Prospective Value of Perfusion and X-Ray Attenuation Imaging With Single-Photon Emission and Transmission Computed Tomography in Acute Cerebral Ischemia

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Background and Purpose—The aim of the present study was to test the hypothesis that perfusion single-photon emission computed tomography (SPECT), carried out in addition to transmission computed tomography (TCT), improves the predictive value of brain imaging within the therapeutically relevant time window after acute cerebral ischemia.

Methods—Using TCT and \(^{99m}\text{Tc}\)-ethyl cysteinate dimer (ECD)-SPECT within 6 hours after symptom onset, we examined 108 patients (44 women, 64 men; mean age 65±13 years) with acute ischemic stroke attributed to the territory of the middle cerebral artery (MCA). In each case, 3 experts prospectively evaluated the early SPECT and TCT images. We correlated these ratings with follow-up TCT findings for the final infarction as well as with clinical outcome (Scandinavian Stroke Scale, Barthel Index, Modified Rankin Scale) after 30 and 90 days.

Results—Severe activity deficits on SPECT, not caused by local atrophy on TCT, were the best predictors (positive predictive value [PPV] 94%, 95% CI 89% to 99%; negative predictive value [NPV] 90%, 95% CI 78% to 100%; \(P<0.001\)) for evolving cerebral infarction. Complete MCA infarctions were predicted with significantly higher accuracy with early SPECT (area under receiver operating characteristic curve [AUC] index 0.91) compared with early TCT (AUC index 0.77) and clinical parameters (AUC index 0.73, \(P<0.05\)). Logistic regression analysis revealed 1 independent predictor for completed MCA territory infarction: SPECT activity deficits in the corresponding areas (PPV 88%, 95% CI 65% to 100%; NPV 96%, 95% CI 92% to 100%; \(P<0.001\)). Furthermore, death after stroke was optimally predicted by \(^{99m}\text{Tc}\)ECD-SPECT. Clinical outcome up to 90 days after the stroke event best correlated with the degree of activity deficits in early SPECT (\(r=0.53\), \(P<0.001\)).

Conclusions—\(^{99m}\text{Tc}\)ECD brain perfusion SPECT that completes TCT definitely improves the predictive value of brain imaging after acute cerebral ischemia. Thus, the combined imaging of brain edema and of cerebral perfusion early after stroke is recommended for clinical use. (Stroke. 2001;32:1588-1597.)

Key Words: cerebral ischemia — stroke, acute — tomography, emission computed — tomography, x-ray computed
TCT, especially at very early time points after the stroke, is controversial, as discussed in the literature, and must be further investigated. There also is evidence from the literature that the predictive value of brain imaging in acute ischemia could be improved by the addition of information regarding blood flow to information regarding early ischemic edema, which is obtained with TCT.

In a previous study, we demonstrated that single-photon emission computed tomography (SPECT) of the brain with [99mTc]ethyl cysteinate dimer ([99mTc]ECD) within 6 hours after the onset of stroke symptoms is able to differentiate between reversible cerebral ischemia and evolving cerebral infarction. In the case of evolving infarction within the MCA territory, [99mTc]ECD-SPECT, performed at the acute stage, allows a prediction of complete (“malignant”) infarction. Even clinical outcome can be reliably predicted with early [99mTc]ECD-SPECT.

Until now, no studies have compared brain TCT with [99mTc]ECD-SPECT within the therapeutically relevant time window of 6 hours, particularly with respect to the identification of (1) patients with spontaneously good prognosis, who do not need specific treatment, (2) patients with evolving infarctions, who would profit from adequate therapy, and (3) patients with the risk of complete (malignant) MCA territory infarctions, in whom clinical outcome probably could be improved by alternative treatment strategies such as decompressive hemicraniectomy or hypothermia. Thus, in the present study, we prospectively tested the hypothesis that [99mTc]ECD-SPECT, performed in combination with TCT, can improve the predictive value of non–contrast-enhanced TCT alone early after stroke.

Subjects and Methods

Subjects

In this study of combined TCT and SPECT, 108 consecutive patients (44 women, 64 men; mean age 65 ± 13 years) were prospectively enrolled. All patients had acute neurological deficits attributed to ischemia within the MCA territory, no stroke history, Scandinavian Stroke Scale (SSS) score of <40 points on admission, and TCT as well as SPECT imaging within 6 hours after the time point at which the acute neurological deficit was first observed. Exclusion criteria were presence of coma, rapid improvement in symptoms during the TCT and SPECT investigations, signs of intracerebral hemorrhage on acute TCT, and symptoms of vertebrobasilar stroke. The study was approved by the Ethics Committee of the University of Leipzig. Of the 108 patients, 39 represent the first group of patients, who were included at the University of Leipzig in an ongoing double-blind, placebo-controlled trial (ECASS II [Second European-Australian Acute Stroke Study]) and were treated in a randomized manner with recombinant tissue plasminogen activator (n=20) or placebo (n=19). The SPECT results for the patients who were included in the ECASS II trial at the University of Leipzig were recently published.

Protocol and Clinical Investigation

Immediately after admission to the hospital, all patients were clinically examined, including blood pressure measurement, evaluation of consciousness, eye inspection with respect to putative gaze palsy or conjugate eye deviation, cardiac examination, and SSS (46 points maximum, without “gait”). Clinical examination was followed by TCT and SPECT imaging. To save time, in 43 patients the radiopharmaceutical agent for SPECT imaging was administered directly before TCT. TCT was repeated 7 days after the stroke to evaluate extent and localization of definitive infarctions. SSS was assessed again 30 and 90 days after stroke. Additional functional and disability outcomes were scored after 90 days using the Barthel Activity of Daily Living Index (0 to 100 points) and the Modified Rankin Disability Scale (0 to 6 points).

Brain Imaging

For TCT, all patients underwent non–contrast-enhanced cranial TCT with a Somatom Plus S scanner (Siemens Inc). Axial slices of the whole brain were obtained parallel to the orbitomeatal line. The slice thickness was 5 mm (lower part of brain up to sellar region) and 10 mm (upper part of brain), respectively. Window width equaled 128 Hounsfield units, with the center level at 36 Hounsfield units. For SPECT, all patients were injected intravenously with 400 to 600 MBq [99mTc]ECD. SPECT acquisition was begun 15 minutes after the injection. Photons were registered with a brain-dedicated SPECT camera (Ceraspect; DSI) with 3 rotating parallel-hole collimators. The SPECT data were acquired, reconstructed, attenuation-corrected, and reoriented according to a standard protocol that has been described elsewhere.

Image Analysis

Interpretation of the acute TCT and SPECT images was performed visually.

Separate Analysis of Early TCT Images

The TCT images were independently evaluated by 3 experienced interpreters. The extent of putative hypodensity and brain swelling in MCA territory (<33%, 33% to 66%, or >66% of MCA territory) was rated, as well as the additional involvement of anterior or posterior cerebral artery territories. On the basis of the TCT findings, the outcome was rated as “transient ischemia,” “nontotal MCA infarction,” or “total MCA infarction.” The experts were aware of the affected side but blinded to the severity of symptoms.

Separate Analysis of Early SPECT Images

In the same manner as for the TCT images, the SPECT images (transverse, coronal, and sagittal slices) were independently evaluated by 3 experienced interpreters. These interpreters were also aware of the side of the symptoms but were blinded to the results of the TCT scoring and symptom severity. Extent of local activity deficits within the MCA territory (<33%, 33% to 66%, or >66% subtotal and total MCA territory) was scored, as well as severity (0=no, 1=mild, 2=moderate, 3=severe decrease in activity). Outcome was predicted as described for TCT images.

Combined Analysis of Early SPECT and TCT Images

The SPECT images were reinterpreted as described together with the corresponding individual TCT images.

Categorization

The follow-up TCT images were analyzed by 3 of the experts, who were blinded to the ratings of the initial TCT and SPECT images, concerning the occurrence of hypodensities. According to these findings, the patients were separated into 3 groups: group A (n=24) had no hypodensities, group B (n=73) had hypodensities in subtotal MCA territory, and group C (n=11) had hypodensities in total MCA territory. This grouping was performed with consideration for possible subsequent pooling of the study population according to the different hypotheses to be tested: prediction of evolving subtotal (groups B plus C versus group A) or total (group C versus groups A plus B) MCA territory infarctions.

Statistical Analysis

Differences between the patient groups in the number of SPECT and TCT findings, the patients were separated into 3 groups: group A (n=24) had no hypodensities, group B (n=73) had hypodensities in subtotal MCA territory, and group C (n=11) had hypodensities in total MCA territory. This grouping was performed with consideration for possible subsequent pooling of the study population according to the different hypotheses to be tested: prediction of evolving subtotal (groups B plus C versus group A) or total (group C versus groups A plus B) MCA territory infarctions.

Differences between the patient groups in the number of SPECT and TCT findings were tested for significance using the Student’s t test for independent samples after verification of normal distribution with the statistical software package SPSS. Normal values were given with 1 SD. Significance levels for differences were set at P<0.05, P<0.01, and P<0.001. Interobserver variability of the visual SPECT
and TCT analyses was assessed by calculating the *κ* statistics for the ratings of each of the 3 independent experts. Receiver operating characteristic (ROC) parameters for results of SPECT and TCT image analyses, as well as clinical findings, were calculated with the software CLABROC for continuously distributed variables and CORROC2 for categorical rating-scale variables. ROC curves were fitted by application of the software ROCFIT. Accuracy, positive predictive value (PPV), negative predictive value (NPV), and relative risk were calculated after cutoff values were defined with the help of the corresponding ROC data and that of cross-tables, respectively. Proportions were presented with 95% CI values. After these univariate analyses, multivariate analyses were performed to identify independent parameters for the prediction of infarction, total MCA territory infarction, or death after stroke. For that, logistic regression analysis was carried out using stepwise forward selection of variables with Wald’s testing. Correlations between clinical, TCT, and SPECT data on admission and clinical follow-up parameters were characterized by calculation of Kendall’s *τ* rank correlation coefficients and (linear) regression analyses.

### Results

#### Patient Characteristics

Group characteristics concerning individual and clinical data for the patients are listed in Table 1. No significant differences were found between groups A (no hypodensities on final TCT), B (subtotal MCA territory hypodensities on final TCT), and C (total MCA territory hypodensities on final TCT) with respect to age and sex distribution or regarding systolic and diastolic blood pressure and occurrence of cardiac arrhythmia. SSS score on admission was significantly higher in group A patients than in group B and C patients (mean ± SD 36 ± 3 versus 29 ± 8 and 25 ± 7, respectively), whereas the difference between groups B and C was insignificant. Impairment of consciousness, evaluated on admission, was observed significantly more often in group C than in group B. Gaze palsy/conjugate eye deviation occurred in only 4% of patients in group A in comparison to 25% of patients in group B (Table 1).

#### Analysis of Early TCT and Perfusion SPECT Images

In early TCT, hyperdense MCA sign was observed significantly more often in group B than in group A (10% versus 0%, *P* < 0.05), as well as focal hypodensities (64% versus 8%, *P* < 0.001) and brain swelling (51% versus 4%, *P* < 0.001). In a comparison of the findings between groups B and C, a highly significant group difference was found regarding the

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**TABLE 1. Clinical Data for the Different Patient Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (No Final Infarction)</th>
<th>Group B (Final Subtotal MCA Territory Infarction)</th>
<th>Group C (Final Total MCA Territory Infarction)</th>
<th><em>P</em> (Group A vs Group B)</th>
<th><em>P</em> (Group B vs Group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>66 ± 14</td>
<td>65 ± 12</td>
<td>67 ± 14</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, % female (F/M)</td>
<td>42 (10/24)</td>
<td>38 (28/73)</td>
<td>55 (6/11)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Side of ischemia, % left hemisphere</td>
<td>46 (11/24)</td>
<td>64 (47/73)</td>
<td>27 (3/11)</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Time of SPECT,* h†</td>
<td>4.2 ± 1.9</td>
<td>4.0 ± 1.6</td>
<td>3.7 ± 1.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SSS score, points‡</td>
<td>36 ± 3</td>
<td>29 ± 8</td>
<td>25 ± 7</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg‡</td>
<td>155 ± 20</td>
<td>161 ± 24</td>
<td>170 ± 25</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg‡</td>
<td>89 ± 10</td>
<td>87 ± 13</td>
<td>89 ± 11</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Impaired consciousness, % (n)‡</td>
<td>4 (1/24)</td>
<td>15 (11/73)</td>
<td>36 (4/11)</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Eye signs, % (n)§</td>
<td>4 (1/24)</td>
<td>25 (18/73)</td>
<td>55 (6/11)</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac arrhythmia, % (n)‡</td>
<td>17 (4/24)</td>
<td>36 (26/73)</td>
<td>50 (5/10)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.  
*Values are mean ± SD.  
†Duration between onset of stroke symptoms and injection of radiopharmaceutical agent.  
‡Status on admission.  
§Gaze palsy/conjugate eye deviation.

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**Figure 1.** Early TCT (left), SPECT (middle), and follow-up TCT (right) images of a patient with a final infarction in the total right MCA territory. Early hypodensities and brain swelling are shown in the complete right MCA territory (arrows) on acute TCT, with corresponding activity deficit in the total MCA territory on acute SPECT. The patient underwent decompressive hemicraniectomy 2 days after the stroke event.
occurrence of focal hypodensities/brain swelling in >66% of the MCA territory (3% versus 36%, \(P<0.001\)). Interobserver variability concerning the early TCT analysis, defined as mean variation among the ratings of the 3 experts, was 17.1% (\(k=0.33, P<0.001\)), and that of early SPECT analysis was 4.4% (\(k=0.75, P<0.001\)). SPECT imaging was carried out 1.3 to 6.0 hours (mean 4.0±1.6 hours) after the onset of stroke symptoms, without significant differences within that period, defined as duration between symptom onset and injection of the radiopharmaceutical agent, among the 3 patient groups (Table 1). With respect to the early SPECT findings, highly significant differences were found between all patient groups: Activity deficits with an extent of >33% of the MCA territory were more often observed in group B than in group A (76% versus 21%, \(P<0.001\)), and those in the total MCA territory were more often observed in group C than in group B (64% versus 1%, \(P<0.001\)). Highly significant differences between groups A and B were further found concerning the frequency of activity deficits with a degree of >1 in the visual scoring (17% versus 97%, \(P<0.001\)). Figures 1 and 2 give examples of early imaging results of 2 patients from group C: although in the case of the patient in Figure 1, early TCT revealed hypodensities and brain swelling in the total MCA territory, in the case of the patient in Figure 2, hypodensities were rated only in the left putaminal area. Early SPECT imaging, however, showed activity deficits in complete MCA territories in both patients.

**Prediction of Evolving Infarction**

Patients with final infarctions (groups B and C) were pooled and compared with the patients without final infarction (group A). Predictive values, calculated relative risk in case of the presence of clinical signs on admission, and TCT and SPECT findings for

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups B and C (n=84)</th>
<th>Group A (n=24)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Relative Risk for Infarction</th>
<th>(P^*)</th>
<th>(P^t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS‡, &lt;33 points (n=60)</td>
<td>56</td>
<td>4</td>
<td>93 (87–100)</td>
<td>42 (28–56)</td>
<td>1.60</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Eye signs‡§ (n=25)</td>
<td>24</td>
<td>1</td>
<td>96 (88–100)</td>
<td>28 (18–37)</td>
<td>1.33</td>
<td>0.012 NS</td>
<td></td>
</tr>
<tr>
<td>At least 1 “early sign”‖ in TCT (n=65)</td>
<td>62</td>
<td>3</td>
<td>95 (90–100)</td>
<td>49 (34–64)</td>
<td>1.86</td>
<td>&lt;0.001 NS</td>
<td></td>
</tr>
<tr>
<td>Focal hypodensity in TCT (n=58)</td>
<td>56</td>
<td>2</td>
<td>97 (92–100)</td>
<td>44 (30–58)</td>
<td>1.72</td>
<td>&lt;0.001 NS</td>
<td></td>
</tr>
<tr>
<td>Hypodensity in basal ganglia in TCT (n=21)</td>
<td>20</td>
<td>1</td>
<td>95 (86–100)</td>
<td>26 (17–36)</td>
<td>1.29</td>
<td>0.032 NS</td>
<td></td>
</tr>
<tr>
<td>Brain swelling in TCT (n=46)</td>
<td>45</td>
<td>1</td>
<td>98 (94–100)</td>
<td>37 (25–49)</td>
<td>1.56</td>
<td>&lt;0.001 0.059</td>
<td></td>
</tr>
<tr>
<td>Focal hypodensity/swelling &gt;33% MCA territory in TCT (n=13)</td>
<td>13</td>
<td>0</td>
<td>100 (100–100)</td>
<td>25 (17–34)</td>
<td>1.34</td>
<td>0.04 NS</td>
<td></td>
</tr>
<tr>
<td>SPECT activity deficit of any extent (n=102)</td>
<td>84</td>
<td>18</td>
<td>82 (75–90)</td>
<td>100 (100–100)</td>
<td></td>
<td></td>
<td>&lt;0.001 NS</td>
</tr>
<tr>
<td>SPECT activity deficit extent &gt;33% MCA territory (n=72)</td>
<td>67</td>
<td>5</td>
<td>93 (87–99)</td>
<td>53 (36–69)</td>
<td>1.97</td>
<td>&lt;0.001 NS</td>
<td></td>
</tr>
<tr>
<td>SPECT activity deficit severity &gt;1 (n=88)</td>
<td>82</td>
<td>6</td>
<td>93 (88–98)</td>
<td>90 (77–100)</td>
<td>9.32</td>
<td>&lt;0.001 NS</td>
<td></td>
</tr>
<tr>
<td>SPECT activity deficit severity &gt;1, not caused by local atrophy in TCT (n=87)</td>
<td>82</td>
<td>5</td>
<td>94 (89–99)</td>
<td>90 (78–100)</td>
<td>9.90</td>
<td>&lt;0.001 &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*All relevant parameters with significant \(P\) values after univariate \(x^2\) testing are listed.*

*Univariate \(x^2\) testing.

*Multivariate logistic regression analysis.

*Status on admission.

*Gaze palsy/conjugate eye deviation.

*Hyperdense MCA sign, focal hypodensity, or brain swelling.

*Not calculated, because no false-negative cases were observed.
The prediction of evolving cerebral infarction are listed in Table 2. The highest PPVs and NPVs were found for a parameter of combined interpretation of early TCT and SPECT images: activity deficits in SPECT with a severity of >1 in visual scoring, which were not caused by local atrophy (PPV 94%, NPV 90%). An example of false-positive scoring in the separate interpretation of the early SPECT images due to local atrophy is illustrated in Figure 3. Multivariate logistic regression analysis revealed both SSS scoring on admission and severity of activity deficits in SPECT to be independent predictors of evolving infarction. Combination of information from these 2 independent predictors resulted in an accuracy of 91% for the prediction of evolving infarction (Table 3). The application of the optimal clinical, TCT, and SPECT predictors and the combination of their predictive impact according to the course of events within the clinical setting (clinical examination, TCT, brain perfusion SPECT) resulted in stepwise improvement in accuracy from 70% to 83% and 93%. This improvement in accuracy was attributed to an improvement in NPV (Figure 4).

**Prediction of Total MCA Territory Infarction**

The group of patients with a final total MCA territory infarction (group C) was compared with a pool of patients without a final total MCA territory infarction (groups A and B). The highest impact on the prediction of total MCA territory infarction among all clinical and early TCT and SPECT parameters was calculated for the extent of activity deficits in SPECT. Deficits with an extent of 100% of the MCA territory were found in 7 of 11 group C patients and in only 1 of 97 group A and B patients. Multivariate analysis revealed the extent of SPECT defects to be the only independent predictor of total MCA territory infarction (Tables 3 and 4). ROC analysis resulted in a significant larger area under the ROC curve (AUC) concerning the extent of the activity deficit scored in the early SPECT images (AUC index 0.91) compared with that concerning SSS scoring on admission (AUC index 0.73) and the extent of hypodensities/brain swelling rated on early TCT images (AUC index 0.77, P<0.05) (Figure 5). The combination of optimal clinical and early TCT predictors resulted in an improvement in accuracy from 58% to 92%, with further improvement after the addition of SPECT information (94%). This stepwise improvement was the result of substantially higher PPV by adding the parameters of brain imaging to the clinical score (Figure 6).

**Prediction of Clinical Outcome**

Death after stroke occurred in 12 patients (11%). Among all clinical, TCT, and SPECT parameters, it was optimally predicted with the information on the extent of activity deficits in SPECT (PPV 88%, NPV 95%, P<0.001). Activity deficits on SPECT in the total MCA territory, as well as coinvolvement of the territories of the anterior and posterior cerebral arteries to the MCA territory, were revealed to be independent predictors of death after stroke (P<0.001 and <0.012 after multivariate logistic regression analysis). The combination of these 2 independent predictors resulted in an accuracy of 93% (Table 3). Correlations between parameters of clinical outcome (SSS after 30 and 90 days, Barthel Index after 90 days, and Modified Rankin Scale after 90 days) and clinical parameters on admission as well as early TCT and SPECT parameters are shown in Table 5: whereas in the case of SSS scoring after both 30 and 90 days, the highest coefficients were calculated for correlation with SSS scoring on admission (r=0.50 and 0.52), with respect to the Barthel Index after 90 days and the Modified Rankin Scale after 90 days, the highest coefficients were found for the correlation with the degree of activity deficits on early SPECT (r=0.46 and 0.53).

**Discussion**

The present study was initiated to test whether brain SPECT with [⁹⁹mTc]ECD, carried out in combination with TCT, can improve the prospective value of brain imaging within 6 days, the highest coefficients were calculated for correlation with SSS scoring on admission (r=0.50 and 0.52), with respect to the Barthel Index after 90 days and the Modified Rankin Scale after 90 days, the highest coefficients were found for the correlation with the degree of activity deficits on early SPECT (r=0.46 and 0.53).

**TABLE 3. Optimal Predictive Values of Combined Information on Clinical Status on Admission and Early TCT and Perfusion SPECT Imaging**

<table>
<thead>
<tr>
<th>Event</th>
<th>Parameter</th>
<th>Accuracy, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction</td>
<td>SPECT/TCT + CD</td>
<td>91 (85–96)</td>
<td>90 (80–96)</td>
<td>94 (82–100)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Total MCA territory infarction</td>
<td>SPECT₁</td>
<td>95 (91–99)</td>
<td>88 (65–100)</td>
<td>96 (92–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death after stroke</td>
<td>SPECT₁ + SPECT₂</td>
<td>93 (88–98)</td>
<td>100 (100–100)</td>
<td>92 (87–97)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Combinations of all independent parameters (result of multivariate logistic regression analyses) were tested.

*P<0.05 after multivariate logistic regression analysis.

SPECT/TCT, activity deficit severity >1 in SPECT, not caused by local atrophy in TCT; CD, SSS scoring <33 points; SPECT₁, activity deficit in total MCA territory; SPECT₂, coinvolvement of ACA and PCA territory.
hours after the onset of stroke symptoms. Both imaging modalities were first applied in a time window in which decisions regarding treatment can be derived from the obtained diagnosis. Previous studies that compared brain perfusion SPECT and TCT in early stages (within 48 hours) of stroke were carried out, with the only exception being a study by Giubilei et al33 of 32 patients, 6 hours after stroke symptom onset.34–39 Because until now optimal treatment strategy beyond the 6-hour time window has not been found, diagnosis at this time after stroke in most cases lacks therapeutical relevance. Therefore, in the present study, we included only patients (n = 108) who underwent both TCT and [99mTc]ECD-SPECT imaging within 6 hours after the onset of symptoms.

Furthermore, we compared TCT with SPECT images obtained using the radiopharmaceutical agent [99mTc]ECD in the acute stage after stroke. The cited studies were exclusively carried out using the local cerebral blood flow (lCBF) tracer [99mTc]hexylmethylpropylene amineoxine (HMPAO) or 133Xe,35 respectively. SPECT studies with 133Xe have lower spatial resolution than 99mTc studies (6 to 7 mm with high-resolution SPECT systems31) due to physical characteristics of the isotope. Two brain perfusion radiopharmaceutical agents labeled with 99mTc are available: in comparison to the originally introduced [99mTc]HMPAO,40 the second-generation lCBF tracer [99mTc]ECD41 offers a number of advantages. First, there is a stronger correlation between the uptake of the radiopharmaceutical agent and cerebral blood flow in lower flow rates, which results in higher sensitivity for the detection of smaller infarctions.42 Second, in contrast to the brain uptake of [99mTc]HMPAO, that of [99mTc]ECD is codetermined by metabolic integrity and viability of the brain tissue.43,44 Third, as reported by our group, image quality and radiochemical stability are higher with the use of [99mTc]ECD, even compared with the recently introduced stabilized [99mTc]HMPAO compounds.45

Figure 4. Prediction of evolving infarction corresponding to the course of events in the clinical setting. There is improvement after the stepwise addition of information on early TCT and SPECT imaging to information on clinical symptomatology on admission.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group C (n = 11)</th>
<th>Groups A and B (n = 97)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Relative Risk for Total MCA Territory Infarction</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia of right hemisphere (n = 47)</td>
<td>8</td>
<td>39</td>
<td>17 (6–28)</td>
<td>95 (90–100)</td>
<td>3.46</td>
<td>0.039</td>
<td>NS</td>
</tr>
<tr>
<td>SSS‡ &lt; 32 points (n = 54)</td>
<td>10</td>
<td>44</td>
<td>19 (8–29)</td>
<td>96 (95–100)</td>
<td>10.00</td>
<td>0.004</td>
<td>NS</td>
</tr>
<tr>
<td>Conjugate eye deviation‡ (n = 4)</td>
<td>2</td>
<td>2</td>
<td>50 (1–99)</td>
<td>91 (86–97)</td>
<td>5.78</td>
<td>0.007</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP‡ &gt; 165 mm Hg (n = 39)</td>
<td>7</td>
<td>32</td>
<td>18 (6–30)</td>
<td>94 (89–100)</td>
<td>3.10</td>
<td>0.045</td>
<td>NS</td>
</tr>
<tr>
<td>Impaired consciousness‡ (n = 16)</td>
<td>4</td>
<td>12</td>
<td>25 (4–46)</td>
<td>92 (84–98)</td>
<td>3.29</td>
<td>0.034</td>
<td>NS</td>
</tr>
<tr>
<td>All “early signs”§ in TCT (n = 6)</td>
<td>3</td>
<td>3</td>
<td>50 (10–90)</td>
<td>92 (87–97)</td>
<td>6.38</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Focal hypodensity/swelling &gt; 53% MCA territory in TCT (n = 13)</td>
<td>5</td>
<td>8</td>
<td>38 (12–65)</td>
<td>94 (89–99)</td>
<td>6.09</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Focal hypodensity/swelling &gt; 66% MCA territory in TCT (n = 6)</td>
<td>4</td>
<td>2</td>
<td>67 (29–100)</td>
<td>93 (88–98)</td>
<td>9.71</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>SPECT activity deficit extent &gt; 66% MCA territory (n = 42)</td>
<td>9</td>
<td>33</td>
<td>21 (9–34)</td>
<td>97 (93–100)</td>
<td>7.07</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>SPECT activity deficit extent 100% MCA territory (n = 8)</td>
<td>7</td>
<td>1</td>
<td>88 (65–100)</td>
<td>96 (92–100)</td>
<td>21.88</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPECT activity deficit MCA + ACA/PCA territory (n = 11)</td>
<td>6</td>
<td>5</td>
<td>55 (25–84)</td>
<td>95 (90–100)</td>
<td>10.58</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

All relevant parameters with significant P values after univariate $\chi^2$ testing are listed.

*Univariate $\chi^2$ testing.
†Multivariate logistic regression analysis.
‡Status on admission.
§Focal hypodensity, brain swelling, or hyperdense MCA sign.
By using $^{99m}$TcECD for high-resolution SPECT and comparing its prognostic impact with that of parameters of clinical status on admission and early TCT, an improvement in the prediction of evolving infarction was achieved. This is particularly evident in borderline situations concerning therapeutic decisions. The combination of admission symptomatology and information obtained with TCT and SPECT allows the prediction of evolving cerebral infarctions with an accuracy of 93% (95% CI 88% to 98%). Symptom severity and severity of perfusion deficits in SPECT were revealed to be the only independent predictors of evolving infarction. However, in cases of an infarction, involvement of the total MCA territory is predicted with a similar accuracy of 94% (95% CI 89% to 98%). Multivariate regression analysis showed potential to independently predict total MCA territory infarction only for SPECT perfusion defects in total MCA territory, not for any early signs of infarction on TCT or clinical data. This advantage of early $^{99m}$TcECD-SPECT was clearly confirmed by additional ROC analysis.

Despite the limited comparability to the above studies, our results of a higher predictive value with brain perfusion SPECT compared with TCT are not hampered by a lack of quality in early TCT evaluation: Fiorelli et al.\(^47\) evaluated the occurrence of early signs of cerebral infarction in TCT (within 5 hours after symptom onset) in a study of 158 patients and reported a PPV of 97% (95% CI 93% to 100%; present results, 95% to 100%) and an NPV of 40% (95% CI 29% to 51%; present results, 25% to 49%) for focal parenchymal changes. In addition, von Kummer et al.\(^14\) reported a PPV of 70% to 85% and an NPV of 83% to 88% of hypodensities and focal brain swelling covering $>$50% of the MCA territory for the prediction of fatal clinical outcome (Oxford Handicap Scale $>$3). In the present study, focal brain swelling/hypodensities in $>$66% of MCA territory predicted total MCA territory infarction with a PPV of 67% (95% CI 29% to 100%) and an NPV of 93% (95% CI 88% to 98%). However, the PPV and NPV of our early TCT evaluation are in accordance with those of Fiorelli et al.\(^47\) and von Kummer et al.\(^14\).

![Figure 5](http://stroke.ahajournals.org/)

**Figure 5.** ROC curves of clinical parameters on admission, as well as early TCT (‘focal hypodensity or brain swelling’) and SPECT, for the prediction of total MCA territory infarction. FPF indicates false-positive fraction; TPF, true-positive fraction.

![Figure 6](http://stroke.ahajournals.org/)

**Figure 6.** Stepwise improvement in the prediction of total MCA territory infarction after rating of the early TCT and SPECT images in addition to clinical evaluation on admission, corresponding to the sequence of event in the clinical setting.
An interesting finding resulted from the analyses of predictive values of early TCT and \([^{99m}Tc]\)ECD-SPECT for the prediction of evolving cerebral infarctions. Optimal PPV and NPV were calculated for perfusion defects that were not caused by local atrophy, whereby this information was obtained from the combined TCT and SPECT image interpretation. In the future, such combined measurements of different pathophysiological parameters could play an important role, particularly in the determination of ischemic penumbra,\(^56\) which represents the target of most stroke therapies\(^49\) and could be diagnosed by combining evaluations of brain tissue viability and blood flow/oxygen concentration.\(^18,9,50\)

Weir et al.\(^51\) investigated a subgroup of 28 stroke patients within 16 hours of symptom onset by using \([^{99m}Tc]\)HMPAO-SPECT and concluded that the accuracy of clinical follow-up prediction decreases the longer the SPECT imaging is delayed, so we focused on the prediction of clinical outcome of the stroke patients within the early time window of 6 hours. In the comparison of early brain perfusion SPECT with TCT has the potential to become a valuable diagnostic tool in the acute phase after stroke.

In conclusion, the hypothesis that the prospective value of TCT analyses was confirmed by von Kummer et al.\(^53\) This problem with the quality of TCT analysis resulted, for example, in the inclusion of 52 patients in the ECASS I trial (8.4% of the ECASS I population) despite extended hypodensitization in early TCT, which was detected by additional retrospective evaluation.\(^44\) It can be speculated that in the future, not only diagnosis of acute cerebral ischemia but also quality of studies for the testing of new therapeutic strategies of acute stroke can be improved by including such additional diagnostic information, which can be obtained with lower interobserver variability.

A possible limitation of the present study must be considered. Discrimination of the patient groups was performed depending on the results of a follow-up TCT examination after 7 days. Because Baron and Marchal\(^55\) noted that TCT with TCT within this period after stroke onset is not optimum for assessment of the extent of the final infarction due to vasogenic edema and mass effects, it cannot be guaranteed that all patients were correctly grouped. In addition, it cannot be completely excluded that the “fogging” effect, in which initially hypodense ischemic areas become isodense compared with normal brain tissue,\(^56\) could have compromised the quality of the follow-up TCT evaluation. However, literature shows that many stroke investigators schedule the follow-up TCT to evaluate the final infarction within the time range of \(\approx 5\) to \(7\) days,\(^36,39,57\) even in large multicenter trials.\(^6,26\)

In conclusion, the hypothesis that the prospective value of brain imaging within 6 hours after the onset of cerebral ischemia is improved by the application of \([^{99m}Tc]\)ECD brain perfusion SPECT in addition to TCT can be confirmed by our results. In the case of irreversible cerebral ischemia, total MCA infarction is predicted with high reliability. Furthermore, the prediction of clinical outcome after acute stroke is improved. Thus, early brain perfusion SPECT in combination with TCT has the potential to become a valuable diagnostic tool in the acute phase after stroke.

### Table 5. Coefficients for Correlation of Clinical and Imaging Data on Admission With Parameters of Clinical Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SSS After 30 d</th>
<th>SSS After 90 d</th>
<th>Barthel Index After 90 d</th>
<th>Modified Rankin Scale After 90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.032</td>
<td>-0.034</td>
<td>-0.132</td>
<td>0.080</td>
</tr>
<tr>
<td>SSS*</td>
<td>0.501</td>
<td>0.520</td>
<td>0.414</td>
<td>-0.460</td>
</tr>
<tr>
<td>Impaired consciousness*</td>
<td>-0.277§</td>
<td>-0.283§</td>
<td>-0.265§</td>
<td>0.286§</td>
</tr>
<tr>
<td>Eye signs*</td>
<td>-0.242§</td>
<td>-0.270§</td>
<td>-0.278§</td>
<td>0.288§</td>
</tr>
<tr>
<td>Systolic BP*</td>
<td>-0.126</td>
<td>-0.120</td>
<td>-0.170†</td>
<td>0.141</td>
</tr>
<tr>
<td>Diastolic BP*</td>
<td>-0.074</td>
<td>-0.070</td>
<td>-0.056</td>
<td>0.062</td>
</tr>
<tr>
<td>Extent of hypodensity in TCT</td>
<td>-0.361†</td>
<td>-0.359†</td>
<td>-0.341§</td>
<td>0.361†</td>
</tr>
<tr>
<td>Extent of brain swelling in TCT</td>
<td>-0.324†</td>
<td>-0.314†</td>
<td>-0.305§</td>
<td>0.318†</td>
</tr>
<tr>
<td>Number of <em>early signs</em>† in TCT</td>
<td>-0.380</td>
<td>-0.372§</td>
<td>-0.311§</td>
<td>0.356†</td>
</tr>
<tr>
<td>Degree of activity deficit in SPECT</td>
<td>-0.475§</td>
<td>-0.475§</td>
<td>-0.457§</td>
<td>0.527§</td>
</tr>
<tr>
<td>Extent of activity deficit in SPECT</td>
<td>-0.441†</td>
<td>-0.431†</td>
<td>-0.410§</td>
<td>0.432†</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

*Status on admission.
†Hyperdense MCA sign, focal hypodensity, or brain swelling.
‡P<0.05, §P<0.01, and ||P<0.001 (Kendall τ testing).
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References

Prospective Value of Perfusion and X-Ray Attenuation Imaging With Single-Photon Emission and Transmission Computed Tomography in Acute Cerebral Ischemia

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