99mTc Technetium-Ethyl-Cysteinate-Dimer Single-Photon Emission CT Can Predict Fatal Ischemic Brain Edema

Jörg Berrouschot, MD; Henryk Barthel, MD; Rüdiger von Kummer, MD; Wolfram H. Knapp, MD; Swen Hesse, MD; Dietmar Schneider, MD

Background and Purpose—We sought to study the prognostic value of early 99mTc-ethyl-cysteinate-dimer single-photon emission CT (99mTc-ECD SPECT) for fatal ischemic brain edema in patients with middle cerebral artery (MCA) stroke compared with the prognostic value of CT and of clinical findings.

Methods—We prospectively studied 108 patients clinically, with 99mTc-ECD SPECT, and with CT within 6 hours of symptom onset (Scandinavian Stroke Scale < 40 points) appropriate to MCA ischemia. The follow-up consisted of Scandinavian Stroke Scale and CT on days 1 and 7, Barthel Index, and Modified Rankin Scale after 3 months. An activity deficit of the complete MCA territory on the SPECT scans and a parenchymal hypoattenuation of the complete MCA territory on CT scans were considered as predictors for a fatal MCA infarction due to mass effect and midbrain herniation.

Results—In 11 of 108 patients (10%), the MCA infarction was the cause of death. The sensitivity of SPECT for fatal outcome was 82% in both visual and semiquantitative analyses, while specificity was 98% and 99%, respectively. The sensitivity and specificity of baseline CT were 36% and 100%, respectively; the sensitivity and specificity of clinical findings (Scandinavian Stroke Scale, depressed level of consciousness, gaze deviation) varied from 36% to 73% and from 45% to 88%, respectively. In a multivariate logistic regression model, only SPECT findings were found to be independent predictors of malignant MCA infarction/death.

Conclusions—We were able to identify patients with fatal MCA infarction with high accuracy by using 99mTc-ECD SPECT within 6 hours of stroke onset. This technique offers great potential to select stroke patients for specific therapies, eg, decompressive hemicraniectomy, soon after onset of symptoms. (Stroke. 1998;29:2556-2562.)

Key Words: brain edema ■ cerebral infarction ■ mortality ■ stroke, ischemic ■ tomography, emission computed
urgently required for 2 reasons: (1) Patients with extended ischemic edema may not benefit from neuroprotection or reperfusion therapy. Moreover, treatment attempts with thrombolysis or hypervolemic hemodilution may bear the risk of edema aggravation and secondary intracerebral hemorrhages.²⁻²³,²⁴ (2) Specific but risky treatments such as decompressive hemicraniectomy, which may reduce mortality by 40%,²⁵⁻²⁷ or mild hypothermia²⁸ seem to be more appropriate for these patients. If the diagnosis of malignant MCA infarction could be proved early, the patients would be transferred immediately to the intensive care unit or to special centers where decompressive hemicraniectomy can be performed.

Single-photon emission CT (SPECT) allows immediate determination of the size and extent of impaired cerebral blood flow after the onset of stroke.²⁹⁻³¹ Using ⁹⁹ᵐTc–hexamethylpropyleneamine oxime (HMPAO) SPECT, Limburg et al.³² showed that the initial flow deficit was closely correlated with early death from transtentorial herniation. Five patients with the largest flow deficits died within the first 6 days after stroke, whereas only 1 of 21 patients with smaller flow deficit died. These SPECT examinations were performed, however, within the first 24 hours after the onset of stroke symptoms. A few SPECT studies performed within 6 hours of stroke onset relied on small patient numbers and did not address the prediction of death after stroke.²⁹,³³⁻³⁶ These studies exclusively used the tracer ⁹⁹ᵐTc–HMPAO, which assesses cerebral blood flow. By contrast, the tracer ⁹⁹ᵐTc–ethyl-cysteinate-dimer (ECD) reflects not only perfusion but also the metabolic status of the brain tissue and may be more specific for revealing the degree of irreversible brain lesions.³⁷⁻⁴⁰ In a study with a time window of 6 hours after the onset of symptoms, ⁹⁹ᵐTc-ECD SPECT was used to obtain a clearer distinction between transient cerebral ischemia and ischemic infarction.⁴¹

The goal of this prospective study was to ascertain the predictive value of ⁹⁹ᵐTc-ECD SPECT for the development of fatal ischemic brain edema compared with the predictive value of CT and clinical findings in the setting of acute stroke within the first 6 hours of stroke onset.

Subjects and Methods

Between February 1996 and September 1997, 293 patients with ischemic stroke were admitted to our Neurological Critical Care Unit. One hundred eight of these patients (64 men, 44 women) who met the following inclusion and exclusion criteria were enrolled into this prospective study. The inclusion criteria were as follows: age 18 to 85 years; sudden onset of a focal neurological deficit in the territory of the MCA; first stroke; a Scandinavian Stroke Scale (SSS) score <40 points at the time of injection of ⁹⁹ᵐTc-ECD; and SPECT and CT examination within 6 hours after the onset of symptoms. Patients were excluded if they had a verteobasilar stroke, if they had improved rapidly by the time of SPECT examination, or if the CT findings were inconsistent with focal ischemia in the MCA territory (eg, intracerebral hemorrhage).

Patients were treated after CT and injection of ⁹⁹ᵐTc-ECD. Sixty-two patients received heparin intravenously to prevent secondary stroke by doubling the apparent activated partial thromboplastin time for ≥24 hours and generally until a cardiac embolism source had been safely ruled out. Thirty-nine patients were enrolled for an ongoing double-blind, placebo-controlled trial and were randomly treated with recombinant tissue plasminogen activator administered intravenously or placebo. These patients received heparin intravenously corresponding to the above criteria, but no earlier than 24 hours after the initiation of therapy and always after the exclusion of an intracerebral hemorrhage in the follow-up CT at 22 to 36 hours after the start of therapy. Seven patients were enrolled for an ongoing double-blind, placebo-controlled trial and were randomly treated with the neuroprotective agent lubeluzole administered intravenously or placebo. These patients were also treated with heparin administered intravenously. The investigators remained blinded to the treatment arms in these 2 trials. The study was approved by the local ethics committee.

⁹⁹ᵐTc-ECD SPECT Analysis

Resting patients with their eyes open were injected with 400 MBq ⁹⁹ᵐTc-ECD in a quiet, dimly lit room. After the injection of the radiopharmaceutical, the subjects were kept in the same condition for an additional 5 minutes. Imaging was started 10 to 15 minutes after injection. Photons were registered with the use of a brain-dedicated SPECT camera (Ceraspect, DSI) with 3 rotating parallel hole collimators. The spatial resolution obtained with the system is ≈7 mm. Within 20 minutes (360° rotation, 120 projections), 1 to 1.5 million counts were collected in a 128 x 128 x 64 matrix. The data were reconstructed by standard filtered back projection with a 2-dimensional Butterworth filter (cutoff 0.95, order 10). Images were corrected for attenuation Chang’s first order method (attenuation coefficient μ=0.15 cm⁻¹). For reorientation, the transverse slices were inclined 15° to the canthomeatal line, corresponding to the stereotaxic system of coordinates of Talairach and Tournoux.⁴² The addition of 4 contiguous slices each resulted in a slice thickness of 6.8 mm (corresponding to the spatial resolution of the system).

SPECT data were analyzed both (1) visually and (2) semiquantitatively with region of interest (ROI) analysis. Visual analysis was based on brain slices in 3 plane orientations (coronal, sagittal, and transverse). Images were assessed in terms of (1) the extent of the activity deficit in the territory of the MCA (no activity deficit; <33%; 33% to 66%; 66% to 99%; complete MCA territory) and (2) the pattern of the activity deficits in comparison to the contralateral region (no right-left difference; small difference; marked difference; and complete lack of activity). On the basis of these observations, the prognosis was estimated with regard to survival versus malignant MCA infarction/death (activity deficit of the complete MCA territory). Although the investigators knew the side of neurological deficit, they were blinded to the severity of the neurological symptoms (SSS) on admission and the outcome of the patients.

For semiquantitative ROI analysis, 5 transverse and 3 coronal slices were selected at predefined distances from the commissura anterior–commissura posterior line (transverse slices: Talairach coordinates = −20 mm, ±1, +8, ±21, ±34 mm) and from the line perpendicular to the commissura anterior–commissura posterior line cutting the commissura anterior (coronal slices: Talairach coordinates = ±5, −16, −37 mm) respectively. In these 8 slices, 88 ROIs were generated with a commercial program (Ceraspect, DSI) and were assigned to anatomic structures according to the stereotaxic atlas.⁴² Count densities of ROIs of the symptomatic hemisphere were related to those of the corresponding contralateral regions and classified as abnormal if a deficit was >10% (ratio 0.90), in agreement with widely accepted standards.²⁹⁻₄₀ In accordance with Hanson et al.,²⁹ we also used the SPECT graded scale, a measure of the intensity and spatial extent of activity deficits. Each ROI was given a score of 0 to 9, whereby 0 indicated a ratio ≥0.91, 1 indicated a ratio of 0.81 to 0.90 (corresponding to 81% to 90% activity compared with the contralateral side), 2 indicated a ratio of 0.71 to 0.80, etc. The scores for all individual ROIs were added to produce the SPECT graded scale.

CT Analysis

Nonenhanced cranial CT scans (Siemens, Somatom Plus S) were obtained immediately after admission within 6 hours of onset of symptoms. A second CT scan was obtained after 24 to 36 hours and a third after 7 ±2 days or after clinical deterioration. Patients with normal second CT and no neurological deficit after 24 hours did not undergo a third CT scan.
The admission CT scans were analyzed by an experienced external neuroradiologist (R. von K.) blinded to the severity of the neurological symptoms (SSS) on admission, the outcome of the patients, and the SPECT findings. He categorized the size of parenchymal hypoattenuation in the territory of the MCA (no hypoattenuation; <33%; 33% to 66%; 66% to 99%; complete MCA territory) and predicted fatal brain edema if the hypoattenuation completely covered the MCA territory.

Clinical Investigations and Follow-Up

The SSS score (46 points maximum; without gait) was determined immediately before the injection of $^{99m}$Tc-ECD, 24 ± 2 hours after the onset of symptoms, and after 7 ± 1 days. In particular, history of hypertension, atrial fibrillation, an impaired level of consciousness (somnolent, stuporous, comatose), and conjugate gaze deviation were registered on admission.

After 30 days, 78 patients underwent a follow-up clinical examination. Concerning the remaining 30 patients, telephone contact was established with them, their relatives, or, alternatively, with the hospitals or rehabilitation centers caring for them to find out whether the patient was still alive.

After 3 months, the Modified Rankin Scale (0 to 6) and the Barthel Index (0 to 100 points) were performed. Seventy-four patients were personally examined; the other 34 patients or their next of kin were contacted by telephone.

All patients who died during the period covered by the study were classified on the basis of the clinical findings, the course of disease, and the CT scans as either neurological death (malignant MCA infarction was defined as MCA infarction that caused mass effect and fatal midbrain herniation) or nonneurological death. Patients with malignant MCA infarction and a secondary nonneurological complication (eg, pneumonia, sepsis, cardiac arrest) were classified under the category of neurological death if they were still comatose at the time of nonneurological complication.

Two groups of patients were formed: those who died because of their stroke (neurological death) and those who were still alive 3 months after stroke or died of a nonneurological death.

Statistical Analysis

Clinical data, SPECT, and CT findings of both groups were compared with the Mann-Whitney U test as well as Student’s t test for unpaired data based on a level of significance of 0.05. Intraobserver variability of visual SPECT analysis was calculated with the Kendall W test after repeated analysis of 40 studies. Interobserver variability of visual analysis was calculated with the Kendall W test after we compared the scores of 3 independent observers. The sensitivity, specificity, and accuracy of clinical and radiological findings for neurological death and the relative risk of neurological death associated with these findings were calculated for visual SPECT analysis, semiquantitative SPECT analysis, CT analysis, and clinical parameters after cutoff values were defined for the parameters with the help of corresponding scatterplots. To identify independent parameters for differentiation between neurological death and survival/nonneurological death, logistic regression was performed with stepwise forward and backward selection of variables with Wald’s test and the statistical software SPSS. Logistic regression analysis was first performed on each of the following variables: age, history of hypertension, atrial fibrillation, neurological findings, and SPECT and CT parameters. Significant risk factors at $P<0.05$ were then entered into a final logistic model. Proportions are presented with the limits of the 95% CI taken from the Ciba-Geigy tables.46

Results

Clinical Findings

The patients’ average age was 65 ± 13 years, and the mean SSS score on admission was 30 ± 8 points (95% CI, 8 to 39 points). On average, the CT and SPECT examinations were performed 4 ± 2 hours after the onset of symptoms.

At 90 days after stroke, 13 (12%) of the 108 patients had died. The cause of death was neurological in 11 patients (10%); 2 patients suffered a nonneurological death. One of these patients was the 76-year-old man with a moderate infarction (33% to 66% of the MCA territory) who died from cardiac arrest on day 9 after stroke, while the other was a 76-year-old woman who also suffered a moderate infarction (33% to 66% of the MCA territory) and died on pneumonia on day 46 after stroke.

Of the 11 patients with neurological death, a 68-year-old male patient with an initially moderate infarction (33% to 66% of the MCA territory) suffered from a recurrent stroke 4 days later, with MCA infarction and secondary parenchymal hemorrhage causing death 3 days later.

Ten patients died from a complete MCA infarction with mass effect and midbrain herniation (malignant MCA infarction). Three of these 10 patients also had severe extracerebral complications (pneumonia, sepsis, cardiac arrest). Four patients also had a secondary parenchymal hemorrhage. These patients were part of a double-blind, placebo-controlled trial and were treated randomly with recombinant tissue plasminogen activator or placebo. Seven of 10 patients died within 10 days. Two patients who underwent hemisarcnecctomy died on days 21 and 28 without ever regaining consciousness (Table 1).

Ninety-five of 108 patients survived their stroke. After 3 months they had an average Barthel Index of 79 ± 28 points. Forty-two patients (39%) had a Modified Rankin Scale score of 0 to 1; 27 patients (25%) had a score of 2 to 3; and 26 patients (24%) had a score of 4 to 5.

Univariate analyses found an association between neurological death and SSS score on admission <27 points, an impaired level of consciousness and conjugate gaze deviation on admission, and a right-sided stroke. The sensitivity and specificity of the clinical findings for fatal outcome varied from 36% to 73% and from 45% to 88%, respectively (Table 2).

SPECT Findings

A technically satisfactory SPECT scan was obtained from all 108 patients. Interobserver variability of the visual SPECT analysis was 2.0% ($W=0.97$, $P<0.001$), and intraobserver variability of the visual scoring ($n=40$) was 3.4% ($W=0.95$, $P=0.003$). In the visual SPECT analysis, 9 of 11 patients with neurological death had an activity deficit covering the complete MCA territory and were prognosticated to suffer a malignant MCA infarction/death (Table 1). The remaining patients had an activity deficit in 33% to 66% of the MCA territory and were predicted to survive. One patient later suffered a parenchymal hemorrhage (>30% of the infarcted area), and it remained uncertain whether death was caused solely by the intracerebral hemorrhage or the MCA infarction. The second patient had a recurrent stroke with parenchymal hemorrhage. Two of 97 surviving patients or patients with nonneurological death had an activity deficit of the entire MCA territory and were predicted to die from malignant MCA infarction. Both patients survived with a subtotal (66% to 99%) MCA infarction subsequently assessed by CT.
TABLE 1. Clinical, SPECT, and CT Findings of 11 Patients With Neurological Death After Ischemic Hemispheric Stroke

<table>
<thead>
<tr>
<th>No./Age, y/Sex</th>
<th>SSS on Admission</th>
<th>Depressed Level of Consciousness</th>
<th>Conjugate Gaze Deviation</th>
<th>Baseline CT: Parenchymal Hypodensity in MCA Territory</th>
<th>SPECT Visual Analysis, Activity Deficit in MCA Territory</th>
<th>SPECT Graded Scale</th>
<th>Time of Death, d</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/80/F</td>
<td>10</td>
<td>Somnolent</td>
<td>Conjugate eye deviation</td>
<td>100%</td>
<td>Complete lack</td>
<td>143</td>
<td>16</td>
<td>Malignant MCA infarction + pneumonia</td>
</tr>
<tr>
<td>2/76/F</td>
<td>26</td>
<td>Somnolent</td>
<td>Gaze palsy</td>
<td>&lt;33%</td>
<td>Complete lack</td>
<td>146</td>
<td>10</td>
<td>Malignant MCA infarction</td>
</tr>
<tr>
<td>3/62/M</td>
<td>20</td>
<td>Stuporous</td>
<td>Gaze palsy</td>
<td>&lt;33%</td>
<td>Complete lack</td>
<td>142</td>
<td>9</td>
<td>Malignant MCA infarction</td>
</tr>
<tr>
<td>4/77/F</td>
<td>37</td>
<td>No</td>
<td>No</td>
<td>&lt;33%</td>
<td>Complete lack + PCA</td>
<td>161</td>
<td>4</td>
<td>Malignant MCA infarction + PH2</td>
</tr>
<tr>
<td>5/42/M</td>
<td>24</td>
<td>No</td>
<td>No</td>
<td>&lt;33%</td>
<td>Complete lack</td>
<td>141</td>
<td>28</td>
<td>Malignant MCA infarction + cardiac arrest</td>
</tr>
<tr>
<td>6/61/M</td>
<td>31</td>
<td>No</td>
<td>No</td>
<td>100%</td>
<td>Complete lack</td>
<td>150</td>
<td>3</td>
<td>Malignant MCA infarction + PH2</td>
</tr>
<tr>
<td>7/75/F</td>
<td>31</td>
<td>Somnolent</td>
<td>Gaze palsy</td>
<td>&lt;33%</td>
<td>Complete lack</td>
<td>85</td>
<td>5</td>
<td>Malignant MCA infarction + PH2</td>
</tr>
<tr>
<td>8/68/M</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>33–66%</td>
<td>Marked difference</td>
<td>47</td>
<td>7</td>
<td>Recurrent infarction + PH2</td>
</tr>
<tr>
<td>9/40/F</td>
<td>26</td>
<td>No</td>
<td>Conjugate eye deviation</td>
<td>100%</td>
<td>Complete lack + PCA</td>
<td>143</td>
<td>21</td>
<td>Malignant MCA infarction + sepsis</td>
</tr>
<tr>
<td>10/78/F</td>
<td>24</td>
<td>No</td>
<td>No</td>
<td>&lt;33%</td>
<td>Complete lack + ACA</td>
<td>235</td>
<td>3</td>
<td>Malignant MCA infarction + PH2</td>
</tr>
<tr>
<td>11/76/M</td>
<td>26</td>
<td>No</td>
<td>Gaze palsy</td>
<td>100%</td>
<td>Complete lack + ACA/PCA</td>
<td>184</td>
<td>6</td>
<td>Malignant MCA infarction</td>
</tr>
</tbody>
</table>

PCA indicates posterior cerebral artery; ACA, anterior cerebral artery; and PH2, parenchymal hemorrhage. >30% of the infarcted area.

In the semiquantitative SPECT analysis, 9 of 11 patients with neurological death had a SPECT graded scale >140, whereas 96 of 97 surviving patients or patients with nonneurological death had a SPECT graded scale ≤140.

Independent risk factors for neurological death were an activity deficit of the complete MCA territory and a SPECT graded scale >140. The sensitivity of admission SPECT for neurological death was 82% (95% CI, 48% to 98%) in visual and semiquantitative analysis, while specificity was 98% (95% CI, 93% to 100%) and 99% (95% CI, 94% to 100%), respectively (Table 2).

**CT Findings**

The follow-up CT scans showed 85 patients with an infarction; the remaining 23 patients had a normal CT. Four of 11 patients with neurological death had a parenchymal hypodensity of 66% of the MCA territory. The specificity of the baseline CT for fatal outcome was 100% (96% to 100%), whereas the sensitivity was only 36% (11% to 69%) (Table 2).

**Comparison of the Predictive Value of Clinical, CT, and SPECT Parameters Regarding the Prognosis of Malignant MCA Infarction/Death**

The only independent parameters for differentiation between neurological death and survival in the final logistic regression analysis were an activity deficit of the complete MCA territory in the visual SPECT analysis on admission (relative risk for neurological death, 40; 95% CI, 10 to 161) and a SPECT graded scale >140 in the semiquantitative SPECT analysis (relative risk for neurological death, 79; 95% CI, 11 to 569) (Table 2).

**Discussion**

This prospective study was designed to assess the predictive value of SPECT for early mortality due to cerebral causes in the setting of acute ischemic stroke within the first 6 hours of onset of symptoms. Our patients did not differ from the general stroke population with respect to age or admission neurological status. The overall outcome is remarkably similar to that known for the natural history of this disease.

Among various clinical variables and CT and SPECT findings, the visually analyzed 99m Tc-ECD SPECT (activity deficit of the complete MCA territory) and the SPECT graded scale >140 were the only independent predictors for early neurological death. The sensitivity of SPECT for neurological death was 82% (95% CI, 48% to 98%) and seems clearly superior to CT, which had a sensitivity of only 36% (95% CI, 11% to 69%). Because of the rather small number of neurological deaths, the 95% CIs overlap, and we cannot really prove the superiority of SPECT over CT in this regard. The same is true in comparison to the other variables that showed a significant association with early neurological death in univariate tests.

The SPECT observation of an activity deficit of the complete MCA territory was a highly specific finding pre-
dicting neurological death; it was more specific than the clinical findings and as specific as CT. With 2 exceptions, all patients with activity deficits that were less than complete either survived or died of extracerebral causes. The clinical course of these 2 patients with incomplete activity deficit was complicated by recurrent stroke and brain hemorrhage, which may have contributed to fatality after the SPECT examination was done.

In the whole series of 108 patients, only 2 patients with malignant MCA infarction underwent decompressive hemicraniectomy. Both patients died. Since these patients already showed signs of brain stem compression (unilateral pupillary dilatation), the operation may have been performed too late.

In our study, SPECT examinations lasted 20 to 30 minutes. Visual assessment took no longer than 1 to 2 minutes. Since the waiting time for the main laboratory tests takes 30 to 40 minutes, both CT and SPECT can be performed without any significant delay. Moreover, the SPECT scanning time could easily be reduced for visual analysis (which is sufficient in acute situations), which would save even more time.

There are few SPECT data on its predictive value for poor outcome in the setting of acute ischemic stroke within 6 hours of onset of symptoms. Giubilei et al\(^49\) who found reperfusion using 99m Tc-HMPAO SPECT in some of their patients. Ueda et al\(^34\) (1994; 20 patients), and Alexandrov et al\(^36\) (1995; 30 patients) provided no data regarding early mortality. The only SPECT study to address this question that we are aware of had a time window of 24 hours\(^13\) (26 patients; \(^{201}\)Tl)diethyldithiocarbamate SPECT). All 5 patients with the largest flow deficits died within the first 6 days after stroke, whereas only 1 patient died of 21 patients with smaller flow deficits.

The SPECT graded scale in our semiquantitative SPECT analysis is a combination of the size and extent of ischemia and had a high sensitivity and specificity to predict malignant MCA infarction/death. This confirms the results of Hanson et al,\(^29\) who also found a strong association between the severity of ischemia (SPECT graded scale) on the initial SPECT scan and poor long-term outcome (Barthel Index), albeit among just 15 patients examined within 6 hours.

The cerebral uptake of 99m Tc-ECD reflects not only perfusion but also the metabolic status of brain tissue and correlates with the cerebral metabolic rate of oxygen.\(^47,48\) The retention of 99m Tc-ECD requires the presence of cytosolic esterase, which in turn depends on the viability of cells. The complete activity deficit of the whole MCA territory thus may indicate not only low blood flow but also a metabolic breakdown and ongoing irreversible tissue damage. This is supported by our observation that no patient with such a large activity deficit showed reperfusion, in contrast to Baird et al,\(^49\) who found reperfusion using 99m Tc-HMPAO SPECT in some of their patients.

In contrast to SPECT, CT detects ischemic edema that causes a decrease in x-ray attenuation.\(^50\) Ischemic edema occurs in brain areas of severe perfusion deficit <10 to 15

---

**TABLE 2. Sensitivity, Specificity, and Relative Risk of Clinical, SPECT, and CT Findings Within 6 Hours After Onset of Symptoms Between Patients With Neurological Death and Survivors or Patients With Nonneurological Death**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survival/ Neurological Death</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Relative Risk for Neurological Death (CI)</th>
<th>(P^*)</th>
<th>(P^†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 years</td>
<td>20 (n=97) 5 (n=11)</td>
<td>45 (17–77)</td>
<td>79 (70–87)</td>
<td>2.1 (1.0–4.7)</td>
<td>0.06</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53</td>
<td>73 (39–94)</td>
<td>45 (34–56)</td>
<td>1.9 (0.6–4.7)</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>28</td>
<td>45 (17–77)</td>
<td>71 (62–80)</td>
<td>2.3 (0.7–6.7)</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>SSS on admission &lt;27 points</td>
<td>25</td>
<td>73 (39–94)</td>
<td>74 (64–83)</td>
<td>2.8 (1.7–4.6)</td>
<td>0.001</td>
<td>0.4</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>39</td>
<td>73 (39–94)</td>
<td>60 (49–69)</td>
<td>1.8 (1.2–2.8)</td>
<td>0.03</td>
<td>0.2</td>
</tr>
<tr>
<td>Disturbances of consciousness on admission</td>
<td>12</td>
<td>36 (11–69)</td>
<td>88 (79–93)</td>
<td>2.9 (1.1–7.5)</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Gaze deviation on admission</td>
<td>19</td>
<td>55 (23–83)</td>
<td>80 (71–88)</td>
<td>2.8 (1.4–5.5)</td>
<td>0.009</td>
<td>0.5</td>
</tr>
<tr>
<td>Visual SPECT analysis: activity deficit of the complete MCA territory</td>
<td>2</td>
<td>82 (48–98)</td>
<td>98 (93–100)</td>
<td>40 (10.0–161.0)</td>
<td>&lt;0.001</td>
<td>0.04§</td>
</tr>
<tr>
<td>Visual SPECT analysis: complete lack of activity</td>
<td>36</td>
<td>91 (59–100)</td>
<td>63 (52–72)</td>
<td>2.4 (1.8–3.4)</td>
<td>&lt;0.001</td>
<td>0.2</td>
</tr>
<tr>
<td>Semiquantitative SPECT analysis: SPECT graded scale &gt;140</td>
<td>1</td>
<td>82 (48–98)</td>
<td>99 (94–100)</td>
<td>79 (11.0–569.0)</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>CT: parenchymal hypodensity of entire MCA territory</td>
<td>0</td>
<td>36 (11–69)</td>
<td>100 (86–100)</td>
<td>‡</td>
<td>&lt;0.001</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NND indicates nonneurological death.

*χ² test.

†Multivariate logistic regression.

‡Relative risk was not calculated since all patients with neurological death had parameters below the risk level.

§Without the parameters of the semiquantitative SPECT analysis.
ml/100 g per minute. In animal models of MCA occlusion, the net water uptake after MCA occlusion is 2.3% in 4 hours.⁵⁰,⁵¹ According to von Kummer and Weber,⁵⁰ it takes ≈2 to 3 hours until the drop in x-ray attenuation becomes visible on CT scans after MCA occlusion under experimental conditions. This explains the low sensitivity but high specificity of CT in comparison to SPECT. Plain CT does not detect perfusion but the sequelae of low perfusion if a state of edema, which means irreversible tissue damage, has developed. Hypoattenuation of the entire MCA territory, which was 100% (95% CI, 96% to 100%) specific for early cerebral death, was detected by CT within the first 2 hours in 2 patients and at 3 and 5 hours in the other 2 patients in this study. We presume that parenchymal hypoattenuation on CT scans detected earlier than 2 hours after stroke onset means a more severe ischemic damage causing earlier brain edema. In 7 patients who died from cerebral death, CT showed parenchymal hypodensity in less than one third of the MCA territory. Thus, CT does not exclude the possibility of an extended and severe perfusion deficit even if it is normal or shows only small areas of subtle hypoattenuation.¹³ This was recently confirmed by Grond et al.⁵² The initial stages of parenchymal hypodensity on CT scans are very subtle and sometimes difficult to detect. Interrater agreement is moderate even among experienced readers.⁵³ It was shown that parenchymal hypodensity is a reliable sign of irreversible brain tissue damage.¹²,¹₅,²₂,⁵₄

We could not identify clinical variables as independent predictors for early cerebral death after ischemic stroke. Censori et al¹² found among 172 patients with ischemic stroke admitted within 6 hours a Canadian Neurological Scale score <6.5 at entry and atrial fibrillation associated with a significant handicap or death after 30 days. A similar situation was encountered by Fiorelli et al,¹⁴ who studied 300 patients with ischemic stroke admitted within 6 hours after the onset of symptoms. Patients older than 70 years and with a Canadian Neurological Scale score ≈4.5 had a high risk of death or disablement 4 months after the stroke. The smaller the time window between the onset of symptoms and clinical examination, the smaller was the predictive value of clinical parameters. This is explained by the time required for the development of brain edema and increase of intracranial pressure and subsequent disturbances of consciousness or complete hemisepsis in hemisphere strokes. Conversely, the more time that passes, the more precise the prognostic reliability of a clinical score becomes, but this is of little help in the acute situation.

In summary, we were able to identify patients with malignant MCA infarction who later died from midbrain incarceration with high sensitivity and specificity by using ⁹⁹mTc-ECD SPECT within 6 hours of the onset of symptoms. Both visual SPECT analysis (which is simple, quick, and reliable to perform) and semiquantitative ROI analysis had a high predictive value. We found that the CT finding of parenchymal hypoattenuation of the entire MCA territory is 100% specific for fatal ischemic edema, but CT may miss patients at this risk because of its low sensitivity in this regard. Using ⁹⁹mTc-ECD SPECT, we can identify patients with a fatal risk from hemispheric stroke within the first few hours after the onset of symptoms, and we can immediately initiate treatment that may be specific for the increasing intracranial pressure, such as early decompressive hemipanectomy and hypothermia.

References


99mTc-Ethy-Cysteinate-Dimer Single-Photon Emission CT Can Predict Fatal Ischemic Brain Edema
Jörg Berrouschat, Henryk Barthel, Rüdiger von Kummer, Wolfram H. Knapp, Swen Hesse and Dietmar Schneider

Stroke. 1998;29:2556-2562
doi: 10.1161/01.STR.29.12.2556

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/29/12/2556

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/