Sonographic Evaluation of Hemorrhagic Transformation and Arterial Recanalization in Acute Hemispheric Ischemic Stroke

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Background and Purpose—We conducted this prospective study to evaluate the time course of hemorrhagic transformation (HT) and arterial recanalization in the early phase of ischemic stroke using transcranial sonography (TCS).

Methods—Fifty-five patients with acute ischemic hemispheric stroke <32 hours after symptom onset were studied. A 2-MHz sector probe was used to evaluate brain tissue by TCS and basal cerebral arteries by transcranial color-coded sonography. Follow-up investigations were performed up to 6 days. Lesion size and localization were determined by cranial computed tomography.

Results—Of 20 patients with HT, 18 displayed by computed tomography could be identified by TCS. In 1 patient, TCS provided a wrong positive result, and in another 2 patients with small cortical HT, a wrong negative result was provided (sensitivity 90.0%, specificity 97.4%). HT was detected in the first 60 hours after symptom onset in 62.5% of patients treated with tissue plasminogen activator in comparison to 33.3% without thrombolysis. Recanalization of middle cerebral artery occurred earlier in tissue plasminogen activator-treated patients compared to those without tissue plasminogen activator treatment (in the first 60 hours after symptom onset: 78.5% vs 50.0%, respectively; \( P = 0.34 \)). There was a significant time difference between middle cerebral artery recanalization and HT occurrence (\( n = 13, \) median time interval: 20 vs 60 hours; \( P = 0.035 \)).

Conclusions—Transcranial ultrasound is a useful bedside method to depict and closely monitor HT in patients with acute hemispheric stroke. The strong influence of tissue plasminogen activator treatment on HT could be demonstrated. HT development is dependent on the time of artery recanalization. (Stroke. 2009;40:119-123.)

Key Words: acute ischemic stroke • brain tissue monitoring • hemorrhagic transformation • transcranial sonography

Neurosonology offers several modalities in the evaluation of the human brain. For several years extracranial and transcranial Doppler analysis of cerebral macrocirculation has been a basic part of ischemic stroke diagnostics.\(^1\)\(^-\)\(^3\) In recent years, pathological structures within the brain parenchyma could be imaged by transcranial grayscale sonography (TCS). With this noninvasive ultrasound method, primary intracerebral hemorrhage, midline shift after space-occupying ischemic stroke, and brain tumors could be visualized.\(^4\)\(^-\)\(^8\) This technology enables close monitoring of both the vascular and the parenchymal status after ischemic stroke at the bedside of the patient.

Hemorrhagic transformation (HT) of infarction in ischemic stroke is common and represents almost a natural event in the process of cerebral infarction.\(^9\)\(^-\)\(^12\) Moreover, an increasing rate of intracranial bleeding is reported after treatment with tissue plasminogen activator (tPA).\(^13\) Because HT mostly appears in the early phase of ischemic stroke and is not obligatorily associated with clinical deterioration or unfavorable clinical outcome,\(^14\) the presence of HT is often unknown. With respect to early secondary prevention with aspirin, we know from primary intracerebral hemorrhage that regular aspirin use preceding the onset of hemorrhage is an independent predictor of death.\(^15\) We conducted this prospective study to evaluate the time course of HT and artery recanalization in the early phase of ischemic stroke.

Methods

Patients

Fifty-five consecutive patients with acute ischemic stroke in the territory of the internal carotid artery (54 patients with middle cerebral artery [MCA] infarction, 1 patient with anterior choroidal artery infarction) were included and underwent transcranial color-coded sonography and TCS monitoring. Inclusion criteria of the study were acute onset of sensorimotor hemiparesis, neglect or incomplete aphasia <32 hours before sonography, a score of ≥6 according to the National Institutes of Health Stroke Scale, and presence of a sufficient acoustic bone window. All patients had at least 1 cranial computed tomography (CCT) scan as part of our

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Ultrasound Evaluation

Color-coded duplex sonography of the brain supplying arteries and TCS were performed with a SONOS 5500 ultrasound system (Philips Medical Systems) by experienced investigators. We used a 2-MHz sector transducer (S3/S4 probe; Philips) for the transtemporal evaluation of the basal cerebral arteries and a 7.5-MHz linear probe (L7540 probe; Philips) for the extracranial brain-supplying arteries. First, we assessed the status of the extracranial and intracranial cerebral arteries using color-coded duplex sonography.

Occlusion of MCA (M1-segment) was considered in cases with no MCA stem signal on the color display, no Doppler signal when tracing the lateral fissure visible in B-mode, and a detectable distal internal carotid artery or anterior cerebral artery Doppler signal. Diagnosis of occlusion of a large branch or of multiple branches (M2-segment) of the MCA was based on the asymmetry index of Zanette et al.16 This means a diminution of mean flow of the MCA of 21%. For a diagnosis of stenosis of the MCA (M1 segment) maximum peak systolic velocity must exceed 160 cm/sec.3

TCS was then performed with an insonation depth of 16 cm in axial imaging planes parallel to the orbitomeatal line. The symptomatic hemisphere was scanned from the contralateral side of the skull base to the parietal lobe. We digitally recorded a loop of 62 axial imaging planes, which included the standard axial imaging planes. Transtracranial color-coded sonography and TCS follow-up investigations were performed daily up to 6 days. To identify intracerebral blood, we scanned the TCS images for pathological hyperechogenicities as described earlier.8 Ultrasound system settings were adjusted so that nonhemorrhagic brain tissue (thalamus in the diencephalic scanning plane) was scanned with an intermediate echogenicity (between pineal gland [bright] and ventricular system [dark]). The individual system setting (gain, power, and time gain compensation) of the first investigation was documented in a numeric way and used for the follow-up investigations. Diagnosis of HT was made if a hyperechogenicity (compared to the surrounding tissue) was found in a region where no anatomic hyperechogenicities occur. The ultrasound investigator at the patient’s bedside was blinded to CT results while performing the scan.

After the investigation, analysis of the TCS scans was performed offline by an experienced examiner without any knowledge of the CT or MRI imaging information.

Statistical Analysis

We used mean and median values as well as standard deviations and interquartile ranges to describe the data. For sensitivity and specificity, Clopper-Pearson 95% CI was calculated. Positive and negative predictive values were calculated using the Bayes formula with an a priori possibility for hemorrhagic transformation of 50%. The nonparametric Wilcoxon test was used for statistical comparison of the time distribution between MCA recanalization and HT detection (SPSS 15.0). Recanalization rate of MCA in the tPA treatment group compared to the non-tPA treatment group was performed using Fisher exact test. Significance was assigned for values of $P<0.05$.

Results

Mean age of 55 included patients (20 female) was 60.4 (SD, 14.5) years. All patients were admitted with acute hemispheric ischemic stroke in the territory of internal carotid artery <32 hours after symptom onset (with the exception of 1 patient with anterior choroidal artery infarction, all patients had MCA infarction). Mean National Institutes of Health Stroke Scale was 13.7 (SD, 4.8; median, 14; interquartile range, 7). The first CCT was performed immediately after stroke symptom onset (mean, 3.3 hours; SD, 3.0; median, 2.0; interquartile range, 3.75). Follow-up CCT in each patient and cranial MRI in 8 patients provided information about localization and size of the infarction (mean, 35.8; SD, 40.2; interquartile range, 9.5; median, 27 hours after stroke symptom onset). A third CCT scan was performed in 18 patients (mean, 163; SD, 129; interquartile range, 155.5; median, 111 hours after stroke symptom onset). According to our standard stroke protocol, transcranial color-coded sonography was performed immediately in the acute phase of stroke. Mean time of first TCS was 10.6 hours (SD, 7.2; median, 8.5; interquartile range, 6.5 hours) after stroke symptom onset. Follow-up investigations were performed daily up to 6 days.
In 20 patients, CCT revealed HT of infarction (Figure 1). Using TCS, we detected 18 HTs on the symptomatic hemisphere. In 1 patient, TCS provided a wrong positive result because of a reverberation artifact; in 2 other patients, TCS was unable to detect the small cortical HT (sensitivity, 90.0%; 95% CI, 68.3–98.8%; specificity, 97.4%; 95% CI, 86.2–99.9%; positive predictive value, 96.8%; 95% CI, 95.8–97.1%; negative predictive value, 90.7%; 95% CI, 89.6–90.9%). Systemic tPA thrombolysis (0.9 mg/kg within the first 3 hours after symptom onset) was performed in 19 of 55 patients, and HT occurred in 8 of them. In 62.5% (5/8) of these patients, HT was diagnosed in the first 60 hours after symptom onset. HT occurred in 12 of 36 patients without tPA treatment. In 33.3% (4/12), HT could be diagnosed in the first 60 hours after symptom onset (Figure 2A).

**Figure 2.** A, Diagram shows time course of hemorrhagic transformation of infarction (HT) in 20 patients. Time intervals (hours) is plotted against rate of HT. Patients without tPA (dark gray, n=12) and with tPA treatment (light gray, n=8) are displayed. B, Diagram shows time course of middle cerebral artery recanalization in 22 patients with M1 occlusion. Time intervals (hours) is plotted against rate of artery recanalization. Patients without tPA (dark gray, n=8) and with tPA treatment (light gray, n=14) are displayed. C, Box plots of MCA recanalization and hemorrhagic transformation in non-tPA–treated (n=6) and tPA-treated (n=7) patients with initial MCA occlusion. Time intervals (hours) after symptom onset are displayed.
In the initial investigation we found an occlusion of MCA (M1 segment) in 22 patients. In 2 patients we diagnosed MCA (M1 segment) stenosis, in 7 patients had occlusion of M2 segment (with patent MCA main stem), and in the remaining 24 patients normal Doppler spectra in the MCA was found. Recanalization of occluded M1 segment (n=22) in the first 60 hours after symptom onset occurred earlier in tPA-treated patients (n=14) compared with non-tPA–treated patients (n=8; 78.5% [11/14 patients] vs 50.0% [4/8 patient]), respectively (Figure 2B). This difference was not statistically significant (Fisher exact test, P = 0.34).

HT could be detected in 13 patients with documented M1 segment recanalization. HT occurred a median of 40 hours later than the artery recanalization. This effect for the whole group was strong influenced by the subgroup of the tPA-treated patients (Figure 2C). There was a significant difference of time distribution between M1 segment recanalization and HT detection in the whole group (n=13; Wilcoxon test, P = 0.04).

The CT classification of the intracerebral hemorrhages was performed according to the criteria of Berger et al.20 We differentiated between hemorrhagic infarction with petechiae within the infarcted area (HT1/HT2) and parenchymal hematoma with extensive hemorrhage (PH1/PH2). In 13 of 20 patients with a hemorrhagic transformation displayed in the follow-up CCT, we found a hemorrhagic infarction type HT1 or HT2. In 7 of 20 patients, CCT revealed a parenchymal hematoma type PH1 or PH2. On the basis of the echogenicity characteristics provided by TCS, it was not possible to differentiate between HT and PH.

Discussion
The purpose of our present transcranial ultrasound study was to evaluate the sensitivity of TCS in the diagnosis of HT and the time course of HT in the early phase of ischemic stroke. According to the findings of our preliminary study,8 TCS again provided both a high sensitivity (90%) and specificity (97.4%) in depicting HT. Ultrasound monitoring showed HT in the first 60 hours after symptom onset in 62.5% of patients treated with tPA and 33.3% of patients who did not receive tPA. In the same time interval transcranial color-coded sonography displayed MCA recanalization in 78.5% of tPA-treated patients and in 50.0% of non-tPA–treated patients. HT occurred with a median delay of 40 hours after the artery recanalization.

The temporal profile of arterial recanalization after tPA-treatment was evaluated in several studies.17–19 The majority of tPA-induced recanalizations occur during the first hour after treatment. Recanalizations during the following hours are rare but still related to clinical improvement if achieved within 6 hours from onset. The development of HT depends on the time to artery recanalization,19 which is mainly caused by an increase of disturbance of the blood–brain barrier in ischemic tissue. Thrombolyis-related hemorrhagic transformation was interpreted as a marker of early successful recanalization, which leads to a reduced infarct size and improved clinical outcome.19 Our present study shows that the time of HT development is linked to the time of artery recanalization, especially in the subgroup of tPA-treated patients. Hemorrhagic transformation occurs not directly after artery recanalization, the time interval could be >24 hours after thrombolysis.

TCS is a reliable method for depicting HT and offers a useful bedside modality to monitor parenchymal and vascular status in the acute phase of ischemic stroke. Unlike its high diagnostic potential in displaying the echomorphology of intracerebral blood, TCS has its limits in spatial resolution. Therefore, discriminating between hemorrhagic infarction and parenchymal hematoma was not feasible, and small cortical HTs were not diagnosed. CCT or cranial MRI provides more information about the subtype of HT, thus allowing a prognostic statement about the clinical outcome to be made.14,20 The most important advantage of TCS compared with standard diagnostic tools, such as CT and MRI, is the ability to perform close monitoring at the bedside of the patient.

In conclusion, TCS is an easy-to-perform bedside method for depicting and closely monitoring HT of hemispheric ischemic stroke. This method is of particular interest in treating critically ill patients who are at risk for clinical deterioration if transported to receive a CT or MRI scan. Further studies on TCS in acute ischemic stroke are necessary because our data are purely descriptive.

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Disclosures
None.

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