Reperfusion After Thrombolytic Therapy in Ischemic Stroke Measured by Single-Photon Emission Computed Tomography

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Background and Purpose We used $^{99m}$Tc-hexamethylpropyleneamine oxime single-photon emission computed tomography (SPECT) to study cerebral perfusion in patients treated with streptokinase for acute ischemic stroke in an open and prospective study. Our primary aims were (1) to compare the extent of reperfusion between patients who had received thrombolytic therapy and a control group studied during the same period, in patients who were ineligible to receive such therapy and (2) to determine if, among all patients, reperfusion led to improved outcome.

Methods Fifty-seven patients (22 treated with streptokinase) had two SPECT studies performed, the first before streptokinase administration and the second 24 hours later.

Results On the first SPECT study hypoperfusion was present in the middle cerebral artery or anterior cerebral artery territories in 40 patients (17 treated with streptokinase). Patients in the treatment and control groups with initial hypoperfusion on SPECT were well matched for the volume of the perfusion defect and the severity of neurological deficit. A greater number of patients who received streptokinase developed at least partial reperfusion (streptokinase, 65%; control, 52%) on the second study but not significantly so ($P=0.43$). Similarly, the proportion of each hypoperfused region that reperfused ($P=0.74$) and the reduction in the size of the perfusion defect ($P=0.06$) were higher in the streptokinase group but did not reach statistical significance. When all patients were considered, those who did not reperfuse had higher mortality rates ($P=0.008$), less neurological improvement ($P=0.016$), and more functional disability ($P<0.001$) than patients who had reperfusion or normal perfusion initially.

Conclusions These findings suggest that at least some reperfusion during the first 48 hours of ischemic stroke is a common natural occurrence and is of prognostic significance. The observed trend toward better reperfusion indexes among patients treated with streptokinase is encouraging, but larger controlled trials are required to answer this definitively. (Stroke. 1994;25:79-85.)

Key Words • reperfusion • streptokinase • thrombolytic therapy • tomography, emission computed

The administration of thrombolytic therapy in ischemic stroke is targeted at restoring cerebral perfusion acutely, leading to salvage of the ischemic penumbra, smaller infarct size, and improved outcome. While clinical end points are the most important parameters in evaluating therapy, useful additional information may come from imaging reperfusion and tissue salvage; this may help to identify the subgroups that benefit most from therapy and reveal insights into the pathophysiology of acute stroke and early recovery. Until recently, the only way of measuring "reperfusion" after therapy has been by measuring arterial patency with angiography and transcranial Doppler ultrasonography; these techniques, however, do not quantify the extent of tissue ischemia or reperfusion. In addition, angiography is invasive and may delay the commencement of therapy.

Functional imaging techniques such as single-photon emission computed tomography (SPECT) measure tissue perfusion as opposed to arterial patency. SPECT is attracting interest in the evaluation of patients with stroke because it may demonstrate the site and extent of ischemia acutely when standard computed tomography (CT) and magnetic resonance imaging (MRI) studies are usually normal. In evaluating acute stroke therapy, SPECT may provide semiquantitative measurements of reperfusion and tissue salvage, is relatively noninvasive, and is practical because it does not delay treatment. The fixation of $^{99m}$Tc-hexamethylpropyleneamine oxime (HMPAO) within 2 minutes of injection with minimal redistribution allows scanning to be performed up to 4 hours after injection.

In this study repeated $^{99m}$Tc-HMPAO SPECT studies were used to assess cerebral perfusion in patients with acute ischemic stroke who were treated with streptokinase (SK) either intravenously or intra-arterially and control subjects studied during the same period who were ineligible to receive thrombolytic therapy for various reasons. We also wished to determine if reperfusion among all patients led to improved outcome.
Subjects and Methods

The study was conducted between May 1991 and October 1992. Patients with the sudden onset of a focal neurological event of ischemic stroke who presented at either of the two study centers (Austin and Royal Melbourne Hospitals) within 4 hours of symptom onset, had normal CT scans, and no contraindications to thrombolytic treatment were recruited into the pilot phase of the Australian Streptokinase Trial. Patients presenting between 4 and 24 hours after symptom onset were recruited into the Intra-arterial Streptokinase Trial at the Austin Hospital. Patients in whom thrombolytic therapy was contraindicated but who otherwise fulfilled the entry criteria during the period of the study were recruited as control subjects. Contraindications to thrombolytic therapy among the control group included potential for gastrointestinal tract bleeding (5 patients), current anticoagulation (3), surgery in preceding 48 hours (3), uncertain time of stroke onset (3, found collapsed or woke up with deficit but still within 24 hours of onset), improvement before therapy administered (4), refused consent (2), newly diagnosed lung carcinoma (1), intra-arterial facilities not available (4), recent transient ischemic attack or possible stroke (3), deficit too mild (3), and other (6).

Object ROI was fitted to cover the defect; this ROI was mirrored (symmetry axis) was manually selected. The transaxial slice was weighted in proportion to the severity of hypoperfusion, and the perfusion defect on day 2 subtracted from that on day 1. As seen from the above formula, a study of normal perfusion would have zero perfusion defect, and the perfusion defect size on a study of maximal ischemia would approach the physical volume. It is important to recognize that this measure provides an index of cerebral blood flow; SPECT does not provide quantitative flow data.

The formula (volume day 1 − volume day 2)/volume day 1) × 100 was used to calculate percent reperfusion. Regions of hyperperfusion were defined as (maximum) 100% reperfusion in view of the recent report of HMPAO hyperfixation relative to cerebral blood flow. When the perfusion defect increased on the second study, a negative reperfusion value was applied (11 patients).

The following definitions of perfusion change were used: (1) hypoperfusion: perfusion level of 12% or less of the homologous region; (2) hyperperfusion: perfusion level of greater than 12% of the homologous region; (3) reperfusion and reperfusion rate: the number of patients in each of the SK and control groups who had reperfusion greater than 25% by volume on the second HMPAO study (patients with normal initial perfusion scans were excluded from the analysis of reperfusion); and (4) change in perfusion volume: the volume of perfusion defect on day 2 subtracted from that on day 1.

Results are presented as the mean±SEM. Statistical analysis was performed by using Student’s t test and one-way analysis of variance (ANOVA) for comparison of unpaired parametric variables. In the analysis of admission perfusion defect volume, the Mann-Whitney U test for nonparametric variables was used (indicated in Table 2). Proportions between groups were compared by χ2 analysis. An analysis of covariance was performed (using time to 99mTc-HMPAO injection as the covariate in a two-way ANOVA model) to correct for the difference in time to first 99mTc-HMPAO injection between the treatment and control groups (shown in the “Corrected” columns in Tables 1 and 2). Results were considered statistically significant if the two-tailed probability was less than .05.

Results

All Patients

Fifty-seven patients were entered into the study: 55 patients from the Austin Hospital and 2 from the Royal Melbourne Hospital. Twenty-two patients were treated with SK; the 35 control patients received no thrombolytic therapy. Both groups otherwise received best medical treatment, which included aspirin in 20 of 22 SK-treated patients and 33 of 35 control subjects. The demographic data for the two groups are listed in Table 1. SK was administered intravenously (less than 4 hours) in 12 cases and intra-arterially (4 to 24 hours) in 10 patients (Table 1). The mean time to SK infusion was automatically used as the reference ROI on the remaining transaxial slices over which the perfusion defect extended. To segment gray matter activity from scalp and ventricular activity a lower cutoff value on the unaffected cerebral hemisphere was chosen (approximately 50% of the maximal count in the study); in this process the white matter was segmented in addition to the scalp and ventricular activity. On each slice the count rate was compared between homologous voxels in the affected and unaffected hemispheres; a count rate of 12% or lower was defined as hypoperfusion. Each hypoperfused voxel was weighted in proportion to the severity of hypoperfusion using the following formula:

\[ \text{Perfusion Defect Index (cm}^2) = \sum \frac{C[n] - C[a]}{C[n]} \Delta V \]

where \(C[n]\) is counts in voxel in unaffected hemisphere, \(C[a]\) is counts in voxel in affected hemisphere, and \(\Delta V\) is voxel size (13.17/1000 cm\(^3\)).
6.5±1.0 hours. Although patients were recruited up to 24 hours after the onset of symptoms and the overall time of the admission SPECT was 8.4±0.73 hours, patients treated with SK were studied significantly earlier than control subjects (SK, 5.4 hours; control, 10.3 hours; P=.001, t test). Patients in the SK-treated group had slightly worse neurological deficits on admission (P=m, t test; Table 1).

The time between HMPAO injections was 24.4±0.2 hours for all patients (SK, 24.3 ±0.4 hours; control, 24.4±0.2 hours). The mean time after stroke onset that the follow-up study was performed was 32.8±0.8 hours (SK, 29.6±0.9 hours; control, 34.7±1.0 hours).

Patients With Initial Perfusion Defect on SPECT

Perfusion abnormalities (in the clinically relevant vascular territory) were present on the first SPECT study in 40 of the 57 patients. Thirty-nine patients had focal areas of hypoperfusion in the territory of the middle cerebral (MCA) and/or anterior cerebral arteries (ACA), and 1 patient had areas of both focal hyperperfusion and hypoperfusion in the MCA territory. Seventeen patients had been treated with SK, and there were 23 control subjects; the two patient groups were well matched for age, sex, severity of neurological deficit, and size of initial hypoperfusion defect (Table 1). The SK group was studied at an earlier mean time than the control group (SK, 5.5 hours; control, 10.0 hours).

The remaining patients with normal perfusion studies had subcortical ischemia in 12 cases (brain stem, capsular, and two anterior choroidal territory infarcts based on clinical and CT grounds), MCA reversible ischemic neurological deficits in 4 cases (most probably had reperfused at the time of the first HMPAO study), and in 1 patient the location of the ischemic area was uncertain.

Reperfusion on the Second SPECT Study (24 to 48 Hours)

Reperfusion on the second SPECT study could only be assessed in the 40 patients who had abnormal admission scans; the remaining 17 patients again had normal studies on the second day. Reperfusion was seen in 23 (57.5%) of 40 patients (Table 2); in the majority of cases reperfusion was partial, although complete reperfusion occurred in 3 cases and hyperperfusion was present in reperfused zones in 2 cases. In 1 case the previously mentioned hyperperfused region became hypoperfused on the second study. In 11 cases the perfusion defect increased in size.

Reperfusion rates (SK, 65%; control, 52%; P=A3, x² analysis) and the proportion of each hypoperfused region that reperfused (SK, 36.5%; control, 22.1%; P=J4, t test) were higher in SK-treated patients but not significantly so (Table 2). The mean change in volume was also higher in the streptokinase group and approached significance (P=.064 after correction for the covariate factor by two-way ANOVA).

Outcome (All Patients)

Eight patients died; 5 patients with large MCA or ICA territory infarcts died of neurological causes during the first 2 weeks after stroke onset, and the 3 other patients died of respiratory causes (2 within the first 2 weeks, the other patient at 2 months).

When outcome was correlated with perfusion change on SPECT (Table 3), patients who did not develop reperfusion on the second SPECT study had significantly higher mortality (F=.008, one-way ANOVA, Table 3), significantly less improvement in neurological score (P=.016, one-way ANOVA), and more functional
Table 2. Demographic and Reperfusion Data of 40 Patients With Abnormal Admission Perfusion Scans

<table>
<thead>
<tr>
<th>Group</th>
<th>Streptokinase</th>
<th>Control</th>
<th>P*</th>
<th>Corrected†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 intravenous, 7 intra-arterial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68.4±2.4</td>
<td>70.7±2.7</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>8/9</td>
<td>11/12</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>Time of admission SPECT, h</td>
<td>5.5±1.0</td>
<td>10.0±1.2</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Admission neurological score (MCNS)</td>
<td>3.6±0.4</td>
<td>4.7±0.7</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Volume of perfusion defect on admission SPECT, cm³</td>
<td>69.9±12.1</td>
<td>56.0±13.2</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Reperfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (%)</td>
<td>11 (65)</td>
<td>12 (62)</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Percent reperfusion</td>
<td>36.5±13.2</td>
<td>22.1±11.7</td>
<td>.42</td>
<td>.74</td>
</tr>
<tr>
<td>Change in volume, mL</td>
<td>29.4±9.1</td>
<td>7.8±5.7</td>
<td>.041</td>
<td>.064</td>
</tr>
</tbody>
</table>

The streptokinase and control groups were well matched for admission neurological score and perfusion defect volume. SPECT indicates single-photon emission computed tomography; MCNS, modified Canadian Neurological score.

*Student's t test was used for statistical analysis except where otherwise indicated.
†Probability value after covariate analysis using two-way analysis of variance (correction for the different time to first ⁹⁹mTc-hexamethylpropyleneamine oxime injection).
‡Mann-Whitney U test.
§*2 analysis.

disability (<.001, one-way ANOVA) than patients with normal perfusion scans and those with reperfusion.

When outcome was compared between the treatment and control groups (Table 1), the improvement in MCNS score at 3 months was significantly higher in the SK-treated patients compared with control subjects (P=.002, two-way ANOVA); however, there was no difference between the two groups in the Barthel index at 3 months. Two of the deceased patients had been treated with SK (Table 1, P=.33, x² analysis).

Angiographic Correlation of Perfusion Changes

Ten patients treated with intra-arterial SK were studied sequentially with DSA and SPECT. Reperfusion on SPECT at 24 to 48 hours correlated with arterial recanalization on DSA in 2 cases (one of which is shown

Table 3. Relation Between Perfusion and Outcome

<table>
<thead>
<tr>
<th>Reperfusion</th>
<th>Normal Scans*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥25%</td>
<td>&lt;25%</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Age, y</td>
<td>70.2±2.5</td>
<td>69.1±2.8</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>10/13</td>
<td>9/8</td>
</tr>
<tr>
<td>Time of admission SPECT, h</td>
<td>7.3±1.1</td>
<td>9.1±1.4</td>
</tr>
<tr>
<td>Admission neurological score (MCNS)</td>
<td>5.0±0.6</td>
<td>3.1±0.6</td>
</tr>
<tr>
<td>Volume of perfusion defect on admission SPECT, cm³</td>
<td>61.1±10.2</td>
<td>63.1±16.7</td>
</tr>
<tr>
<td>Outcome‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in MCNS at 3/12 mo</td>
<td>3.4±0.7</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>Barthel index at 3/12 mo</td>
<td>72.9±7.7</td>
<td>32.8±9.1</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Patients with normal perfusion scans and those who developed reperfusion (≥25%) on the second study had significantly better outcome than patients who had not reperfused on the second scan. SPECT indicates single-photon emission computed tomography; MCNS, modified Canadian Neurological score.

*One patient in whom the location of ischemia was uncertain was excluded.
†One-way analysis of variance was used for statistical analysis.
‡Three control patients with recurrent stroke during the follow-up period were excluded from outcome analysis.
Hemorrhagic Transformation

Hemorrhagic transformation (Table 1) occurred in 6 patients and was not associated with clinical deterioration; 4 patients who developed haemorrhagic transformation had been treated with SK (P = .14, χ² analysis, Table 1). Hemorrhagic transformation occurred adjacent to reperfused regions in 2 cases and in a region of increased ⁹⁹mTc-HMPAO uptake in 1 case.

Discussion

In this study of reperfusion after thrombolytic therapy in acute ischemic stroke, reperfusion was found to be common during the first 48 hours of ischemia, usually partial, and was of prognostic significance. The higher reperfusion indexes (and neurological improvement) seen in the SK-treated group are encouraging; however, a blinded and randomized study involving larger numbers of patients is required to answer this definitively.

The majority of previous studies of reperfusion in stroke have evaluated arterial patency with angiography and more recently with transcranial Doppler ultrasound. There has been one previous report using SPECT; ⁹⁹mTc-HMPAO SPECT was used to evaluate perfusion change after treatment with intravenous recombinant tissue plasminogen activator in five patients. One patient developed reperfusion and had good outcome; another developed partial reperfusion without significant recovery, and the remaining three patients had minimal reperfusion and poor neurological outcome; visual inspection was used to analyze perfusion. The results from this study and our study suggest that reperfusion documented by SPECT is a practical and noninvasive method for evaluating stroke therapy in MCA territory ischemia. Two of the major limitations of this technique are its moderately low resolution (1.2 cm on our camera at full width, half maximum in a resolution phantom) and relative insensitivity for detecting white matter ischemia. These limitations were responsible for the high number of normal scans in this series (17 of 57 patients). Stable xenon CT and diffusion-weighted MRI are additional modalities by which perfusion may be assessed.

Very little is known about the natural history and prognostic value of reperfusion in human ischemic stroke; this information is vital if perfusion techniques are to be used to evaluate treatment as well as in planning therapeutic trials. Although the control group in this study was matched imperfectly to the treatment group with respect to the time of first ⁹⁹mTc-HMPAO injection, it provided new insights into the natural history of reperfusion. Reperfusion occurred in 52% of patients in the control group within 48 hours; it was usually partial (volumetrically measured at 22±11.7%) and was often seen at the periphery of the hypoperfused area or in the distribution of one of the MCA divisions. In addition, four patients with reversible ischemic deficits in the MCA territory and normal perfusion scans had almost certainly reperfused at the time of initial study. Previous data are scant and come from single (as opposed to sequential) cerebral perfusion studies; reperfusion was inferred from the presence of focal hyperemias (planar xenon [¹³³Xe] studies) or luxury perfusion (positron emission tomography [PET]). In one study using planar [¹³³Xe] imaging focal hyperemias were seen in 8 of 21 patients with MCA occlusion within 4 days of stroke onset.¹³ A PET study of 12 patients studied within 48 hours of stroke onset demonstrated that at least some reperfusion had occurred in 4 of 12 patients.¹⁴ A more recent PET study of 18 patients found hyperperfusion in 6 of 18 patients studied between 5 and 18 hours after stroke onset.¹⁵ Angiographic studies have demonstrated arterial occlusion rates of up
to 76%\(^{18}\) within the first 6 hours of MCA territory ischemia, with up to 25% to 33% of occlusions having cleared by 24 to 48 hours\(^{18}\) and 95% by 2 to 3 weeks.\(^{19}\) However, it should be made clear that arterial recanalization may not be associated with tissue reperfusion, as shown in one of our 10 patients in whom combined angiographic and SPECT studies were performed; this may occur when recanalization is incomplete, emboli have lodged in distal branches, or a "no-reflow" phenomenon is operative.

The duration of tissue viability in human ischemic stroke is not known; factors such as the severity of ischemia and extent of collateral circulation are important determinants of viability. Studies in animal models have indicated that a window period of 4 to 8 hours may exist in tissue with blood flow at penumbral levels.\(^{20,21}\)

The results in this study indicate a clear prognostic benefit of reperfusion during the first 48 hours of stroke. Because measurements were performed 24 hours apart (to wait 4 half-lives for decay of \(^{99m}\)Tc) it was not possible to determine exactly when reperfusion occurred or to stratify outcome according to time of reperfusion. A study of angiography and transcranial Doppler ultrasonography in MCA territory ischemic stroke has shown that outcome is improved and infarction is restricted to the striatocapsular region in patients in whom arterial reopening occurs within 8 hours in the presence of good collateral circulation.\(^{22}\)
Reperfusion After Thrombolytic Therapy

Higher reperfusion indexes were present in the SK group but were not statistically significant. The change in volume of perfusion defect approached significance, and this suggests that while proportional reperfusion was similar in the two groups, reperfusion occurred in larger perfusion defects in the SK group.

The results in this study indicate that perfusion measurements by SPECT are feasible and provide useful additional information in the evaluation of thrombolytic therapy. It would be worthwhile to pursue a randomized, blinded, and strictly time-based study of reperfusion in larger numbers of patients.

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