rCBF-SPECT in Brain Infarction: When Does It Predict Outcome?

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We prospectively studied 26 patients with ischemic stroke within 24 hr, after 2 wk, and after 6 mo with thallium-201diethyldithiocarbamate single-photon emission computed tomography (SPECT) and neurologic and functional assessments. The admission flow deficits correlated with outcome. The admission and 6-mo scores correlated with clinical conditions at each time. At 2 wk, the flow deficits were smaller and did not correlate with clinical parameters. Nor did the presence or absence of hyperfixation of the radiopharmaceutical. Six months after the infarct, the flow defect had decreased in 9 of 15 patients in whom three serial scans were available, with better clinical improvement than in the remaining six whose flow deficits increased. More patients in the first group had been treated randomly with the calcium-entry blocker flunarizine. SPECT imaging of rCBF within 24 hr after stroke correlates with clinical outcome and condition, whereas rCBF imaging at 2 wk after the stroke shows no clinical correlation.

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redictions of outcome after ischemic stroke have not always been consistent when they were based on singlephoton emission computed tomography (SPECT) of regional cerebral blood flow (rCBF) (1.2). Some of the discrepancies found in previous studies may be explained by the lack of a fixed time interval between stroke onset and examination by rCBF-SPECT. The results of rCBF-SPECT might depend on the time interval between brain infarction and imaging. In a previous paper (3), we reported the strong relationship between a large flow deficit present within 24 hr after stroke onset and early death from transtentorial herniation. The size and the intensity of the flow deficit at admission on the one hand and the outcome 6 mo after the stroke with respect to overall functional outcome and the Activities of Daily Living (ADL) on the other hand were also related (3). Hayman et al. (1) observed only poor correlations between rCBF-SPECT results

and clinical condition or outcome in 49 patients examined with [123 I]iodoamphetamine (IMP) SPECT. Further they reported that the flow deficits in the subacute period were smaller than those found at admission. Lee et al. (2) found that larger flow disturbances seen with IMP-SPECT were also not always correlated with a poorer outcome, as was found by Bushnell et al. (4). However, their SPECT scans (1,2) were not always made at equal intervals after stroke onset, and information about rCBF-SPECT changes was derived from different patients studied at different time intervals (2).

In this paper, we present the results of consecutive rCBF-SPECT imaging at fixed intervals after acute brain infarction and correlated them with the clinical condition and outcome in 26 patients.

PATIENTS AND METHODS

Consecutive patients admitted with an acute supratentorial cortical brain infarction were studied. They were included in a double-blind randomized pilot study with the calcium-entry blocking agent flunarizine (5). Inclusion criteria were: stable or progressing clinical signs of focal cerebral ischemia, hemiparesis, age over 18 yr, and admission and administration of the radiopharmaceutical within 24 hr after onset of clinical signs. Patients with disabling previous stroke, serious or disabling other chronic disorders, or with one of the classic lacunar syndromes (6) were excluded, as well as patients using calcium-entry blockers. The present study was performed with 26 patients (9 male, 17 female) (Table 1). Informed consent was obtained from the patients or nearest relatives and the study was approved by the local Medical Ethical Committee.

The patients were examined clinically at admission, Days 3, 7, and 14, and after 1, 3, and 6 mo. The following scales were used:

- 1. The Motricity Index (7) for motor function, which is a derivative of the Medical Research Council motor scale and scores 0 for no muscle contraction and 100 for normal strength.
- 2. The Barthel Index (8) for evaluating ADL with a maximal score of 100.
- 3. The five-grade Rankin scale (9) as an overall disability measure. Death was added as a sixth class on the Rankin outcome scale.

A hemiparesis with a Motricity Index score of less than 34 was considered severe, a Motricity Index score between 33

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 TABLE 1

 Entry and Outcome Characteristics in 26 Patients with Supratentorial Brain Infarction

and 67 moderate, and more than 66 light. The Barthel Index and the Rankin Scale were used at 1, 3, and 6 mo. The date and cause of death were documented. The outcome was measured at 6 mo with the Motricity Index, Barthel Index, and Rankin scale.

The rCBF study was performed within 24 hr after stroke onset and was repeated after 2 wk and 6 mo. SPECT imaging was done 10 min after the i.v. injection of 110-150 MBq of thallium-201-diethyldithiocarbamate (201Tl-DDC) (10). In some patients admitted after office hours, ²⁰¹TI-DDC was administered immediately after arrival in the hospital, but the imaging procedure was postponed until the next morning. This is possible with ²⁰¹Tl-DDC, in view of its physical halflife of 73 hr and lack of redistribution after injection for almost 24 hr. A rotating gamma camera (Technicare, Omega 500) fitted with a 30° slant-hole collimator was used with a 6° stepwise rotation for 360° and 30 sec of acquisition time for each step. Two energy windows of 20% were set at 73-89 keV and 167 keV, respectively. For the reconstruction, a Butterworth filter with a cutoff of 0.35 was used. After attenuation correction, photographs of the images, with a lower threshold set at 30% of the maximum pixel value, were analyzed by two observers blinded to the clinical and computed tomography (CT) results of the patients. The size and the degree of the cerebral flow deficits were analyzed visually in a semiquantitative way and expressed on an arbitrary scale, as described elsewhere (3). The observers were only informed about the side of the lesion. Scans with controversial results were discussed and reassessed by the two observers together; the final lesion size was the mean of the results of the two observers separately and their joint revision.

The change in lesion size after 2 wk was expressed as a percentage of the initial score:

relative SPECT change = $\{[(D0-D14)/D0] \times 100\},\$

where D0 is the SPECT score at admission and D14 is the SPECT score at two weeks.

CT (Siemens Somatom DR3, or Philips Tomoscan 350) performed within 24 hr after stroke onset excluded other relevant pathology. CT was repeated after 2 wk and after 6 mo for a clear depiction of the infarct. CT scans were reviewed by one observer blinded to the SPECT scan results but who was informed about the side of the neurologic deficit.

The Mann-Whitney test was used for comparison of the groups (11). Correlations were computed with Spearman's Rank Correlation (11,12). The p values mentioned are two-tailed, unless stated otherwise. Differences between proportions were tested with Fisher's exact test (12).

RESULTS

The characteristics of the 26 patients studied are presented in Table 1. Six patients died within six days after the stroke from transtentorial herniation, diagnosed by the typical clinical syndrome and repeat CT. Autopsy performed on two patients (6 and 14) showed an occluded internal carotid artery in both. In Patient 25, angiography demonstrated a proximally occluded middle cerebral artery. One patient (17) died after 9 wk from a new brainstem infarction, and another patient (22) died after 6 wk from a myocardial infarction. The evolution in time of the motor strength (Motricity Index) is shown in Figure 1. Apart from the six patients who deteriorated and died in the first week, eight other patients had a decrease in motor strength after admission, but subsequently showed some improvement.

Eleven patients had a poor outcome at 6 mo: eight had died (see above), and three more had become functionally dependent (Rankin > 3).

The final CT diagnosis (Table 1) was made from the best CT scan available in each patient. In three patients who presented with a sensory-motor deficit, the lesion proved to be a lacunar infarction. All patients had a clearly demarcated infarct on the CT scan, except for Patient 17, in whom a final anatomical diagnosis could only be based on clinical and rCBF-SPECT information.

The rCBF defects at admission, after 2 wk, and after 6 mo are presented in Figure 2A. Figure 2B demonstrates the results from the 15 patients in whom three consecutive rCBF-SPECT scans could be obtained. Two surviving patients refused (Patients 12 and 24). The admission rCBF-SPECT scan of Patient 4 could not be quantified for technical reasons, but was incompatible with a lesion of a large size; this was confirmed by later rCBF-SPECT and CT scans. The median lesion size after 2 wk was smaller than at admission (6 versus 22; p < 0.005). The rCBF-SPECT results at admission correlated with the Motricity Index at admission (r = -0.52, p < 0.05), with the Motricity Index at 2 wk (r = -0.54, p < 0.05), and with the ADL (Barthel Index) (r



FIGURE 1

Development of motor strength (Motricity Index) in a group of 26 patients with acute supratentorial brain infarction during the first 6 mo. The median, upper, and lower quartiles are presented.



FIGURE 2

Development of rCBF deficits on consecutive SPECT images at admission, 2 wk, and 6 mo after a supratentorial ischemic stroke in 26 patients. The flow deficit is expressed vertically in a visual semiquantitative scale. A high score means a large flow disturbance. (A) Medians, upper, and lower quartiles of all observations. (B) Results in the 15 patients in whom three consecutive examinations were possible.

= -0.49, p < 0.05) and the overall Rankin score (r = 0.51, p < 0.05) at 6 mo.

The images at 2 wk demonstrated no correlation with motor strength (Motricity Index) after 2 wk and after 6 mo, or with ADL (Barthel Index) and functional (Rankin) outcome at 6 mo. The relative decrease in size of the flow deficit at 2 wk was not related to Motricity Index at 2 wk (r = 0.13; p > 0.20), Motricity Index at 6 mo (r = 0.33; p > 0.20), or Barthel Index at 6 mo (r = 0.14; p > 0.01) (see equation in Methods Section).

The flow deficit at 6 mo again correlated with both the Motricity Index (r = -0.49, p < 0.05, one-tailed)



FIGURE 3

Consecutive SPECT and CT scans from a 60-yr-old woman (Patient 21) with a severe left-sided hemiparesis. Initially, CT shows only slight hypodensity in the right frontoparietal region, but finally the full extent is evident. The initial flow deficit on SPECT after 2 wk becomes "filled in" with mixed normal activity to hyperactivity.

and the Rankin score (r = 0.67, p < 0.05) at that time. The size and intensity of the lesion 6 mo after the stroke were somewhat smaller than at admission (Fig 2A), but this was statistically nonsignificant (p > 0.33).

In six patients, a region of unusual increased concentration of the radiopharmaceutical was found, usually at the rim of the lesion (Fig. 3). This hyperactivity was only encountered in the rCBF-SPECT image made after 2 wk. There was no difference in the size of the initial flow deficits between patients with hyperfixation and those without (p < 0.35). When comparing the groups of patients with hyperactivity at 2 wk to those without, no differences in functional (Rankin), ADL (Barthel Index), or motor (Motricity Index) outcome after 6 mo were encountered, nor were differences found in degree of amelioration of motor function at 2 wk or 6 mo as compared to admission (expressed as a percentage of the initial motor score). Similar to results in the other patients, the later CT images demonstrated a clearly demarcated infarct.

From the patients in whom serial scans were available, two groups could be recognized due to changes in perfusion deficit between admission and 6 mo. In Group A (n = 9), the defect had grown smaller, between 5 to 15 arbitrary units, median 8.5. The motor strength had significantly improved (p < 0.01) in parallel with this decrease. Initially, three had severe, four moderate, and two light hemiparesis; six months later all had a light hemiparesis. In Group B (n = 6), the flow disturbance increased or remained equal after 6 mo as compared to admission. This increase ranged from 0 to 28 arbitrary units, median 13.5. In this group, there was also some motor improvement, but this was statistically insignificant (p < 0.15). Initially, five patients had severe hemiparesis and one had light hemiparesis; later one had severe hemiparesis, four moderate, and one light hemiparesis. There was no difference in average functional outcome (Rankin) and ADL (Barthel Index) between the two groups. The flow disturbances at admission in both groups were the same and were not statistically different.

The timing of the initial SPECT was somewhat different. In Group A, the median was 6.5 hr (range 1.5–24) after stroke onset; in Group B, the median was 11.25 hr (range 1.5–20). This difference was not statistically significant.

In Group A, six patients received flunarizine and three received a placebo; in Group B, two patients received flunarizine and four received a placebo (p = 0.23).

DISCUSSION

In this series of consecutive rCBF-SPECT studies in patients with ischemic stroke, we found that the initial lesion decreased substantially after 2 wk, and that it increased again to a size comparable to admission size after 6 mo.

The lesion size at admission predicted transtentorial herniation and correlated negatively with the motor performance at 2 wk; it also correlated with the overall Rankin outcome and ADL after 6 mo, as shown in our previous report (3).

Apart from this "prognostic" value, there was also a relationship between the rCBF deficit and the "same time" clinical status. On the initial rCBF-SPECT scan, lesion size correlated inversely with motor strength at admission. The rCBF-SPECT taken 6 mo after the stroke correlated weakly with motor strength and moderately with the Rankin outcome score at that time.

The existence of an ischemic penumbra (13) might be suggested by our finding of a decrease in lesion size in 9 (Group A) out of 15 assessable patients. This was accompanied by a substantial improvement of the motor strength. These rCBF-SPECT scans were made between 3.75 and 24 hr after the stroke, suggesting that tissue with an ischemia of 24 hr duration may still partly regain useful reflow and function. Recently, Mountz et al. (14) described better recovery for patients with a larger lesion on rCBF-SPECT as compared to CT. This phenomenon must be based on some other mechanism, as there is no evidence that an ischemic penumbra might last more than 5 yr. The median time interval between brain infarct and rCBF-SPECT in their study was 4 mo, and the maximum was 5.50 yr.

The patients in Group A (more improvement, decrease in rCBF deficit) were investigated with rCBF-SPECT somewhat earlier than the patients in Group B (no significant improvement, increase in rCBF deficit). Although this difference was statistically not significant, it seems plausible that a longer duration of ischemia is less readily followed by improvement.

Another interesting feature was that more patients in Group A received flunarizine than in Group B, again without statistical significance. Like the clinical results of the pilot study (5), this is compatible with a therapeutic cytoprotective effect of flunarizine. Fieschi et al. (15) found a similar result in seven patients who received the calcium-entry blocker nimodipine. The lack of correlation between the SPECT scan at 2 wk and relevant clinical parameters was striking. The flow defects were smaller or absent or there was a hyperfixation. A decrease in the flow defect after 10 days was also found by Rango et al. (16) and Hayman et al. (1). Thefollow-up rCBF-SPECTs (16) were again abnormal, as in our patients. No clinical relevance of this phenomenon was detected, as in our study.

The patients with hyperfixation did not differ from the others in terms of clinical characteristics and outcome variables. Hyperfixation in the subacute period (between 1 and 4 wk) after brain infarction has been demonstrated with several radiopharmaceuticals: tri-

([¹²³]] methyl-hydroxy-iodobenzyl-propanediamine HIPDM) (16,17), [123I]IMP (17), and 99mTc-HMPAO (16,19,20). Hyperfixation has been linked to good prognosis (21), but in other studies (2,16,22), including the present one, this was not confirmed. Various mechanisms might be responsible for this hyperfixation (18, 22,23): hyperperfusion, focal vasodilatation and loss of autoregulation, new capillaries, decreased degradation, passage of hydrophilic radiopharmaceutical metabolites through an altered blood-brain barrier, and retention in macrophages and leukocytes. The presence of an altered blood-brain barrier is demonstrated by contrast enhancement on CT (24) and positive technetiumpertechnetate brain scans in the second and third week (25). In this period, hyperemia as demonstrated with ¹³³Xe can be found in about 10% of cases (23,26,27), and luxury perfusion (decreased oxygen extraction fraction) can be shown with positron emission tomography. This is often coupled to an unfavorable outcome (28), especially if the rCBF falls below 20 ml/100 g/min (29). The findings cannot be explained by redistribution. Apart from one published observation (10), on many more occasions early and delayed scanning after i.v. Tl-DDC injection failed to disclose any redistribution. Even if present, it would not change our results since delayed imaging was only performed in some patients admitted and injected with the radiopharmaceutical within 24 hr after stroke. All further examinations, at 2 wk and at 6 mo, were done by protocol (10) with imaging starting 10 min after i.v. injection, thereby excluding any redistribution.

On the basis of our experience and the above-mentioned results with other radiopharmaceuticals, we believe that the results of rCBF-SPECT in acute ischemic stroke are heavily dependent on the interval between stroke and imaging. The rCBF-SPECT image obtained is not the sole product of regional cerebral perfusion, since in the subacute period a whole array of processes is at hand. As a result, the rCBF-SPECT information has no or only a poor correlation with the clinical condition in the period around 2 wk after the stroke.

On the other hand, early rCBF-SPECT immediately performed after brain infarction produces information unattainable by CT or clinical examination (3). Images from a time period well beyond the 2-wk period have a good correlation with the clinical situation. With these limitations, rCBF-SPECT imaging gives additional information on clinical condition and prognostication above CT scanning and physical examination, which at present seems to be of particular value in the assessment of early stroke therapies (30).

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