DIAS I: Duplex-Sonographic Assessment of the Cerebrovascular Status in Acute Stroke
A Useful Tool for Future Stroke Trials
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Background and Purpose—A number of controlled trials have evaluated the benefit of intravenous thrombolysis in acute stroke with inconsistent results. None of these studies assessed the initial vascular status or provided information regarding the recanalization rate after therapy. Further trials need to clarify whether certain subgroups might possibly benefit more than others from intravenous thrombolysis. Therefore, a fast and valid method for assessment of cerebrovascular status is needed. In this multicenter study, we evaluated the potentials and limitations of color-coded duplex sonography (TCCS) for cerebrovascular status assessment in acute stroke patients before and after therapy. Furthermore, we compared the recanalization rate for patients referred to thrombolytic and conservative medical therapy.

Methods—Fifty-eight patients suffering from hemispheric stroke were enrolled consecutively in 8 centers. Duplex sonography was performed on admission, 2 hours after start of therapy, and 24 hours after onset of symptoms. Therapy was started within 6 hours.

Results—Intravenous thrombolysis was performed in 18 patients, conservative medical therapy in 39 patients, and early thromboendarterectomy in 1 patient. The middle cerebral artery (MCA) mainstem was patent in 29 patients (53.7%), occluded in 25 (46.3%), and was not assessable in 4 patients. Recanalization of the occluded MCA after 2 and 24 hours was diagnosed in 50% and 78% of the patients treated with rtPA and in 0% and 8% in the conservatively treated patients.

Conclusions—Intravenous thrombolysis is highly effective in restoring blood flow after MCA occlusion. TCCS is suitable for assessment of the cerebrovascular status in acute stroke and therefore might define therapeutically relevant subgroups of patients in future stroke trials on the basis of their vascular pathology. (Stroke. 2000;31:2342-2345.)

Key Words: cerebral arteries ■ diagnostic imaging ■ thrombolysis ■ ultrasonography, Doppler, duplex

During the last decade a considerable number of large, randomized, placebo-controlled trials have been performed to evaluate the benefit of thrombolytic therapy in acute stroke with the use of intravenous rtPA. The results are controversial and have been intensively debated: although the NINDS study demonstrated functional improvement after intravenous thrombolysis compared with placebo, the ECASS trials failed to show a clear benefit from this therapy.

In contrast to angiographic trials (PROACT II), none of the large intravenous thrombolysis studies evaluated the presence of vessel occlusion before therapy, although their aim was to recanalize occluded arteries. Therefore, it is likely that a number of patients were referred to intravenous thrombolysis despite a normal cerebrovascular status and therefore probably could not profit from this particular therapy. Furthermore, these trials did not provide any information regarding the recanalization rate after thrombolysis.

It is likely that there are considerable variations in therapeutic responses to intravenous thrombolysis according to the underlying vascular pathology. Future stroke trials must be performed to clarify which subgroups of patients will profit most from this therapy. Therefore, a fast and valid method for the assessment of cerebrovascular status is of utmost importance.

Extracranial and transcranial color-coded duplex sonography (TCCS) is a bedside technique for the evaluation of the brain-supplying arteries, and it can therefore identify patients with arterial occlusions. The purpose of the DIAS study was to assess the cerebrovascular status in acute stroke patients within the first 6 hours after onset of symptoms and to monitor recanalization of occluded arteries after thrombolytic and conservative medical therapy. We aimed to investigate the potential of intravenous thrombolysis in restoring middle cerebral artery (MCA) blood flow and its evaluation by TCCS for future stroke trials.
Furthermore, we wanted to estimate the proportion of patients with occlusion of the MCA in a recent thrombolytic trial by creating inclusion criteria analogous to those of ECASS II. With respect to the pending registration of rtPA for stroke treatment in Europe, the present investigation was purely observational in character. Assuming a certain degree of uncertainty in the choice of treatment, the decision for therapy was left up to each center.

**Subjects and Methods**

DIAS was carried out in 8 centers in Germany and Switzerland. Over a period of 9 months, 58 consecutive patients with symptoms of a moderate to severe hemispheric stroke (Scandinavian Stroke Scale score <30) who fulfilled the inclusion criteria were prospectively enrolled in this study. Female and male patients >18 years of age who could be treated within 6 hours after onset of symptoms were eligible. Stroke symptoms had to be distinguishable from hypoglycemia, migraine, global ischemia, and epileptic seizures. Rapid spontaneous clinical improvement, possibly indicating transient ischemic attacks, led to exclusion from this study. Further exclusion criteria were severe heart failure (NYHA class IV), galactosemia, septic emboli, and unknown time of stroke onset. A CT scan was performed before inclusion to identify patients with intracranial or intracerebral bleeding, neoplasm, arteriovenous malformation, or aneurysm and was read according to the ECASS II criteria. Inclusion and exclusion criteria of the ECASS II-trial were documented.

Color-coded duplex sonography of the extracranial brain-supplying arteries and the basal cerebral arteries were performed on admission, 2 hours after start of therapy, and 24 (>2) hours after onset of symptoms. Extracranial internal carotid arteries (ICAs) and common carotid arteries (CCAs) were classified as "normal", "stenosed" or "occluded" according to literature. A "preocclusive signal" was diagnosed when the extracranial duplex of the ICA revealed a typical high-resistance signal without of diastolic flow. ECASS II criteria. Inclusion and exclusion criteria of the ECASS II-trial were documented.

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TCCS was performed by using the transtemporal approach, as described previously. Angle-corrected blood flow velocities were obtained from contrast-enhanced measurements if available, otherwise from unenhanced TCCS investigations. "Siphon occlusion" was diagnosed when the intracranial portion of the ICA was assessable by TCCS but no color signal or Doppler spectrum could be obtained, or when extracranial duplex sonography of the ICA revealed a preocclusive signal. "MCA mainstem occlusion" was considered to have occurred when no color signal or Doppler trace could be obtained in the lateral fissure but the anterior cerebral artery (ACA) and the P1 and P2 segments of the posterior cerebral artery (PCA) were sufficiently assessable (Figure). "MCA stenosis" was ascertained when Doppler spectral analysis demonstrated circumscribed acceleration of mean systolic blood flow velocity (>120 cm/s) and a side-to-side difference of >21%, as well as spectral signs of disturbed flow, in accordance with published criteria. According to Zanette et al, "multiple MCA branch occlusion" was diagnosed when the asymmetry index of the angle-corrected mean blood flow velocity of the M1 segment exceeded 21%. Asymmetry index was calculated only if supplying carotid arteries and contralateral MCA could be assessed without relevant stenosis or occlusion. Furthermore, flow direction of the ACA was documented. An investigation of an arterial segment was considered satisfactory when a diagnosis could be obtained according to the above-mentioned criteria. Each extracranial and transcranial duplex examination was recorded on video tapes. The duration of the examination time was determined offline.

Contrast enhancement (Leovist, Schering) was used in all TCCS examinations if ipsilateral basal cerebral arteries or the contralateral M1 segment of the MCA were not visible to full extent or the ipsilateral carotid siphon was not assessable. In these cases, 4 g Leovist was administered at a concentration of 300 mg/mL as single or multiple bolus injection or infusion. Ready-to-use Leovist is a suspension of air and galactose microparticles. Palmitic acid (0.1%) guarantees stability of microbubbles for several minutes, and their small diameter permits passage through capillary beds. This results in a sufficient signal enhancement of the basal cerebral arteries for approximately 3.5 minutes. Each injection was followed by a flush of 10 mL of saline. If necessary, overenhancement of the color signals (blooming effect) was reduced by decreasing the insonation power and gain.

Therapy was started within 6 hours from onset of symptoms according to the local therapy regimes (eg, aspirin, heparin, thrombolysis). When a participating center chose thrombolytic therapy, intravenous rtPA was applied according to the ECASS II protocol.

For comparison of the frequency of MCA mainstem occlusions in the entire DIAS and the ECASS II analogous collective and of the recanalization rate between different therapy groups we used Fisher’s exact 2-tail test.

**Results**

Fifty-eight patients (36 men and 22 women) were included in this study. Their median age was 64 years (range 38 to 89 years), and median NIH stroke scale (NIHSS) score on admission was 14. Inclusion profiles of 35 patients were in complete accordance with ECASS II criteria. Their median age, NIHSS on admission, and sex are presented in Table 1. Differences in the inclusion criteria in the remaining 23 patients referred to age >80 years (4 patients), hypodensity in >1/3 of the MCA territory (3 patients), hemiplegia plus fixed eye deviation (5 patients), use of steroid medication (1 patient), noncontrollable blood pressure >180 mm Hg (1 patient), additional cerebral neoplasm (1 patient), no use of contraceptives (1 patient), and severe aphasia (7 patients).

Intravenous thrombolysis in accordance with the ECASS II protocol was performed in 18 patients (31.0%). Twenty-two

| TABLE 1. Conformity of the Baseline Features of ECASS II Patients and ECASS II–Analogous DIAS Patients |
|-----------------------------------------------|----------------|----------------|----------------|
| ECASS II–Analogous DIAS Patients | ECASS II Patients | **Total DIAS Patients** | **ECASS II Patients** |
| (n=35) | **(n=58)** | **(n=800)** | **(n=800)** |
| Median age, y | 64 | 68 | 62 |
| Men:women | 1.6 | 1.4 | 1.6 |
| NIHSS score on admission | 14 | 11 | 11 |

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patients (39.9%) received dose-adjusted intravenous heparin so that the partial thromboplastin time was at least doubled, and 17 (29.3%) received aspirin or no antithrombotic therapy (conservative treatment). Early carotid endarterectomy was carried out in 1 patient. Administration of Levovist was well tolerated in all patients without side effects.

Vascular Status on Admission

Initial duplex examination was performed a mean of 3.4 (SD 1.2) hours after onset of symptoms (mean; SD 1.2 hours). Levovist was used in 51 of 58 transcranial examinations (88%). In the overall analysis of the DIAS collective, the ipsilateral MCA was patent in 29 patients (53.7%), occluded in 25 (46.3%), and not assessable in 4 patients. In patients with a patent M1 segment, an asymmetry index of mean blood flow velocity could be calculated in 19 of 29 patients. In 11 of these 19 patients, the asymmetry index exceeded 21%, indicating multiple MCA branch occlusion.

In the subgroup analogous to ECASS II, we found the ipsilateral MCA not assessable in 1 patient, patent in 24 (70.6%), and occluded in 10 (29.4%; Table 2). Asymmetry index could be calculated in 16 patients. In 8 of them, multiple MCA branch occlusion was diagnosed.

Comparing the entire DIAS collective with those patients analogous to ECASS II, MCA mainstem occlusions were significantly less frequent in the ECASS II–analogous collective ($P<0.05$).

Recanalization rate

In the DIAS collective, recanalization of the occluded MCA-mainstem 2 hours after therapy and 24 hours after onset of symptoms was diagnosed in 50% and 78%, respectively, of the patients treated with rtPA. In patients referred to conservative treatment, only 1 M1-recanalization could be detected 24±2 hours after onset of symptoms (Table 3). Therefore, recanalization rate of MCA mainstem occlusions 2 hours after therapy and 24 hours after onset of symptoms differed significantly between the thrombolytic and conservative medical treatment groups ($P<0.05$).

Discussion

TCCS has been proved to be a valid method for detection of intracranial vessel occlusion, with a high diagnostic agreement between TCCS and angiography. $^5,6$ For the first time, this study evaluated the vascular pathology of acute stroke patients in a multicenter setting using TCCS. Early, noninvasive TCCS has been proved to be a valid method for detection of intracranial vessel occlusion, with a high diagnostic agreement between TCCS and angiography. $^5,6$
Assessment of Vascular Status in Acute Stroke

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Evasive evaluation of the neurovascular status may be of particular relevance for future stroke trials, because it allows the selection of patients for intravenous thrombolysis, taking into account their vascular status.

Our ECASS II–analogous collective closely matched the actual ECASS II population with regard to inclusion and exclusion criteria, demographic and baseline data. In this subgroup, the MCA mainstem as depicted by ultrasound was patent in 71% of patients, whereas 29% revealed an occlusion. Based on our data, we can assume that only one third of patients in the ECASS II trial actually had an MCA mainstem occlusion. Given the fact that thrombolytic therapy primarily aims at recanalizing occluded vessels, this emphasizes the importance of the assessment of the vascular status in future stroke trials. These future studies also need to clarify the relationship between cerebrovascular status and benefit from intravenous thrombolysis.

The recanalization rates of 50% and 78% 2 hours after therapy and 24 hours after onset of stroke in patients who underwent thrombolytic therapy, compared with rates of 0% and 8% in those without thrombolysis, illustrate the effectiveness of intravenous rtPA application in restoring MCA blood flow. These results are comparable to the recanalization rates found with intra-arterial application of prourokinase and confirmed by digital subtraction angiography (recanalization rates of 58% [versus placebo 14%] and 66% [versus heparin 18%], respectively).4

Because our study design was observational and did not allow randomization, the probative force to prove the clinical benefit of intravenous thrombolysis is limited. However, it has been shown previously7,8 that successful early recanalization is closely associated with a favorable outcome. Unlike diagnostic angiography, TCCS carries no risks but enables reliable screening of stroke patients for MCA occlusion and monitoring of treatment without procedural delay.

Our findings encourage attempts to define neurovascular pathology for stroke trials in general and thrombolysis in particular and to select patients who are more likely to benefit from therapy than the cohort as a whole. Despite the use of an ultrasound contrast agent, 7% of our patients could not be investigated sufficiently because of ultrasound attenuation by the skull. This is the most important limitation of this method. Nevertheless, DIAS shows that TCCS is a useful bedside technique for the fast and valid evaluation of the initial cerebrovascular status and for monitoring the efficiency of intravenous thrombolysis in restoring MCA blood flow in >90% of all acute stroke patients. It therefore renders the definition of subgroups of patients in future stroke trials with respect to the underlying vascular pathology.

Appendix

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