI was performed using a commercially available echo planar instrument operating on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). The imaging protocol consisted of T2*-weighted gradient echo (repetition time [TR]/echo time [TE] = 600/17 ms, flip angle 30°), a diffusion-weighted echo planar (TR/TE = 8000/70 ms) imaging series, and intracranial and extracranial MR angiography.

A neurologist determined the NIHSS scores before and 24 h after t-PA infusion. Remarkable recovery was defined as a ≥8-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. Good recovery 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 [15].

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

All patients had baseline blood samples drawn in the emergency room before MRI. The leukocyte count, erythrocyte count, and platelet count, as well as $HbA1_C$, CRP, creatinine, glucose, and D-dimer levels, were determined.

Using clinical, radiological, cardiac, and ultrasound test results, an experienced stroke neurologist assessed each patient according to modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [16] 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. Undetermined stroke was used when no etiological source of emboli could be identified.

Statistical analysis was performed using StatView version 5 statistical software. The frequencies of early recanalization and remarkable and good recovery 24 h after t-PA infusion were compared between the two groups. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann–Whitney *U* test and Kruskal–Wallis *U* test for continuous variables. Values of $p<0.05$ were considered significant.

3. Results

A total of 90 consecutive stroke patients were treated with t-PA. Three patients were excluded because they had a pacemaker. Eighteen patients had no occlusion and twelve had vertebral-basilar stroke. Of the remaining 57 patients, initial MRA demonstrated M1 occlusion in 22 patients and M2 occlusion in 22 patients. Of these, four were excluded because of renal impairment (2), malignancy

(1), and registration error (1). Thus, 40 patients (23 men, 17 women; mean age, 76.4 ± 8.2 years, median 79 years) were enrolled in the present study.

Twenty-three patients were assigned to the Edaravone group, and seventeen were assigned to the Non-Edaravone group. Table 1 shows the clinical characteristics of the two groups. The proportion of females was higher in the Edaravone group than in the Non-Edaravone group (60.9% vs. 17.6%, P = 0.0097). However, other clinical characteristics did not differ between the two groups.

Follow-up MRA within 60 min after t-PA infusion revealed early recanalization in 15 (37.5%) patients (complete in 6 patients, partial in 9) and no recanalization in 25 (62.5%). Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072)(Table 2 and Fig. 2). The occurrence of hemorrhagic transformation 24 h after t-PA infusion did not differ between the two groups (60.9% vs. 64.7%, P = 0.9999) Symptomatic intracranial hemorrhage was observed in 2 Non-Edaravone group patients (Table 2).

Before t-PA infusion, the NIHSS scores did not differ between the two groups (12.7 ± 6.4 for the Edaravone group vs. 12.8 ± 6.4 for the Non-Edaravone group, P = 0.9455). Remarkable recovery, good recovery and worsening were 65.2% for the Edaravone group vs. 29.4% for the Non-Edaravone group, 13.0% vs. 5.9%, and 4.4% vs. 17.6%, respectively. Therefore, remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (78.3% vs. 35.3%, P = 0.0061). However, worsening was not different between the two groups (4.4% vs. 17.6%, P = 0.1657). Immediately after t-PA infusion, endovascular therapy was performed in 8 patients (2 in Edaravone group, and 6 in Non-Edaravone group). When those patients were excluded from the analysis of neurological recovery 24 h after t-PA infusion, remarkable recovery, good recovery and worsening were 66.7% for the Edaravone group vs. 36.4% for the Non-Edaravone group, 14.3% vs. 9.1%, and 4.8% vs. 18.2%, respectively. Thus, remarkable and good recoveries were more frequently observed in the Edaravone group than in the Non-Edaravone group (80.1% vs. 45.5%, P = 0.0396). However, worsening was not different between the two groups (4.8% vs. 18.2%, P = 0.2661) (Table 2 and Fig. 3).

Table 1
Clinical characteristics of the two groups.

Clinical symptoms (%)	Edaravone group	Non-Edaravone group	P
	No = 23	No = 17	
Female	14(60.9%)	3(17.6%)	0.0097
Age (years)	76.9 ± 7.3	75.8 ± 9.5	0.8055
Hypertension	13(56.5%)	12(70.6%)	0.3637
Diabetes mellitus	5(21.7%)	6(35.3%)	0.3426
Hyperlipidemia	4(17.4%)	2(11.8%)	0.6223
Smoking	2(8.7%)	1(5.9%)	0.9999
Atrial fibrillation (AF)	17(73.9%)	13(76.5%)	0.9999
Stroke type			0.6833
Cardioembolic stroke	17(73.9%)	13(76.5%)	
Large artery disease	1(4.4%)	0(0%)	
Others	5(21.7%)	4(23.5%)	
Baseline NIHSS score	12.7 ± 6.4	12.8 ± 6.4	0.9455
Systolic blood pressure (mm Hg)	137.5 ± 20.0	149.2 ± 19.7	0.0591
Diastolic blood pressure (mm Hg)	77.6 ± 14.3	82.2 ± 12.5	0.3523
Time from symptom onset to t-PA infusion, min	140.4 ± 27.5	131.2 ± 45.2	0.7017
Laboratory data			
HbA1C (%)	5.7 ± 0.7	6.2 ± 2.3	0.7426
Glucose (mg/dl)	139.1 ± 33.7	166.5 ± 111.6	0.9346
CRP (mg/dl)	0.9 ± 1.3	1.1 ± 2.3	0.6815
Leucocytes (/μl)	7309.6 ± 2074.1	7409.4 ± 2790.2	0.6916
Erythrocytes (X10000/μl)	441.4 ± 55.4	411.6 ± 67.6	0.1470
Platelets (X10000/μl)	19.5 ± 6.0	17.9 ± 4.6	0.4601
Creatinine (mg/dl)	0.7 ± 0.3	0.8 ± 0.2	0.1255
PT-INR	1.1 ± 0.2	1.8 ± 3.1	0.8374
Site of occlusion			0.9999
M1	11(47.8%)	9(52.9%)	
M2	12(52.2%)	8(47.2%)	
Baseline DWI-ASPECTS	7.2 ± 1.9	7.1 ± 1.8	0.8161
M1 SVS on T2*	1(4.3%)	3(17.6%)	0.2941

Table 2
Early recanalization rate, hemorrhagic transformation, and neurological recovery of the two groups.

Clinical symptoms (%)	Edaravone group	Non-Edaravone group	P
	No = 23	No = 17	
Early recanalization	13(56.5%)	2(11.8%)	0.0072
Complete	5(21.7%)	1(5.9%)	
Partial	8(34.8%)	1(5.9%)	
Hemorrhagic transformation	14(60.9%)	11(64.7%)	0.9999
Symptomatic	0(0.0%)	2(11.8%)	0.1744
Baseline NIHSS score	12.7 ± 6.4	12.8 ± 6.4	0.9455
NIHSS score 24 h after t-PA infusion	6.9 ± 6.8	10.9 ± 8.7	0.0924
Remarkable recovery	15(65.2%)	5(29.4%)	0.0252
Good recovery	3(13.0%)	1(5.9%)	0.6235
Worsening	1(4.4%)	3(17.6%)	0.2941
Dramatic and good recovery	18(78.3%)	6(35.3%)	0.0061
Excluding 8 patients with endovascular therapy after t-PA infusion			
	No = 21	No = 11	
Baseline NIHSS score	12.9 ± 6.5	12.4 ± 7.5	0.7062
NIHSS score 24 h after t-PA infusion	7.3 ± 6.9	9.5 ± 9.2	0.5386
Remarkable recovery	14/21(66.7%)	4/11(36.4%)	0.1422
Good recovery	3/21(14.3%)	1/11(9.1%)	0.9999
Worsening	1/21(4.8%)	2/11(18.2%)	0.2661
Dramatic and good recovery	17/21(80.1%)	5/11(45.5%)	0.0396

4. Discussion

Early recanalization was more frequently observed in the Edaravone group than the Non-Edaravone group. Thus, administration of edaravone during t-PA infusion in acute stroke patients should enhance early recanalization of the occluded artery.

Vascular endothelium releases massive amounts of t-PA as an acute thromboprotective response when intravascular clotting occurs. [9] Therefore, it is important to avoid vascular endothelial cell injury when embolus occludes the artery. Pharmacological studies using cultured bovine aorta have demonstrated that edaravone inhibits vascular endothelial cell injury. [11] Simultaneous administration of edaravone and t-PA should inhibit endothelial cell injury, and release of t-PA from endothelial cells may be maintained. Therefore, t-PA released from vascular endothelial cells in addition to intravenously administered t-PA should enhance early recanalization.

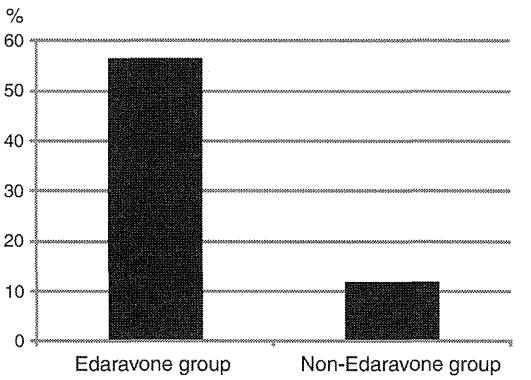

Fig. 2. The early recanalization rate for the Edaravone and Non-Edaravone groups. Early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group (56.5% vs. 11.8%, P = 0.0072).

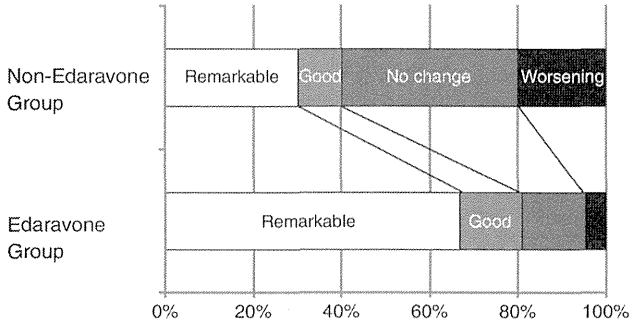

Fig. 3. The frequency of neurological recovery 24 h after t-PA infusion for the Edaravone and Non-Edaravone groups. Remarkable and good recovery was more frequently observed in the Edaravone group than in the Non Edaravone group (80.1% vs. 45.5%, $P = 0.0396$).

Recently, the EDO trial demonstrated that edaravone was effective for the treatment of acute noncardioembolic ischemic stroke within 24 h of onset. [17] Edaravone inhibited brain edema, prevented infarct expansion, improved the neurological symptoms, and attenuated delayed neuronal cell death in ischemic animal models. [18–22] Uno et al. [23]. reported that edaravone reduced oxidative damage in patients with acute stroke. Furthermore, several investigators reported that edaravone inhibited rt-PA-induced cerebral hemorrhage in the ischemic brains of rats. [10,24] The reason for this was that edaravone inhibited the dissociation of the basement membrane and prevented endothelial cell damage and BBB disruption in acute ischemic stroke. Therefore, edaravone should also be effective for acute stroke patients treated with t-PA.

The internationally recommended dosage of t-PA is 0.9 mg/kg, but in Japan, the 0.6 mg/kg dose has been selected according to the J-ACT study results. [12] Therefore, there may be a problem of dosage efficacy. However, J-MARS showed that the frequency of favorable outcome at 3 months in patients between 18 and 80 years with a baseline NIHSS score <25 was 39%, which suggested that 0.6 mg/kg intravenous alteplase should be safe and effective. [25] In J-MARS, edaravone was used in 74.6% of 7492 patients (unpublished), but it was not known when edaravone was administered before and after t-PA infusion. Furthermore, J-ACT II showed that the frequency of early recanalization of the occluded MCA within 6 h after t-PA infusion was about 50% and induced a favorable clinical outcome, compatible to that previously reported with the 0.9 mg/kg dose [26]. In the Edaravone group in the present study, the frequency of early recanalization of the occluded MCA was about 50%, which was similar to the J ACT II results. In J-ACT II, 91.4% of patients were treated with edaravone (unpublished), but it was not known when edaravone was administered before and after t-PA infusion. In J-ACT II and J-MARS, it is possible that edaravone enhanced early recanalization, resulting in favorable outcomes.

The present study had several limitations. Firstly, MRA is somewhat inaccurate for detection of vessel occlusion or stenosis. [27] Secondly, MRI cannot be performed in patients with implantation of metallic materials such as pacemakers and metal clips; three patients were excluded from our study. Thirdly, the results of patients treated without edaravone for 7 days were not examined. Therefore, the effects on patient outcome and hemorrhagic transformation between patients with and without use of edaravone for 7 days were not established. Fourthly, the distribution of the number of patients between the two groups was not even due to use of the envelope method. Finally, although the sample size was small, the difference in the frequency of early recanalization between the two groups was very significant. We believe that edaravone should enhance early recanalization.

In conclusion, early recanalization was more frequently observed in the Edaravone group than in the Non-Edaravone group. Thus, administration of edaravone during t-PA infusion in acute stroke patients should enhance early recanalization of the occluded artery. Edaravone should be given for acute stroke patients as soon as possible.

Conflicts of interest

The authors have no conflict of interests to disclose.

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Low DWI-ASPECTS is associated with atrial fibrillation in acute stroke with the middle cerebral artery trunk occlusion

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ABSTRACT

Background and purpose: For optimal acute stroke management and secondary prevention, discrimination of stroke etiology is crucial. We hypothesized that a low Alberta Stroke Program Early CT Score (ASPECTS) on diffusion-weighted imaging (DWI) immediately after stroke onset was associated with the presence of atrial fibrillation (AF).
Methods: Consecutive patients admitted within 24 h from stroke onset with an occlusion at the horizontal segment of the middle cerebral artery (M1) on initial MRA were retrospectively enrolled. AF was diagnosed based on continuous electrocardiogram monitoring during acute hospitalization or its confirmed history.
Results: Of the 206 patients (95 women, median age 77 [IQR 69–85] years, NIHSS score 18 [13–23]) enrolled, AF was identified in 138 patients (AF group): chronic AF in 89, known paroxysmal AF (pAF) in 13, and masked pAF on admission in 36. The ASPECTS score on the initial DWI, performed a median of 2.5 h after onset, was lower in the AF group than in the others (4 [2–6] vs. 7 [4–8], $p<0.001$). With the optimal cut-off value of ≤ 6 (sensitivity, 78%; specificity, 57%; area under the ROC curve, 0.682), DWI-ASPECTS was independently associated with the presence of any AF (OR 5.05, 95%CI 2.36 to 10.8), as well as the presence of any pAF (OR 8.64, 95%CI 3.00 to 24.9) and that of masked pAF on admission (OR 10.0, 95%CI 3.06 to 32.9).
Conclusion: Extensive early ischemic change assessed by DWI-ASPECTS predicts the presence of AF, even initially masked pAF, in acute stroke patients with M1 occlusion.

1. Introduction

The etiological mechanisms of cardioembolic stroke differ from those of other ischemic strokes, and accordingly, there are unique strategies for acute management and secondary prevention, including urgent anticoagulant therapy and rapid exploration for cardiac thrombi. Thus, prompt diagnosis of cardioembolic stroke is crucial, especially in the hyperacute phase. However, detection of atrial fibrillation (AF), the leading cause of cardioembolic stroke, is often difficult due to the existence of paroxysmal AF (pAF) [1].

Diffusion-weighted magnetic resonance imaging (DWI, MRI) depicts ischemic lesions clearly [2]. Combined with magnetic resonance angiography (MRA), DWI contributes to rapid and accurate diagnosis of ischemic stroke subtype [3]. Although the presence of atherosclerotic changes of the responsible artery on MRA is a good indicator to distinguish atherothrombotic infarction from cardioembolism [3], this information is not available when MRA reveals complete arterial occlusion. Large infarct volume is another promising factor to distinguish cardioembolic infarcts with high-risk emboligenic sources from infarcts with internal carotid artery (ICA) atherosclerosis [4], and it is applicable to patients with arterial occlusion. The Alberta Stroke Program Early CT Score (ASPECTS) on DWI is a semi-quantitative topographic score that can simply estimate the extent of infarct area immediately after stroke [5,6], and it has been proven to correlate inversely with DWI lesion volume [7,8]. The aim of this study was to examine the hypothesis that acute stroke patients with occlusion at the horizontal segment (M1) of the middle cerebral artery (MCA) who had AF had lower DWI-ASPECTS scores than those without AF.

2. Methods

2.1. Subjects

Consecutive acute ischemic stroke patients who underwent MRI/MRA on admission to our stroke center within 24 h from stroke onset from April 2006 through August 2011 and were diagnosed as having

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M1 occlusion with compatible acute neurological deficits were retrospectively enrolled. Patients with contraindications to MRI were excluded.

This study was approved by the institutional ethics committee.

2.2. Clinical backgrounds and characteristics

Clinical backgrounds, including sex, age, and cardiovascular risk factors, were reviewed. Cardiovascular risk factors were defined as: 1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg before or ≥2 weeks after stroke onset; 2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥200 mg/dl, or glycosylated hemoglobin ≥6.5% on admission; 3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level ≥220 mg/dl; and 4) current smoking and alcohol intake. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

2.3. Identification of atrial fibrillation

For detecting AF, a 12-lead electrocardiogram (ECG) on admission and continuous ECG monitoring for the initial several days of hospitalization (at least 24 h) were conducted in all patients. These examinations were repeated during acute hospitalization when patients were suspected to have AF based on complaints of palpitations. Patients with AF (the AF group) were classified into three subgroups: those with chronic AF (cAF), those with known paroxysmal AF (pAF) as a confirmed history or identification on the initial ECG, and those with masked pAF on admission that was later identified. Patients who did not have a history of AF or in whom AF was not detected on ECG were defined as the non-AF group.

2.4. Neuroimaging

MRI studies including DWI and MRA were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Siemens MAGNETOM Vision or MAGNETOM Sonata scanner, Erlangen, Germany). DWI was obtained using the following parameters: TR/TE, 4000/100 ms; b values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 96×128; and slice thickness, 4.0 mm, with a 1.0-mm intersection gap.

DWI-ASPECTS was scored by a neurologist (Y.S.) who was blinded to all clinical information, based on the method described by Barber et al. [5]. The MCA territory was allotted 10 points, and a single point was subtracted for an area of hyperintensity on initial DWI. A score of 0 indicated complete ischemic involvement throughout the MCA territory. The inter-rater reliability of DWI-ASPECTS was evaluated using scores by another neurologist (T.O.) with weighted κ statistics. The intra-rater reliability was examined with scores recorded after a 2-month interval from the initial evaluation by the same neurologist (Y.S.). The site of arterial occlusion was determined on the initial MRA. M1 occlusion was judged irrespective of the presence of ipsilateral ICA occlusion. Patients with the horizontal distance from the ICA bifurcation to the distal end of the flow signal at M1 in an anteroposterior view <5 mm were defined as having M1 proximal occlusion, while those in whom this residual vessel length was ≥5 mm were defined as having M1 distal occlusion [9].

2.5. Statistical analysis

Clinical backgrounds and characteristics were compared between the AF and non-AF groups. Univariate analyses were performed using the chi-square test, Fisher's exact test, or the Mann–Whitney U test as appropriate. The data are presented as median values (interquartile range [IQR]) or frequencies (%). To obtain the optimal cut-off value of DWI-ASPECTS for discriminating the AF group from the non-AF group, receiver-operating characteristic (ROC) curve analysis was conducted. Multivariate logistic regression analyses were performed to identify independent factors associated with the presence of AF. DWI-ASPECTS and all variables of clinical manifestations identified on univariate analyses with p values <0.1 were entered into the model. Multivariate analyses were also performed to identify factors related to the presence of pAF after removing patients with cAF from the cohort, while factors related to the presence of masked pAF were identified after removing patients with cAF and those with known pAF.

All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Results were considered significant at $p<0.05$.

3. Results

Overall, 1461 patients with acute ischemic stroke were admitted to our stroke center during the study period (Fig. 1). Of these, 123 patients were excluded due to: MRI contraindicated in 105; missing the MRA sequence on the initial MR examination in 12; and difficult evaluation of the imaging due to motion artifact in 6. Of the remaining 1338 patients, arterial occlusion at M1 was observed in 206 patients. Finally, these 206 patients (95 women, median age 77 [IQR 69–85] years, NIHSS score 18 [13–23]) were enrolled in the present study.

AF was observed in 138 patients (AF group), while it was not observed in the remaining 68 patients (non-AF group). In the AF group, 89 (65%) patients had cAF, 13 (9%) had known pAF, and the remaining 36 (26%) had masked pAF. The clinical characteristics of the included patients are presented in Table 1. Patients in the AF group were older ($p<0.001$) and had a higher NIHSS score ($p=0.004$) than those in the non-AF group. Male sex ($p=0.037$), hyperlipidemia ($p=0.005$), and current smoking ($p=0.001$) were less common, and the plasma D-dimer ($p=0.029$) level was higher in the AF group than in the non-AF group.

The initial MRI was performed a median 2.5 h (IQR 1.5–8.2 h) after stroke onset. Overall, 121 patients (59%) had M1 proximal occlusion. The DWI-ASPECTS was significantly lower in the AF group than in the non-AF group (median 4 [IQR 2–6] vs. 7 [4–8], $p<0.001$, Table 1). The inter-rater reliability of DWI-ASPECTS was $\kappa=0.69$, and intra-rater reliability was $\kappa=0.72$. The proportion of patients with AF decreased along with the increase in DWI-ASPCETS ($r=-0.843$, $p=0.001$ with Spearman's rank correlation test, Fig. 2). Using the ROC curve, the optimal cut-off value of DWI-ASPECTS distinguishing the AF group from the non-AF group was ≤6 (sensitivity, 78%; specificity, 57%; area under the ROC curve, 0.682).

The results of multivariate regression analysis for association with AF are presented in Table 2. DWI-ASPECTS ≤6 (OR 5.05, 95%CI 2.36 to 10.8, $p<0.001$) and advanced age (OR 1.47, 95%CI 1.03 to 2.09, $p=0.034$ for every 10 years) were positively associated, and hyperlipidemia (OR 0.48, 95%CI 0.24 to 0.99, $p=0.047$) and current smoking (OR 0.31, 95%CI 0.13 to 0.73, $p=0.007$) were inversely associated with having AF. DWI-ASPECTS ≤6 was associated with having AF when the analysis was done only for patients with M1 proximal occlusion (OR 6.92, 95%CI 2.11 to 22.7, $p=0.001$) and only for those with M1 distal occlusion (OR 6.95, 95%CI 1.96 to 24.6, $p=0.003$). DWI-ASPECTS was also associated with having AF as a continuous variable (OR 0.76, 95%CI 0.65 to 0.88 for every 1 point).

The results of multivariate analyses for association with pAF are presented in Table 3. DWI-ASPECTS ≤6 was positively associated with the presence of any pAF (both known and masked pAF, OR 8.64, 95%CI 3.00 to 24.9) and with the presence of masked pAF (OR 10.0, 95%CI 3.06 to 32.9).

4. Discussion

In the present study, a significant association between the initial DWI-ASPECTS and the presence of AF was demonstrated in acute ischemic stroke patients with M1 occlusion. DWI-ASPECTS of 6 or less could predict AF irrespective of the M1 occlusion site. Moreover,

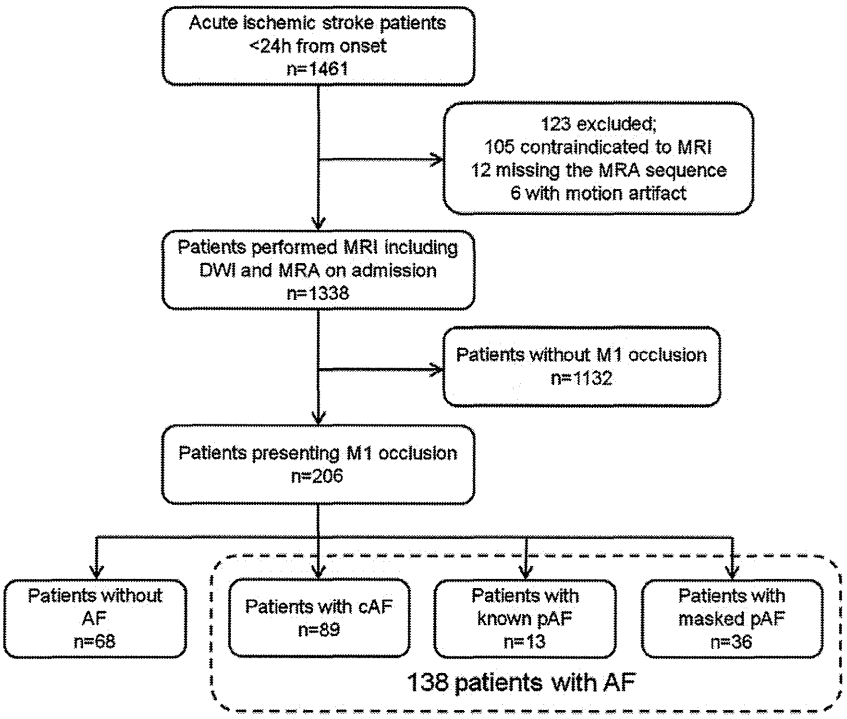

Fig. 1. Patient flow chart.

DWI-ASPECTS could distinguish patients with unidentified AF at presentation that was later documented from those with sinus rhythm.

The finding that DWI-ASPECTS discriminates patients with AF from those without AF was partly consistent with previous reports that showed a larger infarct volume on DWI in patients with cardioembolism than in those with internal carotid artery disease [4]. For acute stroke patients with M1 occlusion, AF seems to cause sudden main trunk occlusion and poor collateral circulation, and it may result in extensive ischemia [10]. However, visual assessment of the infarct volume depends on the reader's experience and skill and is time-consuming, and the intra-rater and inter-rater reliabilities are not sufficiently high [11]. On the other hand, DWI-ASPECTS can be scored promptly with good inter-rater reliability [5], and it is a simple and handy indicator in the emergent clinical setting. The cut-off of DWI-ASPECTS >6 was proven to be associated with complete or functional independency 3 months after IV t-PA [6,12]. The one-third of cerebral hemisphere rule on CT [13] appears to generally coincide with this cut-off of ASPECTS. In addition, AF was recently reported to predict poor outcome after IV t-PA [14,15]. The positive association of AF with DWI-ASPECTS ≤6 in our cohorts can be a good explanation for poor outcome of AF patients after thrombolysis.

The occluded sites of the M1 affect various clinical characteristics, including neurological severity, initial ASPECTS, and response to thrombolytic therapy [9]. It is interesting that DWI-ASPECTS ≤6 predicted

Table 1
Baseline characteristics.

Variables	Total	AF group	Non-AF group	p
	n=206	n=138	n=68	
Male sex, n (%)	111 (54)	67 (49)	44 (65)	0.037
Age, y, median (IQR)	77 (69–85)	80 (71–88)	74 (68–79)	<0.001
Vascular risk factors, n (%)				
Hypertension	144 (70)	95 (69)	49 (72)	0.747
Diabetes mellitus	28 (14)	14 (10)	14 (21)	0.051
Hyperlipidemia	69 (34)	37 (27)	32 (47)	0.005
Current smoking	41 (20)	18 (13)	23 (34)	0.001
Alcohol intake	77 (37%)	48 (35%)	29 (43%)	0.461
Blood pressure on admission, median (IQR)				
Systolic, mm Hg	156 (136–169)	153 (134–165)	160 (140–176)	0.115
Diastolic, mm Hg	83 (70–91)	82 (70–91)	84 (72–91)	0.777
Time from onset to initial MRI, h, median (IQR)	2.5 (1.5–8.2)	2.5 (1.5–7.9)	2.6 (1.5–8.7)	0.873
NIHSS score, median (IQR)	18 (13–23)	20 (15–23)	16 (12–20)	0.002
M1 proximal occlusion, n (%)	121 (59)	82 (59)	39 (57)	0.880
DWI-ASPECTS, median (IQR)	5 (3–7)	4 (2–6)	7 (4–8)	<0.001
Biochemistry results on admission, median (IQR)				
Leukocyte count, /μl	7300 (5700–9000)	7200 (5600–8900)	7900 (6200–9300)	0.120
hs-CRP, mg/dl	0.13 (0.06–0.53)	0.14 (0.06–0.59)	0.13 (0.06–0.45)	0.571
D-dimer, μg/ml	1.9 (1.2–3.5)	2.2 (1.3–4.0)	1.6 (1.0–2.6)	0.017

AF indicates atrial fibrillation; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health stroke scale; M1, middle cerebral artery horizontal segment; hs-CRP, high-sensitivity C-reactive protein; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

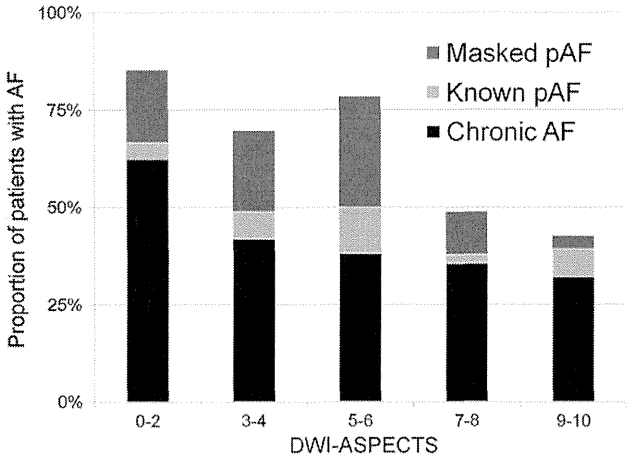

Fig. 2. The frequency of atrial fibrillation and the DWI-ASPECTS. The frequency of atrial fibrillation decreases along with the increase in DWI-ASPECTS ($r = -0.843$, $p = 0.001$ with Spearman's rank correlation test).

the presence of AF irrespective of the occluded sites. Atherosclerotic change in the MCA occurs predominantly in the stem [16], and embolic occlusion due to AF seems to be relatively common in the distal trunk where the caliber becomes smaller. Similar percentages of M1 proximal occlusion in the present AF and non-AF groups suggest that our cohort included many patients having large cardiogenic emboli.

Paroxysmal AF has similar risks of ischemic stroke to cAF [17,18] and is more prevalent than cAF in acute stroke patients [19]. Although guidelines recommend 24-h holter monitoring for patients with ischemic stroke of unknown cause [20], 24-h monitoring was reported to misdiagnose pAF in more than half of patients with confirmed pAF using 7-day Holter monitoring [1]. The left atrial volume index divided by diastolic velocity on echocardiogram and frequent atrial premature beats on ECG were other predictors of pAF in acute stroke [21,22], but their predictive values are not known. The present finding that DWI-ASPECTS predicted masked pAF even after removal of patients with cAF and previously known pAF helps in the quick selection of possible cardioembolic cases from cryptogenic stroke patients.

This study had some limitations. First, the retrospective design might have contributed to some selection bias. Second, ASPECTS is validated for ischemic strokes in the MCA territory, and the present finding cannot be applied to patients developing ischemic stroke in the posterior circulation. In addition, patients with MCA branch occlusion were not evaluated. Third, although every attempt was made to detect AF, some patients with pAF might have been overlooked. Fourth, most of the included patients were admitted and performed MRI in ultra-early phase in the present study. The median onset-to-MRI time was 2.5 h in this study, and our results should be carefully interpreted in generalization.

Table 2
Multivariate logistic regression analysis for predicting the presence of atrial fibrillation.

Variables	OR	95% CI	P
Male sex	0.65	0.30–1.41	0.276
Age (for every 10 years)	1.47	1.03–2.09	0.034
Diabetes mellitus	0.43	0.16–1.14	0.090
Hyperlipidemia	0.48	0.24–0.99	0.047
Current smoking	0.31	0.13–0.73	0.007
Initial NIHSS (for every 1 point)	1.01	0.96–1.07	0.635
DWI-ASPECTS ≤6	5.05	2.36–10.8	<0.001
D-dimer (for every 1.0 μg/ml)	1.04	0.91–1.19	0.587
DWI-ASPECTS (for every 1 point)	0.76	0.65–0.88	<0.001

NIHSS indicates the National Institutes of Health stroke scale; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

Table 3
Multivariate logistic regression analyses for predicting the presence of paroxysmal atrial fibrillation (pAF).

Variables	OR	95% CI	p
Any pAF (both known and masked)			
Male sex	0.42	0.16–1.12	0.084
Age (for every 10 years)	1.66	1.00–2.75	0.050
Diabetes Mellitus	0.11	0.02–0.64	0.014
Initial NIHSS (for every 1 point)	1.04	0.96–1.13	0.306
DWI-ASPECTS ≤6	8.64	3.00–24.9	<0.001
D-dimer (for every 1.0 μg/ml)	0.98	0.84–1.15	0.820
Masked pAF			
Male sex	0.49	0.17–1.43	0.191
Age (for every 10 years)	1.80	1.05–3.06	0.031
Diabetes mellitus	0.16	0.03–0.90	0.038
Initial NIHSS (for every 1 point)	1.02	0.94–1.12	0.582
DWI-ASPECTS ≤6	10.0	3.06–32.9	<0.001

NIHSS indicates National Institutes of Health stroke scale; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging.

In conclusion, extensive early ischemic change assessed by DWI-ASPECTS can discriminate the presence of AF from sinus rhythm in patients with acute ischemic stroke due to M1 occlusion, irrespective of the type of AF and the occluded site. DWI-ASPECTS ≤6 is a good indicator for thorough investigation of AF, including, for example, using implantable cardiac monitors.

Role of funding source

None.

Conflict of interest statement

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Visibility of the Lesser Sphenoid Wing Is an Important Indicator for Detecting the Middle Cerebral Artery on Transcranial Color-Coded Sonography

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Key Words
Cerebrovascular disease · Lesser sphenoid wing · Middle cerebral artery · Transcranial color-coded sonography · Stroke

Abstract
Background: Failure to detect the sphenoidal segment of the middle cerebral artery (M1) on transcranial color-coded sonography (TCCS) results from either M1 occlusion or an insufficient temporal bone window (TBW). We sought to identify a simple indicator on B mode images for M1 evaluation. ***Methods:*** Consecutive acute ischemic stroke patients with an intact M1 segment underwent prospective TCCS evaluation. Visibilities of the contralateral temporal bone (CTB), midbrain (MB) and lesser sphenoid wing (LSW) on B mode images were defined as follows: 'invisible', 'poor' if the contour was less than 50% visible, 'fair' if more than 50% visible and 'good' if totally visible. M1 detectability on color Doppler images was defined as follows: 'INVISIBLE', 'POOR' if the M1 was detected as color dots, 'FAIR' if linearly but discontinuously detectable, and 'GOOD' if linearly and continuously detectable. The relationship between each structure's visibility and M1 detectability was assessed. ***Results:*** Seventy-six patients with 152 TBWs were evaluated. The CTB was 'invisible' in 2%, 'poor' in 22%, 'fair' in 36% and 'good' in 40%. Visibility of the MB was 36, 24, 26 and 14%, respectively. Visibility of the LSW was 16, 22, 29 and 32%, respectively. The M1 was 'INVISIBLE' in 51%, 'POOR' in 7%, 'FAIR' in 7% and 'GOOD' in 35%. Spearman's rank correlation coefficient between each structure's visibility and M1 detectability was 0.68 for the CTB, 0.66 for the MB and 0.80 for the LSW, respectively ($p < 0.001$ for all). ***Conclusion:*** Visibility of the LSW on B mode appears to be a better indicator than other structures for M1 evaluation.

Background

Transcranial color-coded duplex sonography (TCCS) is widely used to evaluate the intracranial arterial system in patients with acute stroke [1–4]. There have been insufficient data to compare the ability of ultrasonographic examination to visualize intracranial structures and vessels through the skull bone in different races [5–7]. There is some reported data on success rates for Doppler ultrasound in different races, with the highest success rates in northern Europeans, and lower in most other populations (Asians, African Americans, Hispanics) [8–10].

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There is much less reported data on relative success rates in different races for intracranial B mode imaging. Asian populations have a high frequency of poor temporal bone windows (TBWs) [8–10]; failure to detect the sphenoidal portion of the middle cerebral artery (M1) on TCCS could be secondary to M1 occlusion or to an inadequate TBW, or sometimes to poor technique or wrong gain settings. The hyperechoic lesser sphenoid wing and superior margin of the petrous pyramid were proposed to be indicators for the identification of the middle and posterior cerebral arteries [11]. This study aimed to clarify the relationship between visibilities of the contralateral temporal bone (CTB), midbrain (MB) and ipsilateral lesser sphenoid wing (LSW) on B mode images and the detectability of the ipsilateral M1 on color Doppler images by TCCS. We have attempted to develop a simple indicator to determine whether failure to detect flow in the M1 is secondary to local arterial disease or to an inadequate bone window.

Subjects and Methods

Consecutive patients with acute ischemic stroke admitted to our stroke center within 7 days after stroke onset between January 2009 and July 2009 were prospectively registered. They were evaluated by intracranial magnetic resonance imaging (MRI) for brain and intracranial magnetic resonance angiography (MRA) for intracranial arteries with a 1.5-tesla system (Magnetom Vision; Siemens, Germany), and carotid duplex ultrasonography for the common carotid artery and the extracranial internal carotid artery (ICA) using a Hitachi EUB-8500 ultrasound machine (Hitachi Medical Corp, Tokyo, Japan) with a 7.5-MHz linear probe on admission. Patients having an M1 or an ICA with luminal stenosis >50% or occlusion on baseline intracranial MRA or carotid ultrasonography, those having a pacemaker, or those who had an extracranial-intracranial arterial bypass were excluded from our study.

TCCS Examination

TCCS examination using a Hitachi EUB-8500 ultrasound machine with a 2- to 2.5-MHz sector probe was performed transtemporally in horizontal projection within 24 h after initial MRA and carotid US evaluations. Patients were lying in a supine, left lateral or right lateral decubitus position according to the side of the TBW examined and the patient's condition. With a scanning depth of 15.5 cm as a fixed depth, the CTB was visualized first for orientation, and the visibilities of the CTB, MB and LSW were assessed. On B mode images, the MB is hypoechoic and butterfly-shaped, and it is surrounded by hyperechoic subarachnoid cisterns, and the LSW has a hyperechoic outline of the bony structures at the skull base [11]. The B mode gain was initially set at 20 and adjusted to optimize structure delineation in the ultrasound image. Then color Doppler ultrasound was used to identify the intracranial arteries. The color gain was set at 38 as a default value and adjusted to obtain an optimum color display to the setting just below that in which background noise first becomes apparent. The velocity color scale was initially set at ±27.3 cm/s. To mitigate aliasing, color flow velocity settings were changed between ±2.3 and ±54.7 cm/s. The M1 at a depth of 4–6 cm was evaluated as a unidirectional flow toward the probe on color Doppler images. If color dots or discontinuous color were initially detected, whether the vessel was the M1 or not was judged based on the depth, the positional relationships with the probe and the intracranial structures, and the direction of blood flow, and further attempts to manipulate the probe superiorly and inferiorly to identify the remainder of the M1 were performed. If the MB and LSW could not be clearly identified, we carefully measured the intracranial head diameter by using the B mode and used the actual depth to guide the examination. Two experienced vascular neurologists who knew the information of the M1 on baseline MRA assessed the visibilities of the MB, LSW and CTB on B mode images and assigned patients into 4 categories as follows: 'invisible' if the hyperechoic CTB within the echo window, the peduncle of the MB or the hyperechoic LSW within the echo window was not visible at all; 'poor' if it was visible less than 50%; 'fair' if it was visible more than 50%, and 'good' if it was almost totally visible (fig. 1, 2). The detectability of the M1 was assessed on color Doppler images and assigned into similar categories as follows: 'INVISIBLE' if the M1 was undetected, 'POOR' if detected as color dots, 'FAIR' if linearly but discontinuously detectable and 'GOOD' for being linearly and continuously detectable (fig. 2, 3). When the M1 was assigned into the category 'INVISIBLE', the detectabilities of the anterior and posterior cerebral arteries from the same TBW were also evaluated to ascertain the absence of a proper TBW according to the recent consensus recommendations [4]. The posterior cerebral artery was detectable if the precommunicating segment, proximal or distal postcommunicating segment was detected. The interrater and intrarater agreements for each of the categories (invisible, poor, fair and good), by kappa statistic, were 0.45 and 0.64 for the MB, 0.62 and 0.85 for the LSW, 0.61 and 0.71 for the CTB, and 0.89 and 0.96 for the M1, respectively, according to the offline video monitoring evaluations of 20 randomly selected patients by the above-mentioned two experienced vascular neurologists.

Contrast-Enhanced TCCS Examination

Contrast-enhanced TCCS examination was performed in the initial 10 patients who had 'INVISIBLE', 'POOR' or 'FAIR' detection of the M1 on color Doppler images after they had given their informed consent. Levovist (Bayer Health Care, Leverkusen, Germany), an ultrasound contrast agent consisting of granules composed of 99.9% galactose and 0.1% palmitic acid, was used. Levovist was injected at a dose of 2.5 g diluted in 7 ml of 0.9% saline resulting in a concentration of 300 mg/ml (total volume, 8.5 ml). A 4.25-ml bolus of Levovist was injected into an antecubital vein within 10 s, followed by a 10-ml saline chaser bolus for the one side. A second injection for the other side was administered after the first contrast effect had faded out. Detectability improvement on contrast-enhanced TCCS examination was defined as improvement of M1 detectability on contrast-enhanced TCCS by one or more categories compared with that on non-contrast-enhanced examination.

Data Analysis

The percentages of each finding were calculated for all patients, by sex and by age (<70 years old or ≥70 years old). The percent-

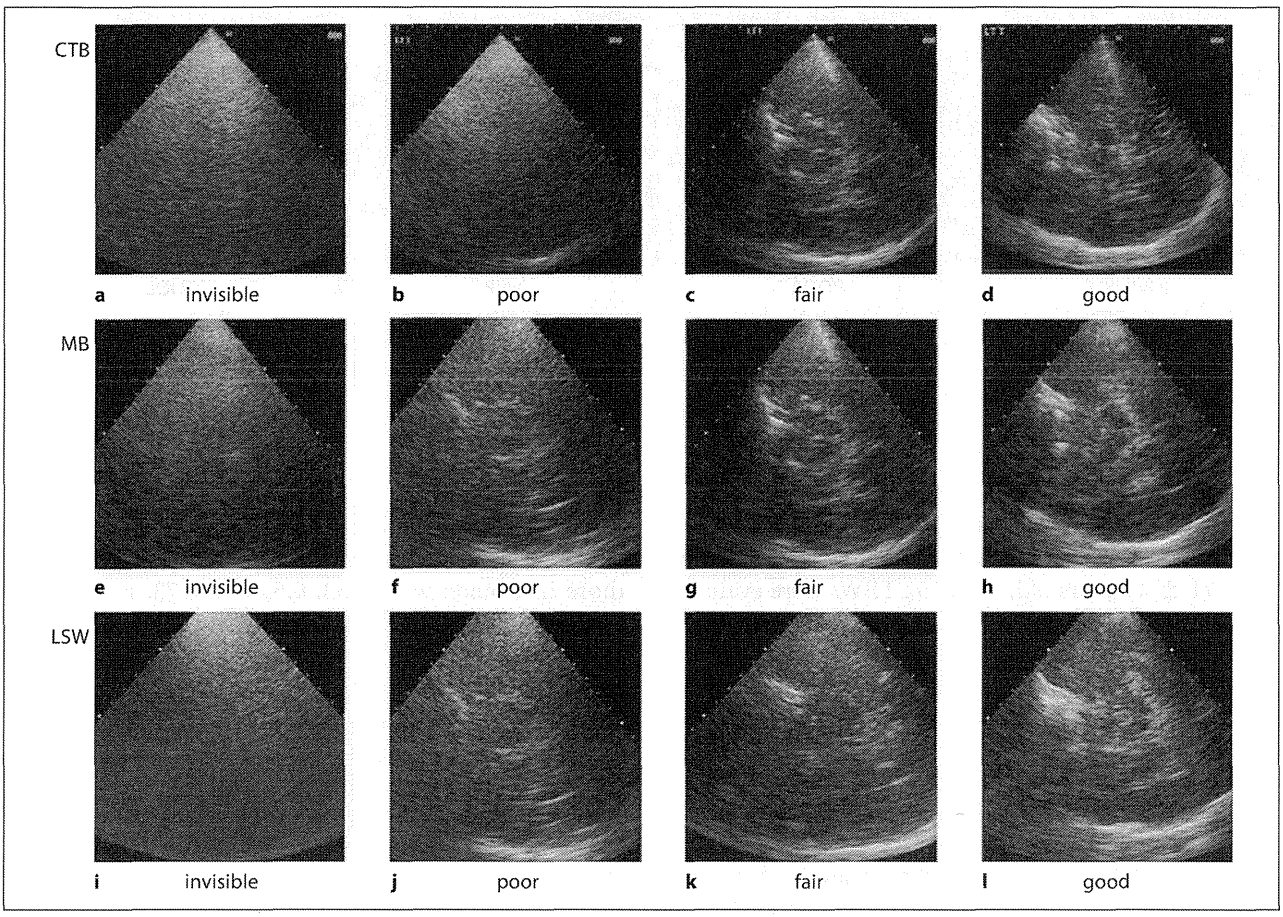

Fig. 1. Visibilities of CTB (**a–d**), MB (**e–h**) and LSW (**i–l**) on B mode images. invisible = The contour is not visible; poor = the contour is less than 50% visible; fair = the contour is more than 50% visible; good = the contour is almost totally visible.

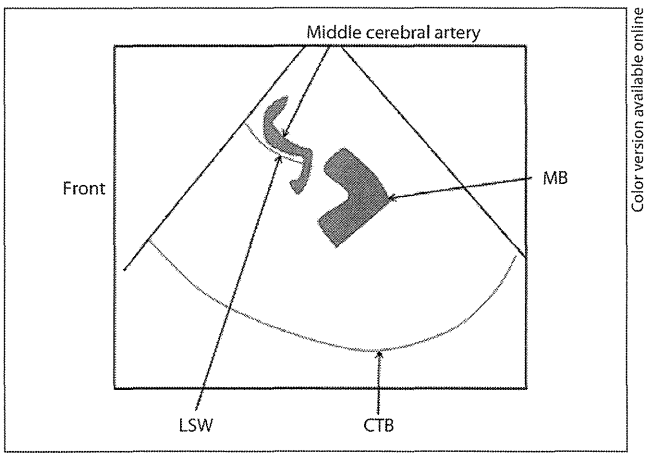

Fig. 2. A schema of CTB, MB, LSW and middle cerebral artery.

Color version available online

ages of each category were compared by sex and by age using the χ^2 test. The relationship between each structure's visibility and M1 detectability was analyzed using Spearman's rank correlation. The percentages of M1 detection improvement by categorical visibility of each structure on B mode images were calculated.

Results

One hundred and twenty-four acute ischemic stroke patients admitted to our stroke center during the study period were investigated. Forty-six patients who had vascular abnormality on MRA (13 ICA occlusion, 5 ICA stenosis ≥50%, 1 ICA pseudo-occlusion, 14 middle cerebral artery M1 occlusion, 13 middle cerebral artery M1 stenosis ≥50%), 1 patient having a pacemaker, and 1 patient

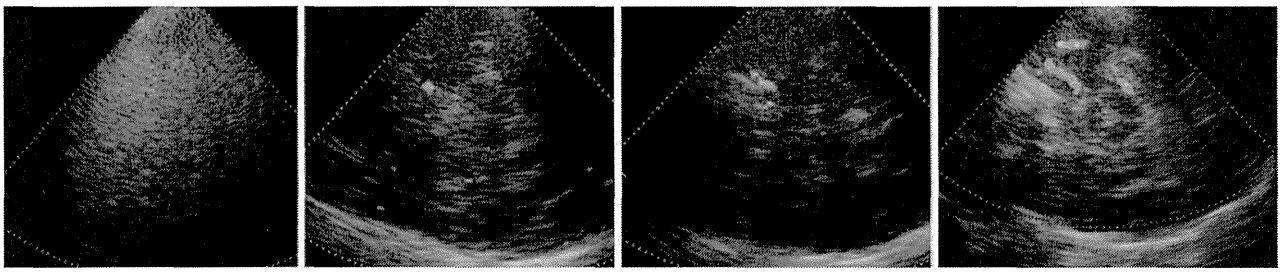

Fig. 3. M1 detectability on color Doppler images. **a** The M1 is undetectable (INVISIBLE). **b** The M1 is detected as color dots (POOR). **c** The M1 is linearly but discontinuously detectable (FAIR). **d** The M1 is linearly and continuously detectable (GOOD).

who had superficial temporal artery/middle cerebral artery anastomosis were excluded. Seventy-six patients (48 men, 71 ± 12 years old) with 152 TBWs were evaluated by TCCS. None of these had a large infarction which caused brain displacement on MRI. Table 1 summarizes the percentages of each structure's visibility on B mode images and M1 detectability on color Doppler images for all patients, by sex and by age. There were 38 TBWs of women aged ≥70 years, 42 TBWs of men aged ≥70 years, 18 TBWs of women aged <70 years and 54 TBWs of men <70 years. The CTB, MB and LSW were visible on B mode in 98, 64 and 84%, respectively; levels of visibility are shown in table 1. The M1 was detected in 49% on color Doppler images, and M1 detectability was 'POOR' in 7%, 'FAIR' in 7% and 'GOOD' in 35%. Structural visibilities on B mode and M1 detectability were better in men than in women and in younger adults (<70 years old) than in older adults (≥70 years old). Among 77 TBWs with an 'INVISIBLE' M1, the anterior cerebral artery was detectable only through 4 TBWs, and the PCA was detectable through 25 TBWs (table 2).

The correlation coefficient between each structure's visibility and M1 detectability was 0.68 for the CTB, 0.66 for the MB and 0.80 for the LSW ($p < 0.001$ for all; table 3). The M1 was detectable as 'GOOD' in 40 (82%) out of 49 TBWs with 'good' LSW visibility, although it was so in 43 (70%) out of 61 TBWs with 'good' CTB visibility and in 17 (77%) out of 22 TBWs with 'good' MB visibility. When the LSW was invisible, the M1 was not detected. When the LSW was less than 50% visible, the M1 was detected in 9%. When the LSW was more than 50% visible, the M1 was detected in 55%. When the LSW was almost totally visible, the M1 was detected in 98%. The correlation coefficients between each structure's visibility and M1 detectability in men were 0.62 for the CTB, 0.60 for the MB and 0.74 for the LSW ($p < 0.001$ for all); those in women were 0.58, 0.53 and 0.72, respectively ($p < 0.001$ for all). Those of younger adults were 0.61, 0.58 and 0.74, respectively ($p < 0.001$ for all); those of older adults were 0.71, 0.70 and 0.80, respectively ($p < 0.001$ for all).

Contrast-enhanced TCCS examination was performed in 20 TBWs of 10 patients (table 4). In 8 of 20 TBWs (40%), the M1 was identified with 1 or more category improvements compared with that on non-contrast-enhanced examination. The detection improvement of the M1 was ascertained for no TBWs with 'invisible' LSW, 50% with 'poor' LSW, 57% with 'fair' LSW and 50% with 'good' LSW.

Discussion

In this study, categorical visibilities of the CTB, MB and LSW on B mode images and categorical M1 detectability on color Doppler images by TCCS were determined in Japanese acute ischemic stroke patients without stenotic lesions of the M1 or ICA on baseline MRA or carotid ultrasonography. The major findings were as follows: first, the M1 was detectable by TCCS in 49% in this study of patients with a known patent M1. Second, visibilities of the CTB, MB and LSW on B mode images had positive correlations with M1 detectability on color Doppler images. Third, LSW visibility was a better indicator than CTB and MB visibilities for evaluation of the M1. Fourth, contrast-enhanced TCCS examination provided better M1 detection than nonenhanced examination in half of the TBWs through which each structure was vis-

Table 1. Structural visualization and M1 detectability by TCCS

Structural visualization on B mode image		invisible	visible			p
			poor	fair	good	
Structural visualization on B mode image						
CTB	Total (152 TBWs)	3 (2)	34 (22)	54 (36)	61 (40)	
	Women (56 TBWs)	3 (5)	25 (45)	16 (29)	12 (21)	<0.0001[a]
	Men (96 TBWs)	0	9 (9)	38 (40)	39 (51)	
	Aged ≥70 years (80 TBWs)	3 (4)	23 (29)	30 (38)	24 (30)	0.0163[b]
	Aged <70 years (72 TBWs)	0	11 (15)	24 (33)	37 (51)	
	Women aged ≥70 years (38 TBWs)	3 (8)	20 (53)	10 (26)	5 (13)	0.0689[c]
	Women aged <70 years (18 TBWs)	0	5 (28)	6 (33)	7 (39)	
	Men aged ≥70 years (42 TBWs)	0	3 (7)	20 (48)	19 (45)	0.3486[d]
	Men aged <70 years (54 TBWs)	0	6 (11)	18 (33)	30 (56)	
MB	Total (152 TBWs)	55 (36)	36 (24)	39 (26)	22 (14)	
	Women (56 TBWs)	37 (66)	10 (18)	7 (13)	2 (4)	<0.0001[a]
	Men (96 TBWs)	18 (19)	26 (27)	32 (33)	20 (21)	
	Aged ≥70 years (80 TBWs)	39 (49)	22 (28)	17 (21)	2 (3)	<0.0001[b]
	Aged <70 years (72 TBWs)	16 (22)	14 (19)	22 (31)	20 (28)	
	Women aged ≥70 years (38 TBWs)	30 (79)	6 (16)	2 (5)	0	0.0061[c]
	Women aged <70 years (18 TBWs)	7 (39)	4 (22)	5 (28)	2 (11)	
	Men aged ≥70 years (42 TBWs)	9 (21)	16 (38)	15 (36)	2 (5)	0.0046[d]
	Men aged <70 years (54 TBWs)	9 (17)	10 (19)	17 (31)	18 (33)	
LSW	Total (152 TBWs)	25 (16)	34 (22)	44 (29)	49 (32)	
	Women (56 TBWs)	15 (27)	23 (41)	10 (18)	8 (14)	<0.0001[a]
	Men (96 TBWs)	10 (10)	11 (11)	34 (35)	41 (43)	
	Aged ≥70 years (80 TBWs)	16 (20)	22 (28)	23 (29)	19 (24)	0.0700[b]
	Aged <70 years (72 TBWs)	9 (13)	12 (17)	21 (29)	30 (42)	
	Women aged ≥70 years (38 TBWs)	13 (34)	16 (42)	5 (13)	4 (11)	0.1649[c]
	Women aged <70 years (18 TBWs)	2 (11)	7 (39)	5 (28)	4 (22)	
	Men aged ≥70 years (42 TBWs)	3 (7)	6 (14)	18 (43)	15 (36)	0.3460[d]
	Men aged <70 years (54 TBWs)	7 (13)	5 (9)	16 (30)	26 (48)	
M1 detectability on color Doppler images		INVISIBLE	POOR	FAIR	GOOD	p
M1	Total (152 TBWs)	77 (51)	11 (7)	11 (7)	53 (35)	
	Women (56 TBWs)	42 (75)	3 (5)	2 (4)	9 (16)	<0.0001[a]
	Men (96 TBWs)	35 (36)	8 (8)	9 (9)	44 (46)	
	Aged ≥70 years (80 TBWs)	46 (58)	8 (10)	7 (9)	19 (24)	0.0198[b]
	Aged <70 years (72 TBWs)	31 (43)	3 (4)	4 (6)	34 (47)	
	Women aged ≥70 years (38 TBWs)	29 (76)	3 (8)	1 (3)	5 (13)	0.5002[c]
	Women aged <70 years (18 TBWs)	13 (72)	0	1 (6)	4 (22)	
	Men aged ≥70 years (42 TBWs)	17 (40)	5 (12)	6 (14)	14 (33)	0.1146[d]
	Men aged <70 years (54 TBWs)	18 (33)	3 (6)	3 (6)	30 (56)	

Values are represented by numbers of TBWs, with percentages in parentheses.
[a] Women versus men by χ^2 test. [b] Aged ≥70 years versus aged <70 years by χ^2 test. [c] Women aged ≥70 years versus women aged <70 years by χ^2 test. [d] Men aged ≥70 years versus men aged <70 years by χ^2 test.

ible ('poor', 'fair' or 'good'), whereas TBWs with 'invisible' MB or LSW could not gain any contrast improvement for M1 detection.

TCCS is widely used to evaluate the intracranial arterial system in patients with acute stroke. The main limitation of TCCS arises from poor acoustic insonation conditions via the TBW, particularly in Asians, women and older patients. The failure rate because of an insufficient acoustic bone window is approximately 10–20% of patients in Western countries [8–10] and 20–30% of

Table 2. Anterior (ACA) and posterior cerebral artery (segment 1 and 2) detectabilities of 77 TBWs with 'INVISIBLE' M1

	INVISIBLE	POOR	FAIR	GOOD
ACA	73	3	1	0
P1	71	5	1	0
Proximal P2	59	10	6	2
Distal P2	57	4	11	5

Values are represented by numbers of TBWs.

Table 3. Relationship between structural visualization and M1 detectability

		M1 detectability				Spearman's ρ	p
		INVISIBLE	POOR	FAIR	GOOD		
CTB	invisible (3 TBWs)	3	0	0	0	0.68	<0.0001
	poor (34 TBWs)	33	0	1	0		
	fair (54 TBWs)	32	8	4	10		
	good (61 TBWs)	9	3	6	43		
MB	invisible (55 TBWs)	48	5	1	1	0.66	<0.0001
	poor (36 TBWs)	19	3	4	10		
	fair (39 TBWs)	7	2	5	25		
	good (22 TBWs)	3	1	1	17		
LSW	invisible (25 TBWs)	25	0	0	0	0.80	<0.0001
	poor (34 TBWs)	31	2	1	0		
	fair (44 TBWs)	20	6	5	13		
	good (49 TBWs)	1	3	5	40		

Values are represented by numbers of TBWs.

patients in Asian countries [4, 5]. In our study, this rate was 51%. Low M1 detectability in women and older patients was consistent with previous reports [9, 10]. Therefore, simple indicators to judge acoustic insonation conditions via the TBW are important to evaluate the M1 segment.

Insonations of B mode and color Doppler seem to be similarly affected by the temporal bone, because structural visibilities on B-mode images had significantly positive correlations with M1 detectability on color Doppler images for all patients, by sex and by age. The closer spatial relationship of the M1 with the LSW than with the CTB or MB seems to explain the present results that LSW visibility had the best correlation with M1 detectability. When the M1 was 'INVISIBLE' on color Doppler images, the precommunicating segment, proximal and distal postcommunicating segments were detected in 32% but the anterior cerebral artery was rarely detectable via the same TBW. Based on our results, the following criteria for

Table 4. M1 detectability improvement by contrast enhancement

		Improvement of M1 detectability
CTB	invisible (0 TBWs)	–
	poor (4 TBWs)	0
	fair (5 TBWs)	1 (20)
	good (11 TBWs)	7 (64)
MB	invisible (6 TBWs)	0
	poor (7 TBWs)	4 (57)
	fair (4 TBWs)	3 (75)
	good (3 TBWs)	1 (33)
LSW	invisible (5 TBWs)	0
	poor (6 TBWs)	3 (50)
	fair (7 TBWs)	4 (57)
	good (2 TBWs)	1 (50)

Values are represented by numbers of TBWs, with percentages in parentheses.

M1 evaluation on TCCS were developed. If the LSW is almost totally visible, M1 occlusion may be considered in patients with M1 invisibility. If the LSW is invisible or less than 50% visible, M1 invisibility on TCCS does not directly indicate M1 occlusion, and an additional imaging modality, such as MRA or CT angiography, is required. If the LSW is more than 50% visible and the M1 is not detectable, more than 50% or totally, visibility of the CTB and MB indicates probable M1 occlusion.

The addition of an ultrasound contrast agent allows adequate diagnosis in about 80–90% of patients with insufficient bone windows [12–20]. In our Japanese stroke patients, 40% of TBWs had an improved detection of the M1 on contrast-enhanced examination. In patients with invisible structures on B mode images, the administration of a contrast agent did not result in vessel identification. Therefore, TBWs with poor, fair and good visibility and insufficient M1 detection seem to be appropriate candidates for contrast-enhanced TCCS examination.

There were some limitations in this study. First, M1 occlusion on TCCS cannot be discussed from our findings because of the study exclusion of patients with luminal stenosis >50% or occlusion of the M1 or ICA on MRA and those with large infarction which may cause brain displacement. Second, severe atherosclerosis often causes arterial tortuosity and calcification. Arterial tortuosity might shift the M1 further from the LSW, and calcification might prevent ultrasound insonation. Third, machine specificity might affect structural visibility and M1 detectability. Fourth, the small sample size might affect the statistical correlation between the M1 detectability and the visibility of each anatomical structure, and a larger study might be needed to confirm our results. Finally, because our vascular neurologists knew that all the patients had a patent M1, the results might be overestimated.

Conclusion

The visibility of the LSW on B mode images was well correlated with M1 detection in Japanese aged patients with acute ischemic stroke having a patent M1. Our findings warrant future studies to determine detailed criteria of M1 occlusion using TCCS in patients with acute ischemic stroke.

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Disclosure Statement

None.

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Identification of Internal Carotid Artery Dissection by Transoral Carotid Ultrasonography

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Key Words
Transoral carotid ultrasonography · Cerebrovascular disease · Internal carotid artery dissection · Stroke

Abstract
Background and Purpose: Conventional transsurface carotid ultrasonography (TSCU) via the cervical surface often fails to detect dissection of the extracranial internal carotid artery (ICA). The role of transoral carotid ultrasonography (TOCU) in the detection of ICA dissection was examined. ***Method:*** Patients with unilateral extracranial ICA dissection identified by digital subtraction angiography (DSA) from our database of patients with ischemic stroke or transient ischemic attack (TIA) were reviewed. Findings of dissection were compared between TSCU and TOCU. ***Results:*** Eight patients (7 men, 37–69 years old), including 7 with ischemic stroke and 1 with TIA, had ICA dissection. By DSA, dissection was identified between the first and third vertebrae in 4 patients and from the third cervical vertebra to the intracranial level in the remaining 4. TOCU images revealed an intimal flap as definite evidence of dissection in all patients. In 7 patients, color flow signals were not seen in false lumens, indicating thrombosed lumens. Four patients showed morphological changes of dissection on follow-up TOCU, including a patient with recovery of color flow signals in false lumens. The diameter of the dissected ICA was 7.3 ± 0.7 mm and that of the contralateral ICA was 4.9 ± 0.6 mm ($p = 0.008$). In contrast, TSCU did not enable any conclusive findings of ICA dissection to be made in any patient. Six patients had intramural hematoma on T_1-weighted MRI, and 2 had an intimal flap with a double lumen on magnetic resonance angiography. ***Conclusion:*** TOCU has advantages over TSCU in achieving an accurate diagnosis and follow-up evaluation of ICA dissection.

Introduction

Internal carotid arterial (ICA) dissection accounts for approximately 2–3% of all ischemic strokes [1, 2] and is one of the important causes of stroke in young and middle-aged patients [3–6]. The pathogenesis of ICA dissection is often unknown. Most ICA dissections occur spontaneously or follow a sudden head movement, a chiropractic manipulation, and many types of sports activities [7, 8]. Because ICA dissection sometimes causes brain ischemia and subarachnoid hemorrhage [6], immediate vascular evaluation and treatment are necessary. Among the diagnostic tools for identifying dissections, including

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