Sonographic Monitoring of Midline Shift in Space-Occupying Stroke
An Early Outcome Predictor

T. Gerriets, MD; E. Stolz, MD; S. König; S. Babacan; I. Fiss; M. Jauss, MD; M. Kaps, MD

Background and Purpose—Transcranial color-coded duplex sonography (TCCS) allows bedside imaging of intracranial hemodynamics and parenchymal structures. It provides reliable information regarding midline shift (MLS) in space-occupying hemispheric stroke. We studied the value of MLS measurement to predict fatal outcome at different time points after stroke onset.

Methods—Forty-two patients with acute, severe hemispheric stroke were enrolled. Cranial computed tomography (CCT) and extracranial duplex sonography were performed on admission. TCCS was carried out 8 ± 3, 16 ± 3, 24 ± 3, 32 ± 3, and 40 ± 3 hours after stroke onset. Lesion size was determined from follow-up CCT.

Results—Twelve patients died as the result of cerebral herniation (group 1); 28 survived (group 2). Two patients received decompressive hemicraniectomy and were therefore excluded from further evaluation. MLS was significantly higher in group 1 as early as 16 hours after onset of stroke. Specificity and positive predictive values for death caused by cerebral herniation of MLS ≥ 2.5, 3.5, 4.0, and 5.0 mm after 16, 24, 32, and 40 hours were 1.0.

Conclusions—TCCS helps to estimate outcome as early as 16 hours after stroke onset and thus facilitates identification of patients who are unlikely to survive without decompressive craniectomy. Because of its noninvasive character and bedside suitability, sonographic monitoring of MLS might be a useful tool in management of critically ill patients who cannot undergo repeated CCT scans. (Stroke. 2001;32:442-447.)

Key Words: brain edema ■ cerebral infarction ■ stroke outcome ■ ultrasonography, Doppler, duplex

Transcranial color-coded duplex sonography (TCCS) allows imaging of intracranial arteries, veins, and parenchymal structures.1–4 Because of its noninvasive character and suitability for bedside application, TCCS can be used in the acute phase of stroke and for repeated monitoring at short intervals even in critically ill patients. It reveals reliable information regarding the lateral displacement of the third ventricle as a criterion for midline shift (MLS) in space-occupying hemispheric stroke.5–8 Lateral displacement of midline structures resulting from progressive postischemic edema has been found to correlate closely with a poorer outcome in stroke patients.5–9,10–14 In a subgroup of stroke patients with rapid progressive edema, the mortality rate reaches 80% as the result of axial brain stem herniation.15,16 Several open, prospective studies indicate that decompressive hemicraniectomy can decrease mortality rates up to 50% in so-called “malignant” middle cerebral artery (MCA) stroke, that is, postischemic edema unresponsive to treatment.17–19 Nevertheless, patient selection and an optimal timing are crucial for this therapy: Early surgical intervention can prevent irreversible damage to adjacent brain structures and improve outcome but may be performed on patients who would not have required this invasive procedure. Thus, an early predictor of stroke outcome, suitable as well for patients who cannot be assessed clinically, is of utmost importance.

In a recent study, sonographic assessment of MLS 32 ± 4 hours after stroke onset was shown to identify MCA stroke patients who are unlikely to survive.7 Furthermore, horizontal displacement of the septum pellicudum and the pineal gland, derived from cranial computed tomography (CCT) scans, is used as an inclusion criterion in a randomized trial testing hemicraniectomy versus medical therapy in severe hemispheric stroke (Derk W. Krieger, MD, personal communication, 2000).

The purpose of this study was to evaluate the temporal dynamics of MLS in hemispheric stroke patients in short intervals within the first 40 hours. We hypothesized that measurement of MLS at defined time intervals may serve as an early outcome predictor and facilitates indication for aggressive treatments such as hypothermia or decompressive hemicraniectomy.

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Subjects and Methods

Patients and General Study Design

Forty-two consecutive patients (31 men, 11 women; mean age, 61.0 years; SD 14) with acute, severe MCA territory stroke were enrolled prospectively in this study. Patients were included within 16 hours after onset of stroke if the exact time of symptom onset was known (±30 minutes). Patients with a Scandinavian stroke scale (SSS) >35 on admission were excluded from this study.20

Neurosonologic Methods

Extracranial color-coded duplex sonography of the brain-supplying arteries was performed on admission (Hewlett Packard; SONOS 2000 or 5500; 5.0-MHz sector and 7.5-MHz linear scanner). TCCS was performed by 3 investigators through the transtemporal acoustic bone window with the use of a 2.5-MHz sector scanner as described earlier.3 Angle-corrected systolic and diastolic blood flow velocity of the MCA and the supraclinoid part of the internal carotid artery was obtained from the ipsilateral and contralateral sides. By tilting the ultrasound probe ≈10 degrees upward, the third ventricle could be displayed at a depth of 6 to 8 cm. This structure was easily identified by its hyperechogenic margins, the surrounding hyperechogenic thalamus, and the hyperechogenic pineal gland. The distance between the TCCS probe and the center of the third ventricle was measured in a line perpendicular to the walls of the third ventricle (Figure 1) from both the ipsilateral (A) and contralateral (B) sides, and the deviation from the presumed midline was calculated by the equation MLS = (A - B)/2.

TCCS was carried out 8±3, 16±3, 24±3, 32±3, and 40±3 hours after stroke onset.

Computed Tomography

CCT was performed on admission to exclude patients with intracerebral hematoma and during the first 2 weeks to determine the size of the infarct. Diagnosis of old territorial infarcts (>1.5 cm) and space-occupying bleeding complications during the first 40 hours after stroke were exclusion criteria for this study. MLS was calculated from follow-up images if the time delay between CCT and TCCS was <6 hours, in a fashion analogous to that of TCCS by measuring the distance between the external tabula of the skull to the middle of the third ventricle on both sides, with the use of the previously stated formula. CCT examiners were blinded to TCCS findings and vice versa.

Statistics

Sensitivity, specificity, and predictive values were calculated from cross-tables. MLS of patients in both outcome groups (death versus survival) were compared by a nonparametric test for unrelated samples (Mann-Whitney U test). Differences in sex, age, and extracranial and intracranial vascular status were tested by Fisher’s exact test. MLS values obtained from TCCS and CCT images were compared by linear regression analysis. Significance was assigned for values of P<0.05.

Results

Median SSS on admission was 16.4–35 TCCS allowed examination of the MCA in 40 of 42 patients (95.2%) and imaging of the third ventricle in all patients. Duplex sonography revealed MCA occlusion in 31 of 40 patients (82.5%) and carotid T occlusion in 16 of 40 patients (40.0%). Intravenous thrombolysis according to the ECASS II protocol was carried out in 9 patients (21.4%). Recanalization of MCA occlusion was observed in 5 of 9 patients after thrombolysis and in 7 of 22 conservatively treated patients 10.5 hours (mean, 3.25 to 23.75) and 21.1 hours (mean, 9 to 35.5) after onset of stroke.

Follow-up CCT demonstrated infarction of <50% of the MCA territory in 9 and >50% in 33 patients. In 5 patients, an additional anterior or posterior cerebral artery infarction was found. Sixteen of 42 patients (38.1%) were sedated and artificially ventilated during the first 48 hours.

Thirty-eight CCT images were performed within 6 hours before or after a TCCS examination. Mean MLS was 1.18 mm (SD 1.15) on CCT and 1.25 mm (SD 1.30) on TCCS images. The difference of MLS between both methods was ±0.075 mm in 31 (81.6%), 0.75 to 1.5 mm in 6 (15.8%), and >1.5 mm in 1 (2.6%) data pairs. MLS values correlated well with both imaging techniques (r=0.88; P<0.0001).

Twelve patients (28.6%) died secondary to cerebral herniation with clinical signs of rostrocaudal deterioration such as decerebral posturing or pupillary dilation and no other cause of death (group 1). Death occurred between 24 and 168 hours after onset of stroke (mean, 78.3 hours). Median SSS on admission was 10 (range, 4 to 30). Twenty-eight patients (71.4%) survived (group 2; median SSS =16; range, 4 to 35). The difference of SSS on admission was not significant between both groups (P>0.05). Two men received decompressive hemicraniectomy 27 and 30 hours after stroke and survived. Both were excluded from further statistical evaluation.

MLS monitoring was possible in 33, 29, 26, 29, and 23 patients in each 8-hour time interval. Data are presented in Table 1 and Figure 2. Missing values were due to admission after >11 hours, performance of other diagnostic or therape-
animal studies,26-28 the benefit of this therapy in patients is still under debate.16,18,29-32 For appropriate patient selection, treatment procedures within an examination time interval, or death. MLS was significantly higher in patients who died compared with survivors 16, 24, 32, and 40 hours after onset of stroke but not after 8 hours. Specificity and positive predictive values (PPV) of MLS of 1.25, 2.5, 3.5, 4.0, and 5.0 mm were 1.0 (Table 2).

No statistically significant differences were found between both groups concerning sex (P>0.1), age (P>0.1), MCA occlusion (P>0.1), and carotid T occlusion (P>0.1). There was a nonsignificant trend toward a better outcome after early (within 12 hours; P=0.06) as well as late MCA recanalization (within 40 hours; P=0.06). Death caused by herniation occurred significantly more often in patients with an infarct size >50% of the MCA territory depicted by late follow-up CCT (P<0.05; Fisher’s exact test).

**Discussion**

Within the first days after onset of stroke, postischemic vasogenic brain edema with subsequent cerebral herniation is the most common cause of death.21-25 Although decompressive hemicraniectomy has been shown to be effective in animal studies,26-28 the benefit of this therapy in patients is still under debate.16,18,29-32 For appropriate patient selection and an optimal timing of therapy, an early and reliable predictor of outcome is crucial.

**Midline Shift**

The first to describe a method for measuring MLS by means of TCCS were Seidel and coworkers in 1996. Various studies evaluated its reliability in revealing information regarding the diameter and lateral displacement of the third ventricle. A comparative study revealed a high correlation of the diameter of the third ventricle depicted by CCT and TCCS (r=0.96).33 Seidel et al demonstrated a good interobserver and intraobserver reproducibility for determining the diameter of the third ventricle on TCCS images. The correlation of MLS apparent on CCT and TCCS in this study is in agreement with various other studies that report correlation coefficients between 0.87 and 0.93.5,6,8 Concerning the precision of sonographic MLS measurement, Stolz et al reported a ±0.89-mm, 2-SD confidence interval of TCCS findings compared with CCT. It is likely, however, that the CCT measurements in these studies contain some error because they were based on manual readings of the CCT scans and thus that the precision of the sonographic MLS measurements was underestimated.

The comparison between CCT and TCCS revealed a marked discrepancy in 1 of 38 examinations (TCCS, 4.35 mm; CCT, 6.1 mm). In this patient, a severe compression of the third ventricle was visible on the CCT image, which probably led to difficulties in identification of this structure on the TCCS images.

In this study, patients with large hemispheric stroke were prospectively investigated. Other midline structures such as the pineal gland or the septum pellucidum have not been monitored because of their poor display on TCCS scans. Nevertheless, there is a close correlation of the lateral displacement of the septum pellucidum and the pineal gland (r=0.82) as demonstrated on CCT.12 TCCS findings were monitored in 8-hour time intervals during the first 40 hours after onset of stroke. Extracranial vascular status was investigated on admission with duplex sonography. TCCS proved to be a reliable method in assessing intracranial vessel occlusion and was used for assessment of MCA occlusion and recanalization on follow-up.

Twelve patients died as the result of cerebral herniation; 28 survived. Death occurred after day 1 and before day 7 (mean, 3.3 days); 4 of 12 patients (33%) died within the first 48 hours. This clinical course is representative and agrees with clinicopathological16,23,24 and epidemiological studies,25 where 19% to 47% of all deaths caused by herniation occurred significantly more often in patients with an infarct size >50% of the MCA territory depicted by late follow-up CCT (P<0.05; Fisher’s exact test).

**TABLE 2. Results: Sensitivity, Specificity, and Predictive Values**

<table>
<thead>
<tr>
<th>TCCS</th>
<th>Time, h</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLS &gt;1.25 mm</td>
<td>8±3</td>
<td>0.56</td>
<td>0.83</td>
<td>0.56</td>
<td>0.83</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>MLS &gt;2.5 mm</td>
<td>16±3</td>
<td>0.83</td>
<td>1.00</td>
<td>1.00</td>
<td>0.96</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLS &gt;3.5 mm</td>
<td>24±3</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLS &gt;4.0 mm</td>
<td>32±3</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLS &gt;5.0 mm</td>
<td>40±3</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, and predictive values of MLS of 1.25, 2.5, 3.5, 4.0, and 5.0 mm, indicating fatal outcome 8, 16, 24, 32, and 40 hours after stroke.

Probability values indicate statistical difference of MLS between patients who died and those who survived.
occurred within 48 hours after onset of stroke. Silver and coworkers\(^\text{21}\) analyzed the course of 38 patients with malignant MCA infarction whose cause of death was transtentorial herniation. They reported no deaths occurring within the first 24 hours or after day 10. Furthermore, our results concur with a clinicopathological study, where MLS, as a measure of brain edema, reaches a maximum between day 2 and day 4 after stroke onset.\(^\text{23}\)

Two patients of our cohort survived after decompressive hemicraniectomy. MLS of one patient exceeded 3.5 mm after 24 hours (Figure 2), giving anecdotal evidence that hemicraniectomy can be a life-saving therapy in space-occupying stroke.\(^\text{22}\)

MLS differed significantly between both outcome groups as early as 16 hours after onset of stroke. For calculation of sensitivity, specificity, and predictive values, we set limiting values for MLS to 1.25 mm after 8 hours, 2.5 mm after 16 hours, 3.5 mm after 24 hours, 4.0 mm after 32 hours, and 5.0 mm after 40 hours to obtain a maximum PPV. In agreement with our previous study,\(^\text{7}\) all patients with a MLS >4 mm after 32 hours died (PPV=1.0). In addition, the present study demonstrates that MLS is a reliable outcome measure even as early as 24 and 16 hours (PPV=1.0 and 1.0) after onset of symptoms. Nevertheless, the difference of 1.4 and 1.0 mm between the highest MLS of survivors and the lowest fatal MLS at 24 and 32 hours indicates a certain overlap between survivors and fatalities.

Besides horizontal shift, vertical displacement has also been shown to be relevant for survival. Horizontal rather than downward displacement is closely related to the level of consciousness.\(^\text{11,14}\) Downward displacement is also important, although it does not correlate well with outcome.\(^\text{38,39}\) It is clearly an advantageous coincidence that horizontal displacement can be depicted accurately by means of TCCS.\(^\text{5}\)

Our findings agree with those of Pullicino and coworkers,\(^\text{12}\) who evaluated lateral displacement of the pineal gland by using CCT scans performed between 0 and 48 hours after the onset of clinical symptoms; they found a specificity of 0.89 and a sensitivity of 0.46 for predicting patient 14-day mortality rates. Displacement >4 mm was associated with a low probability of 14-day survival, although the relation between time of stroke onset and time of CCT scan was not precisely defined. Haring et al\(^\text{13}\) found a low sensitivity (0.19) but a high specificity (0.97) of MLS-obtained CT scans within the first 18 hours after stroke onset for the development of malignant MCA infarction. In contrast, various other studies with less clearly defined time points of measurements could not find a positive correlation between MLS and outcome (Table 3).

We conclude that MLS measurements performed very early (ie, within the first 16 hours from stroke onset) or not strictly correlated with time after infarct fail to predict fatal outcome in patients with severe MCA infarctions.

### Clinical Scores

In our previous study,\(^\text{7}\) we found no significant difference in modified SSS between patients who died and those who survived 32 hours after stroke, whereas MLS differed significantly between both groups at this time point. This suggests that MLS measurements might predict outcome earlier than clinical findings. In the present study, SSS on admission again did not correlate with outcome. These results are in accordance with findings of other groups who could not find an association between clinical scores on admission and fatal outcome.\(^\text{13,15,16}\) On the contrary, Berrouschot et al\(^\text{41}\) reported a good correlation between an SSS <27 on admission and fatal outcome (P<0.001) but with a moderate sensitivity and specificity of SSS on admission for predicting cerebral herniation of 0.73 and 0.74.

In the present study, assessment of SSS during follow-up was not possible in 16 patients because of sedation and artificial ventilation, resulting in a selection bias. Thus, we did not compare the time course of MLS and SSS. This reflects a common problem in the clinical assessment of critically ill stroke patients. Clinical scores are of limited help in predicting outcome in patients with severe MCA stroke who require ventilator therapy.

### Cerebrovascular Status

Several studies have demonstrated the significance of the cerebrovascular status as an early predictor of functional outcome. Patency of the MCA was identified as an independent predictor of early improvement,\(^\text{42,43}\) whereas diminished blood flow velocity or occlusion of the MCA predicted early

### TABLE 3. Literature Review: Significance of MLS for Indicating Fatal Outcome in Patients With Hemispheric Stroke

<table>
<thead>
<tr>
<th>MLS Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum MLS(^\text{15})</td>
<td>0–120</td>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>MLS on admission(^\text{16})</td>
<td>0–12</td>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>MLS present/absent(^\text{13})</td>
<td>0–18</td>
<td>0.19</td>
<td>0.97</td>
<td>0.86</td>
<td>0.55</td>
<td>62 vs 62</td>
</tr>
<tr>
<td>MLS on admission(^\text{16})</td>
<td>0–24</td>
<td></td>
<td></td>
<td></td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>MLS &gt;4 mm(^\text{12})</td>
<td>0–48</td>
<td>0.46</td>
<td>0.89</td>
<td></td>
<td></td>
<td>118</td>
</tr>
<tr>
<td>MLS after 10 h(^\text{7})</td>
<td>7–13</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>MLS &gt;4 mm after 32 h(^\text{7})</td>
<td>28–36</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

*Time interval after stroke onset in which measurement was performed. †Case-control study: fatal outcome vs survival. ‡Horizontal shift of septum pellucidum. §Lateral and vertical shift of pineal gland and horizontal shift of septum pellucidum. ¶Lateral displacement of the third ventricle obtained from TCCS scans.
deterioration. An association between normalization of MCA blood flow and a better functional outcome has been reported in several studies. In the present study, the vascular status on admission failed to predict fatal outcome. This discrepancy may be due to differences in the chosen outcome measures. Functional outcome scores (CNS, NIHSS, ESS, and modified Rankin scale) were used in the above-mentioned studies, whereas we differentiated between death and survival within the first 2 weeks because of the considerable number of severely impaired patients on ventilator therapy who were not clinically assessable.

In contrast to others who found a good correlation between vascular status on admission and recanalization (P<0.001 and P<0.01) and who reported a high sensitivity, specificity, PPV, and negative predictive value (NPV) (0.53, 0.83, 0.47, and 0.85) for the diagnosis of a carotid T occlusion in predicting fatal outcome, we only found a vague correlation for early (<24 hours) or late (≥24 hours) recanalization of the occluded MCA (P=0.06) and no correlation for vascular findings on admission (P>0.1).

CCT Findings
Several studies indicate a good correlation between early CCT signs of cerebral ischemia and outcome. PPVs for indicating fatal outcome range from 0.36 to 1.00. We to estimate outcome as early as 16 hours after stroke onset and cannot otherwise be monitored adequately. TCCS helps its noninvasive character and suitability for bedside applicability. Findings suggest that TCCS monitoring of MLS, because of its noninvasive character and suitability for bedside application, is a diagnostic alternative in critically ill patients, who are not able to cooperate, not fit for repeated transportation, and cannot otherwise be monitored adequately. TCCS helps to estimate outcome as early as 16 hours after stroke onset and thus facilitates identification of patients who are unlikely to survive without decompressive craniectomy.

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