Prediction of Early Neurological Deterioration Using Diffusion- and Perfusion-Weighted Imaging in Hyperacute Middle Cerebral Artery Ischemic Stroke

Juan F. Arenillas, MD; Álex Rovira, MD; Carlos A. Molina, MD; Elisenda Grivé, MD; Joan Montaner, MD; José Álvarez-Sabin, MD, PhD

Background and Purpose—Early neurological deterioration (END) occurs during the acute phase in approximately one third of all ischemic stroke patients and is associated with a significantly greater morbidity and mortality.1–4 Previous studies demonstrated that the extension of early focal hypodensity and mass effect on initial CT scan represent the strongest predictors of END among clinical, neuroradiological, and biochemical variables.1,2 Thus, END has been suggested to be determined mainly by cerebral edema provoked by the ischemic injury that follows an arterial occlusion.2 Moreover, clinical worsening during the first 48 hours after onset of cerebral ischemia may be influenced by various and heterogeneous factors, including the underlying vascular lesion, the capacity of collateral circulation, and biochemical processes such as excitotoxic neurotransmission and neuroinflammation.5–8 In this setting, experimental and human stroke studies provide evidence that early rather than later application of neuroprotective and aggressive therapies that may modify the aforementioned mechanisms underlying END could lead to a better outcome.9–11

MRI has proven to be extremely sensitive to cerebral ischemia. Several studies have shown good correlations...
between MRI findings, stroke severity, and long-term clinical outcome in acute hyperacute and hyperacute ischemic stroke patients. Furthermore, diffusion-weighted imaging (DWI) is able to detect restricted interstitial water diffusion related to cellular energetic failure, membrane dysfunction, and subsequent cytotoxic edema within ischemic parenchyma, but earlier within the hyperacute phase of ischemic stroke and with a greater sensitivity than CT scan. Moreover, DWI lesion volume obtained within 14 hours after onset of middle cerebral artery (MCA) occlusion was recently found to be an independent predictor of malignant MCA infarction. How-ever, evidence of the usefulness of ultra-early (≤6 hours) DWI and perfusion-weighted imaging (PWI) findings to predict early clinical evolution in MCA stroke is lacking. In addition, the impact of the time course of arterial recanalization on early clinical and radiological outcomes has not been systematically assessed in previous MRI studies with MCA stroke patients.

The purpose of this study was to investigate the value of DWI and PWI performed within the first 6 hours after onset of documented MCA occlusion to predict END, which would help to define the role of MRI in the selection of patients who would obtain benefit from early neuroprotective or aggressive therapeutic strategies. We also sought to determine the relationship between time to artery recanalization as detected by transcranial Doppler ultrasonography (TCD), DWI lesion enlargement, and the occurrence of END.

Subjects and Methods

Inclusion criteria were as follows: patients presenting with symptoms attributable to MCA territory ischemia; performance of DWI, PWI, and MR angiography (MRA) within the first 6 hours from symptom onset; DWI signal hyperintensity within MCA territory; MRA demonstration of occlusion affecting intracranial internal carotid artery (ICA) or MCA; and informed consent obtained from the patients or their relatives. Exclusion criteria comprised the following: initial DWI defect outside MCA territory; absence of arterial occlusion on admission MRA; previous disability related to stroke or known neurological illness; END associated with parenchymal hematoma on control cranial CT scan; END as result of new ischemic events caused by occlusion of initially nonaffected vessels demonstrable by means of control MRA or TCD; and END after reocclusion of the previously recanalized and initially occluded vessel demonstrated by TCD.

This study was approved by the local ethics committee.

Patient Selection

Between August 1999 and November 2001, of a total of 610 hyperacute stroke patients attended at our Cerebrovascular Unit, 38 underwent DWI, PWI, and MRA within the first 6 hours from symptom onset. Eight patients had to be excluded. In 2 of them, DWI displayed posterior cerebral artery territory infarctions. MRA showed no arterial occlusion in 2 patients who had anterior choroidal artery infarctions on DWI. Proximal MCA stenosis, but not occlusion, was observed on initial MRA in 1 patient, who was also excluded. One patient suffered a severely disabling myopathy that made it very difficult to interpret National Institutes of Health Stroke Scale (NIHSS) scores. Two patients who presented END showed parenchymal hematomas on control CT scan. Finally, 30 patients fulfilled all criteria to enter this study.

Clinical Assessment

Baseline examinations included a medical history, physical examination, routine blood biochemistry and blood count, ECG, and chest x-ray. Stroke onset was defined as the last time the patient was known to be without any neurological deficit. Neurological examinations were performed on admission and at 6, 12, 24, and 48 hours after stroke onset. Stroke severity was assessed with the NIHSS. All clinical scores were obtained by a video-trained stroke neurologist or a senior neurology resident, certified to apply the NIHSS. END was defined as an increase in the NIHSS score by ≥4 points during the first 48 hours after symptom onset.

Age, sex, cigarette smoking (defined as present if the patient had smoked at least an average of 10 cigarettes per day during the past 5 years), and medical history of hypertension, diabetes, hypercholesterolemia, diagnosed coronary heart disease, and intermittent claudication were recorded. Systolic and diastolic blood pressure values, body temperature, and glucose level were determined on admission. Leukocyte count and fibrinogen levels were obtained from baseline blood samples and recorded for further analysis.

Clinical outcome at day 90 was evaluated by means of the modified Rankin Scale (mRS). A score ≥2 was considered indicative of poor outcome.

MRI Protocol

MRI was performed with a 1.5-T whole body imager system with 24-mT/m gradient strength, 300-ms rise time, and an echo-planar–capable receiver equipped with a gradient override (Magnetom Vision Plus, Siemens Medical Systems). The images obtained included the following: (1) axial diffusion-weighted echo-planar spin-echo sequence (4000/100/2 [repetition time (TR)/echo time (TE)/acquisitions]); (2) axial perfusion-weighted echo-planar gradient-echo sequence (2000/60/40 [TR/TE/acquisitions]); and (3) MRA (30/5.4/15 [TR/TE/flip angle]).

Diffusion-weighted (DW) images were obtained with a single-shot spin-echo echo-planar pulse sequence with diffusion gradient b values of 0, 500, and 1000 s/mm² along all 3 orthogonal axes over 15 axial sections, 5-mm-thick sections, interslice gap of 1.5 mm, 240-mm field of view, and 96 × 128 matrix. The acquisition time for the DW images was 56 seconds. To minimize the effects of diffusion anisotropy, the DW data were automatically processed to yield standard isotropic DW images.

Perfusion-weighted (PW) images were acquired by using the dynamic first pass of a 0.1-mmol/kg bolus of gadolinium-based contrast material (Magnevist, Schering AG) for selected 13- to 15-section positions measured 40 times sequentially (acquisition time, 2 seconds for each measure). The bolus of 15 mL of contrast material was injected in the antecubital vein by using an MR-compatible power injector (Spectris, Medrad Inc) and an injection speed of 5 mL/s for 3 seconds, starting 5 seconds after initiating the sequence, followed by a flush with 15 mL saline. The PW sequence generated a time-to-peak (TTP) map for each section position that was immediately available for interpretation at the console with all the other images. Perfusion images were obtained with the use of 5-mm-thick sections, interslice gap of 1.5 mm, 240-mm field of view, and 128 × 128 matrix.

Tissue abnormality was considered in areas of high signal intensity on both DW images (reflecting decreased water motion) and TTP maps (reflecting delayed bolus arrival).

Volume measurements of the extension of tissue abnormality on DW images and on TTP maps were performed by a manual tracing technique by a neuroradiologist (A.R.), who was blind to clinical and TCD data. The perimeter of the area of abnormal high signal intensity was traced on each DW image and TTP map. All measured areas were multiplied by the slice distance to obtain the total lesion volumes for both DW images and TTP maps.

For MRA, we used a 3-dimensional time-of-flight sequence, with 1.5-mm-thick sections, 200-mm field of view, and 200 × 512 matrix, with a total acquisition time of 156 seconds.

In most patients, a follow-up MRI examination was performed between days 3 and 5 after stroke onset. This examination included DW images, MRA, and an additional transverse T2-weighted fast spin-echo (3000/85/2 [TR/TE/excitations]) or fast fluid-attenuated inversion recovery (FLAIR) (9000/110/2200/2 [TR/TE/inversion time/excitations]) sequence.
Computed Tomography

Fifteen patients (50%) underwent cranial CT scan on admission. The remaining 15 were included in the study before local approval of thrombolytic therapy. Cranial CT scan was performed systematically at the time END occurred to rule out hemorrhagic transformation. Presence and type of hemorrhagic transformation were defined according to previously published criteria.24,25 We excluded patients in whom a parenchymal hematoma was considered the cause of END.

TCD Protocol

Serial TCD examinations were conducted on admission and at 6, 12, 24, and 48 hours from stroke onset. Baseline and follow-up studies were performed by the same stroke neurologist. TCD recordings were performed with the use of a Mult-Dop X/TCD (DWL Elektronische Systeme GmbH) device, with a hand-held transducer in a range-gated, pulsed-wave mode at a frequency of 2 MHz. A standard method of insonation without compression testing, as previously described, was used.26,27 MCAs, anterior cerebral arteries, and posterior cerebral arteries were insonated through the temporal window at a depth between 45 and 65 mm. Mandatory initial MRA occlusion corresponded to TCD findings in all cases. Proximal MCA occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA, accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery. Distal MCA occlusion was defined as a diffuse dampening of the mean blood flow velocity in the affected MCA >21% compared with the contralateral MCA.28 Recanalization on follow-up TCD recordings was diagnosed when a dampened or normal waveform appeared in a previously demonstrated proximal MCA occlusion or when a previously dampened waveform came within the normal range in a previously occluded distal MCA.26 No change in the abnormal waveforms indicated that no recanalization had occurred.

Therapeutic Considerations

Five patients were included in clinical trials of potentially neuroprotective drugs shortly after MRI had been performed. After local approval of thrombolytic therapy (July 2000), 7 patients of the finally 30 included received intravenous recombinant tissue plasminogen activator (rtPA). Thrombolysis was performed according to European Cooperative Acute Stroke Study (ECASS) II criteria within the 6-hour time window.29 The indication for rtPA was based solely on the clinical status and CT findings, so that MRI in no case supposed a delay in the beginning of the treatment. Anticoagulant therapy was started in the absence of hemorrhagic transformation on the control CT scan performed at 48 hours after stroke onset, when indicated. Until then, all patients received subcutaneous low-molecular-weight heparin as prophylaxis for deep venous thrombosis.

Blood pressure, temperature, and glucose levels were managed following the European Stroke Initiative recommendations.30

Statistical Analysis

Statistical analyses were made by use of the SPSS statistical package, version 9.0. We used χ² tests to compare rates or proportions of discrete variables and Mann-Whitney U tests to assess statistical differences between continuous variables. The Spearman test was used to study the correlation between baseline NIHSS score and initial DWI and PWI lesion volumes. Baseline variables were compared to detect potential predictors of END, and those showing a P<0.05 were included in a logistic regression model. To calculate the sensitivity and specificity of baseline DWI or PWI volumes to predict END, a receiver operator characteristic (ROC) curve was configured, and cutoff values with the highest sensitivity and specificity were included in the final logistic regression analysis. Results were expressed as adjusted odds ratios and corresponding 95% CIs. Follow-up variables were compared to detect factors associated with END. Kruskal-Wallis Tests were performed to analyze the distribution of initial DWI and PWI lesion volumes according to site of arterial occlusion and to study the relationship between duration of vessel occlusion and DWI defect volume expansion from baseline to control examination at days 3 to 5. A value of P<0.05 was considered statistically significant.

Results

Baseline Variables

Seventeen women and 13 men were finally included. Demographic characteristics of the study population and vascular risk factors are shown in Table 1. Mean age was 70.6±12.4 years (range, 41 to 90 years). Forty percent of patients were hypertensive.

Mean time from stroke onset to baseline MRI was 223.2±95.6 minutes (range, 95 to 359 minutes). Initial MRA showed an intracranial ICA occlusion in 7 patients (23.3%), a proximal MCA occlusion in 14 (46.6%), and an occluded distal MCA in the remaining 9 (30%). Median NIHSS score on admission was 16.5 (range, 5 to 22). Median baseline PWI and DWI lesion volumes were 226 cm³ (range, 3 to 366 cm³) and 15 cm³ (range, 1 to 366 cm³), respectively. Twenty-eight patients (93.3%) had a PWI-DWI mismatch >20% on baseline MRI. In the remaining 2 cases (1 patient with an intracranial ICA occlusion and another 1 with a distal MCA occlusion), no mismatch was observed.

A significant positive correlation was observed between initial NIHSS score and DWI volume (Spearman’s r=0.674, P<0.001) but not between baseline NIHSS score and PWI lesion volume (r=0.257, P=0.196).

Figure 1 shows the significant differences in initial DWI and PWI volumes according to location of arterial occlusion. Patients with more proximal arterial occlusions had significantly greater PWI lesion volumes (P=0.003, Kruskal-Wallis test), DWI volumes (P=0.49), and a more reduced PWI-DWI mismatch (P=0.022) on initial MRI.

Potential Predictors of END

END occurred in 7 patients (23.3%). In 5 of them (71.4%), NIHSS score increase was mainly due to a decrease of the level of consciousness initiated between 36 and 48 hours after stroke onset. All of these patients died within the next 5 days because of massive cerebral edema, raised intracranial pressure, and transtentorial herniation. The remaining 2 patients had a worsening in limb strength, survived, and scored 5 on the mRS at day 90. Presence of END was significantly associated with a poor long-term outcome (P=0.002). Table 2 summarizes MRI, clinical, and TCD data from these 7 patients. None of them had received rtPA therapy. Of the remaining 23 patients, only 1 died of a nonneurological cause, at day 21 after stroke onset.
Table 3 shows baseline variables associated with the posterior occurrence of END. Baseline NIHSS score (P=0.049), proximal occlusion (P=0.002), initial DWI (P=0.002) and PWI (P=0.003) volumes, and reduced PWI-DWI mismatch (P=0.038) were significantly associated with END in the univariate analysis. A trend toward significance was observed for higher glucose levels (P=0.074). Furthermore, there were no significant differences in time to MRI between the patient groups. Only hyperacute DWI lesion volume remained as an independent predictor of END when a logistic regression model was applied (odds ratio, 11.5; 95% CI, 2.31 to 57.1; P=0.0028). A ROC curve provided a cutoff point of DWI hypodensity >89 cm³ (sensitivity, 85.7%; specificity, 95.7%) that better predicted END.

Follow-Up Variables Associated With END
Control MRI and TCD follow-up data were compared to detect variables associated with END. A second MRI could not be performed in 4 of the 7 patients that suffered END because of their deteriorated clinical state. Median DWI volume at day 3 to 5 was 27.5 cm³ (range, 1 to 451 cm³). An enlargement of initial DWI lesion volume was observed in 22 of 26 patients (84.6%). Initial and final DWI volumes coincided in 2 patients (7.7%). A partial reversal of initial DWI defect was noted in 2 patients (7.7%) in whom very early recanalization occurred. Greater DWI lesion volumes observed on control MRI (P=0.018) and more pronounced DWI lesion enlargement between baseline and control examinations (P=0.01) were the radiological variables associated with END. Control cranial CT scan performed after END had been detected, in those patients who could not undergo DWI, showed large carotid territory hypodensity and signs of space-occupying brain edema such as midline shift. Figure 2 shows baseline and control MRI of patient 6 of Table 2. Moreover, TCD-determined duration of arterial occlusion was significantly associated with END (P<0.001). Of the 7 END patients, 5 showed no recanalization of intracranial ICA, and in the remaining 2, proximal MCA recanalized between 12 and 24 hours. No patient with arterial occlusion duration of <12 hours suffered END in our series. Furthermore, in none of the patients with baseline DWI defect volumes >89 cm³, the cutoff value that better predicted END, was arterial recanalization detected within the first 12 hours.

In addition, a graded response was observed in DWI volume expansion in relation to duration of arterial occlusion, as shown in Figure 3 (P=0.017, Kruskal-Wallis test).

Discussion
The present study demonstrates that DWI lesion volume obtained within the first 6 hours after intracranial ICA or MCA occlusion is a powerful predictor of further neurological deterioration and provides scientific evidence that END is mainly determined by the severity and extent of early ischemic injury.

Previous studies have identified extension of early CT scan hypodensity as an independent predictor of END in acute stroke patients.1,2 Furthermore, CT scan may detect cytotoxic postischemic cerebral edema that causes a decrease in x-ray attenuation, which would be visible earlier after more severe ischemic damage.31 Moreover, large hyperacute CT scan hypodensity32–34 and diffusely attenuated corticomedullary contrast35 have been shown to be highly specific, but only moderately sensitive, to predict fatal ischemic brain edema.

Table 2. Summary of Data From Patients Who Experienced END

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/Sex</th>
<th>Occluded Artery</th>
<th>Time to MRI, min</th>
<th>Baseline NIHSS</th>
<th>PWI, cm³</th>
<th>Baseline DWI, cm³</th>
<th>PW-DW Mismatch, %</th>
<th>Recanalization, h*</th>
<th>Control DWI, cm³</th>
<th>3-Month Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>L proximal MCA</td>
<td>359</td>
<td>21</td>
<td>305</td>
<td>126</td>
<td>58.7</td>
<td>12–24</td>
<td>250</td>
<td>mRS=5</td>
</tr>
<tr>
<td>2</td>
<td>75/M</td>
<td>L proximal MCA</td>
<td>244</td>
<td>13</td>
<td>182</td>
<td>4</td>
<td>97.8</td>
<td>12–24</td>
<td>50</td>
<td>mRS=5</td>
</tr>
<tr>
<td>3</td>
<td>56/F</td>
<td>R intracranial ICA</td>
<td>135</td>
<td>19</td>
<td>320</td>
<td>211</td>
<td>35.1</td>
<td>No</td>
<td>…</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>67/M</td>
<td>R intracranial ICA</td>
<td>289</td>
<td>18</td>
<td>320</td>
<td>108</td>
<td>66</td>
<td>No</td>
<td>…</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>71/M</td>
<td>R intracranial ICA</td>
<td>145</td>
<td>18</td>
<td>366</td>
<td>366</td>
<td>0</td>
<td>No</td>
<td>…</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>80/F</td>
<td>R intracranial ICA</td>
<td>120</td>
<td>22</td>
<td>349</td>
<td>244</td>
<td>24</td>
<td>No</td>
<td>451</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>57/M</td>
<td>R intracranial ICA</td>
<td>230</td>
<td>22</td>
<td>350</td>
<td>228</td>
<td>30.7</td>
<td>No</td>
<td>…</td>
<td>Death</td>
</tr>
</tbody>
</table>

L indicates left; R, right. PWI and DWI values are lesion volumes. All reported deaths occurred within the first week after stroke onset. None of these patients received rtPA. Patients 1 and 7 were included in clinical trials of neuroprotective agents.

*Time interval in which recanalization was detected.
and ominous stroke outcome. In this context, comparative studies have shown that PWI and DWI are much more sensitive and reliable than CT in the detection of early ischemic underlying pathology. In our study, ultra-early DWI lesion volume emerged as the most robust predictor of END among a series of clinical and neuroradiological variables. These findings are in agreement with recent studies showing that DWI lesion volume within the first few hours after MCA or intracranial ICA occlusion strongly predicts clinical deterioration due to massive postischemic edema. All of our patients were imaged within the first 6 hours after stroke onset, the most attractive time window in which early decisive therapeutic decisions may have to be taken. In contrast to previous MRI studies, presence and location of arterial occlusion and time course of recanalization were systematically assessed.

In our series, END appeared basically in the context of severe postischemic cerebral edema, which may lead to neurological worsening through mass effect and raised intracranial pressure, with conversion of areas of oligemia to critically hypoperfused tissue and compromise of regional blood flow in previously clinically silent neighbor territories. Although the impossibility of performing a follow-up MRI in 4 patients limited our analysis of other factors related to END, DWI lesion expansion was significantly associated with clinical deterioration. However, despite the marked increase of irreversible lesion volume observed during the first days in most patients (84.6%), only 23.3% of patients experienced END, which is in agreement with previous studies. Thus, recruitment of ischemic penumbra within the infarct core may not always correspond to clinical progression in stroke patients. In addition, our analysis of the variables associated with END is limited by the fact that 5 patients participated in clinical trials of neuroprotective agents and 7 were treated with rtPA, because of the potential impact on tissue viability of these substances.

### TABLE 3. Univariate Analysis of Potential Predictors of END

<table>
<thead>
<tr>
<th>Age, mean±SD, y</th>
<th>67 ± 9</th>
<th>71.7± 13.2</th>
<th>0.169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F), No. (%)</td>
<td>2 (29)</td>
<td>15 (65)</td>
<td>0.190</td>
</tr>
<tr>
<td>Hypertensive, No. (%)</td>
<td>4 (57)</td>
<td>8 (35)</td>
<td>0.392</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>2 (29)</td>
<td>3 (13)</td>
<td>0.565</td>
</tr>
<tr>
<td>Hypercholesterolemia, No. (%)</td>
<td>2 (29)</td>
<td>5 (22)</td>
<td>0.708</td>
</tr>
<tr>
<td>Coronary disease, No. (%)</td>
<td>2 (29)</td>
<td>2 (9)</td>
<td>0.225</td>
</tr>
<tr>
<td>Time to MRI, mean±SD, min</td>
<td>217.4± 89.0</td>
<td>225±100.53</td>
<td>0.856</td>
</tr>
<tr>
<td>Left hemisphere, No. (%)</td>
<td>2 (29)</td>
<td>13 (57)</td>
<td>0.390</td>
</tr>
<tr>
<td>rtPA, No. (%)</td>
<td>0 (0)</td>
<td>7 (30)</td>
<td>0.518</td>
</tr>
<tr>
<td>Neuroprotective trials, No. (%)</td>
<td>2 (29)</td>
<td>3 (13)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline NIHSS score, mean±SD</td>
<td>19±3.1</td>
<td>14.9±4.9</td>
<td>0.049*</td>
</tr>
<tr>
<td>Temperature, mean±SD, °C</td>
<td>36.7±0.56</td>
<td>36.5±0.4</td>
<td>0.618</td>
</tr>
<tr>
<td>Systolic blood pressure, mean±SD, mm Hg</td>
<td>159.2±39.8</td>
<td>150.0±27.7</td>
<td>0.645</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean±SD, mm Hg</td>
<td>91.1±21.5</td>
<td>87.7±24.7</td>
<td>0.604</td>
</tr>
<tr>
<td>Glucose levels, mean±SD, mg/dL</td>
<td>223.5±89.9</td>
<td>168.5±95.4</td>
<td>0.074</td>
</tr>
<tr>
<td>Leukocytes, mean±SD, mm³</td>
<td>10257±4077</td>
<td>8219±2234</td>
<td>0.243</td>
</tr>
<tr>
<td>Fibrinogen, mean±SD, μmol/L</td>
<td>4.82±1.8</td>
<td>3.77±1.13</td>
<td>0.135</td>
</tr>
<tr>
<td>Intracranial ICA occlusion, No. (%)</td>
<td>5 (71)</td>
<td>2 (9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>DWI volume, mean±SD, cm³</td>
<td>183.8±116.1</td>
<td>21.1±25.5</td>
<td>0.002*</td>
</tr>
<tr>
<td>PWI volume, mean±SD, cm³</td>
<td>312.8±67.9</td>
<td>168.1±89.0</td>
<td>0.003*</td>
</tr>
<tr>
<td>Percent PW-DW mismatch, ±SD</td>
<td>42.7±32.8</td>
<td>79.05±25.8</td>
<td>0.038*</td>
</tr>
</tbody>
</table>

Results of univariate analysis of baseline variables potentially associated with the posterior occurrence of END are shown.

*Variables included in the final logistic regression model (see Results).

---

Figure 2. a. Initial DWI obtained 2 hours after onset of left hemiplegia in an 80-year-old woman (patient 6 in Table 2). b. Follow-up T2-weighted image performed at day 3, showing enlargement of the infarcted area and severe mass effect. The patient died at day 5.
Hyperacute MRI findings may provide information about the dynamic evolution of ischemic brain tissue. Ultra-early DWI volume better discriminated the patients that later deteriorated among the patients with greater baseline PWI lesions. Moreover, larger hyperacute DWI lesions may reflect a more severe early ischemic insult with a more rapid transition from ischemia to infarction, which may be conditioned by a proximal arterial occlusion and a poor collateral circulation. In this setting, early DWI volume might be considered a surrogate marker of the intensity of the molecular response triggered by cerebral ischemia, which includes all the biochemical mechanisms that have been previously related to END. These comprise the release of neuroexcitatory amino acids, which contribute to cytotoxic edema formation, and neuroinflammation, which leads to further cellular destruction. Our study supports previous observations showing that both extent and severity of the initial ischemic insult determine the risk of developing massive brain edema that leads to early neurological worsening. The altered hemodynamic conditions, set by the initial arterial occlusion, and the hypoperfused tissue viability thresholds may vary over time depending on the evolution of the affected vessel and on the state of collateral circulation. Therefore, early MRI findings may reflect only the worst possible clinical and morphological course if the arterial occlusion persists. In this context, duration of occlusion was associated with the occurrence of END in our series. Previous studies have demonstrated that even delayed recanalization is associated with smaller infarct size and better clinical outcome. In accord with these findings, a graded response was observed in DWI volume enlargement in relation to duration of arterial occlusion. Interestingly, partial reversal of initial DWI volume was seen in 2 patients with ultra-early recanalization, as reported previously. Nevertheless, we failed to demonstrate whether earlier recanalization may abort the fatal evolution predicted by larger hyperacute DWI lesions. In agreement with previous studies, we observed that patients with more proximal occlusions had larger PWI and DWI lesions at baseline and longer duration of arterial occlusions.

In the present study the extension and severity of the initial ischemic injury were estimated by DWI lesion volume quantitative measurement, which can be obtained rapidly with current processing techniques. Moreover, apparent diffusion coefficient maps better discriminate irreversibly damaged tissue within the heterogeneous DWI hypersignal, and their use might have improved the predictive power of our model. In addition, our system uses TTP maps to obtain PWI. The impact of other techniques of dynamic susceptibility contrast imaging, such as the more sensitive mean to transit time maps determined by deconvolution, on the predictive value of PWI deserves further study.

In conclusion, patients showing hyperacute DWI larger lesions after intracranial ICA or MCA occlusion are at a higher risk of END, a process with a severe outcome. We suggest that ultra-early MRI evaluation may identify, with very high sensitivity and specificity, the subset of ischemic stroke patients who would obtain benefit from early administration of neuroprotective therapies, including aggressive strategies such as hypothermia and decompressive craniectomy.

References


Diffusion-Weighted MRI: Back to the Future

The accompanying article demonstrates the capacity of diffusion-weighted imaging (DWI) to be a powerful predictor of early neurological deterioration. The authors have elegantly performed a study of 38 patients with middle cerebral artery stroke in which they found an increase in the National Institutes of Health Stroke Scale (NIHSS) score >4 in patients to be associated with acute DWI signs that can predict this deterioration. Imaging was performed within 6 hours of onset, which represents the time window for studies of thrombolysis. While the number of patients studied is still small, this report raises an important issue, namely, the capacity of DWI to serve not only as a marker of stroke but as a report of its severity. This article clearly answers this question positively: indeed, all patients who presented early neurological deterioration had greater DWI lesion volumes on the acute scan. This is of extreme importance since the aim of imaging should be not only to determine the presence of ischemia but to demonstrate evolution, be it positive or negative. Indeed, CT has been demonstrated to be a predictor of bad outcome: not only could it demonstrate absent hemorrhage, but it could show signs heralding malignant ischemic transformation. This is why CT has remained the method of choice for evaluation of patients in studies of thrombolysis.

With the introduction of modern echo-planar fast MR technology, the ability of DWI to image acute changes associated with ischemia was demonstrated. Together with further refinements in MR angiography, perfusion imaging, and spectroscopy, it is able to obtain in vivo data that were previously obtainable only in animal models of ischemia. However, from a clinical perspective, DWI has not been as thoroughly studied as CT. Indeed, DWI has entered our current armamentarium for imaging of acute stroke with few validation studies being available. After the initial enthusiasm about a method often thought to demonstrate acute stroke unequivocally, more questions were raised than answered about its implementation. Initial studies showed it to be sensitive and to correlate with neurological status, but more data were needed for DWI to gain wide acceptance. In an era of evidence-based medicine, when solid data were needed to strengthen initial resistance to thrombolysis, it almost looked as though the bright future of DWI was behind it.

However, with studies such as that reported in the accompanying article, DWI is now showing its capacity to fulfill the early promises made in the laboratory setting: DWI demonstrates its capacity not only as a diagnostic tool but also as a research tool. The authors again report that DWI correlates strongly with initial NIHSS score, further strengthening the clinical validity of previous studies.

DWI not only provides us with important clinical information by acutely showing lesion extension but is also able to deliver important physiopathological data through measures of the apparent diffusion coefficient (ADC). Indeed, despite contradictory findings concerning the exact nature of the changes underlying the acute decrease in ADC, many recent reports tend to point to its validity. Reports have shown reversal of lesions to be possible after intervention, when both DWI volumes and ADC lesions are measured.

Most importantly, Oppenheim et al found a slight marked decrease in the ADC in areas that would present infarct growth. In another study they found that patients with a lower ADC measured in the lesion would develop hemorrhagic transformation. Oppenheim et al found that lesion volume and ADC value measurements together could predict malignant infarction better than DWI lesion alone. The authors of the accompanying article are encouraged to further investigate this phenomenon, which would undoubtedly strengthen their assertions.

In addition to well-established MRI methods such as T2-weighted imaging and MR angiography, newer techniques such as diffusion tensor imaging are opening the way for new approaches to clinical ischemia management and research. Indeed, changes in water anisotropy might occur at an early point, heralding structural changes taking place in the penumbra.

Additionally, it is becoming clear that the changes seen on any kind of neuroimaging study should not be interpreted alone but are to be seen as part of a whole. This was recently pointed out in an important study by Baird et al, who found that factors such as DWI/perfusion-weighted imaging changes, NIHSS score, and time from onset of symptoms should be taken into account; this was more recently summarized as a 4-factor model. This stresses not only the multimodality of methods but the multidisciplinary management that is becoming increasingly evident in the treatment of acute stroke. This is important to take into account when the data presented in the accompanying article are considered.

Therefore, we conclude that, as stated by the authors, DWI seems to be usable as an early means to select patients for more aggressive therapy. Thus, DWI has again found its place both in the present as a clinical tool and in the future as a source of clinical experimentation.

Karl-Olof Lövblad, MD, Guest Editor
Neuroradiology Unit
Department of Radiology
University Hospital of Geneva
Geneva, Switzerland

References


Prediction of Early Neurological Deterioration Using Diffusion- and Perfusion-Weighted Imaging in Hyperacute Middle Cerebral Artery Ischemic Stroke

Juan F. Arenillas, Álex Rovira, Carlos A. Molina, Elisenda Grivé, Joan Montaner and José Álvarez-Sabín

*Stroke*. 2002;33:2197-2205
doi: 10.1161/01.STR.0000027861.75884.DF
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/33/9/2197

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/