Prediction of Malignant Middle Cerebral Artery Infarction by Early Perfusion- and Diffusion-Weighted Magnetic Resonance Imaging

Götz J. Thomalla, MD; Thomas Kucinski, MD; Volker Schoder, MSc; Jens Fiehler, MD; Rene Knab, MSc; Herrmann Zeumer, MD; Cornelius Weiller, MD; Joachim Röther, MD

Background and Purpose—We tested the hypothesis that early diffusion- and perfusion-weighted MRI (DWI and PWI, respectively) allows the prediction of malignant middle cerebral artery (MCA) infarction (MMI).

Methods—Thirty-seven patients with acute MCA infarction and proximal vessel occlusion (carotid-T, MCA main stem) were studied by DWI, PWI, and MR angiography within 6 hours of symptom onset. Eleven patients developed MMI, defined by decline of consciousness and radiological signs of space-occupying brain edema. Lesion volumes were retrospectively defined as apparent diffusion coefficient \(<80\%\) (ADC<sub>core</sub>) and time to peak \(>4\) seconds (TTP<sub>4s</sub>) compared with the unaffected hemisphere. ADC decrease within the infarct core (ADC<sub>core</sub>) and relative ADC within the ADC<sub><30%</sub> lesion (rADC<sub>lesion</sub>) were measured. Neurological deficit at admission was assessed with the National Institutes of Health Stroke Scale (NIHSS).

Results—Patients with MMI showed larger ADC<sub>core</sub> (median, 157 versus 22 mL; \(P<0.001\)) and TTP<sub>4s</sub> (208 versus 125 mL; \(P<0.001\)) lesion volumes, smaller TTP/ADC mismatch ratio (1.5 versus 5.5; \(P<0.001\)), lower ADC<sub>core</sub> values (290 versus 411 mm<sup>2</sup>/s; \(P<0.001\)), lower rADC<sub>lesion</sub> (0.60 versus 0.66; \(P=0.001\)), higher frequency of carotid-T occlusion (64\% versus 15\%; \(P=0.006\)), and higher NIHSS score at admission (20 versus 15; \(P=0.001\)). Predictors of MMI were as follows for sensitivity and specificity, respectively: ADC<sub><30%</sub> >82 mL, 87\%; TTP<sub>4s</sub> >162 mL, 83\%, 75\%; TTP/ADC mismatch ratio <2.4, 80\%, 79\%; ADC<sub>core</sub> <300 mm<sup>2</sup>/s, 83\%, 85\%; rADC<sub>lesion</sub> <0.62, 79\%, 74\%; and NIHSS score at admission \(\geq 19\), 96\%, 72\%.

Conclusions—Quantitative analysis of early DWI and PWI parameters allows the prediction of MMI and can help in the selection of patients for aggressive tissue-protective therapy. (Stroke. 2003;34:1892-1900.)

Key Words: brain edema • magnetic resonance imaging, diffusion-weighted • magnetic resonance imaging, perfusion-weighted • stroke, acute

Large infarctions in the middle cerebral artery (MCA) territory may develop space-occupying brain edema, leading to midline shift, raised intracranial pressure, and herniation.\(^1,2\) The clinical course in these patients is characterized by deterioration of consciousness and signs of brain stem herniation usually occurring within 2 to 5 days.\(^2,3\) This subgroup of MCA strokes has been labeled malignant MCA infarction (MMI).\(^4\)

Whereas mortality in overall acute MCA stroke ranges between 5\% and 25\%,\(^5-7\) mortality of large MCA infarction varies between 40\% and 100\%.\(^3,5-7,10\) Conservative treatment results in mortality rates of approximately 80\%.\(^3,8\) Therefore, aggressive therapeutic approaches are recommended for this group of patients.

Decompressive craniectomy has been shown to reduce mortality and to improve outcome in patients with MMI in several case series\(^10,11\) (see Steiner et al\(^12\) for review). There is some evidence that early craniectomy is more effective than decompression at later time points. In a prospective case series, a stepwise reduction of time between stroke onset and surgery from 39 to 21 hours resulted in a further reduction of mortality from 27\% to 16\%.\(^11\) Therefore, the early identification of patients likely to develop MMI appears crucial.

A number of possible predictors of MMI have been identified, as follows: (1) clinical and/or laboratory findings such as coma on admission\(^13\); nausea, vomiting, or systolic blood pressure >180 mm Hg within the first 24 hours\(^14\); and history of hypertension, history of heart failure, or elevated white blood cell count\(^9\); (2) cranial CT (CCT) findings such as major early signs of ischemia covering >30\%\(^15\) or >50\% MCA territory,\(^9,14,16,17\) CCT lesion volume >240 mL\(^18\) or >400 mL,\(^13\) hyperdense MCA sign,\(^6\) local brain swelling,\(^17\) or midline shift\(^11\); (3) angiographic findings such as carotid-T occlusion\(^15\); (4) perfusion parameters such as cerebral blood

Received January 21, 2003; final revision received March 20, 2003; accepted April 11, 2003.

From the Klinik und Poliklinik für Neurologie (G.J.T., R.K., C.W., J.R.); Neuroradiologische Abteilung, Klinik und Poliklinik für Radiologie (T.K., J.F., H.Z.); and Institut für Mathematik und Datenverarbeitung in der Medizin (V.S.), Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.


Correspondence to Götz Thomalla, MD, Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg-Eppendorf, Martinistraße 52, D-20246 Hamburg, Germany. E-mail: thomalla@uke.uni-hamburg.de

© 2003 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000081985.44625.B6
flow measured by xenon CT\textsuperscript{19} or \textsuperscript{99m}technetium-ethylcysteinate-dimer single-photon emission CT\textsuperscript{20}; and (5) MRI findings such as diffusion lesion volume \textgreater 145 mL within 14 hours of symptom onset and apparent diffusion coefficient (ADC) decrease in different regions of interest (ROIs).\textsuperscript{21}

Multiparametric MRI has been proposed as a new diagnostic standard of acute stroke management.\textsuperscript{22,23} Acute stroke MRI combining diffusion- and perfusion-weighted MRI (DWI and PWI, respectively), MR angiography (MRA), and heme-sensitive MR images (T2* -weighted images) supplies information on ischemic tissue (DWI), perfusion deficit (PWI), and vessel occlusion (MRA) and detects intracerebral hemorrhage (T2*-weighted images) within 1 session with examination times of \textless 20 minutes.\textsuperscript{24–28} We tested the hypothesis that acute stroke MRI provides parameters that allow the prediction of MMI within the first 6 hours of stroke onset.

**Subjects and Methods**

**Patients**

We retrospectively analyzed data of patients admitted to our hospital from January 2000 to November 2001 for the diagnosis of acute stroke. Inclusion criteria were as follows: (1) acute MCA stroke with well-defined onset; (2) stroke MRI (PWI, DWI, MRA) performed within 6 hours of symptom onset; and (3) proximal vessel occlusion (carotid-T or MCA main stem occlusion) shown by MRA. Patients enrolled in randomized trials of neuroprotective agents or thrombolytic drugs were excluded from the analysis.

Diagnosis of MMI was based on clinical course and follow-up imaging (CCT or MRI) according to the following criteria: (1) secondary neurological deterioration including at least decline of consciousness as defined by 1 or more points on the level of consciousness item of the National Institutes of Health Stroke Scale (NIHSS) and (2) large space-occupying MCA infarction on follow-up MRI or CCT (covering more than two thirds of the MCA territory with compression of ventricles or midline shift) assessed in consensus by an experienced neurologist (J.R.) and neuroradiologist (T.K.). All patients were admitted to the stroke unit or neurological intensive care unit. Patients were treated by intravenous or intra-arterial thrombolysis according to Second European-Australasian Acute Stroke Study Investigators (ECASS II)\textsuperscript{29} or Prolyse in Acute Cerebral Thromboembolism (PROACT II)\textsuperscript{30} criteria. Decompressive hemicraniectomy was performed in consensus by an experienced neurologist and neurosurgeon according to an institutional protocol.

**Clinical Assessment**

Severity of neurological deficit at admission was assessed by a neurologist using the NIHSS.\textsuperscript{31} Outcome was assessed with the Barthel Index\textsuperscript{32} and the modified Rankin Scale\textsuperscript{33} at day 90. Etiology of stroke was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.\textsuperscript{34}

**MRI Protocol**

MRI studies were performed with a 1.5-T scanner equipped with a 20-mT/m gradient system (Magnetom Symphony, Siemens). DWI, PWI, T2*-weighted imaging, fluid-attenuated inversion recovery (FLAIR) sequence, and a time-of-flight MRA were acquired within a standardized protocol within approximate 20 minutes. Details of the MRI protocol and the postprocessing procedure were reported recently.\textsuperscript{35} Diagnosis of vessel occlusion was based on MRA and dichotomized into carotid-T and MCA main stem occlusion. Occlusion of the extracranial internal carotid artery with accompanying MCA main stem occlusion was classified as MCA main stem occlusion. Examples of MRI studies are shown in the Figure.

**A:** NIHSS 14, MRI 1.5 h after symptom onset, i.v. thrombolysis, non MMI

A Patient with severe right hemiparesis and aphasia (NIHSS score 14). MRI 1.5 hours after symptom onset reveals a large PWI/DWI mismatch with a small diffusion lesion in the left basal ganglia (DWI, ADC) and a large area of hypoperfusion (TTP). MRA shows left M1 occlusion. Patient was treated by intravenous thrombolysis. FLAIR at day 1 shows only a small striatocapsular infarction. B, Patient with right hemiplegia, complete aphasia, and somnolence (NIHSS score 21). MRI 2 hours after symptom onset reveals a large diffusion lesion (DWI, ADC), a perfusion lesion covering the entire MCA territory (TTP), and no relevant PWI/DWI mismatch. MRA shows left carotid-T occlusion. DWI 5 hours after initial MRI reveals further lesion growth. Patient developed malignant MCA infarction and was treated with hemicraniectomy 24 hours after stroke onset. T2-WI indicates T2-weighted imaging.
Volume Measurement and ROI Analysis

Diffusion and perfusion lesion volumes were measured on ADC and time to peak (TTP) maps with a semiautomatic threshold procedure. First, the average ADC value of the unaffected hemisphere was determined with an upper threshold of ADC/H$_1$ $\geq$ 1000 mm$^2$/s to eliminate partial volume effects resulting from high ADC values from cerebrospinal fluid. Second, the lesion area was traced manually with a generous safety margin. Third, a threshold function was applied within this area with the use of an 80% threshold of the contralateral mean ADC. A similar procedure was performed on the TTP maps, first defining the mean TTP of the unaffected hemisphere, then tracing the visible lesion, and finally applying a threshold of a TTP delay of 4 seconds compared with the contralateral mean TTP for each slice. Pixel numbers resulting from this procedure were multiplied with voxel size to obtain ADC/80% lesion volumes. TTP/ADC mismatch ratio (ADC/80%/TTP/$\leq$ 4s) was calculated. The readers of the MRI scans (G.J.T. and T.K.) were blinded to the clinical status of the patients.

ADC changes were assessed in different ROIs as previously suggested. ADC decrease within the infarct core (ADC$_{core}$) was measured in a 9 $\times$ 9-voxel ROI centered in the area with the smallest ADC values within the infarct core. Relative ADC within the ADC$_{80%}$ lesion (rADC$_{80%}$) was calculated as the mean ADC value within the ADC$_{80%}$ lesion compared with the mean ADC in the unaffected hemisphere.

Statistical Analysis

Patients were divided into MMI and non-MMI patients. Data are presented as median (range) for continuous variables and counts (percentage) for categorical variables. The 2 groups were compared for demographic, clinical, and MRI parameters with the Mann-Whitney $U$ test for continuous parameters and Fisher exact test for categorical variables (SPSS 9.0.1, SPSS Inc). All probability values are interpreted descriptively in the context of an exploratory data analysis. For parameters that showed group differences with $P < 0.01$, conventional binormal receiver operating characteristic (ROC) analysis was performed with the use of statistical software (ROCKIT 0.9B; www.radiology.uchicago.edu/klar/t toppage11.html). From these curves, sensitivity, specificity, positive predictive values, and negative predictive values for the prediction of MMI were calculated. Thresholds result from the smoothed ROC curves and were chosen to maximize sensitivity and specificity equally. Addi-

### Table 1. Demographic and Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>MMI ($n$=11)</th>
<th>Non-MMI ($n$=26)</th>
<th>Group Comparison</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [y], median (range)</td>
<td>60 (38–89)</td>
<td>61 (39–89)</td>
<td></td>
<td>0.46*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>6 (54)</td>
<td>8 (33)</td>
<td></td>
<td>0.16†</td>
</tr>
<tr>
<td>Left MCA infarction, n (%)</td>
<td>7 (64)</td>
<td>20 (77)</td>
<td></td>
<td>0.33†</td>
</tr>
<tr>
<td>NIHSS at admission, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>20 (19–25)</td>
<td>15 (8–24)</td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>Right MCA infarction</td>
<td>20.5 (19–25)</td>
<td>11.5 (8–22)</td>
<td></td>
<td>0.08*</td>
</tr>
<tr>
<td>Left MCA infarction</td>
<td>20 (19–23)</td>
<td>15.5 (8–24)</td>
<td></td>
<td>0.02*</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>3 (27)</td>
<td>8 (31)</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>4 (36)</td>
<td>11 (42)</td>
<td></td>
<td>0.52†</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td></td>
<td>0.49†</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>4 (36)</td>
<td>5 (19)</td>
<td></td>
<td>0.24†</td>
</tr>
<tr>
<td>Infarct classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete MCA territory</td>
<td>8 (73)</td>
<td>1 (4)</td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Deep+ superficial MCA territory (incomplete)</td>
<td>3 (27)</td>
<td>15 (58)</td>
<td>0.09†</td>
<td></td>
</tr>
<tr>
<td>Striatocapsular infarction</td>
<td>0 (0)</td>
<td>7 (27)</td>
<td></td>
<td>0.06†</td>
</tr>
<tr>
<td>Superficial MCA territory</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td></td>
<td>0.34†</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolyis</td>
<td>2 (18)</td>
<td>16 (62)</td>
<td></td>
<td>0.02†</td>
</tr>
<tr>
<td>Intra-arteral thrombolyis</td>
<td>1 (9)</td>
<td>4 (15)</td>
<td></td>
<td>0.52†</td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>7 (64)</td>
<td>…</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid-T occlusion, n (%)</td>
<td>7 (64)</td>
<td>4 (15)</td>
<td></td>
<td>0.006†</td>
</tr>
<tr>
<td>Time from symptom onset to MRI (min), median (range)</td>
<td>210 (100–300)</td>
<td>168 (90–285)</td>
<td>0.27*</td>
<td></td>
</tr>
<tr>
<td>Time to MRI $\leq$ 3 h, n (%)</td>
<td>5 (46)</td>
<td>17 (65)</td>
<td>0.35†</td>
<td></td>
</tr>
<tr>
<td>Outcome parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRS, median (range)</td>
<td>4 (3–6)</td>
<td>1 (0–6)</td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BI, median (range)</td>
<td>13 (0–45)</td>
<td>100 (0–100)</td>
<td></td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Mann-Whitney $U$ test; †Fisher’s exact test.
Five of these patients were excluded for the following reasons: early death due to cardiac failure (n=1) and enrollment in randomized clinical trials (n=4; 1 of these patients developed MMI). Sixty-three patients did not meet the inclusion criteria: in 43 patients MRA showed only MCA branch or no vessel occlusion and in 19 patients the MRI protocol was incomplete (2 of these developed MMI). One patient had symptomatic hemorrhage after intravenous thrombolysis; this patient was not categorized as having MMI. Thirty-seven patients were finally included; 11 developed MMI, and 26 did not.

Demographic and clinical features are summarized in Tables 1 and 2. MMI and non-MMI patients were similar regarding age, sex, side of infarction, etiology, and time from symptom onset to MRI. The number of infarctions covering the complete MCA territory was higher in the MMI group (73% versus 4%). Patients with MMI presented with higher NIHSS score at admission (20 versus 15; \(P=0.001\)) and a higher frequency of carotid-T occlusion (64% versus 15%; \(P=0.006\)). A greater number of patients were treated by thrombolysis in the non-MMI group. Clinical outcome at 3 months was worse in the MMI group, with all surviving patients being dependent compared with a large number of independent patients in the non-MMI group (modified Rankin Scale score, 4 versus 1 \([P<0.001]\); Barthel Index score, 13 versus 100 \([P=0.001]\)).

Within the MMI group, 7 patients were treated with hemicraniectomy 6 to 36 hours from symptom onset (≤12 hours in 5 patients, 13 to 36 hours in 2 patients). Four patients were treated conservatively. All patients treated with hemicraniectomy survived, with modified Rankin Scale score of 3 to 4 (median, 4) at day 90. Three of the 4 conservatively treated patients died 2 to 7 days after onset; the surviving patient presented at day 90 with a modified Rankin Scale score of 4 (see Tables 1 and 2 for clinical data of MMI patients).

Patients with MMI showed larger ADC_{core} lesion volumes (157 versus 22 mL; \(P<0.001\)), more extensive TTP_{>4s}/ADC_{core} mismatch ratio (1.5 versus 5.5; \(P<0.001\)) (Table 3). ADC_{core} (290 versus 411 mm²/s; \(P<0.001\)) and rADC_{lesion} (0.60 versus 0.66; \(P=0.001\)) were lower in MMI patients.

The following MRI parameters predicted MMI with high sensitivity and specificity (Table 4): ADC_{core>82} >82 mL (87% sensitivity; 91% specificity), TTP_{>4s}/ADC_{core} mismatch ratio <2.4 (80% sensitivity; 79% specificity), TTP/ADC mismatch ratio <1.5 (80% sensitivity; 74% specificity), and rADC_{lesion} <0.62 (79% sensitivity; 74% specificity). NIHSS score at admission ≥19 appeared to predict MMI with high sensitivity (96%) but rather low specificity (72%). Carotid-T occlusion seemed to be only a moderate predictor with only 64% sensitivity but rather low specificity (72%).

### Results

Within the study period, 105 patients with acute MCA stroke and well-defined symptom onset were studied by MRI within the first 6 hours. Forty-two patients met the inclusion criteria. Within the study period, 105 patients with acute MCA stroke were treated in our hospital; 43 patients MRA showed only MCA branch or no vessel occlusion and in 19 patients the MRI protocol was incomplete (2 of these developed MMI). One patient had symptomatic hemorrhage after intravenous thrombolysis; this patient was not categorized as having MMI. Thirty-seven patients were finally included; 11 developed MMI, and 26 did not.

Demographic and clinical features are summarized in Tables 1 and 2. MMI and non-MMI patients were similar regarding age, sex, side of infarction, etiology, and time from symptom onset to MRI. The number of infarctions covering the complete MCA territory was higher in the MMI group (73% versus 4%). Patients with MMI presented with higher NIHSS score at admission (20 versus 15; \(P=0.001\)) and a higher frequency of carotid-T occlusion (64% versus 15%; \(P=0.006\)). A greater number of patients were treated by thrombolysis in the non-MMI group. Clinical outcome at 3 months was worse in the MMI group, with all surviving patients being dependent compared with a large number of independent patients in the non-MMI group (modified Rankin Scale score, 4 versus 1 \([P<0.001]\); Barthel Index score, 13 versus 100 \([P=0.001]\)).

Within the MMI group, 7 patients were treated with hemicraniectomy 6 to 36 hours from symptom onset (≤12 hours in 5 patients, 13 to 36 hours in 2 patients). Four patients were treated conservatively. All patients treated with hemicraniectomy survived, with modified Rankin Scale score of 3 to 4 (median, 4) at day 90. Three of the 4 conservatively treated patients died 2 to 7 days after onset; the surviving patient presented at day 90 with a modified Rankin Scale score of 4 (see Tables 1 and 2 for clinical data of MMI patients).

Patients with MMI showed larger ADC_{core} lesion volumes (157 versus 22 mL; \(P<0.001\)), more extensive TTP_{>4s}/ADC_{core} mismatch ratio (1.5 versus 5.5; \(P<0.001\)) (Table 3). ADC_{core} (290 versus 411 mm²/s; \(P<0.001\)) and rADC_{lesion} (0.60 versus 0.66; \(P=0.001\)) were lower in MMI patients.

The following MRI parameters predicted MMI with high sensitivity and specificity (Table 4): ADC_{core>82} >82 mL (87% sensitivity; 91% specificity), TTP_{>4s}/ADC_{core} mismatch ratio <2.4 (80% sensitivity; 79% specificity), TTP/ADC mismatch ratio <1.5 (80% sensitivity; 74% specificity), and rADC_{lesion} <0.62 (79% sensitivity; 74% specificity). NIHSS score at admission ≥19 appeared to predict MMI with high sensitivity (96%) but rather low specificity (72%). Carotid-T occlusion seemed to be only a moderate predictor with only 64% sensitivity but rather low specificity (72%).

### Discussion

We tested the value of a routine stroke MRI protocol for the prediction of MMI in acute stroke patients within 6 hours of symptom onset. We identified several parameters that predicted MMI with high sensitivity and specificity within the 6-hour time window: diffusion lesion volume, perfusion lesion volume, perfusion/diffusion-mismatch ratio, ADC de-
crease within the lesion, and severity of neurological deficit at admission.

**Predictive Parameters**

Clinical parameters have previously been used to predict the development of MMI. Coma on admission and early nausea and vomiting were found to correlate with fatal brain edema, and initial NIHSS score at admission was higher in patients who were dead or dependent 1 month after stroke. Similarly, carotid-T occlusion has been reported to predict early signs of ischemia were found to be predictive of fatal brain edema. A recently published MRI study reports a 100% sensitivity and 94% specificity in the prediction of MMI for a DWI lesion volume of >145 mL within 2 to 14 hours of symptom onset. It seems obvious that the predictive value of CCT or MRI will be higher the later the MRI data are acquired.

We focused on the 6-hour time window because the majority of severely affected stroke patients arrive within the first 6 hours. It is at this early stage of stroke development that therapeutic decisions must be made. Because hemicraniectomy appears to be more effective the earlier it is performed, it is important to identify patients at risk of MMI as early as possible.

Infarct volume has been proposed as a predictor of MMI, and several studies have focused on CCT findings. Major early signs of ischemia were found to be predictive of fatal brain edema or early deaths. Likewise, final lesion volume measured by CCT predicted fatal brain swelling. A recently published MRI study reports a 100% sensitivity and 94% specificity in the prediction of MMI for a DWI lesion volume of >145 mL within 2 to 14 hours of symptom onset. It seems obvious that the predictive value of CCT or MRI will be higher the later the MRI data are acquired.

We focused on the 6-hour time window because the majority of severely affected stroke patients arrive within the first 6 hours. It is at this early stage of stroke development that therapeutic decisions must be made. Because hemicraniectomy appears to be more effective the earlier it is performed, it is important to identify patients at risk of MMI as early as possible.

---

**TABLE 4. Prediction of MMI: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV (%) (95% CI)</th>
<th>NPV (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCcore lesion volume &gt;82 ml</td>
<td>87 (59-98)</td>
<td>91 (47-97)</td>
<td>82 (48-98)</td>
<td>92 (75-99)</td>
</tr>
<tr>
<td>TTP &gt;4 s lesion volume &gt;162 ml</td>
<td>83 (53-97)</td>
<td>75 (43-94)</td>
<td>53 (27-79)</td>
<td>86 (65-97)</td>
</tr>
<tr>
<td>TTP/ADC mismatch ratio &lt;2.4</td>
<td>80 (50-95)</td>
<td>79 (47-95)</td>
<td>64 (35-87)</td>
<td>91 (72-99)</td>
</tr>
<tr>
<td>rADCcore &lt;0.62</td>
<td>79 (51-98)</td>
<td>74 (42-88)</td>
<td>57 (29-82)</td>
<td>91 (72-99)</td>
</tr>
<tr>
<td>ADCcore &lt;300 mm²/s</td>
<td>83 (45-93)</td>
<td>85 (58-100)</td>
<td>62 (32-86)</td>
<td>88 (68-97)</td>
</tr>
<tr>
<td>NIHSS at admission &gt;19 (all patients)</td>
<td>96 (42-100)</td>
<td>72 (47-89)</td>
<td>61 (36-83)</td>
<td>100 (85-100)</td>
</tr>
<tr>
<td>NIHSS at admission &gt;17 (right MCA infarction)</td>
<td>96 (40-100)</td>
<td>82 (36-100)</td>
<td>77 (28-100)</td>
<td>98 (46-100)</td>
</tr>
<tr>
<td>NIHSS at admission &gt;19 (left MCA infarction)</td>
<td>99 (59-100)</td>
<td>70 (46-88)</td>
<td>54 (25-81)</td>
<td>100 (77-100)</td>
</tr>
<tr>
<td>Carotid-T occlusion</td>
<td>64 (31-89)</td>
<td>85 (65-96)</td>
<td>64 (31-89)</td>
<td>85 (65-96)</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; CI, confidence interval.

---

**TABLE 5. Group Comparison Thrombolysis Versus No Thrombolysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Thrombolysis (n=23)</th>
<th>No Thrombolysis (n=14)</th>
<th>Group Comparison p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMI, n (%)</td>
<td>3 (13)</td>
<td>8 (57)</td>
<td>0.007†</td>
</tr>
<tr>
<td>Age [y], median (range)</td>
<td>60 (38-89)</td>
<td>68.5 (44-89)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7 (30)</td>
<td>7 (50)</td>
<td>0.20†</td>
</tr>
<tr>
<td>Left MCA infarction, n (%)</td>
<td>9 (64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS at admission, median (range)</td>
<td>17 (8–24)</td>
<td>19.5 (9–25)</td>
<td>0.39*</td>
</tr>
<tr>
<td>Carotid-T occlusion, n (%)</td>
<td>4 (17)</td>
<td>7 (50)</td>
<td>0.04†</td>
</tr>
<tr>
<td>Time to MRI [min], median (range)</td>
<td>165 (90–285)</td>
<td>192.5 (120–300)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Outcome parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRS, median (range)</td>
<td>1 (0–6)</td>
<td>4 (3–6)</td>
<td>0.007*</td>
</tr>
<tr>
<td>BI, median (range)</td>
<td>100 (0–100)</td>
<td>20 (0–60)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Lesion volume ADCcore [ml], median (range)</td>
<td>24 (0–168)</td>
<td>99 (2–233)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Lesion volume TTPcore [ml], median (range)</td>
<td>138 (19–213)</td>
<td>192 (56–252)</td>
<td>0.01*</td>
</tr>
<tr>
<td>TTP/ADC mismatch ratio, median (range)†</td>
<td>4.3 (0.6–528)</td>
<td>1.7 (0.6–52)</td>
<td>0.08*</td>
</tr>
<tr>
<td>rADCcore, median (range)</td>
<td>0.66 (0.59–0.72)</td>
<td>0.62 (0.57–0.76)</td>
<td>0.02*</td>
</tr>
<tr>
<td>ADCcore [mm²/s], median (range)</td>
<td>417 (274–603)</td>
<td>343 (210–638)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test; †Fisher’s exact test; ‡after exclusion of 2 cases with no measurable ADC lesion (division by zero impossible) in thrombolysis group.
In our study an ADC$_{<80\%}$ > 82 mL assessed within the first 6 hours (median, 3 hours) of symptom onset predicted the development of MMI with 87% sensitivity and 91% specificity. The early time point of our MRI study may be the reason why the predictive diffusion lesion volume we found was smaller than the 145 mL reported previously. It is well known from the literature that DWI lesions grow over time within and even beyond the first 24 hours. Cases of small lesions in early initial DWI but with large final infarctions and malignant course have been reported. We had a similar case within our sample: in this patient initial ADC lesion of ischemia.25,43 ADC within the group of patients not treated by thrombolysis. To address the question of the extent to which thrombosis influences the prediction of MMI, we compared patients treated with thrombosis with those not treated with thrombosis (Table 5). Because of small sample size, ROC analysis was not performed separately for subgroups.

Because of the exclusion criteria for thrombosis (early ischemic signs covering more than one third of MCA territory), lesion volumes were larger and carotid-T occlusion was more frequent in the group not treated by thrombosis, whereas the severity of the neurological deficit appeared to be similar for both groups. Because diffusion lesion volume was found to be a powerful predictor of MMI, it is not surprising that the number of patients developing MMI was larger within the group of patients not treated by thrombosis.

The optimal time window for MRI to predict MMI has yet to be established. In cases in which initial MRI remains doubtful, an early follow-up MRI or CCT within the first 12 hours is required.

The degree of the ADC decrease within the infarct core (ADC$_{core}$ $<$ 300 mm$^2$/s) as well as within the entire lesion (rADC$_{lesion}$ $<$ 0.62) predicted MMI with high sensitivity and specificity. These findings are in agreement with the results from a previous MRI study in which ADC decrease in different ROIs predicted MMI.1 From a pathophysiological point of view, this can be easily explained because the extent of the ADC decrease is a function of the severity and duration of ischemia.25,43

The predictive value of the perfusion lesion volume may seem surprising. Previous studies of the predictive value of the initial perfusion lesion have been controversial. The initial PWI lesion was found to correlate only moderately with final infarct volume or clinical outcome. In contrast, infarct growth was predicted well by a severe perfusion deficit defined as regional cerebral blood flow $<$ 12 mL/100 g per minute, TTP $>$ 4 seconds, or mean transit time $>$ 4 seconds. In the present study, with the use of the TTP$_{4s}$/ADC$_{<80\%}$ threshold, a perfusion lesion volume $>$ 162 mL predicted MMI with 83% sensitivity and 75% specificity.

The PWI/DWI mismatch is assumed to represent “tissue at risk of infarction” and has been suggested as a possible target for reperfusion therapy. In our study a small mismatch ratio (TTP$_{4s}$/ADC$_{<80\%}$ $<$ 2.4) predicted MMI with high sensitivity and specificity. In the absence of a multivariate analysis, it remains to be determined whether the PWI/DWI mismatch independently predicts MMI. Because the area of PWI/DWI mismatch depends directly on the DWI lesion volume, the predictive value of the mismatch may well be an effect of the DWI lesion volume itself.

In summary, we found different MRI and clinical parameters to be strong predictors of MMI. Because CIs overlap and multivariate analysis was not performed, we cannot judge which parameter acts as the strongest independent predictor. Nevertheless, there seems to be a tendency for diffusion lesion volume to be the most powerful predictor of MMI at this early stage.

Subgroup Analysis: Thrombolysis Versus No Thrombolysis

Thrombolysis has been shown to result in higher recanalization rates, smaller final lesion volumes, and better outcome in patients with acute occlusion of the MCA. It is obvious that successful thrombolysis resulting in early nutritive reperfusion may substantially alter the risk of developing MMI in patients with carotid-T occlusion or MCA main stem occlusion. To address the question of the extent to which thrombosis influences the prediction of MMI, we compared patients treated with thrombosis with those not treated with thrombosis (Table 5). Because of small sample size, ROC analysis was not performed separately for subgroups.

Because of the exclusion criteria for thrombosis (early ischemic signs covering more than one third of MCA territory), lesion volumes were larger and carotid-T occlusion was more frequent in the group not treated by thrombosis, whereas the severity of the neurological deficit appeared to be similar for both groups. Because diffusion lesion volume was found to be a powerful predictor of MMI, it is not surprising that the number of patients developing MMI was larger within the group of patients not treated by thrombosis.

Misclassifications

Although MRI-derived parameters resulted in a good prediction of MMI, there were misclassifications that deserve closer analysis. The ADC$_{<80\%}$ lesion volume $>$ 82 mL threshold resulted in 3 misclassifications that were erroneously classified as MMI. In all 3 patients, follow-up MRI revealed large infarctions with at least moderate edema and midline shift. Nevertheless, these patients remained clinically stable and did not deteriorate. They showed neither severe brain atrophy nor any other obvious reason that might explain the more benign development. Particularly when hemicraniectomy is discussed as an option, a false-positive classification as MMI is of major concern because it may result in unnecessary surgical treatment. Therefore, DWI alone is not sufficient for the prediction of MMI and must be supplemented by other clinical or imaging parameters.

In the study by Oppenheim and colleagues, bivariate models combining DWI lesion volume and ADC decrease in different ROIs resulted in a prediction of MMI with 100% sensitivity and specificity. Because of the small size of their sample ($n=28$), these results should be interpreted cautiously. We did not perform multivariate analysis because of the small sample size in our study.

There are limitations to our study. We used a retrospective design, and validation of the results in a prospective study is required. This was not a community-based study. We included all consecutive patients within a 2-year period, and we cannot rule out bias since our hospital is a referral center. Small sample size represents another limitation, leading to wide CIs and precluding multivariate analysis. Predictive models that combine $\geq 2$ parameters may further improve prediction, and some effects may be too small to be detected within such a small sample.

Conclusions

We showed that acute stroke MRI allows the prediction of malignant MCA infarction within a very early time window
Acknowledgments

We acknowledge helpful discussions with our partners within the Kompetenzzentrum Schlaganfall, sponsored by the Bundesministerium für Bildung und Forschung (B5; No. 01GI9902/4). Rene Knab is supported by a grant within this project.

References

Can We Predict Massive Space-Occupying Edema in Large Hemispheric Infarctions?

Approximately 10% of large hemispheric infarctions are associated with massive, so-called malignant, space-occupying cerebral edema resulting in neurological deterioration due to brain tissue shifts, leading to herniation and often death. Increase in intracranial pressure is a late phenomenon that typically does not occur until after clinical signs of herniation have developed. Space-occupying edema is the leading cause of death within the first week of stroke. Mortality rates derived from intensive care unit–based series are as high as 79% despite aggressive medical therapy, and survivors have a poor neurological outcome. These data should be interpreted with caution because of possible selection bias.

There is currently no universally accepted treatment modality for patients who deteriorate as a result of space-occupying hemispheric infarction. Hemicraniectomy with dural patch enlargement has been proposed as a life-saving measure and might be the most promising therapeutic option. The goal of surgery is to reverse mass effect and brain tissue shifts, decrease increased intracranial pressure, improve cerebral perfusion pressure, and prevent secondary neural injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in mortality and, when performed very early, reduction in hemisphere infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury. Laboratory studies of hemicraniectomy for large hemispheric infarction in rats have shown a decrease in injury.

Data in humans have been largely derived from case series and 2 open, nonrandomized, controlled studies. In 1 study 32 patients with clinical deterioration, midline shift, and uncal herniation or obliteration of the cisterns underwent hemicraniectomy, and 21 controls received medical treatment alone. Mean time between symptom onset and surgery was 39 hours. Mortality was 34% in the surgically treated group compared with 78% in the control group. A subsequent study from the same investigators included 31 patients who underwent early hemicraniectomy at a mean of 21 hours after symptom onset. Mortality was reduced to 16%, and functional outcome in the survivors in the surgical group in both studies was improved compared with historic controls. Although these data suggest a potential substantial benefit of decompressive surgery, they cannot be readily translated into clinical practice. Most importantly, nonrandomized enrollment resulted in a control group with older and sicker patients. Furthermore, it remains unclear whether the quality of life in survivors is acceptable enough to advocate surgery as a beneficial treatment, particularly in elderly patients and perhaps in those with dominant hemispheric strokes.

While controversy remains over the beneficial effect of hemicraniectomy in space-occupying hemispheric stroke, randomized controlled trials are presently under way that should provide some more objective efficacy data. The final data of HeADDFIRST, a multicenter pilot study funded by the National Institute of Neurological Disorders and Stroke, are expected to be available in 6 to 12 months. In Europe the HAMLET study is currently randomizing patients with massive space-occupying hemorrhagic infarctions to decompressive surgery or medical treatment to assess differences in mortality and functional outcome at 1 year.

Can we predict massive space-occupying edema in large hemispheric infarctions? If hemicraniectomy proves to be beneficial in patients with life-threatening edema from stroke, it stands to reason that early surgery will result in the best clinical outcomes. Conversely, unnecessary surgical procedures with their associated risks should be avoided. Thus, early and accurate prediction of malignant hemispheric infarction might become crucial in the management of these patients.

Various studies have reported on clinical predictors of malignant middle cerebral artery (MCA) infarction (MMI), including the following: high NIHSS score on admission, history of hypertension or heart failure, increased baseline white blood cell count, early nausea/vomiting, and early elevated blood pressure. However, since the unfavorable...
course of MMI is primarily determined by a large space-occupying lesion with mass effect and tissue shifts, it seems logical that imaging prognosticators will improve predictive accuracy. Indeed, several studies have found that early CT hypodensity involving >50% of MCA territory, involvement of additional vascular territories, early attenuated corticomedullary contrast on CT, and MCA trunk or carotid-T occlusion increase the chance of malignant cerebral edema. Total infarct volume appears to be of particular importance. A prospective study of 99m-technetium-ethyl-cysteinate-dimer single-photon emission CT within 6 hours of symptom onset in 108 patients with MCA infarction predicted mortality with 82% sensitivity and 98% specificity. A prospective study of 53 patients with MCA occlusion showed that hypodensity on CT covering >50% of MCA territory within 6 hours had an 85% positive predictive value for fatal outcome with 94% specificity. Horizontal displacement of the pineal gland of ≥4 mm on CT within 48 hours of stroke is also associated with high mortality. A small retrospective MRI study of 28 patients with MCA or carotid-T occlusion found that a DWI lesion >145 cm³ within 14 hours of stroke onset predicted MMI with 100% sensitivity and 94% specificity. Prediction was further improved by combining DWI lesion volume with ADC measurements.

In the accompanying article, Thomalla et al report on the predictive value of DWI and PWI within 6 hours of stroke onset in 37 patients with MCA stroke and proximal vessel occlusion. MMI was defined as a decline in consciousness demonstrated as at least 1 point on the level of consciousness item on the NIHSS, in conjunction with a large space-occupying infarct and compression of ventricles or midline shift. The authors found that an ADC >82 mL was the most accurate MRI prognosticator, predicting MMI with 87% sensitivity and 91% specificity. Admission NIHSS score had a higher sensitivity than any single MRI prognosticator but had only moderate (72%) specificity. Three patients were misclassified as MMI with use of the 82 mL ADC cutoff. Multivariate analysis could not be performed because of the small sample size.

In conclusion, the study of Thomalla et al contributes unique data on early prediction of space-occupying hemispheric infarction by MRI prognosticators in the 6-hour time window. However, before these parameters can be used in clinical practice, they will need to be validated in a well-designed, prospective study with a larger sample size.

Christine A.C. Wijman, MD
Department of Neurology and Neurological Sciences
Stanford University Medical Center
Stanford Stroke Center
Palo Alto, California

References
Prediction of Malignant Middle Cerebral Artery Infarction by Early Perfusion- and Diffusion-Weighted Magnetic Resonance Imaging

Götz J. Thomalla, Thomas Kucinski, Volker Schoder, Jens Fiehler, Rene Knab, Herrmann Zeumer, Cornelius Weiller and Joachim Röther

*Stroke*. 2003;34:1892-1899; originally published online July 10, 2003;
doi: 10.1161/01.STR.0000081985.44625.B6

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/8/1892