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# Small Centrum Ovale Infarcts on Diffusion-Weighted Magnetic Resonance Imaging

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***Background and Purpose***—A small centrum ovale infarct (SCOI), caused by occlusion of the white matter medullary arteries, is often equated with a lacunar infarct. We sought to clarify the clinical characteristics of a SCOI visualized by diffusion-weighted MRI (DWI) compared with those of a small basal ganglia infarct (SBGI).

***Methods***—Patients with a SCOI (SCOI group; n=38) or SBGI (SBGI group; n=68) ≤15 mm in diameter on conventional MRI and DWI were selected from 582 consecutive patients with acute ischemic stroke. Sex, age, neurological symptoms, vascular risk factors, emboligenic heart disease, arterial occlusive disease in the ipsilateral carotid system, and recurrent stroke within the initial 30 days were compared between the 2 groups.

***Results***—Only 47% of SCOIs but 87% of SBGIs could be identified with the use of conventional MRI, whereas DWI could detect them all. Age, sex, and vascular risk factors were not significantly different between the 2 groups. The SCOI group had more frequently an abrupt onset of symptoms (63% versus 26%; $P=0.0002$), emboligenic heart diseases (34% versus 12%; $P=0.0054$), occlusive carotid and/or middle cerebral artery diseases (53% versus 19%; $P=0.0004$), and recurrent stroke (13% versus 1%; $P=0.0216$) but less frequently a classic lacunar syndrome (50% versus 81%; $P=0.0009$) than the SBGI group. On a multivariate analysis, both arterial and heart diseases were independently associated with the SCOI group.

***Conclusions***—Symptomatic SCOIs detected by DWI may be associated with large-vessel and heart diseases and should be distinguished from lacunar infarcts. (***Stroke*. 2002;33:1541-1544.)**

**Key Words:** cerebral arteries ■ heart disease ■ lacunar infarction ■ magnetic resonance imaging, diffusion-weighted

The subcortical white matter of the cerebral hemispheres receives blood supply via 2 different vascular systems, deep and superficial penetrating arteries, both originating from the middle cerebral artery (MCA).[1-3] The deep penetrating arteries arise directly from the MCA trunk and irrigate the basal ganglia, internal capsule, corona radiata, and caudate head. The superficial penetrating arteries, namely the white matter medullary arteries, arise from the cortical branches of the MCA and supply blood flow to the centrum ovale. A small basal ganglia infarct (SBGI) is often noted as a lacunar infarct, which is caused predominantly by in situ arteriopathy.[4-6] A small centrum ovale infarct (SCOI) has a size and shape similar to those of a SBGI on brain imaging studies. However, the pathogenesis of a SCOI remains unresolved.

Diffusion-weighted MRI (DWI) is a powerful tool for detecting acute ischemic lesions and can clearly discriminate fresh infarcts from old ones.[7,8] In this respect, it is far more sensitive and specific than CT and conventional MRI.

The aim of the present study was to clarify the clinical characteristics of a SCOI detected by DWI and to compare them with those of a SBGI.

## Subjects and Methods

Patients with a SCOI (SCOI group) or SBGI (SBGI group) were selected from 582 consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) who were admitted to our hospital within 7 days of symptom onset between October 1996 and September 2000. We defined a SCOI as an isolated infarct on MRI with a maximal diameter of ≤15 mm located in the territory of the white matter medullary artery arising from the cortical branches of the MCA, according to the templates of Bogousslavsky and Regli.[1] A SBGI was defined as a singular infarct on MRI ≤15 mm in diameter localized in the territory of the deep penetrating artery of the MCA, including putamen, globus pallidus, internal capsule, and caudate head. We excluded patients with an infarct in the thalamus, brain stem, and subcortical white matter of the anterior and posterior cerebral artery territories. To locate the SCOI within the territory of the white matter medullary arteries as accurately as possible, patients with an infarct situated deeper in the corona radiata (ie, in a more paraventricular location, closer to the deep penetrating artery territory) were also excluded from the present study.

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The following clinical characteristics were compared between the 2 patient groups: (1) patient sex and age; (2) mode of symptom onset; (3) National Institutes of Health Stroke Scale (NIHSS) score on admission; (4) frequency of a classic lacunar syndrome; (5) vascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia, and cigarette smoking; (6) emboligenic heart diseases; (7) arterial occlusive diseases in the ipsilateral carotid system; and (8) recurrence of ischemic stroke or TIA within 30 days of symptom onset.

MRI studies were performed with the use of a Siemens MAGNETOM Vision 1.5-T MR unit with echo-planar capability. We performed conventional MRI studies involving T1-weighted (repetition time [TR]/echo time [TE], 630/14), T2-weighted (TR/TE, 5400/99), and fluid-attenuation inversion recovery (FLAIR) images (TR/TE, 9000/105) within 14 days of symptom onset (mean, 5.8 days; range, 1 to 14 days) in all patients. Forty patients underwent MRI studies within the initial 3 days, 49 between 4 and 7 days after stroke onset, and 17 between 8 and 14 days. DWI studies were simultaneously performed with a multislice, single-shot, spin-echo echo-planar imaging sequence. Diffusion gradients were applied in each of the $x$, $y$, and $z$ directions with 2 b values (0 and 1000 s/mm$^2$). To minimize the effects of diffusion anisotropy, an average of the 3 diffusion directions was calculated. MR images were reviewed by a neuroradiologist and a neurologist, both of whom were blinded to clinical data. Infarcts were considered to be symptomatic when they were focally hyperintense on T2-weighted and FLAIR images, isointense or slightly hypointense on T1-weighted images, and located in the vascular region corresponding to the patient's symptoms. Criteria for the diagnosis of fresh infarcts on DWI included focal hyperintensity, judged not to be due to normal anisotropic diffusion or magnetic susceptibility artifact. The infarct sizes were measured both on axial T2-weighted image and DWI, and the infarcts with a maximal diameter of ≤15 mm were included in the present study.

Mode of neurological symptom onset was classified into 3 categories: abrupt, gradual, and unknown. A classic lacunar syndrome included pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria–clumsy hand syndrome, according to previous reports.[2,9,10]

The vascular risk factors were identified as follows: (1) use of antihypertensive agents for hypertension, with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg on admission for hypertension; (2) use of oral hypoglycemic agents, insulin, or glycosylated hemoglobin >6.4% for diabetes mellitus; (3) use of antihyperlipidemic agents or serum cholesterol level >220 mg/dL for hypercholesterolemia; and (4) any cigarette usage within the 28 days preceding the index stroke for smoking.

To detect emboligenic heart diseases, all patients underwent 12-lead ECG, 24-hour ECG monitoring, and transthoracic echocardiography. Emboligenic heart diseases included atrial fibrillation, mitral stenosis, left ventricular aneurysm, prosthetic heart valves, infective endocarditis, sick sinus syndrome, and dilated cardiomyopathy.

We performed color-flow duplex carotid ultrasonography (Toshiba SSA 270A, Toshiba Inc, or Ultramark 9 HDI, ATL) in all cases. Intracranial arteries were evaluated with conventional cerebral angiography or MR angiography in all patients. The grade of extracranial carotid stenosis was determined according to the criteria used in the North American Symptomatic Carotid Endarterectomy Trial.[11] To determine the degree of intracranial stenosis, the vessel being evaluated was measured at its point of maximal narrowing and compared with the normal section of the vessel adjacent to the stenosis. Arterial diseases were considered significant when stenosis >50% or occlusion was evident in the ipsilateral carotid system.

Statistical analyses were performed with the use of a commercially available software package (Stat-View, version 5.0; SAS Institute). We compared the 2 groups with the $\chi^2$ test and Student's $t$ test, and thereafter multivariate logistic regression analysis was performed. Independent variables were sex, age, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, emboligenic heart diseases, and arterial occlusive diseases in the ipsilateral carotid system. A $P$ value of <0.05 was considered statistically significant.

This study protocol followed the principles outlined in the Declaration of Helsinki.

## Results

Among the 582 consecutive patients with acute ischemic stroke or TIA, 38 (6.5%) and 68 patients (11.7%) met the criteria for SCOI and SBGI, respectively. Five SCOI and 2 SBGI patients had a clinical diagnosis of TIA. The subjects consisted of 68 men and 38 women, with an age of 67.4±10.1 (mean±SD) years.

All SCOIs and SBGIs were detected by DWI. In the SCOI group, however, conventional MRI studies could identify a symptomatic infarct in only 18 patients (47%). Because the remaining 20 SCOI patients (53%) had multiple or diffuse white matter lesions, conventional MRI studies failed to distinguish a symptomatic infarct from the white matter lesions because of a similar signal intensity. In the SBGI group, the symptomatic infarcts could be identified in 59 patients (87%) by conventional MRI studies.

The demographic and clinical features of the 2 patient groups are shown in Table 1. Twenty-four patients (63%) in the SCOI group had an abrupt onset of neurological symptoms compared with 18 (26%) in the SBGI group ($P$=0.0002). The neurological presentation was compatible with a classic lacunar syndrome in 55 patients (81%) of the SBGI group but in only 19 (50%) of the SCOI group ($P$=0.0009). Ten patients (26%) in the SCOI group presented a monoparesis, whereas 3 (4%) in the SBGI group did ($P$=0.0017). Sex, age, vascular risk factors, and NIHSS score on admission were not significantly different between the 2 groups.

Emboligenic heart diseases were detected in a total of 21 patients (20%). They consisted of 13 patients (34%) in the SCOI group and 8 (12%) in the SBGI group, indicating a higher incidence in the SCOI group than in the SBGI group ($P$=0.0054). A total of 33 patients (31%) had occlusive carotid and/or MCA disease. It was found in 20 patients (53%) of the SCOI group but in only 13 (19%) of the SBGI group ($P$=0.0004). Five patients had both heart and arterial occlusive diseases: 3 in the SCOI group and 2 in the SBGI group. Thus, a total of 30 patients (79%) in the SCOI group harbored an emboligenic heart disease and/or an arterial occlusive disease, which was a greater proportion than the 19 patients (28%) in the SBGI group ($P$<0.0001).

The results of the multivariate logistic regression analysis are presented in Table 2. After adjustment for sex, age, and vascular risk factors, the presence of an emboligenic heart disease (odds ratio [OR], 5.52; 95% CI, 1.61 to 18.9; $P$=0.0065) and an occlusive carotid and/or MCA disease (OR, 8.13; 95% CI, 2.83 to 23.3; $P$<0.0001) were independently associated with the presence of a SCOI.

Mean (±SD) number of days of hospitalization was 35±23. We followed up all the patients until 30 days after onset of initial ischemic event. During this period, 5 patients (13%) of the SCOI group and 1 (1%) of the SBGI group developed recurrent stroke or TIA ($P$=0.0216). All these patients received anticoagulant or antiplatelet therapy soon

**TABLE 1. Demographic and Clinical Features of the SCOI and SBGI Groups**

| | SCOI Group (n=38) | SBGI Group (n=68) | P* |
|---|---|---|---|
| Male sex | 28 (74) | 40 (59) | 0.1260 |
| Age, y | 67±10 | 68±10 | 0.8811 |
| Hypertension | 24 (63) | 47 (69) | 0.5315 |
| Diabetes mellitus | 12 (32) | 21 (31) | 0.9408 |
| Hypercholesterolemia | 14 (37) | 28 (41) | 0.6617 |
| Smoking | 23 (61) | 41 (60) | 0.9813 |
| Abrupt onset | 24 (63) | 18 (26) | 0.0002 |
| NIHSS score | 3.7±2.1 | 4.3±2.4 | 0.2374 |
| Classic lacunar syndrome | 19 (50) | 55 (81) | 0.0009 |
| Pure motor | 14 (37) | 39 (57) | 0.0428 |
| Pure sensory | 0 | 0 | ... |
| Sensorimotor | 3 (8) | 12 (18) | 0.2467 |
| Ataxic hemiparesis | 2 (5) | 2 (3) | 0.6166 |
| Dysarthria–clumsy hand | 0 | 2 (3) | 0.5357 |
| Nonlacunar syndrome | 19 (50) | 13 (19) | 0.0009 |
| Monoparesis | 10 (26) | 3 (4) | 0.0017 |
| Hemiparesis with major hemispheric symptoms | 4 (11) | 3 (4) | 0.2467 |
| Pure dysarthria | 2 (5) | 3 (4) | >0.9999 |
| Other symptoms | 3 (8) | 4 (6) | 0.6993 |
| Emboligenic heart disease | 13 (34) | 8 (12) | 0.0054 |
| Atrial fibrillation | 7 | 4 | |
| Ventricular aneurysm | 2 | 2 | |
| Mitral stenosis | 2 | 0 | |
| Prosthetic valves | 2 | 0 | |
| Sick sinus syndrome | 0 | 1 | |
| Dilated cardiomyopathy | 0 | 1 | |
| Arterial occlusive disease | 20 (53) | 13 (19) | 0.0004 |
| ICA stenosis>50% | 12 | 5 | |
| ICA occlusion | 2 | 0 | |
| MCA stenosis>50%† | 6 | 8 | |

ICA indicates internal carotid artery. Values are n (%) or mean±SD.

*$\chi^2$ test and Student's $t$ test were used to compare variables between the 2 groups.

†Stenosis at horizontal portion (M1).

after the admission. In each of the 5 SCOI patients with recurrent stroke, DWI scans revealed new lesions in the MCA territory ipsilateral to the initial SCOI. Of these patients, 4 had a significant arterial stenosis of the internal carotid artery, and the remaining 1 patient had an atrial fibrillation, which were the same as initial diagnoses at the time of first stroke. The patient in the SBGI group, however, had a new lesion in the contralateral thalamus on DWI and had neither arterial nor heart disease. None of the patients in the present study had a major complication or died until 30 days after onset of initial ischemic event.

## Discussion

The pathogenesis of the SCOI remains controversial. Bogousslavsky and Regli[1] suggested that a symptomatic SCOI was associated with hypertension and diabetes mellitus and with lacunar syndromes but not with occlusive carotid disease and emboligenic heart disease, indicating that it is caused mainly by in situ small-vessel disease involving the white matter medullary artery. Similarly, the other 2 studies[12,13] reported that patients with SCOI were more likely to have risk factors for small-vessel disease. However, there were some problems in these studies. First, mechanisms other than small-vessel disease may account for a SCOI, because approximately one third of the patients had occlusive carotid disease and/or emboligenic heart disease. Second, patients with multiple or diffuse white matter lesions were usually excluded to avoid false diagnosis of SCOI on CT or conventional MRI scans, although approximately one third of acute stroke patients have been reported to have silent, chronic white matter lesions.[14,15] Third, evaluation of the intracranial arteries with conventional cerebral angiography or MR angiography was performed only in selected patients.

**TABLE 2. Logistic Regression Models for Probability of SCOI**

| | OR | 95% CI | P |
|---|---|---|---|
| Male sex | 2.23 | 0.73–6.82 | 0.1607 |
| Age | 0.99 | 0.94–1.03 | 0.5409 |
| Hypertension | 0.80 | 0.26–2.50 | 0.7021 |
| Diabetes mellitus | 0.45 | 0.15–1.35 | 0.1527 |
| Hypercholesterolemia | 0.92 | 0.35–2.39 | 0.7633 |
| Smoking | 0.76 | 0.26–2.24 | 0.6245 |
| Emboligenic heart disease | 5.52 | 1.61–18.9 | 0.0065 |
| Arterial occlusive disease | 8.13 | 2.83–23.3 | <0.0001 |

In the present study we used DWI, the most sensitive and specific imaging method to detect acute ischemic lesions, and we always evaluated intracranial arteries by conventional cerebral angiography or MR angiography. The SCOI group showed a significantly higher prevalence of occlusive carotid and/or MCA disease and emboligenic heart disease than the SBGI group, although vascular risk factor profiles were similar between the 2 groups. On the multivariate analysis, both arterial occlusive and heart diseases were independently associated with the SCOI. The substudy of the European Carotid Surgery Trial[16] suggested that 66% of patients with a SCOI had ipsilateral carotid stenosis of >50% compared with 40% of those with a SBGI. Waterston et al[17] studied 10 patients with small deep infarcts in association with occlusive carotid artery disease, of whom 7 patients had only a SCOI. Moreover, Lammie and Wardlaw[18] reported, in their pathological study of 12 consecutive autopsy cases with SCOI, that the mechanism of the infarct was definitely or probably cardioembolic in 3 cases, possibly embolic from the heart or aortic arch in 5, and probably embolic from the ipsilateral carotid disease in 2 (ie, 10 of 12 cases had potential sources of emboli). We also found that only one half of the SCOI patients presented a classic lacunar syndrome and that approximately two thirds of them had an abrupt onset. Therefore, we believe that cerebral large-vessel disease and emboligenic heart disease may play an important role in the mechanism of SCOI rather than small-vessel disease. Large-vessel diseases as well as heart diseases can mediate a SCOI

by embolic mechanism. The high incidence of abrupt onset in the SCOI group may support this hypothesis. A hemodynamic mechanism also could be considered in some SCOI patients with large-vessel disease, at least in 2 patients with internal carotid artery occlusion.

Other potential sources of emboli, including right-to-left shunt representing patent foramen ovale[19] and atherosclerotic disease of the aortic arch,[20,21] may have been overlooked in our study because we did not routinely perform transesophageal echocardiography. Further investigations should be necessary to clarify the relation of these emboligenic diseases to SCOIs.

In conclusion, symptomatic SCOIs on DWI studies, unlike SBGIs, were significantly associated with cerebral large-vessel disease and emboligenic heart disease. We therefore should distinguish a SCOI from a lacunar infarct.

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# Relationship between Findings of Conventional and Contrast-Enhanced Transcranial Color-Coded Real-Time Sonography and Angiography in Patients with Basilar Artery Occlusion

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*BACKGROUND AND PURPOSE:* **Contrast-enhanced transcranial color-coded real-time sonography (TCCS) is a promising tool for the evaluation of brain circulation. The purpose of the present study was to assess the diagnostic ability of conventional and contrast-enhanced TCCS in patients with acute stroke and basilar artery occlusion and to compare the findings with those of angiography.**

*METHODS:* **We prospectively performed conventional and contrast-enhanced TCCS within 3 days before or after digital subtraction angiography or MR angiography in 62 consecutive patients with acute ischemic stroke. We assigned the patients to two groups on the basis of angiographic findings: basilar artery occlusion group (n = 7) and control group without basilar artery occlusion (n = 55). We obtained basilar artery flow images showing the direction of blood flow using TCCS through a suboccipital window.**

*RESULTS:* **In the control group, the detection rate of basilar artery flow using conventional and contrast-enhanced TCCS was 76.4% and 98.2%, respectively ($P < .001$), and the flow direction was antegrade in all patients. In the basilar artery occlusion group, neither conventional nor contrast-enhanced TCCS could obtain flow images of the proximal basilar artery in any patient. In five patients with proximal basilar artery occlusion, a reversed flow image in the distal basilar artery obtained by contrast-enhanced TCCS was confirmed by angiography to be blood supply through collateral circulation from the carotid systems. However, two patients with distal basilar artery occlusion did not have this sign.**

*CONCLUSION:* **Contrast-enhanced TCCS is more sensitive in imaging basilar artery flow than is conventional TCCS. When examined with contrast-enhanced TCCS, a combination of absent basilar artery flow and the reversed basilar artery flow sign may be a diagnostic indicator of basilar artery occlusion.**

Transcranial color-coded real-time sonography (TCCS) enables simultaneous and 2D visualization of brain parenchyma and intracranial blood vessels in color-coded B-mode images (1, 2). Therefore, this tool is a reliable method for the noninvasive assessment of the basal cerebral arteries, including not only anterior but also posterior brain circulation. However, the major limitation of TCCS is poor insonation of ultrasound in approximately 16–20% of patients (3, 4). Transpulmonary sonographic contrast agents can overcome this drawback because they increase the echogenicity of the blood with microscopic air bubbles. The agents can also improve the diagnostic capability of intracranial Doppler imaging (5–14).

We described the diagnostic criteria of TCCS for occlusion and stenosis of the middle and posterior cerebral arteries (15, 16). However, the TCCS criteria for basilar artery occlusion have not yet been reported. The purpose of the present study was to assess the diagnostic ability of conventional and contrast-enhanced TCCS for patients with acute stroke and basilar artery occlusion.

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## Methods

Sixty-two consecutive patients (54 men and eight women; age range, 46–90 years; mean age, 67.6 years; median age, 67.0 years; SD, 9.6 years) with acute ischemic stroke or transient ischemic attack were prospectively examined within 1 week after symptom onset with both conventional and contrast-enhanced TCCS between October 1999 and February 2000. Thirty-eight had ischemic stroke in the anterior circulation and 24 in the posterior circulation. TCCS was performed within 1 week of stroke onset (<6 hours in six patients, 6–24 hours in nine, 2–3 days in 29, and 4–7 days in 18). All patients underwent cerebral angiographic examination with digital subtraction angiography (n = 23) or MR angiography (n = 39). The intervals between ultrasonographic and angiographic examinations were <3 days. The patients were divided into two groups, based on angiographic findings: the basilar artery occlusion group (n = 7) and the non-occlusion control group (n = 55).

### *TCCS Examinations*

Two investigators blinded to the angiographic results performed the TCCS examinations. All patients were placed in the right lateral position with the head flexed so that the chin rested on the neck. A probe was placed on the middle of the nape of the neck (suboccipital acoustic bone window) to aim the ultrasound beam upward through the foramen magnum. An Ultramark 9 HDI with a 2- to 3-MHz 90° sector scan was used for TCCS examination. Pulse repetition frequencies ranged from 2,500 to 10,000 Hz, depending on optimal visualization of the vascular structure. The color sonographic gain level was just below the level of the background noise. Blood flow toward the probe (positive Doppler shift) was shown in red, and blood flow away from the probe (negative Doppler shift) was shown in blue (2). We chose a coronal scanning plane that allowed simultaneous visualization of the bilateral vertebral arteries and the basilar artery in one scanning plane. The basilar artery was identified as a flow image distal to the vertebral union. If the vertebral arteries were displayed as only one flow image because of an occluded or aplastic contralateral vertebral artery, we judged that the basilar artery was visualized as linear flow at an insonation depth of approximately 70–100 mm. Soon after conventional TCCS, 4–8 mL of contrast agent (300 mg/mL; Levovist/Schering, Berlin, Germany) was injected within 10 seconds through the antecubital vein (17).

We calculated the detection rate of basilar artery flow using conventional and contrast-enhanced TCCS and compared the rates using the $\chi^2$ test. In each basilar artery flow image, the direction of blood flow (toward or away from the probe) was also noted.

### *Digital Subtraction Angiography or MR Angiography*

Digital subtraction angiography with selective injection of the common carotid and vertebral arteries was performed via the femoral artery in all patients. MR angiography was performed by using a 1.5-T system (MAGNETOM Vision, Siemens) with the following settings: 35/7.6 (TR/TE); flip angle, 20°; section thickness after zero fill interpolation, 0.5 mm; matrix, 245 × 512; field of view, 17.5 × 20 cm; and superior saturation band. MR angiographic images were processed with a maximum intensity projection. Two neuroradiologists blinded to the results of the sonographic studies interpreted the digital subtraction and MR angiographic studies.

## Results

The insonation depth was between approximately 60 and 80 mm for the vertebral union and >60 mm for the basilar artery in the control group. Normal antegrade basilar artery flow was detected by conventional TCCS in 42 (76.4%) patients. After contrast enhancement, the basilar artery was visualized in all except one patient (98.2%, $P < .001$ versus conventional TCCS). On the other hand, the basilar artery image could not be obtained with conventional TCCS in any of the basilar artery occlusion group patients. Using contrast agents, we detected a reversed flow (reversed basilar artery flow sign) in the distal basilar artery in five patients, who had a retrograde basilar artery filling via collateral circulation from the carotid system revealed by digital subtraction or MR angiography (Fig 1). The other two patients did not have the reversed basilar artery flow sign. Their angiograms showed occlusion of the distal basilar artery and did not show blood supply through collateral circulation from the carotid system (Fig 2).

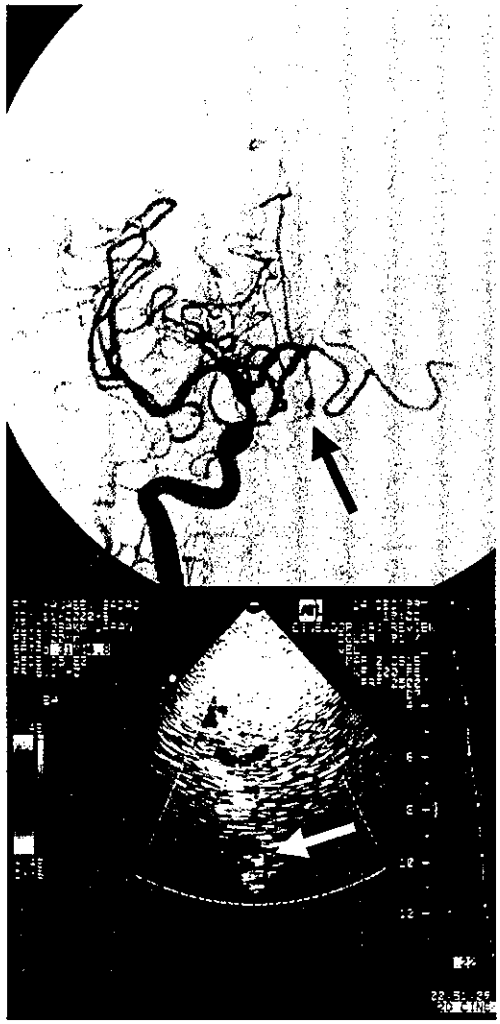

FIG 1. Anteroposterior view angiogram of the right carotid artery shows reversed basilar artery flow through collateral circulation from the carotid systems (*top, arrow*). Reverse basilar artery flow is shown in *red* with contrast-enhanced TCCS (*bottom, arrow*).

## Discussion

Previous studies have indicated that contrast-enhanced TCCS enables adequate diagnosis regarding

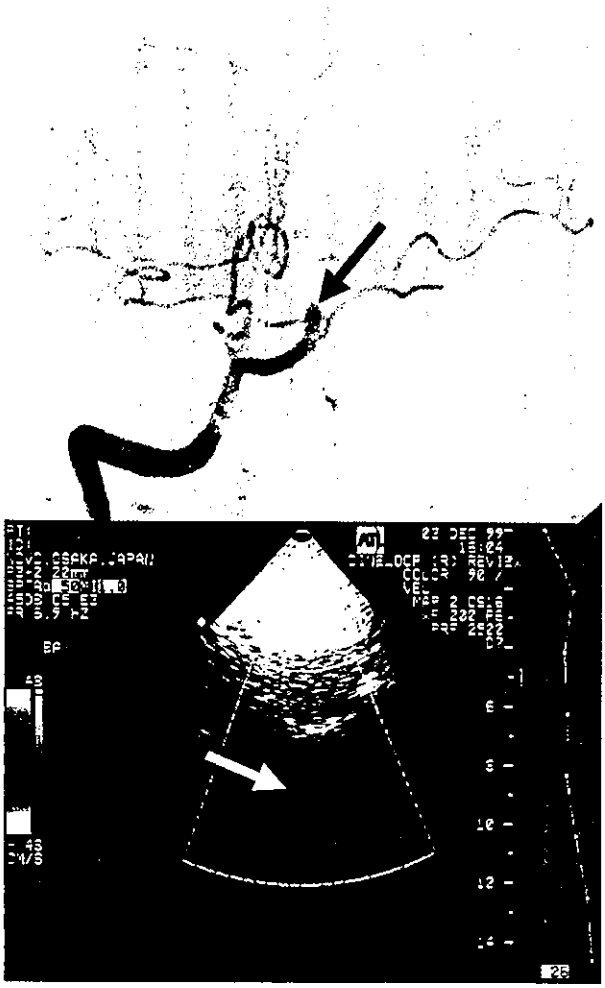

FIG 2. Anteroposterior view angiogram of the right vertebral artery shows distal basilar artery occlusion due to cardioembolism (*top*, *arrow*). No blood supply to the basilar artery was evident on the carotid angiograms (not shown). With contrast-enhanced TCCS, no basilar artery flow was visualized (*bottom*, *arrow*).

brain circulation, even when conventional TCCS is insufficient (5–14). The present study showed that conventional TCCS could visualize normal basilar artery flow through the suboccipital window in only 76.4% of the patients. However, contrast-enhanced TCCS detected 98.2% of the basilar artery flow in these patients. The sonographic findings were highly compatible with those of angiography. Therefore, non-occluded basilar artery was reliably diagnosed by contrast-enhanced TCCS. When normal antegrade basilar artery flow is not visualized with conventional TCCS, a contrast-enhanced study should be added to evaluate the presence of occlusion. If normal antegrade basilar artery flow cannot be imaged by contrast-enhanced TCCS, the presence of basilar artery occlusion should be strongly suspected.

In patients with basilar artery occlusion, basilar artery flow imaged with contrast-enhanced TCCS varied according to the site of occlusion. We obtained the reversed flow in the distal basilar artery in patients with proximal basilar artery occlusion. In these patients, blood supply to the distal basilar artery was confirmed with digital subtraction angiography or MR angiography via collateral circulation from the carotid system.

Conventional transcranial Doppler sonography is a noninvasive method for studying the vertebral and basilar arteries. However, the procedure has several difficulties: identification of a target artery under pathologic conditions, unknown isonation angles, and documentation. It is often difficult to distinguish the basilar artery from other arteries, such as the vertebral, anterior inferior cerebellar, and posterior inferior cerebellar arteries. TCCS is superior to transcranial Doppler sonography in evaluating the vertebral and basilar arteries because TCCS can display color flow images of these major vessels.

There are some potential problems related to the application of TCCS in the evaluation of patients with stroke. First, although this procedure is noninvasive, useful application of this technology is likely to require the availability of experienced operators during initial assessment of the patients. Second, it seems unlikely that contrast-enhanced TCCS will replace CT-assisted angiography or MR imaging supported by perfusion/diffusion sequences and MR angiography for initial evaluation of patients with stroke leading toward inclusion or exclusion from thrombolytic therapy. However, contrast-enhanced TCCS could be useful for making a treatment decision when patients with acute ischemic stroke and basilar artery occlusion are admitted or transferred to a hospital where digital subtraction or MR angiography cannot be performed. Third, there are some diagnostic limitations of the imaging technique, such as difficulties obtaining a proper sonographic window, the effect of obesity, variations in vessel morphology, and the effect of significantly reduced blood flow velocity.

## Conclusion

Contrast-enhanced TCCS visualizes basilar artery flow better than does conventional TCCS. As examined with contrast-enhanced TCCS, the combination of lack of antegrade basilar artery flow imaging and the reversed basilar artery flow sign may be diagnostic of proximal basilar artery occlusion.

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# Combined carotid and transcranial color-coded sonography in acute ischemic stroke

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**Abstract**

The objective of this study is to clarify whether the combination of carotid duplex sonography (CD) and transcranial color-coded sonography (TCCS) can accurately detect occlusive lesions in extra and intracranial brain arteries in acute stroke patients, using angiography as the standard. Just before angiography, we performed CD and TCCS in 40 consecutive patients within 24 h after stroke onset. We assessed 320 vessels in total, bilateral internal carotid arteries, vertebral arteries, M1 segments of middle cerebral arteries (MCAs), and P2 segments of posterior cerebral arteries (PCAs). Out of all vessels, 250 (78.1%) could be evaluated by neurosonography because 32 MCAs and 38 PCAs were excluded due to inadequate acoustic windows for TCCS. Significant occlusive lesions ( > 50%) were observed in 21 out of 250 vessels by neurosonography. Angiography confirmed 20 occlusive lesions as revealed by neurosonography. In the remaining 229 neurosonographically normal vessels, angiography showed no significant lesions except M2 occlusions. The accuracy, sensitivity, and specificity of neurosonography for the detection of occlusive vessels were 99.6, 100 and 99.6%, respectively. Occlusive lesions were observed in 20 of all patients by neurosonography. Nineteen of them were confirmed by angiography. The combination of CD and TCCS can make an accurate diagnosis for significant occlusive lesions in brain arteries in acute stroke patients.


*Keywords:* Carotid duplex sonography; Transcranial color-coded sonography; Angiography; Acute ischemic stroke

## 1. Introduction

The transcranial Doppler (TCD) is a non-invasive tool for studying the basal cerebral arteries, and has been widely used for evaluating ischemic stroke (Aaslid et al., 1982; Wechsler et al., 1986; Kaps et al., 1990). Recently, transcranial color-coded sonography (TCCS) has been introduced as a new method for imaging the basal cerebral arteries (Bogdahn et al., 1990; Martin et al., 1994; Tsuchiya et al., 1991). TCCS, the combination of color-coded Doppler data with B-mode display, can more readily and confidently identify the vessels than TCD. Thus, the diagnostic accuracy of occlusive lesions in the basal cerebral arteries has been reported to be higher with TCCS

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than with TCD (Kimura et al., 1996, 1998a, 2000). Carotid duplex sonography (CD) has been also widely used as a tool to evaluate occlusive lesions in the extracranial brain arteries such as the internal carotid artery (ICA) and vertebral artery (VA) (Steinke et al., 1990; Androulakis et al., 1996; Chang et al., 1995; Kimura et al., 1994, 1997, 1998b).

It is important to detect the pathologic lesions in the carotid and intracranial cerebral arteries in acute ischemic stroke patients. Both conventional digital subtraction angiography (DSA) and magnetic resonance angiography (MRA) provide large amounts of information about cerebral arterial pathologies and hemodynamics (Riles et al., 1992). However, DSA carries a risk of 0.4–0.7% mortality and serious morbidity, and a high risk of minor morbidity (Earnest et al., 1984; Dion et al., 1987; Stevens et al., 1989). The application of DSA or MRA methods may not be easy and rapid. On the other hand, neurosonographic examination is non-invasive, convenient, relatively inexpensive and can be performed at the bedside.

The diagnostic accuracy of the neurosonographic examination has been thought to be high even in acute stroke patients. That, however, remains unclear. We prospectively performed both CD and TCCS in consecutive acute stroke patients immediately before angiography. The aim of this study is to clarify whether the combination of CD and TCCS can accurately detect occlusive lesions in extra- and intracranial brain arteries in acute stroke patients, using angiography as the gold standard.

## 2. Methods

We prospectively studied 40 consecutive acute ischemic stroke patients (30 men, 10 women, aged 63±29 years) within 24 h after stroke onset, including 36 patients examined within 6 h, between April 1, 1998 and March 31, 1999. We diagnosed stroke subtype according to NINDS III (National Institute of Neurological Disorders and Stroke, 1990); cardioembolic brain infarction in 23 patients, atherothrombotic infarction in seven, lacunar infarction in two, transient ischemic attack in four, and other ischemic strokes in the remaining four. Both CD and TCCS were performed immediately before cerebral angiography. Interpreters (K.W. or K.K.) who performed both CD and TCCS had known the symptoms of patients. The other investigators except K.W. or K.K. carried out angiography, and were blinded to the findings of CD and TCCS. The equipment used for the CD and TCCS was a commercially available machine (ATL Ultramark 9 HDI, ATL, Bothell, USA).

### 2.1. Carotid duplex sonographic examinations

The transducer was operated at 5–10 MHz for B-mode imaging and Doppler functions. The pulse repetition frequency was mainly 5000 Hz, and the low-pass filter was 50 Hz. Imaging was performed while the patients were lying in the supine position with the head turned away from the side being scanned and neck extended. The common carotid artery (CCA), ICA origin and VA were examined in longitudinal and transverse planes with anterior, lateral, and posterior approaches using B-mode imaging and color flow imaging. The ICA origin was investigated for morphologic abnormalities. To measure blood flow velocities on longitudinal scans, the sample volume, 5–7 mm in size, was set in the CCA, ICA, and VA, which were displayed as linearly as possible. Special care was taken to keep the incident angle between the CCA, ICA or VA and the beam at 30–60. We measured the end-diastoric flow velocity, peak-systoric flow velocity, and mean flow velocity in the CCA, ICA, and VA. When a B-mode or color flow imaging was indicative of stenotic lesions in the ICA, the sample volume was moved slowly from the proximal to distal segment of the ICA stenosis to obtain the highest flow velocity. These velocities were corrected with the incident angle. In addition, we measured the side-to-side ratio of the end-diastolic flow velocity (ED-ratio) in the CCA which was calculated by dividing the velocity on the side of higher flow velocity by that on the contralateral side.

We used the previously reported criteria for the neurosonographic diagnosis of significant stenosis or occlusion of the ICA and VA (Steinke et al.,

1990; Androulakis et al., 1996; Chang et al., 1995; Kimura et al., 1994, 1997, 1998b; Yasaka et al., 1992) (Table 1).

### 2.2. Transcranial color-coded sonographic examinations

The transducer was operated at 2–3 MHz for B-mode imaging and Doppler functions. The pulse repetition frequency was mainly 3700 Hz, and the low-pass filter was 50 Hz. We routinely obtained color Doppler flow images and measured flow velocity at bilateral M1 segments of the middle cerebral arteries (MCAs) and P2 segments of the posterior cerebral arteries (PCAs) by pulsed-Doppler. If the midbrain or the temporal bone of contralateral side to the attached probe could not be displayed with TCCS, we immediately stopped the test to avoid a loss of time because the echo-window of this patient was thought to be inadequate.

Table 1
Diagnostic criteria for ICA and VA occlusion or stenosis with duplex carotid ultrasonography

| Findings | Sonographic diagnosis |
|---|---|
| *A. ICA origin* | |
| (1) PSFV of ICA | |
| > 210 cm/s | > 70% stenosis |
| > 150 cm/s | > 50% stenosis |
| (2) ED-ratio of CCA | |
| ≥ 1.4 | ICA occlusion or severe stenosis |
| < 1.4 | No occlusion |
| (3) Oscillating thrombus | Embolic ICA occlusion |
| *B. VA* | |
| (1) No signal | Occlusion at origin |
| (2) MFV is detected as integrate flow and EDFV is not detected | Occlusion before branching of PICA |
| (3) MFV < 18 cm/s, VA diameter ≥ 2.5 mm[a] and EDFV is detected | Occlusion after branching of PICA |

CCA, common carotid artery; PSFV, peak-systolic flow velocity; ED-ratio, side-to-side ratio of the end-diastolic flow velocity in CCA, which was calculated by dividing the velocity on the side of higher flow velocity by that on the contralateral side; MFV, mean flow velocity; EDFV, end-diastolic flow velocity; PICA, posterior inferior cerebellar artery.

[a] When MFV < 18 cm/s and the VA diameter < 2.5 mm, the VA was diagnosed as hypoplastic vertebral arteries.

The patients were examined first in the left lateral decubitus position and then in the right lateral decubitus position. Blood flow velocity and direction were displayed in real time as color signals within a subsector of the black-and-white image through a temporal bone window. Particular care was taken to obtain a long axis view of the target vessel by means of tilting, rotating, or shifting the transducer to keep the incident angle between the artery and the pulsed-Doppler beam at 60° or less. A range-gate pulsed-Doppler, with a sample volume of 2 mm, was used to measure the blood flow velocity in the MCA and PCA. The sample volume was moved slowly from proximal to distal of the M1 or P2 segment, and was displayed as color flow images on the B-mode. We measured the peak-systolic and end-diastolic flow velocities corrected with incident angle. The highest flow velocity during five consecutive cardiac cycles was recorded. We calculated the ED-ratio in MCA.

We evaluated occlusive lesions of the M1 and P2 segments based on the criteria reported elsewhere (Kimura et al., 1996, 1998a, 2000) (Table 2).

Table 2
Diagnostic criteria of MCA and PCA occlusion or stenosis with TCCS

| Findings | Sonographic diagnosis |
|---|---|
| *A. MCA (horizontal portion; M1)* | |
| (1) No signal on the contralateral side of hemiparesis and MCA flow can be observed on the ipsilateral side of hemiparesis | M1 occlusion |
| (2) ED ratio of M1 > 1.9 | M1 occlusion of lower side |
| 3) PSFV of M1 > 180 cm/s | M1 stenosis > 50% |
| *B. PCA (P2 segment)* | |
| (1) No signal in P2 | Occlusion |
| (2) PSFV > 200 cm/s | P2 stenosis > 50% |

ED-ratio, side-to-side ratio of the end-diastolic flow velocity in M1 segment, which was calculated by dividing the velocity on the side of higher flow velocity by that on the contralateral side; PSFV, peak-systoric flow velocity.

### 2.3. Angiographic examinations

When patients were suspected to have the occlusive lesions in main brain arteries from their clinical symptoms, informed consent was obtained from patients or their family and selective cerebral angiographic studies were performed via a femoral artery approach immediately after the neurosonographic examinations. Biplane digital subtraction techniques were used. Angiographic findings were considered significant, if the ICA, M1, or P2 had an occlusion or a stenosis greater than 50%, or VA or M2 had an occlusion.

### 2.4. Statistical analysis

We compared the neurosonographic diagnosis with angiographic results as the standard using the contingency table. The diagnostic accuracy, sensitivity, and specificity of neurosonography for the detection of occlusive vessels were calculated. Statistical analysis was performed using a commercially available software package (Stat-View, version 4.5).

## 3. Results

Results of neurosonographic and angiographic examinations are showed in Table 3. We assessed 320 vessels in total, bilateral ICAs, VAs, M1 segments of MCAs, and P2 segments of PCAs. 250 (78.1%) of all vessels could be evaluated by neurosonography because 32 MCAs and 38 PCAs were excluded due to inadequate acoustic windows for TCCS. Significant occlusive lesions were observed in 21 (8.4%) of 250 vessels by neurosonography. Angiography confirmed 20 of 21 occlusive lesions that were detected by neurosonography. The remaining lesion was diagnosed as M2 occlusion by angiography, while as M1 occlusion by neurosonography. In 229 arteries diagnosed as normal using neurosonography, angiography showed M2 occlusions in 6 arteries, but no significant stenotic lesions in the remaining 223 arteries. On the other hand, angiography detected significant occlusive lesions in 35 of 320 vessels. Out of 35 significant lesions detected by angiography, 27 lesions were evaluated through the adequate acoustic windows for TCCS. Of these 27 lesions, seven M2 occlusions were not diagnosed as significant stenotic lesions with TCCS. However, the remaining 20 lesions were correctly detected by neurosonography.

The CD perfectly diagnosed non- or occlusive lesions in ICAs and VAs (Table 4-a). We did not evaluate M2 occlusion using TCCS because TCCS criteria of M2 occlusion have not been established yet. If we consider M2 occlusion on angiography as a normal finding for TCCS, the diagnostic accuracy, sensitivity, and specificity of TCCS for the detection of occlusive lesions are excellent (98.9, 100 and 98.9%, respectively) (Table 4-b). Overall, in total 250 vessels evaluated by the combination of CD and TCCS, the diagnostic accuracy, sensitivity, and specificity of neurosonographic examinations for the detection of occlusive lesions are excellent (99.6, 100 and 99.6%, respectively) (Table 4-c).

Furthermore, in a total of 40 patients, significant occlusive vessels were observed in 20 patients by neurosonographic examinations (Table 5). Angiography confirmed the neurosonographic diagnosis in 19 of these patients. A lesion of the remaining patient was diagnosed as a M2 occlusion by angiography, while as a M1 occlusion by TCCS. On the other hand, angiography showed no significant occlusive lesions in 19 of 20 patients who were considered as normal using neurosonography. Therefore, the diagnostic accuracy, sensitivity, and specificity of neurosonographic examinations for the detection of patients with occlusive lesions were 95.0, 95.0, and 95.0%, respectively.

## 4. Discussion

It is important to evaluate occlusive lesions in the extra and intracranial arteries in acute stroke patients. The combination of CD and TCCS enables us to evaluate the occlusive lesions in not only extracranial but also intracranial arteries. Therefore, we believe that it is useful to perform both CD and TCCS for acute stroke patients.

Table 3
Results of neurosonographic and angiographic examinations

| | Neurosonographic examinations ($n = 250$) | Angiographic examinations | | |
|---|---|---|---|---|
| | | Vessels identified by CD and TCCS ($n = 250$) | Vessels not identified by CD and TCCS ($n = 70$) | All vessels ($n = 320$) |
| *(1) ICA* | | | | |
| No significant occlusive lesions | 70 | 70 | 0 | 70 |
| Stenosis greater than 50% | 1 | 1 | 0 | 1 |
| Occlusion | 9 | 9 | 0 | 9 |
| *(2) VA*[a] | | | | |
| No significant occlusive lesions | 73 | 73 | 0 | 73 |
| Occlusion before branching of PICA | 5 | 5 | 0 | 5 |
| Occlusion after branching of PICA | 2 | 2 | 0 | 2 |
| *(3) MCA* | | | | |
| No significant occlusive lesions | 44 | 38 | 25 | 63 |
| M1 stenosis greater than 50% | 1 | 1 | 0 | 1 |
| M1 occlusion | 3 | 2 | 1 | 3 |
| M2 occlusion | –[b] | 7 | 6 | 13 |
| 4) PCA | | | | |
| No significant occlusive lesions | 42 | 42 | 37 | 79 |
| P2 occlusion | 0 | 0 | 1 | 1 |

[a] All the V0/1-segments of all the patients were investigated with angiography, and no lesions in the V0/1-segments were found.
[b] Neurosonographic criterion of M2 occlusion has not been established.

The CD should now be a standard part of the extracranial carotid vessels imaging. In the present study, CD could perfectly diagnose significant occlusive lesions of ICA and VA. The diagnostic criteria for the ICA and VA occlusion used in this study are practical to evaluate arterial lesions even in acute ischemic stroke patients.

In the present study, TCCS demonstrated a high specificity and sensitivity compared with DSA as the standard. Kenton et al. (1997) reported that TCCS findings agreed closely with MRA in acute stroke patients. Baumgartner et al. (1999) assessed the basal cerebral arteries in ischemic stroke patients with TCCS and showed its usefulness. However, the patients in their report were not only acute stroke patients. The TCD criteria for M1 occlusion is based on the absence or the severe reduction of detectable Doppler signal at a depth of insonation corresponding to the MCA. This criteria is unclear, so it is difficult to attempt to diagnose M1 occlusion by using TCD. On the other hand, TCCS can display the intracranial vessels using color flow imaging. Therefore, TCCS should be superior to TCD to evaluate the MCA and PCA.

However, there are some drawbacks to the TCCS procedure. First, some patients cannot be studied due to inadequate insonation windows for TCCS. The failure rate increases with age and is also higher in women because of the higher prevalence of temporal hyperosteosis. In addition, detection rate of the intracranial artery flow signal using TCD is lower in Japanese than in Caucasians (Itoh et al., 1993; Hashimoto et al., 1992). In the

Table 4
Diagnostic accuracy

| | | Angiographic findings | | Total |
|---|---|---|---|---|
| | | Abnormal | Normal | |
| *(a) The diagnostic accuracy of CD* | | | | |
| Neurosonographic findings | Abnormal[a] | 17 | 0 | 17 |
| | Normal | 0 | 143 | 143 |
| Total | | 17 | 143 | 160 |
| *(b) The diagnostic accuracy of TCCS* | | | | |
| Neurosonographic findings | Abnormal[b] | 3 | 1 | 4 |
| | Normal[c] | 0 | 86 | 86 |
| Total | | 3 | 87 | 90 |
| *(c) The diagnostic accuracy of neurosonographic examinations (the combination of CD and TCCS)* | | | | |
| Neurosonographic findings | Abnormal[d] | 20 | 1 | 21 |
| | Normal[e] | 0 | 229 | 229 |
| Total | | 20 | 230 | 250 |

[a] 'Abnormal' indicates occlusions or significant stenoses ( > 50%) in ICAs or VAs.
[b] 'Abnormal' indicates occlusions or significant stenoses ( > 50%) in PCAs or M1 segments of MCAs.
[c] M2 occlusion on angiography was considered as normal because the ultrasonographic criterion of M2 occlusion has not been established.
[d] 'Abnormal' indicates occlusions or significant stenoses ( > 50%) in ICAs, VAs, PCAs, or M1 segments of MCAs.
[e] M2 occlusion on angiography was considered as normal because the ultrasonographic criterion of M2 occlusion has not been established.

present study population, all patients were Japanese and the majority were older than 60 years. Second, it is not always possible to visualize the M2 branches of MCA using TCCS. To the best of our knowledge, a specific TCCS diagnosis for M2 branch occlusion has not been established yet. Recently, Postert et al. (1998, 1999) reported that transpulmonary echo contrast agents improve the visualization of intracranial arteries. Unfortunately, echo contrast agents could not be used in the present study because the use of an agent was approved in Japan after the end of the present study. Three-dimensional transcranial power Doppler imaging has been developed and provides excellent visualization of the M2 branches of MCA (Kimura et al., 1998c). The combination of three-dimensional transcranial power Doppler imaging with echo contrast agents may make the

Table 5
The diagnostic accuracy of acute ischemic stroke patients by neurosonographic examinations

| | | Angiographic examination | | Total |
|---|---|---|---|---|
| | | Patients with abnormal vessels[a] | Patients without abnormal vessels[b] | |
| Neurosonographic examination | Patients with abnormal vessels[a] | 19 | 1 | 20 |
| | Patients without abnormal vessels[b] | 1 | 19 | 20 |
| | Total | 20 | 20 | 40 |

[a] 'Abnormal' indicates occlusions or significant stenoses ( > 50%) in ICAs, VAs, PCAs, or M1 segment of MCA's.
[b] M2 occlusion on angiography was considered as normal because the ultrasonographic criterion of M2 occlusion has not been established.

ultrasonographic diagnosis of M2 occlusion possible. Future technical innovations may reduce these limitations.

Intravenous thrombolysis with tissue plasminogen activator (t-PA) given to ischemic stroke patients within 3 h of stroke onset can improve long-term outcome (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). In particular, TCCS can identify major vessels more rapidly and certainly than TCD. Therefore, the examinations with combination of CD and TCCS before intravenous administration of t-PA should be useful for acute stroke patients.

In conclusion, if acute stroke patients have adequate insonation windows for TCCS, the combination of CS with TCCS can diagnose significant occlusive lesions in major extra- and intracranial arteries accurately and rapidly without invasion. Therefore, TCCS and CD can be used not only to evaluate the occlusive lesions in the acute stage of stroke, but also to monitor the cerebral circulation in acute stroke patients who have undergone an initial comprehensive MRA or DSA examination.

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# Ultrasonographic prediction of patients' outcome in hyperacute ischemic stroke

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**Abstract**

*Objective*: We examined whether carotid ultrasonographic (US) findings in hyperacute ischemic stroke are useful to predict patients' outcome. *Methods:* We studied 73 consecutive patients with carotid stroke using both computed tomography (CT) and duplex carotid ultrasonogarphy within 6 h of stroke onset. We evaluated early CT findings defined as obscuration of the lentiform nucleus, loss of the insular ribbon and/or cortical effacement, and US findings indicating internal carotid artery (ICA) or middle cerebral artery trunk occlusion. The National Institute of Health Stroke Scale (NIHSS) at admission and modified Rankin scale on day 30 were assessed. *Results:* According to multiple logistic regression analysis, positive US findings ($P = 0.0045$, odds ratio, 11.1) provided the best predictor of modified Rankin scale score $\geq 3$ compared with a baseline NIHSS $\geq 16$ ($P = 0.036$, odds ratio, 7.9) and early CT findings ($P = 0.18$). *Conclusion:* US findings of hyperacute stroke may provide a better predictor of patients' outcome.


*Keywords:* Stroke; Acute-ultrasonography-tomography; X-ray computed-stroke outcome

## 1. Introduction

Neurosonologic examination is widely used to evaluate pathological lesions in extra- and intracranial cerebral arteries in hyperacute ischemic patients. In particular, carotid ultrasonographic (US) findings in acute carotid ischemic stroke or transient ischemic attack (TIA) patients are useful in the diagnosis of severe stenosis or occlusion of the internal carotid artery (ICA; Kimura et al., 1997; Yasaka et al., 1992; Fell et al., 1981; Hoshino et al., 1989). Moreover, US findings may provide the basis for the treatment strategy in hyperacute stroke patients.

During the initial hours after acute carotid ischemic stroke, early computed tomographic (CT) findings of the brain, such as obscuration of the lentiform nucleus, loss of the insular ribbon, cortical effacement and hyperdense middle cerebral artery signs (HMCAS) are often observed (Tomura et al., 1988; Truwit et al., 1990; Bastianello et al., 1991; Tomsick et al., 1990; Leys et al., 1992; Moulin et al., 1996; Büttner et al., 1997;

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