Value of Single-Photon Emission-Computed Tomography in Acute Stroke Therapeutic Trials

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**Background and Purpose:** New therapeutic interventions for acute ischemic stroke are aimed at improving cerebral blood flow in the first 3 to 6 hours after symptom onset. Single-photon emission-computed tomography (SPECT) performed in the setting of clinical therapeutic trials may give us a better understanding of the physiological response to new forms of treatment and could impact acute management decisions.

**Methods:** We prospectively studied 15 patients with hemispheric ischemic stroke with SPECT within 6 hours of symptom onset and again at 24 hours. The ischemic defect was assessed in a semiquantitative manner that used computer-generated regions of interest (SPECT graded scale). This measure was correlated with clinical presentation (National Institutes of Health [NIH] Stroke Scale), initial clinical course (change in NIH Stroke Scale), long-term outcome (Barthel Index at 3 months), and complications of cerebral hemorrhage and edema.

**Results:** The severity of the SPECT graded scale on the admission scan correlated with the severity of neurological deficit (admission NIH Stroke Scale) \(P<.05\) and was positively associated with poor long-term outcome as measured with the Barthel Index \(P<.001\) and the complications of cerebral hemorrhage and massive cerebral edema \(P<.005\). In fact, there was a threshold value for the SPECT graded scale above which all patients suffered poor long-term outcome and the complications of cerebral hemorrhage and edema.

**Conclusions:** The measurement of an ischemic defect using SPECT is a valid assessment of hemispheric stroke severity in the hyperacute setting and may be useful for selecting or stratifying patients in clinical therapeutic trials. *(Stroke. 1993;24:1322-1329.)*

**Key Words** • cerebral blood flow • cerebral infarction • clinical trials • tomography, emission computed

Several studies evaluating the etiologic and prognostic significance of hemispheric asymmetry in isotope uptake using single-photon emission-computed tomography (SPECT) in acute stroke have been published, but there are no clear recommendations for use of this information in the decision-making process in the acute period.\(^1,10\) Only a few investigators have attempted to study patients with SPECT within the first 3 to 6 hours after symptom onset. Animal studies of acute focal ischemia indicate that the first several hours of a focal ischemic insult represent the time window available for intervention, that is, before irreversible injury has occurred.\(^4,6,11\) It follows that any information from SPECT that may assist in making therapeutic decisions should be obtained in these early hours. In addition, beyond the first 24 hours the correlation of blood flow studies with the degree of ischemic injury falls off as recanalization and reperfusion occur, often associated with hyperperfusion.\(^12,13\) Very few investigators have attempted to use cerebral SPECT in their evaluation of patients during therapeutic clinical trials, a setting in which this information would be particularly useful.\(^11\) In addition, variable methods of analysis and techniques of imaging make any synthesis of this literature difficult.

We have studied patients with SPECT within the first 6 hours of the onset of hemispheric stroke symptoms to determine (1) whether we could derive a clinically useful method for measuring SPECT abnormalities in the acute stroke setting that could be used easily and reproducibly and would be amenable for use in a multicenter trial and (2) if a classification of patients according to the type and degree of ischemic injury as defined by SPECT might be possible. In addition, clinical presentation, early clinical course, and long-term outcome were compared with both the initial study and a second study measuring change during a 24-hour period to determine (3) whether SPECT results are representative of early clinical presentation and course and (4) whether this imaging technique can predict long-term outcome.

**Subjects and Methods**

Between June 1991 and April 1992, we attempted to evaluate all patients entering the emergency room of Hermann Hospital, in Houston, Tex, within 5 hours of
symptom onset of a carotid distribution ischemic stroke with technetium-99m-labeled hexamethylpropyleneamino oxime (\(^{99m}\)Tc-HMPAO) SPECT. Those with a history or computed tomography (CT) consistent with previous ischemic stroke were excluded. All patients were also screened for randomization into one of two ongoing clinical therapeutic trials, one with a 3-hour and the other with a 6-hour entry window. Patients received a baseline SPECT before randomization and a second SPECT 24 hours after symptom onset. Each patient received a CT scan at baseline and 1 week. If the patient experienced a clinical deterioration, CT scanning was performed at the time of clinical change to evaluate for the complications of clinically significant cerebral edema or hemorrhagic conversion of ischemic infarction. These complications were defined by the CT evidence for these entities in association with a clinical deterioration. Patients were classified as to stroke mechanism using previously defined criteria.\(^{14}\) The National Institutes of Health Stroke Scale (NIH SS) was performed at baseline and 24 hours after symptom onset as a measure of severity of neurological deficit acutely and to document early clinical change.\(^{15,16}\) This test consists of 13 items with either three or four possible grades per item scored from 0 to 2 or 3, with 0 being the best and 2 or 3 being the worst outcome for that item. The maximum score is 42. The Barthel Index performed 3 months after the qualifying stroke was used as an evaluation of long-term outcome.\(^{17}\) This is a well-validated activities of daily living scale that consists of 10 weighted items, with a maximum score of 100 indicating competence in all 10 items.

For the SPECT, patients received 20 to 25 mCi (740 to 925 MBq) of \(^{99m}\)Tc-HMPAO intravenously for each study. This readily crosses the blood-brain barrier and rapidly localizes in brain tissue in proportion to the blood flow and function at the time of injection. Within a few minutes of injection, the distribution of activity stabilizes and there is minimal redistribution for up to 8 hours after injection, so that scanning can be delayed and still be representative of the ischemic defect present at the time of injection.\(^{18}\) Therefore, if a patient is to be entered into a therapeutic trial, the isotope can be administered and the patient treated with the study drug before scanning, thus avoiding any delay in treatment. Although the isotope has been shown to localize in proportion to blood flow in normal tissue, whether or not it localizes in abnormal tissue in proportion to blood flow equally as well is unclear. It should also be noted that the contribution of decreased blood flow due to the phenomenon of diaschisis cannot be differentiated from the primary ischemic insult.

Scanning was performed 1 to 5 hours after injection using a three-headed rotating gamma camera (Trionix Corporation, Twinsburg, Ohio) using the stop-and-shoot method, at intervals of 3° with 30 seconds per stop (20 minutes total acquisition time). Ultra-high-resolution collimators were used. Transverse tomographic images of 3.56-mm thickness were reconstructed using filtered back-projection with a Hamming filter (Nyquist frequency of 1.404 cycles per centimeter with a high cutoff frequency of 1.05 cycles per centimeter). Images were obliquely resliced to obtain a standardized projection along three axes and then redisplayed in three-pixel-thick (10.7-mm) transverse images. It should be noted that the three-headed rotating gamma cameras are clearly superior in this application when compared with single-head equipment. Somewhat longer imaging times may be required to achieve similar results with other equipment.

For analysis, four transverse images (each of 10.7-mm thickness) were chosen that included a sizable portion of the cerebral cortex and adjacent white matter. These were consecutive images beginning just above and excluding the cerebellum posteriorly and the inferior temporal regions anteriorly. High vertex images were not included. Computer software (Trionix) was used to outline 10 truncated wedges on each transverse image for a region-of-interest (ROI) analysis (Fig 1a). Each wedge in each slice represented one ROI, so that there were a total of 20 ROIs from each hemisphere. There were two reasons for our exclusion of inferior cortical, high vertex, and deep gray matter: first, to exclude regions normally showing greater side-to-side variability\(^{19}\) and second, to ensure an approximate equal sizing of individual ROIs so they could be equally weighted in the analysis. Asymmetry in isotope uptake was calculated by dividing the counts from a single ROI in the symptomatic hemisphere by counts in the comparable contralateral ROI. A difference of 10% or greater (ratio less than or equal to 0.90) was chosen as a significant asymmetry, as previously defined for our Nuclear Medicine department and in accordance with what others have found.\(^{19,20}\) Each ROI received a score from 0 to 10, with 0 corresponding to a ratio greater than 0.91 (signifying no abnormality), 1 corresponding to a ratio of 0.81 to 0.90, 2 corresponding to a ratio of 0.71 to 0.80, etc. The scores for all individual ROIs were added for a total score. This score, called the SPECT graded scale,
Table 1. Summary of Clinical, Single-Photon Emission Computed Tomography, and Computed Tomographic Scan Data

<table>
<thead>
<tr>
<th>Pt/age (y)/sex</th>
<th>Etiology</th>
<th>Clinical presentation</th>
<th>NIH SS (at 0/24 h)</th>
<th>Barthel Index (at 3 mo)</th>
<th>SPECT graded scale (at 0/24 h)</th>
<th>CT scan (at 7 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/67/M</td>
<td>Atherothrombotic (left ICA stenosis by ultrasound)</td>
<td>RHP, aphasia</td>
<td>7/7</td>
<td>100</td>
<td>5/0</td>
<td>No CT scan at 7 d</td>
</tr>
<tr>
<td>2/65/F</td>
<td>Unknown (normal angiogram, ECG, and echocardiogram)</td>
<td>RHP, RHS</td>
<td>16/4</td>
<td>100</td>
<td>0/0</td>
<td>Small subinsular infarct</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/52/M</td>
<td>Cardiomyocardial (dilated cardiomyopathy)</td>
<td>RHP, RHH, aphasia, neglect</td>
<td>19/14</td>
<td>100</td>
<td>16/5</td>
<td>Frontal MCA branch and PCA territory infarct</td>
</tr>
<tr>
<td>4/49/F</td>
<td>Cardiomyocardial (rheumatic valvular disease)</td>
<td>LHP, neglect</td>
<td>10/6</td>
<td>100</td>
<td>4/0</td>
<td>Small subinsular infarct</td>
</tr>
<tr>
<td>5/49/F</td>
<td>Atherothrombotic (left ICA occlusion by angiography)</td>
<td>RHP, RHH, aphasia</td>
<td>24/12</td>
<td>100</td>
<td>32/14</td>
<td>Frontal MCA branch and deep MCA territory infarct</td>
</tr>
<tr>
<td>6/76/M</td>
<td>Cardiomyocardial (atrial and ventricular arrhythmias)</td>
<td>RHP, RHS, aphasia, neglect</td>
<td>15/4</td>
<td>100</td>
<td>29/3</td>
<td>Small putamenal infarct</td>
</tr>
<tr>
<td>7/63/F</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>LHP, neglect</td>
<td>6/0</td>
<td>100</td>
<td>16/0</td>
<td>Small subinsular infarct</td>
</tr>
<tr>
<td>8/74/M</td>
<td>Cardiomyocardial (artificial aortic valve)</td>
<td>RHP, RHH, RHS, aphasia</td>
<td>16/17</td>
<td>80</td>
<td>29/8</td>
<td>Superficial and deep MCA territory infarct</td>
</tr>
<tr>
<td>9/70/F</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>LHP, LHH, LHS, neglect</td>
<td>13/7</td>
<td>80</td>
<td>26/3</td>
<td>Small subinsular infarct</td>
</tr>
<tr>
<td>10/83/M</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>LHP, LHH, LHS, neglect</td>
<td>19/11</td>
<td>75</td>
<td>27/2</td>
<td>Parietal MCA branch infarct</td>
</tr>
<tr>
<td>11/68/F</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>RHP, RHH, RHS, aphasia</td>
<td>22/35</td>
<td>5</td>
<td>31/32</td>
<td>Superficial MCA territory infarct with hemorrhage</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/53/M</td>
<td>Cardiomyocardial (dilated cardiomyopathy)</td>
<td>RHP, RHH, RHS, aphasia</td>
<td>18/22</td>
<td>50</td>
<td>49/29</td>
<td>Superficial and deep MCA territory infarct</td>
</tr>
<tr>
<td>13/73/M</td>
<td>Cardiomyocardial (dilated cardiomyopathy)</td>
<td>LHP, LHH, LHS, neglect</td>
<td>22/23</td>
<td>5</td>
<td>79/0*</td>
<td>Superficial and deep MCA infarct with hemorrhage</td>
</tr>
<tr>
<td>14/73/F</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>RHP, RHH, RHS, aphasia</td>
<td>25/31</td>
<td>0</td>
<td>70/102</td>
<td>Superficial and deep MCA territory infarct with edema</td>
</tr>
<tr>
<td>15/80/F</td>
<td>Cardiomyocardial (atrial fibrillation)</td>
<td>RHP, RHS, aphasia</td>
<td>23/26</td>
<td>Died</td>
<td>51/39</td>
<td>Superficial and deep MCA infarct with edema and hemorrhage</td>
</tr>
</tbody>
</table>

Pt, patient; NIH SS, National Institutes of Health Stroke Scale; SPECT, single-photon emission-computed tomography; CT, computed tomographic; ECG, electrocardiogram; RHP, right hemiparesis; LHP, left hemiparesis; RHS, right hemisensory deficit; LHS, left hemisensory deficit; RHH, right homonymous hemianopsia; LHH, left homonymous hemianopsia; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

*This patient's hyperperfusion on the 24-hour SPECT is not accounted for with this method of analysis.

is similar to a method described by Limburg et al10 in their work with brain SPECT using thallium-201-labeled diethyldithiocarbamate. It is a semiquantitative measure that estimates the severity of asymmetry in isotope uptake but also accounts for the volume of tissue affected by adding together the number of small ROIs affected.

Data were evaluated using the Pearson product moment correlation coefficient using values from the SPECT graded scale tested against initial clinical presentation (NIH SS, time 0) and early clinical change (change in NIH SS over 24 hours). The outcome measures of the Barthel Index and complications of hemorrhage and edema were considered in a dichotomous fashion (good long-term outcome, Barthel Index greater than 60; poor long-term outcome, Barthel Index 60 or less; presence or absence of cerebral edema or hemorrhage defined by the CT scan appearance). This threshold score of 60 is widely accepted as being a valid indicator of supervised independent recovery after stroke.21 The association of SPECT with long-term outcome and presence or absence of these complications was evaluated with the Student’s t test for unpaired data. We also looked for an association between the NIH SS scores and these outcome measures. The level of significance for all statistics was defined as P<.05.

Results

Patient characteristics and their SPECT graded scales are summarized in Table 1. We succeeded in studying 15 patients with SPECT within 6 hours of symptom onset. The range of time periods from onset of symptoms to initial SPECT injection was 1.5 to 6 hours (mean, 3.2 hours). Patients ranged in age from 49 to 83 years (mean, 66.3 years). The etiology for stroke in most of those studied was cardioembolic. Seven were randomized to an intravenous thrombolytic trial and seven to a glutamate antagonist trial. One of the patients was not included in either clinical trial. Both studies are double-blinded, placebo-controlled trials. The investigators involved remain blinded as to the patients' treat-
ment in these trials because the trials are still ongoing, so that any influence of therapeutic intervention on outcome cannot yet be ascertained. The initial CT scans on all but one patient showed no evidence for infarction or hemorrhage. Patient 14 had subtle signs of left middle cerebral artery infarction on the initial CT scan with blurring of sulcal patterns in that vascular territory. Results of the CT scans performed at 1 week are listed in Table 1. Patient 1 did not receive a CT scan at 1 week. The remaining 14 patients all showed evidence of cortical or subcortical infarction in the appropriate middle cerebral artery territory.

The patients could be roughly divided into three groups according to the severity of hemispheric asymmetry on their time 0 SPECT (Table 1). The first group consisted of patients with mild ischemia barely detectable (patient 1) or undetectable (patient 2) with the SPECT graded scale (ranging from 0 to 5). Both patients demonstrated a good long-term recovery (Fig 1b).

The second group, patients 3 through 11, had sizable ischemic defects with a large number of individual ROIs affected (9 to 18 abnormal ROIs per patient) but with only a moderate degree of asymmetry in isotope uptake in each ROI as quantified by the SPECT graded scale (16 to 40) (Fig 1c). Seven of the nine patients in this group showed early clinical improvement with at least a 4-point improvement on the NIH SS, and eight of the nine had a good long-term outcome (Barthel Index greater than 60). Patient 11 was the exception with poor long-term outcome (Barthel Index of 5) following a clinical deterioration that began 24 hours after stroke onset as a result of hemorrhagic conversion of her infarction.

The third group, patients 12 through 15, had severe ischemic insults in both volume (15 to 20 abnormal ROIs per patient) and degree of isotope uptake asymmetry, with a SPECT graded scale ranging from 49 to 79 (Fig 1d). All patients in this group had poor long-term outcome. Patient 15 died at 1 week because of medical complications following deterioration in her level of consciousness as a result of cerebral edema and hemorrhage. The other three patients in this group were severely disabled at 3 months (Barthel Index ranging from 0 to 50). Patient 13 had a severe deficit on his initial SPECT study but at 24 hours had developed marked hyperperfusion detectable with SPECT. (Hyperperfusion is not accounted for in the SPECT graded scale.) There was no clinical improvement with this reperfusion phenomenon. Although the numbers of ROIs affected were similar in patients from groups 2 and 3, the degree of isotope uptake asymmetry was more profound in those from group 3, possibly implicating a comparative lack of collateral blood supply (Fig 1d).

Results of the statistical analysis are summarized in Table 2 and Figs 2 through 5. An abnormality of the SPECT graded scale on the initial scan was detected in 14 of the 15 patients. Pearson’s correlation coefficient for the SPECT graded scale on the initial SPECT scan and clinical presentation (NIH SS at time 0) was .59 with P<.05 (Fig 2). In like manner, the 24-hour SPECT study also correlated well with the 24-hour NIH SS (P<.005) (data not shown). However, when we examined the change in SPECT graded scale over 24 hours, we found no correlation with the change occurring clinically as measured by the change in the NIH SS over 24 hours (P=.45). In fact, there were divergent changes in 7 of the 15 patients (Figs 3, 4a, and 4b). Five patients showed an improvement in SPECT without any corresponding clinical improvement (patients 1, 8, 12, 13, and 15) (Fig 4a and 4b). This discrepancy may be another confirmation of the short time window available for reperfusion to occur to result in improved outcome. The time window may be particularly restricted in those with limited collateral supply. Three of the 5 patients (patients 12, 13, and 15) were in the third group with severe

| Table 2. Pearson’s Product Moment Correlation Coefficient for SPECT Graded Scale (Time 0) and Change in SPECT Graded Scale (Over 24 Hours) Correlated With NIH Stroke Scale (Time 0) and Change in NIH Stroke Scale (Over 24 Hours); t Values Describing Association of SPECT Graded Scale (Time 0) and Change in SPECT Graded Scale (Over 24 Hours) With Outcomes of Barthel Index at 3 Months and Development of Complications of Cerebral Edema and Hemorrhagic Conversion |
|-----------------|-----------------|-----------------|
| NIH Stroke Scale (time 0) | Barthel Index or hemorrhage t (df=13) | Cerebral edema or hemorrhage t (df=13) |
| SPECT graded scale (time 0) | .59* | 4.21† | 3.51‡ |
| NIH Stroke Scale (time 0) | . . . | 2.79* | 2.90* |
| Change in NIH Stroke Scale (0-24 h) | r | .21 | 0.21 | 0.29 |
| SPECT, single-photon emission-computed tomography; NIH, National Institutes of Health. There was also a significant association between the initial NIH Stroke Scale and these outcome measures. *P<.05; †P<.001; ‡P<.005. |

![Fig 2. Scatterplot showing the correlation of single-photon emission-computed tomography (SPECT) defect at time 0 (as measured by SPECT graded scale) with clinical presentation (National Institutes of Health [NIH] Stroke Scale at time 0); r=.59, P<.05.](http://stroke.ahajournals.org/Downloaded From http://stroke.ahajournals.org)
Fig 3. Scatterplot demonstrating the lack of correlation between the change in the single-photon emission-computed tomography (SPECT) graded scale and the change in the National Institutes of Health (NIH) Stroke Scale during a 24-hour period; $r=.21$, $P=.45$. Seven patients with improvement both clinically and with respect to SPECT defect are represented by the data points with both $x$ and $y < 0$. The single patient who worsened both clinically and with respect to SPECT graded scale is represented by the data point with both $x$ and $y > 0$. The other data points represent patients with discrepant changes in the SPECT graded scale and NIH Stroke Scale. They are identified with their patient numbers from Table 1. Some of the discrepancy appears to be due to reperfusion occurring within 24 hours without a concomitant clinical improvement (patients 1, 8, 12, 13, and 15).

Ischemic defects by SPECT, where limited collateral supply may have been an issue. In addition to these 5 patients, there were 2 patients in whom there was no change in the SPECT defect but significant clinical changes occurred (patient 2, clinical improvement; patient 11, clinical deterioration).

There was a strong association between the severity of ischemia on the initial SPECT scan and poor long-term outcome as defined by a Barthel Index less than or equal to 60 ($t=4.21$, $df=13$, $P<.001$) (Fig 5 and Table 2). In fact, there appeared to be a threshold effect for hemispheric asymmetry in isotope uptake on the initial study (SPECT graded scale greater than 40), above which poor outcome was a certainty (Fig 5 and Table 1, patients 12 through 15).

Cerebral edema with mass effect and hemorrhagic conversion of infarction are complications seen with large insults with a severe degree of ischemia. In our study, patients 14 and 15 developed this degree of cerebral edema associated with clinical deterioration, and patients 11, 13, and 15 developed hemorrhagic conversion associated with clinical deterioration. These complications were defined by CT scans performed at the time of clinical deterioration and occurred from 2 to 7 days after symptom onset. As expected, the admission SPECT graded scales in patients with either hemorrhagic conversion or cerebral edema reliably differed (asymmetry in isotope uptake more profound) from those without these complications ($t=3.51$, $df=13$, $P<.005$) (Fig 6 and Table 2). As with long-term outcome, there seemed to be a threshold effect on the initial scan (SPECT graded scale greater than 50), above which these complications would predictably occur (Fig 6 and Table 1, patients 13, 14, and 15).

There was no significant association between the change in SPECT graded scale over 24 hours and the change in NIH SS over this same interval, or the outcome measures of Barthel Index at 3 months ($P=.84$), or the complications of cerebral edema or hemorrhagic conversion of ischemic infarction ($P=.78$) (Table 2).
The NIH SS, performed within the first few hours of symptom onset in tandem with the injection of isotope for the first scan, also correlated well with both outcome measures of Barthel Index ($P < .05$) and the complications of cerebral edema and hemorrhagic conversion of infarction ($t = 3.51$, df = 13, $P < .005$). As in the case with the Barthel Index, there was also a threshold (- -) above which all patients suffered these complications. Note that the highest SPECT graded scales correspond to the most severe SPECT defects.

**Discussion**

In this study, we were able to show a strong association between the severity of an ischemic insult, defined by SPECT performed within 6 hours of symptom onset, and clinical presentation, long-term outcome, and the complications of cerebral edema and hemorrhagic conversion of ischemic stroke.

Much of the work in brain SPECT for cerebrovascular disease has focused on documenting the sensitivity of the modality (versus CT scan), with only a few studies documenting the changes seen within the first 6 hours of symptom onset. Previous studies comparing SPECT with CT or with a concurrent clinical examination concentrating on the subacute and chronic stages of stroke have yielded variable results. Raynaud et al. described the blood flow patterns and metabolism of a peripheral area that surrounds the infarct core during the subacute period with possible implications for treatment in the subacute phase. However, if the information obtained from SPECT is to be clinically useful in stroke management, it must be obtained earlier in the patient’s course, during the window of opportunity for intervention. Our study reveals a close correlation between the severity of the SPECT defect when performed within the first 6 hours and the clinical severity of stroke. It is not possible to gain similar information with commonly performed imaging studies now used in the acute setting (CT or conventional magnetic resonance imaging). Diffusion-weighted imaging with magnetic resonance imaging can yield similar information, but this modality is not yet widely available. In our study, at the time SPECT was clearly abnormal in 13 of 15 patients, CT showed a suggestion of abnormality in only 1.

Limburg et al. found that SPECT performed within 24 hours correlated with an index of motor performance at presentation. We were also able to show a correlation between a scan performed as late as 24 hours after symptom onset and the 24-hour exam; however, there was no clear correlation between change in SPECT and change clinically over 24 hours. This is a matter of some concern if improvement in SPECT is to be used to document efficacy of therapy. The reason for this discrepancy may be the frequent improvement in blood flow that occurs with spontaneous recanalization over the first 24 hours, which is not always mirrored in clinical improvement (demonstrated in five of our patients). The absence of an association between perfusion changes over the first 24 hours, as measured by the SPECT graded scale, and long-term outcome would also support this reasoning. This phenomenon speaks to the issue of the limited time window in which to institute reperfusion therapy. This lack of improvement despite recanalization was well demonstrated by Fieschi et al. in their series of patients studied within 6 hours of symptom onset with angiography and transcranial Doppler and then followed serially with transcranial Doppler. Although it is an attractive hypothesis, the lack of correlation may also be due to inadequacies in our units of measure. The SPECT graded scale is a semiquantitative measure of the severity of an ischemic insult that can only roughly estimate the changes in blood flow. In addition, it cannot account for the difference in relative eloquence of various areas of the brain, so that a small deep infarct with an undetectable flow defect might result in a severe clinical deficit.

In addition to its reflection of the early clinical picture, SPECT has additional prognostic capabilities in patients with acute stroke. Much like the study published by Giubilei et al., we found a strong association between the severity of the SPECT defect detected on the early scan and long-term outcome. Similarly, we found a threshold of severity of hemispheric asymmetry in isotope uptake (SPECT graded scale greater than 40), above which all patients would predictably experience a poor outcome. Patients with a moderately severe defect on their initial scans (SPECT graded scale 16 to 40) did comparatively better, and the two with either mild or no defect (SPECT graded scale 0 to 5) both experienced good long-term outcome. As an example, if these findings were confirmed with larger numbers of patients qualifying for clinical trials, it may be appropriate to include patients with moderately severe SPECT defects in future thrombolytic trials while excluding those with mild defects who could be predicted to improve spontaneously and those with severe defects who may be less likely to respond and are at greater risk for complications.

We also showed a correlation between the development of either massive cerebral edema or hemorrhagic conversion with the severity of the hemispheric asym-
metry in isotope uptake (high SPECT graded scale). Limburg et al.\textsuperscript{10} showed a correlation between severity of the SPECT asymmetry (performed within 24 hours of symptom onset) and early death due to transtentorial herniation in a series of 26 patients studied with SPECT using thallium-201–labeled diethyldithiocarbamate. The same investigators studied patients with SPECT in an open trial of intravenous thrombolytic therapy. Of the five patients they studied, only one patient with a smaller defect responded clinically, also showing resolution of the defect on the second scan. Those with more severe defects did not respond to thrombolytic therapy, and one of these patients developed hemorhagic conversion of her infarction.\textsuperscript{11} For our patients, as with long-term outcome, there appeared to be a threshold effect such that patients with a SPECT graded scale above 50 were likely to develop edema or hemorrhage.

We recognize that 14 of our 15 patients might have received therapy that could have affected their outcome, thereby confounding any correlation between baseline SPECT and clinical outcome. In reviewing the clinical courses of our patients with the complications of cerebral edema or hemorrhage, we concluded that with the exception of one patient, it was doubtful that they were the direct result of treatment within the clinical trials, specifically the thrombolytic trial for which the concern for reperfusion injury is the greatest. Only one of the patients suffering complications of cerebral edema or hemorhagic conversion of their infarct had been entered into the thrombolytic trial. Therefore, most of the complications probably represent the natural course of the patients’ strokes. The strong negative predictive capability of SPECT in this study, in spite of the confounding variable of possible treatment with a potentially efficacious therapy, only strengthens the argument that this test may be able to identify those patients unlikely to respond to reperfusion, in addition to avoiding treatment of individuals at high risk for reperfusion injury (cerebral edema and hemorrhage). However, until the therapeutic studies are unblinded, our conclusions must be considered tentative.

In our study a simple clinical measure of stroke severity, the NIH SS, also correlated well with the outcome measures of the Barthel Index and the complications of cerebral hemorrhage and edema. However, the baseline NIH SS was not as specific as SPECT in predicting poor outcome in our small sample. Furthermore, the NIH SS cannot provide the physiological data that are obtained with SPECT, which may be useful in understanding the clinical response to treatment.

The use of SPECT by other investigators in larger numbers of patients early in clinical trials of potential reperfusion therapies is imperative if the full value of these tests is to be ascertained. If our hypothesis, that the 24-hour time point is too late to determine the adequacy of reperfusion, is correct, methods for rescanning at an earlier time point may be needed to better document the time course and adequacy of reperfusion therapy. Also, rapid acquisition techniques with shorter scanning times may be required to make SPECT more valuable to the practicing clinician who will be dealing with an extremely short time window in which to obtain this information before treatment.\textsuperscript{24}

Our conclusions are as follows: (1) We have shown the feasibility of performing SPECT in the emergency room within the first 6 hours of symptom onset and the methodology for a semiquantitative analysis of SPECT that could be used in multicenter clinical trials. (2) SPECT may be useful for classification of patients by the type and degree of ischemic injury. Further studies are needed to confirm our findings. (3) The change in cerebral perfusion over 24 hours as measured with the SPECT graded scale does not correlate well with clinical change as measured by the NIH SS or long-term outcome. (4) The severity of SPECT abnormalities in the first 6 hours of ischemia is highly predictive of outcome, and there appears to be a threshold effect for the hemispheric asymmetry in isotope uptake, above which all patients have a poor long-term outcome. Further studies are needed to confirm our findings. (5) A threshold of asymmetry in isotope uptake may exist in acutely performed SPECT, above which patients have a high likelihood of developing the complications of edema or hemorrhage, a setting in which reperfusion therapy may yield catastrophic consequences. Further studies are needed to confirm our findings.

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Stroke. 1993;24:1322-1329
doi: 10.1161/01.STR.24.9.1322
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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