Diagnostic Impact and Prognostic Relevance of Early Contrast-Enhanced Transcranial Color-Coded Duplex Sonography in Acute Stroke

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Background and Purpose—We sought to evaluate the diagnostic value of echo-enhanced transcranial color-coded duplex sonography (TCCD) and the clinical relevance of vascular pathology assessed by sonography for early clinical outcome in acute ischemic stroke.

Methods—We present 23 consecutive patients with an anterior circulation stroke in whom clinical examination, CT, and ultrasonography were performed within 5 hours after the onset of symptoms. Transcranial Doppler sonography (TCD) and unenhanced and contrast-enhanced TCCD (Levovist, 4 g, 300 mg/mL) were compared for their ability to detect middle cerebral artery (MCA) occlusion and flow velocity reduction suggesting hemodynamic impairment in the MCA distribution pathway. Sonographic examination times were registered. Baseline clinical characteristics and CT findings were assessed. Neurological deficit was quantified according to the National Institutes of Health Stroke Scale score, with an early clinical improvement defined as decrease of the score by 4 or more points or a complete resolution of the deficit on day 4.

Results—Contrast-enhanced TCCD enabled diagnosis of intracranial vascular pathology in 20 affected hemispheres, whereas unenhanced TCCD and TCD were conclusive in 7 and 14 hemispheres, respectively (P<0.0001). Contrast-enhanced TCCD was superior in evaluating distal carotid (carotid-T) occlusion and differentiating major vessel occlusions from patent arteries with flow velocity diminution. Mean examination time for enhanced TCCD ranged from 5 to 7 minutes, depending on the number of investigated vessels (without or with MCA branches). Logistic regression selected a patent MCA without reduced blood flow velocity as the only independent predictor for an early clinical improvement (P<0.01).

Conclusions—Contrast-enhanced TCCD is a promising tool for early prognosis in anterior circulation stroke. It is considered superior to unenhanced TCCD and TCD. (Stroke. 1998;29:955–962.)

Key Words: cerebral ischemia ▪ contrast media ▪ diagnostic imaging ▪ stroke outcome ▪ ultrasonography, Doppler, duplex

Intravenous recombinant tissue plasminogen activator has been shown to improve the outcome of acute stroke when application is started within 3 hours of the onset of ischemia and might be beneficial within 6 hours of an ischemic anterior circulation stroke in carefully selected patients. However, systemic thrombolysis is not recommended in patients with a large brain infarction, demonstrated by early CT changes. Benefit from intravenous thrombolysis may be less likely in patients with extensive neurological deficit and hyperdense MCA sign, as shown in a small study in which the presence of both findings predicted a poor clinical and radiological outcome. Even in carefully evaluated CTs, however, subtle signs of focal brain swelling or parenchymal hypodensity may be overlooked in a substantial number of patients with large strokes, and a hyperdense MCA sign, diagnosed with considerable interobserver variability, has shown only moderate sensitivity for the detection of an MCA occlusion. Furthermore, in the very early stage of stroke, patients with only transient ischemic attack cannot be identified clinically. Therefore, therapeutic decisions within this time window, based on clinical examination and CT only, must be considered unreliable for the selection of patients for thrombolytic therapy as well as for the exclusion of those with increased risk of intracerebral hemorrhage.

In the periacute phase of ischemic stroke, more predictive and therapeutically guiding information may be obtained from functional brain imaging techniques as well as from the assessment of vascular status. Perfusion- and diffusion-weighted MRI performed within 6 hours after the onset of symptoms in patients with severe clinical deficits enabled...
highly accurate differentiation of patients who would improve from those who would not. A recently published study indicates that patency of the major intracranial arteries as well as the presence of collateral blood supply demonstrated by arterial DSA within 6 hours after the onset of stroke predicted early clinical improvement. Conversely, angiographic evidence of a distal ICA (carotid-T) or MCA trunk occlusion and the absence of collateral blood flow correlates with a poor clinical outcome. Although intra-arterial DSA is considered the gold standard for the assessment of vascular pathology, the time it requires and its invasive character with potentially hazardous complications restrict its use in stroke patients. Instead of DSA, noninvasive techniques, eg, MR angiography or TCD, might be used. Both techniques have shown high specificity and sensitivity compared with angiography in patients with cerebrovascular disorders. Nevertheless, reliability and feasibility in acute stroke patients, who are often restless and without suitable acoustic bone window, must be established before this diagnostic approach is recommended. With the use of TCD, intracranial vessel occlusions are difficult to establish because nondetectable intracranial arteries may also be due to an insufficient ultrasound insonation through the temporal bone window. TCCD might change this situation. Without signal enhancement, however, the rate of diagnostically insufficient investigations seems high.

We report a preliminary analysis of an observational study concerning the additional value of contrast-enhanced TCCD over unenhanced ultrasonography in acute cerebral anterior circulation ischemia.

Subjects and Methods

We present 23 patients (11 men and 12 women; mean age, 67.2 ± 14.2 years) referred to the Department of Neurology, whose diagnostic procedures were completed within 5 hours after the initial onset of symptoms suggesting an acute anterior circulation ischemia. Neurological deficit was quantified at the time of admission and 4 days after stroke onset according to the NIHSS score. Patients who died before the second assessment were assigned the worst score of 42. Neurological improvement was defined as a decrease of NIHSS score by 4 or more points or a complete resolution of the deficit on day 4. At admission, blood pressure was registered, an ECG and a chest x-ray were performed, and a blood sample was drawn for routine diagnosis including coagulation parameters. The medical history was taken from the patient or a relative.

All patients underwent extracranial Doppler, TCD, and TCCD examination according to a standard protocol (Doppler: DWL Multi Dop T, 6- and 4-MHz continuous wave probe, 2-MHz pulsed wave probe; duplex: Toshiba SSH-140HG, 5-MHz linear array transducer for extracranial, 2.5-MHz sector transducer for transcranial examination). The investigation of the extracranial carotid and vertebral artery systems was performed before the transcranial examination. The latter consisted of a pulsed wave Doppler and an unenhanced and an echo-enhanced TCD examination, consecutively performed in this sequence, always starting with the asymptomatic hemisphere. The whole examination was documented on videotape. The sonographer performing the examination was informed about the side of the affected hemisphere but did not know the NIHSS score, assessed by a different investigator. Sonographic data were evaluated off-line by two observers blinded for patient, clinical, and CT data, who simultaneously reviewed all videotapes according to the criteria listed below.

By TCD, the MCA, ACA, and PCA (M1, A1, and P1/2 segments), the distal ICA (C1/2 segment), and the ACoA and PCoA were investigated for detectability (yes, no), peak systolic and mean velocity (centimeters per second), and diagnostic evaluation (diminished flow velocity, normal, increased flow velocity, stenosed, occluded, collateral flow, ineductive). MCA occlusion was diagnosed according to published criteria. Diminished flow velocity was considered in peak systolic values below 40 cm/s, which had been established as the lower limit of the 2 SD range in age-adjusted healthy subjects. Additionally, based on the formula derived by Zanette and coworkers, an interhemispheric asymmetry of MCA mean flow velocities was required for diagnosis. The latter had been found to correlate well with multiple (>3) MCA branch occlusions, if extracranial ICA occlusion had been excluded. According to these criteria, both MCA occlusion and flow velocity diminution suggested hemodynamic impairment in the MCA distribution pathway.

By unenhanced TCCD, visibility and vessel pathology were judged as described for TCD, with the use of corresponding TCCD criteria for MCA occlusion and flow velocity diminution. With respect to the approximately 20% higher velocity measurements by TCCD compared with TCD, the lower limit of the 2 SD range for the normal MCA peak systolic velocity was set to 48 cm/s. Angle-corrected measurements were performed in an axis vessel view more than 2 cm in length that was insonated with an angle of less than 60°.

Contrast-enhanced TCCD followed the same protocol but started with the side of the affected hemisphere. Additionally, we tried to insonate the M2 and M3 segments (MCA main trunk before branching and main branches, respectively) and the A2 segment (ACA distal to the ACoA). For signal enhancement, we used 4 g of a galactose-based suspension of microbubbles (Levovist, Schering AG, commercially available in Germany for this indication since early 1996) in a concentration of 300 mg/mL, slowly injected into an antecubital vein within 30 seconds. A second injection was administered if velocity measurements could not be completed or if the vessels of the anterior part of the circle of Willis could not be visualized sufficiently (concentration 400 mg/mL). For enhanced and unenhanced investigations, the insonation depth was set to 15 cm with a pulse repetition frequency of 3.5 to 4.5 kHz, a 70- to 130-Hz high-pass filter, and a duplex sample volume of 10 mm. If necessary, the color gain was temporally reduced after contrast application to eliminate initial blooming artifacts. Interhemispheric flow velocity indices were calculated separately for enhanced and unenhanced examinations.

Patients underwent unenhanced baseline CT, all initially diagnosed as showing no pathological findings. Twenty-one of the 23 baseline scans were available for reevaluation by two experienced observers blinded for clinical and sonographic data. Observers were required to judge the presence and the side of early signs of cerebral ischemia, ie, abnormally hypodense brain parenchyma and brain swelling and a hyperdense MCA sign. Criteria were defined according to the literature.

Statistical analysis was performed with the use of SPSS software, version 6.1.3. Sonographic techniques were compared by means of nonparametric tests for related samples. Time measurements were analyzed by the Wilcoxon rank sum test and the matched-pairs signed rank test, as appropriate. Fisher’s exact test, Pearson’s correlation coefficient, and stepwise multiple logistic regression.

Selected Abbreviations and Acronyms

ACA = anterior cerebral artery
ACoA = anterior communicating artery
DSA = digital subtraction angiography
ICA = internal carotid artery
MCA = middle cerebral artery
NIHSS = National Institutes of Health Stroke Scale
PCA = posterior cerebral artery
PCoA = posterior communicating artery
TCCD = transcranial color-coded duplex sonography
TCD = transcranial Doppler sonography
were used to analyze parameters affecting clinical outcome. Both overall tests and single comparisons of sets of variables were used when indicated. A $P$ value of less than 0.05 was considered significant.

**Results**

In 20 of the 23 patients, contrast-enhanced TCCD enabled diagnosis of intracranial vascular pathology in the affected hemispheres, whereas TCD and unenhanced TCCD were conclusive in 14 and in 7 patients, respectively ($P=0.0001$) (Figure 1). With contrast-enhanced TCCD, examiners failed to detect a Doppler signal in only 1 patient, whereas TCD and unenhanced TCCD failed in 7 and in 11 patients, respectively. Additionally, transcranial techniques only allowed a partial insonation of the basal cerebral arteries or revealed indecisive sonographic findings that did not enable a definite diagnosis in 2 patients by contrast-enhanced TCCD compared with 4 and 5 patients with TCD and unenhanced TCCD, respectively (Table 1) (Figure 2). In 1 patient, contrast-enhanced TCCD revealed distal ICA (carotid-T) occlusion, which was confirmed by subsequent intra-arterial DSA, whereas TCD findings indicated a nonoccluded MCA with diminished flow velocity. In 1 patient, enhanced TCCD

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**Figure 1. Distal carotid (carotid-T) occlusion.** Axial TCCD images of the basal cerebral arteries, insonated from the affected side before (A) and after (B) signal enhancement. Asterisk indicates ipsilateral brain stem. Note occluded ACA (arrowheads) and MCA (arrows).
detected a high-grade stenosis of an MCA branch (M3 segment), which was not routinely insonated by TCD. In 3 patients with an insufficient visualization of at least the anterior part of the circle of Willis after the first dose of Levovist (300 mg/mL), the diagnostic yield could not be improved by a second or third injection (400 mg/mL). Additional multiple injections (2 in 5 patients, 3 in 2 patients) were administered to complete ipsilateral and contralateral

Figure 2. Axial TCCD image of the basal cerebral arteries, insonated from the affected side after signal enhancement. Asterisk indicates ipsilateral brain stem. Note detectable PCA, undetectable MCA, and ACA (ipsilaterally and contralaterally). Carotid-T occlusion may not be differentiated from insufficient visualization of anterior circulation arteries because of temporal bone window failure.
velocity measurements of MCA branches (M3 segments) according to the standardized examination protocol. On the symptomatic side, MCA branches could not be visualized by enhanced TCCD in 8 of 20 penetrable temporal bone windows. Insonation of the MCA main stem showed an occlusion in 4, a diminished flow velocity in 3, and normal flow velocity in 1 of these patients. Contralaterally, MCA branches could not be detected in 5 of the 20 corresponding asymptomatic hemispheres, all presenting normal flow velocities in the corresponding proximal MCA.

**Time Requirements**

The overall mean examination times of TCD and unenhanced and echo-enhanced TCCD were significantly different ($P<0.05$), with 6.7±3.5 minutes for the contrast-enhanced examination compared with 4.9±2.8 and 4.3±1.5 minutes for the unenhanced TCCD and TCD, respectively. In 7 of the 10 patients with multiple Levovist injections, additional doses were administered to attempt visualization of a possible MCA branch occlusion (M3 segments), which was not tried with the other transcranial techniques. Without this time period, the mean time for enhanced TCCD was 4.7±1.6 minutes, which did not differ from TCD and unenhanced TCCD. In case an insonation was possible, the mean time for the assessment of vascular pathology was prolonged by unenhanced TCCD (7.1±2.0 minutes) compared with TCD (4.3±1.4) and contrast-enhanced TCCD (4.7±1.6) ($P<0.05$).

**Clinical Relevance**

Median NIHSS score at admission, 98±55 minutes after the first onset of symptoms, was 17 (range, 1 to 30). On day 4, 10 of the 23 patients had improved, exhibiting a median score of 1 (range, 0 to 16), whereas 13 had remained stable or deteriorated (median, 19; range, 4 to 42). Table 2 shows the comparison between demographic data, baseline clinical characteristics, vascular risk factors, CT findings, and the clinical course. There were no differences between both subgroups regarding sex, age, systolic and diastolic blood pressure, and median NIHSS score at admission. Except for a nonsignificantly lower frequency of atrial fibrillation, improving patients presented a pattern of vascular risk factors similar to that of nonimproving individuals. Twenty-one of the 23 baseline CTs, performed 117±55 minutes after the onset of stroke, were available for reevaluation. Early findings of brain infarction and a hyperdense MCA sign were diagnosed in a minority of the affected hemispheres without significant differences between nonimproving and improving patients. The frequency of various drug therapies, ie, intravenous heparin, subcutaneous heparin, and antiplatelet agents, did not differ between the two groups. After the application of Levovist, we did not observe an adverse event in any of the patients.

Ultrasonography, performed 148±66 minutes after the onset of symptoms, suggested hemodynamic impairment in the MCA distribution pathway in 10 of the 20 intracranially
evaluated patients. Sonography detected an MCA occlusion in 1 patient, a carotid-T occlusion in 3, an MCA flow velocity diminution due to multiple (>3) MCA branch occlusions in 3, and a diminished MCA flow velocity due to an insufficiently collateralized extracranial ICA occlusion in an additional 3 patients. Of these 10 patients, only 1 improved compared with 9 of 10 who exhibited normal or increased MCA flow velocities in the affected hemisphere ($P=0.001$) (Table 3). Among the demographic data, baseline clinical characteristics, vascular risk factors, sonographic vascular status, and CT findings, a patent MCA without diminished flow velocity, as evaluated by echo-enhanced TCCD, was the only independent predictor of an early improvement by stepwise logistic regression ($P<0.01$).

In patients with MCA occlusion or blood flow velocity reduction, median NIHSS score at admission (17; range, 1 to 30) did not differ from patients without these findings (12; range, 2 to 26) ($P=0.3$). On day 4, patients with MCA occlusion or blood flow velocity reduction exhibited significantly higher NIHSS scores (median, 18; range, 7 to 42) than those with an initially patent MCA with normal blood flow velocity (median, 1; range, 0 to 8) ($P<0.0001$). Most of the patients with an MCA occlusion or blood flow velocity reduction had deteriorated (median NIHSS score difference, +6; range, −4 to 15), whereas the neurological status of the patients without these findings had improved markedly (median NIHSS score difference, −11; range, −18 to −1) ($P<0.0001$).

### Discussion

The clinical value of TCCD for the assessment of intracranial vessel pathology is still under discussion. Angle correction of blood flow velocities, initially considered a major advantage over TCD, has shown only minor clinical relevance.\textsuperscript{22–24} The use of echo-contrast agents for identification of major vessel occlusions and the reduction of bone window failure, both of particular relevance in acute stroke patients, has not been evaluated yet.\textsuperscript{26–28} The purpose of our study was to assess and compare the diagnostic impact of TCD and unenhanced and contrast-enhanced TCCD in acute stroke.

In case of undetectable flow signal, reliable diagnosis of MCA occlusion and its differentiation from technical problems is a well-known problem of transcranial ultrasonography. Successful insonation of the ipsilateral noninvolved basal cerebral arteries, ie, ACA, distal ICA, and PCA, is considered mandatory.\textsuperscript{13,14,26–28} If only the PCA is detectable, a distal ICA (carotid-T) occlusion may be erroneously diagnosed in a considerable number of patients. According to our experience, partial insonation of the circle of Willis, showing only the posterior part, is frequent in older individuals, especially by TCCD, and a reduced flow velocity in the extracranial ICA is a highly variable finding in periacute stroke patients. Reliable sonographic diagnosis of carotid-T occlusion requires a detectable flow signal in the ACoA or the ACA (ipsilateral A2 segment, contralateral A1/2 segment) when insonated from the affected side (Figures 1B and 2).

In our study the incidence of an insufficient temporal bone window for TCD was similar to that reported by others,\textsuperscript{14} whereas the rate for TCCD exceeded most of those reported in the literature,\textsuperscript{15,26–28} as well as that obtained in our laboratory for age- and sex-adjusted patients with chronic cerebrovascular diseases. Supposedly, this can be referred to the use of a 2.5-MHz TCCD probe (compared with 2.25 MHz),\textsuperscript{27,28} the higher proportion of female (52% versus 29%) and older patients (mean age, 67 versus 55 years),\textsuperscript{26} and the acute stroke setting, including increased restlessness of the patients. However, after the application of signal enhancement, the rate of an insufficient bone window decreased to only 13%, which was significantly lower than that of the TCD and the unenhanced examination.

Contrast-enhanced TCCD seems to be more reliable than TCD in differentiating an MCA main stem occlusion from a nonoccluded vessel with highly diminished flow velocity, as demonstrated in one patient. This is of particular relevance if thrombolytic therapy is considered. In most patients enhanced TCCD also enabled the insonation of at least the proximal part of MCA branches, revealing a high-grade stenosis in one patient. Based on the fact that MCA branches could not be visualized in 25% of the unaffected hemispheres, however, nondetectable branches without flow velocity reduction in the proximal MCA do not seem to be a sufficient criterion to diagnose multiple branch occlusions.

With the exception of one patient, in whom angiography 40 minutes after signal-enhanced TCCD confirmed diagnosis of carotid-T occlusion when a patent MCA with reduced blood flow velocity was diagnosed by TCD, sonography was not followed by DSA to compare the diagnostic findings. This was not thought to be ethically justified in an observational
study because of potentially hazardous complications. Nevertheless, all patients with extracranial/intracranial pathologies were sonographically reexamined at short intervals. These examinations invariably supported the initial diagnosis, eg, by visualizing MCA or carotid-T recanalization. These findings are also supported by a recent study showing high accuracy of contrast-enhanced TCCD diagnosis of MCA occlusion and subsequent recanalization when compared with angiography.29

In regard to therapeutic consequences, eg, thrombolysis, the relevance of establishing intracranial vessel pathology in the first hours after stroke is most significant.1,2 Fast and reliable diagnostic procedures are required. In view of former TCD studies that emphasized the need for considerable time, patience, and experience to identify an MCA occlusion,10 we assessed the time needed for sonographic evaluation. The mean time for the conventional examination, including extracranial Doppler/duplex and TCD, was 15.5 minutes. If, with respect to its lower diagnostic yield, TCD was replaced by contrast-enhanced TCCD, the calculated mean examination time was 15 to 17 minutes, depending on the number of vessels investigated (without or with MCA branches). An increase in the experience of examiners investigating peri-
acute stroke patients resulted in a decrease of examination time toward the end of the study; the calculated time required for combined extracranial Doppler/duplex and contrast-enhanced TCCD was 15 minutes or less.

MRA is an additional noninvasive alternative to DSA, which, in contrast to ultrasonography, also allows the demonstra-
onstration of more distal arterial branches.28 However, its feasibility and reliability in acute stroke patients, who are often aphasic and restless, must still be evaluated, as well as the examination time necessary in these situations. Performance of additional functional brain images is a major advantage of MR technique. Early differentiation of structural brain lesions from functionally impaired regions with subsequent clinical outcome prognosis might be enabled by perfu-
sion- and diffusion-weighted techniques. However, with respect to available studies, angiographic and functional imaging findings might correspond in a substantial number of patients.

In our study the absence of an MCA occlusion or blood flow velocity reduction was a strong predictor of early clinical improvement. If insonation was possible, TCD- and TCCD-assessed MCA peak systolic velocity and calculated interhemispheric asymmetry indices corresponded in all patients for the presence or absence of a pathological finding. An increase of the TCCD-assessed Doppler shift (and flow velocity) after signal enhancement, ranging from 20% to 45% (due to a nonlinear conversion of the backscattered Doppler signal intensity into the video signal), has been described.25 However, interhemispheric flow velocity comparisons, which were evaluated separately for unenhanced and enhanced TCCD and, in the latter, with identical device settings between the left/right measurements within a few seconds, should not be influenced. In none of the patients with diminished MCA peak systolic velocity established by TCD and unenhanced TCCD did this velocity exceed 48 cm/s after signal enhancement, confirming that an MCA blood flow velocity reduction was only assumed in markedly decreased flow velocities. Our results correspond with angiographic findings obtained in the early course of acute stroke.10,30,31 In contrast to these studies,10,30 only a minority of our patients demonstrated early CT signs of cerebral ischemia, which did not correlate with the early clinical outcome. However, most of our CTs were performed less than 3 hours after the onset of symptoms, when normal findings do not exclude irreversible ischemic brain damage,12 whereas the other studies included CTs from a wider time window. If we assume that the vascular status in the very early course of stroke is related to the extent of successive brain infarction and neurological outcome, it might be used as an early guide for therapeutic decisions.

In summary, the use of echo-enhanced TCCD for assessing intracranial vascular pathology in periacute stroke patients significantly increased diagnostic efficacy compared with other transcranial sonographic techniques. Sonographically established early vascular pathology seems to be a major predictor—and was in our study the only predictor—of early clinical outcome and might become a promising tool to judge the efficacy of early stroke therapy. Further investigations that include more patients are necessary.

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