tPA-Associated Reperfusion After Acute Stroke Demonstrated by SPECT

James C. Grotta, MD; Andrei V. Alexandrov, MD

Purpose—The aim of our study was twofold: to determine the frequency and magnitude of perfusion defect in stroke patients who qualify for rtPA therapy within 3 hours of stroke onset and to determine the ability of rtPA to improve perfusion by 24 hours.

Subjects and Methods—Patients with suspected hemispheric stroke who fulfilled entry criteria into the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study and also had pretreatment injection of 111mTc-HMPAO, with single-photon emission computed tomography (SPECT) performed using a triple-head camera at baseline and 24 hours, were included.

Results—All 12 patients who qualified for rtPA therapy had perfusion defects on baseline SPECT (SPECT graded scale [SGS] score range, 16 to 79). Mean±SD perfusion defect was comparable in rtPA (n=4) versus placebo (n=5) groups (SGS score, 36±18 versus 39±12; NS) despite earlier injection time in the rtPA group (98±24 versus 141±21 minutes; P=.02). Total SPECT scanning time was 20 to 25 minutes. At 24 hours, reperfusion was greater in rtPA patients compared with the placebo group (SGS score, 7±9 versus 29±17; P=.05), with relative improvement in the region-of-interest scores of 87±16% after rtPA compared with 28±30% with placebo (P=.01).

Conclusions—A substantial perfusion defect exists in stroke patients with larger hemispheric infarcts who meet NINDS criteria for rtPA therapy, and rtPA is better able than placebo to rectify this defect. SPECT is feasible for clinical trials and should be evaluated as a substituted end point in stroke therapeutic trials.

Key Words: cerebral blood flow ▪ plasminogen activator, tissue-type ▪ reperfusion ▪ stroke ▪ tomography, emission computed

Although rtPA therapy within the first 3 hours after the onset of acute stroke symptoms results in improved outcome, the urgency of this therapy precludes extensive diagnostic studies before treatment. Therefore, in the NINDS study that demonstrated the efficacy of rtPA, there was no requirement to demonstrate a perfusion defect prior to treatment. Furthermore, while it is assumed that the effectiveness of rtPA was due to its ability to improve reperfusion during the immediate poststroke period, this was not documented by comparing baseline with 24-hour studies of cerebral blood flow in the rtPA versus placebo groups. At our center, which was one of the participants in the NINDS rt-PA Stroke Study, we tried to obtain SPECT cerebral perfusion studies at baseline and after 24 hours in as many patients as possible during the study. We report the baseline results in all 12 patients who had SPECT scans carried out within 3 hours of symptom onset and the baseline compared with 24-hour SPECT studies in all 5 placebo-treated and 4 rtPA-treated patients.

Subjects and Methods

Selection of Patients
All patients admitted to Hermann Hospital (Houston, Tex), where we carried out the NINDS rtPA study, were considered for inclusion.

The inclusion and exclusion criteria for the NINDS study have been published1 and for the most part were the inclusion and exclusion criteria for the present SPECT analysis, because all patients studied with SPECT were being considered simultaneously for inclusion into the NINDS rtPA trial. In addition, to be included in this SPECT substudy, all patients had to receive the injection of isotope (111mTc-HMPAO) for SPECT within 3 hours of symptom onset but before rtPA administration, all had to have technically adequate SPECT scans carried out at baseline and again after 24 hours, and all had to have suspected hemispheric infarcts. Of the 12 patients meeting these criteria and included in this analysis, 8 were randomized into the NINDS rtPA versus placebo study and one was treated with open-label rtPA soon after the study was completed. Three were not treated with thrombolytics. Some of these patients were included in a previous publication2 that validated our SPECT methodology and correlated results with clinical outcome. The previous analysis did not focus on results within the first 3 hours or compare rtPA versus placebo patients.

SPECT Methodology

Our methods for carrying out SPECT and analyzing data have been published.3 Briefly, all patients received 20 to 25 mCi 111mTc-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, with minimal redistribution within 8 hours. Scanning was performed 1 to 5 hours after injection.
with use of a 3-headed rotating gamma camera (Trionix Corp). Four transverse images (10.7-mm thick) were chosen that began just above the cerebellum posteriorly and inferior temporal lobes anteriorly. Ten truncated wedges were outlined on the cortex of each hemisphere on each image; each wedge represented one ROI. 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. Each ROI received a score of from 0 to 10, with 0 representing 10% asymmetry; 1, 10 to 19% asymmetry, 2, 20 to 29% asymmetry, etc. The sum of all ROI scores (10 ROIs per slice) gave the SPECT graded scale (SGS), which represents both the depth and extent of perfusion defect.

**Results**

All data are presented in Table 1. The mean time to injection of isotope after onset of symptoms was 114±45 minutes. All 12 patients with symptoms of cerebral ischemia persisting for up to 3 hours had a perfusion defect visible on SPECT. The mean SGS score for the 12 patients was 40±18 (range, 16 to 79).

The 4 rtPA and 5 placebo patients had comparable baseline SGS scores (39±12 versus 36±18). Time to isotope injection was faster in the rtPA group (98±24 versus 141±62 minutes; \( P < .05 \)). Improved perfusion occurred in both placebo and rtPA groups over the first 24 hours (Fig 1), but a perfusion defect persisted at 24 hours in all placebo patients (mean SGS score, 29±17). In comparison, flow was virtually normal by 24 hours in all but 1 rtPA patient (mean SGS score, 7±9; \( P = .05 \) versus placebo). The percent improvement in SGS score was significantly greater in the rtPA group compared with placebo (\( P = .01 \); Fig 2). The improved perfusion in rtPA versus placebo-treated patients was paralleled by greater improvement, as measured on the NIH Stroke Scale, over the first 24 hours (Fig 3).

**Comparison of SGS and NIHSS Scores at Baseline and 24 Hours by Group**

<table>
<thead>
<tr>
<th>Patient</th>
<th>SGS Interval, min</th>
<th>SGS Baseline</th>
<th>NIHSS Baseline</th>
<th>SGS at 24 h</th>
<th>NIHSS at 24 hs</th>
<th>SGS % Change</th>
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NIHSS indicates National Institutes of Health Stroke Scale; and SGS interval, time from symptom onset to HMPAO injection.

*Compared with placebo.
Discussion

Our data demonstrate that in patients presenting with a persisting neurological deficit for up to 3 hours after symptom onset and who qualify for rtPA therapy using the NINDS criteria, a substantial perfusion defect exists. Furthermore, our data also demonstrate the ability of rtPA therapy to rectify this perfusion defect compared with placebo. Although the number of patients included in this study is very small, the data are consistent with clinical response observed in our patients and with other studies of cerebral perfusion and thrombolysis in the literature.3–5

One implication of our study is that clinical criteria alone without confirmatory measurement of cerebral perfusion is sufficient to establish that most patients who qualify for rtPA therapy on clinical grounds also have a significant cerebral ischemic lesion. The patient population in this SPECT study did not include those with brain stem infarcts but did include patients suspected of having either cortical or lacunar hemispheric strokes. However, only 1 of our patients had a baseline National Institutes of Health Stroke Scale score of <10 that might have been reflective of a smaller lacunar lesion. Therefore, our conclusions are most valid in the consideration of larger hemispheric lesions.

We2 and others3–13 have shown that SPECT measurement of cerebral perfusion correlates with outcome and response to therapy. SPECT and other methodologies such as positron emission tomography and nuclear magnetic resonance may ultimately (after careful evaluation within the context of randomized therapeutic trials) provide important information for patient selection, especially to help exclude those with such severe and irreversible damage that thrombolysis is ineffective or dangerous. However, our data indicate that at least within the first 3 hours in patients with hemispheric infarcts, such studies are not needed to establish that a perfusion defect exists which can possibly be reversed by intravenous rtPA. This may not be the case if patients are studied longer after the onset of symptoms, after spontaneous reperfusion has occurred.

Our data also suggest that rtPA-induced reperfusion can be documented by SPECT. In this small series we did not detect the hyperemia described by other investigators.6 Furthermore, such reperfusion correlated with clinical improvement in our2 and other3–13 published studies. This suggests the possibility of using SPECT or other physiological measures as a “substituted end point” for clinical trials. Such physiological data may be more sensitive and convenient and less expensive than long-term clinical follow-up, and at the very least can provide important confirmatory information in support of clinical outcome scales.

References


Figure 2. There is significantly greater reperfusion (expressed as percent improvement in SGS score from baseline to 24 hours) in rtPA patients than in placebo patients.

Figure 3. Placebo patient (four scans at left) had a National Institutes of Health Stroke Scale (NIHSS) score of 25 and SGS score of 44 at baseline (top). At 24 hours, the NIHSS score improved to 15, but the SGS score worsened to 54 (bottom). rtPA patient (four scans at right) had an NIHSS score of 20 and SGS score of 60 at baseline (top). At 24 hours, the NIHSS score was 6 and the SGS score 24, with reperfusion of the penumbral region (arrow) in the middle cerebral artery distribution (bottom).


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