Cerebral Glucose Metabolism as a Predictor of Rehabilitation After Ischemic Stroke

Wolf-Dieter Heiss, MD; Heinz-Georg Emunds, MD; Karl Herholz, MD

Background and Purpose: Permanent neurological deficits after ischemic stroke are primarily determined by the location and size of an infarct, but social recovery and rehabilitation also depend on the functional status of brain tissue outside the infarct. Since neuronal loss and functional deactivation in peri-infarct tissue are reflected as changes in flow and metabolism, measurement of glucose consumption may yield an additional measure of rehabilitative capacity.

Methods: Seventy-six nondiabetic patients (48 men, 28 women; mean age, 56.7±14.37 years) with a first unilateral supratentorial ischemic infarct were consecutively enrolled. At stable neurological and clinical condition 9±7.2 days after the attack, cerebral metabolic rate of glucose (CMR_{glu}) in noninfarcted brain regions was measured by positron emission tomography of fluordeoxyglucose. Outcome was assessed 21 to 77 (mean, 50.5±11.7) months after the stroke with a rehabilitation index for daily life activities.

Results: At time of assessment of outcome 16 patients had died (score, 0), 22 were completely recovered (score, 200), and 38 had partially improved (rehabilitation score, 5 to 195). Younger age, absence of arterial hypertension and cardiac disease, but also higher global, ipsilateral, and contralateral CMR_{glu} were significantly related to a better final outcome (P=.001), whereas sex and neurological deficits in the subacute stage after stroke were not related to final outcome. To evaluate the significance of CMR_{glu} further after adjustment for clinical prognostic variables, a multiple regression analysis of the effect of age and CMR_{glu} on rehabilitation score in homogeneous subgroups of partially recovered patients was performed. It revealed a significant positive correlation of CMR_{glu} (P=.016) with recovery in hypertensive subjects, while age was the dominant prognostic factor (P=.07) in patients with normal blood pressure.

Conclusions: These results demonstrate that outcome after stroke is significantly influenced by several factors incapacitating brain function in addition to the ischemic attack. In addition to age and cardiac disease, hypertension is an important factor leading to widespread arteriopathy with neuronal loss and tissue damage. The significant correlation of CMR_{glu} outside the infarct with functional recovery in hypertensive subjects probably reflects the extent of hypertensive tissue damage and subsequently reduced capacity to compensate for the focal ischemic insult. (Stroke. 1993;24:1784-1788.)

KEY WORDS cerebrovascular disorders glucose hypertension prognosis rehabilitation tomography, emission-computed

Although various factors derived from clinical features or patient characteristics have been found to be individually related to outcome after ischemic stroke, only multivariate analysis or stepwise regression of several variables can help to predict probabilities of mortality, survival, and functional recovery in stroke victims. These statistical procedures yield reliable estimates for groups of patients, but their validity in individual cases is limited. For such applications quantitative measures, by which the capability of the brain for compensation of infarct-related defects can be assessed, might be helpful. Because neuronal loss and deactivation in tissue outside the infarct are reflected as changes in physiological variables, the predictive value of glucose metabolism on functional outcome was analyzed in stroke patients by multiple regression analysis in addition to risk factors and clinical data.

Subjects and Methods

Patients

Seventy-six consecutive patients (28 women, 48 men; age, 21 to 77 years [mean, 56.7±14.37 years]) who had suffered a unilateral supratentorial nonhemorrhagic ischemic infarction were studied. Their diagnosis was based on history and thorough clinical workup including neurological and medical examination, electroencephalography, and Doppler ultrasonography of extracranial vessels. Infarcts were verified in all cases by x-ray computed tomography (CT) and, in some cases, by additional magnetic resonance imaging. Infarcts were located in the basal ganglia (23 patients), restricted to cortex and subcortical white matter (31 patients), or involved cortex as well as basal ganglia (22 patients). Exclusion criteria were reversible neurological deficits (transient ischemic attack and prolonged reversible ischemic neurological deficit) and a history of previous strokes or other neurological or acute medical diseases. Patients with diabetes were excluded because of a
possible confounding effect of that condition on cerebral glucose transport and metabolism.3 Thirty-nine patients (51%) suffered from chronic arterial hypertension, and 31 patients (41%) had symptomatic cardiac disease (coronary heart disease or cardiac failure).

During the acute phase after their stroke, all patients received standard treatment (hemodilution with dextran 40 or hydroxyethyl starch), including intensive care if necessary. rehabilitative measures were initiated as early as possible in the neurology department and continued thereafter in a rehabilitative institution. During the subacute phase, 9.2±7.2 days after the ictus when clinical condition and neurological deficit had stabilized, the clinical and neurological states were assessed and glucose metabolism was studied by positron emission tomography (PET). The metabolic data were compared with a control group of 51 healthy subjects (mean age, 44.8±15.03 years; range, 18 to 77 years).

**Positron Emission Tomography**

Cerebral metabolic rate of glucose (CMR_glu) was measured by PET of 2-[(18)F]fluoro-2-deoxy-D-glucose (FDG) in a supine resting condition with eyes closed and ears unplugged with a four-ring, seven-slice positron camera (Scanditronix PC 384, Uppsala, Sweden; full width at half maximum, 7.8 mm; slice thickness, 11 mm). Two intercalated sets of seven slices each were recorded 30 to 40 and 40 to 50 minutes after intravenous injection of approximately 185 MBq FDG, yielding a total of 14 partially overlapping transaxial images in parallel with the canthomeatal line. Multiple arterialized blood samples were drawn from a dorsal hand vein heated by a 44°C water bath, and plasma activity was determined from 0 to 50 minutes after injection. Procedural details as well as normal values were reported previously.6 The cerebral glucose consumption rate was calculated pixel by pixel, with adjustment of K1 and K2 to measured activity and a lumped constant of 0.42.7 The infarct was outlined manually, guided by hypodense areas on simultaneously displayed CT scans. The remaining brain tissue was mapped with a standardized computer-assisted regionalization procedure to sample mainly gray matter.8 Average gray matter CMR_glu of all noninfarcted gray matter regions in the ipsilateral and contralateral hemisphere, the difference between these hemispheric values, and the total average of all noninfarcted brain regions (infratentorial and supratentorial, gray matter and white matter of semioval center) were used for statistical analysis.

**Rehabilitation Score**

Long-term outcome was assessed for an observation period of 21 to 77 (mean, 50.5±11.72) months after the stroke. For this purpose a questionnaire was used that included the Barthel Index9 and 10 additional questions that mainly referred to functioning in daily life with respect to cognitive performance (orientation, memory, comprehension, various language functions), housekeeping (preparing meals, outside responsibilities), and social interaction (visits, participation in excursions and events) as suggested by Sarno et al.10 This index included 20 questions with graded answers yielding a maximum score of 200 for complete rehabilitation. The questionnaire was completed for all patients. Forty-two patients were able to answer the questions without help, in 17 the questionnaires were completed by or with the assistance of relatives or friends, in 7 cases with the help of family doctors or nurses, and in 6 after examination of one of us (H.-G.E.) at home.

**Statistical Analysis**

Descriptive statistics are reported as mean±SD. Nonparametric tests (Wilcoxon, Spearman’s rank correlations) were used preferentially, because rehabilitation scores were not distributed normally in the whole group. Differences among frequencies were examined by Mantel-Haenszel χ2 test. In the subgroup of patients with partial rehabilitation, normal distribution of rehabilitation scores could be achieved by logarithmic transformation (ln[200−x]), and regression analysis was applied. All statistical procedures were based on a commercial software package (SAS Institute, Cary, NC).

**Results**

At the time of the PET study all patients suffered from distinct neurological deficits with a motor and/or sensory hemisindrome present in 63 patients (41 right, 22 left), hemianopsia (visual field defects) in 13, aphasia in 25, moderately impaired consciousness in 18, and extrapyramidal symptoms and epileptic seizures in 1 patient each. Patients could present several symptoms of the various categories (motor, sensory, visual, aphasic, and others) and were classified as monosymptomatic (n=17), disymptomatic (n=25), and polysymptomatic (n=34). Thirty-nine patients suffered from arterial hypertension (multiple increased blood pressure values [diastolic 95 mm Hg or greater, systolic 160 mm Hg or greater] in the subacute phase after stroke or history of treated hypertension); in 31 patients cardiac disease (coronary heart disease, myocardial infarction, arrhythmia, valvular disease, cardiac failure) complicated the picture. Both hypertension and heart disease were found in 20 patients. CMR_glu as measured in the subacute stage after the first ischemic stroke was significantly reduced in the infarcted region (19.4±6.34 µmol/100 g per minute), slightly decreased in the ipsilateral hemisphere outside the infarct (32.0±5.73 µmol/100 g per minute), and in the lower normal range in the contralateral hemisphere (34.1±6.06 µmol/100 g per minute). The ipsilateral/contralateral side difference was 2.2±2.42 µmol/100 g per minute, and the global CMR_glu was 30.2±4.90 µmol/100 g per minute (Table 1).

At the time of assessment of outcome, 50.5±11.72 months after the ischemic stroke, 16 patients had died (rehabilitation index, 0), 22 had recovered completely (rehabilitation index, 200), and in 38 improvement was incomplete (rehabilitation index, between 5 and 195 [mean, 173.7±37.38]). The grade of rehabilitation was significantly correlated to the variables age (Spearman r=−.47, P=.0001) and global, ipsilateral, and contralateral CMR_glu (Table 1), but CMR_glu asymmetry was not related to outcome. A plot of average global, ipsilateral, and contralateral CMR_glu in fully recovered, partially recovered, and deceased patients is shown in Fig 1. Arterial hypertension and cardiac disease were indicative of unfavorable outcome: 13 of the 16 patients who died in the course were hypertensive at the time of their stroke in contrast to 7 of the 22 patients who recovered completely (P=.003). Cardiac disease was manifest in
11 of 16 patients who eventually died, in contrast to 5 of 22 with complete recovery (P=.005). Neither sex nor complexity of neurological deficits was significantly related to outcome (Table 2).

Because the patients' rehabilitation scores were unevenly distributed, with large proportions of maximal (completely recovered) and minimal (deceased) values, statistical analysis of the interaction of various factors on outcome was not feasible. Therefore, the subgroup of partially improved patients was analyzed. In that group rehabilitation scores were normally distributed after logarithmic transformation (ln[200−x]), and a multiple regression analysis of the effect of age and CMRglu was possible. Hypertension was of some prognostic influence in this subgroup (normotensive subjects reached scores of 168±27.3; hypertensive subjects, 146±47.4; P=.17), whereas an effect of cardiac disease on outcome was absent in this group (rehabilitation score of 154±46 in patients without versus 161±27 in patients with cardiac disease; P=.89). Therefore, regression analysis was performed separately for normotensive and hypertensive patients. In normotensive patients (n=19), age was the most important prognostic factor, although this relation did not reach the 5% level of significance (P=.07). Metabolic rates had no significant correlation to rehabilitation in this subgroup (probability values between .62 and .96 for global, ipsilateral, and contralateral CMRglu). In hypertensive patients (n=19), however, glucose metabolism was the only factor significantly correlated to level of outcome (P=.016 for global, P=.038 for ipsilateral, and P=.045 for contralateral CMRglu), whereas age had no significant influence on rehabilitation score (P=.72). Fig 2 shows a scatterplot of rehabilitation score versus global CMRglu (r=−.56) to illustrate that relation (the negative sign is due to the transformation of rehabilitation scores). Because we accounted for the effect of age by multiple regression analysis, the relatively young age of our patient sample (56.7±14.37 years) probably does not bias the results.

Hemispheric metabolic asymmetry was generally not of prognostic significance. Side differences between affected and contralateral hemisphere, however, tended to be smaller (1.9±2.70 versus 2.7±2.98 μmol/100 g per minute; P=.16), and global metabolism was significantly lower (29.2±3.28 versus 31.9±4.43 μmol/100 g per minute; P=.04) in hypertensive than in normotensive subjects, suggesting more severe and less focally accentuated metabolic impairment in patients with hypertension.

**Discussion**

Because typical stroke patients are elderly and have a range of comorbid diseases contributing to functional decline,11,12 it is important in the estimation of long-term prognosis early after the attack to differentiate the effects of age from those of illness.13 Of all the factors investigated, age was the single most important determinant for short-term mortality and long-term outcome1,2 and must be considered as a major factor in multivariate analysis, where heart disease, hypertension, and a measure of neurological function must be included in a predictive model of long-term survival after stroke.2,3 Even in our small sample of 76 nondiabetic patients studied in the subacute stage after their first ischemic hemispheric stroke, the individual factors age, arterial hypertension, and cardiac disease were significantly related (P=.001) to functional outcome assessed by a modified index of activities of daily living 2 to 6.5 years after the ictus. Overall, the CMRglu in the first weeks after stroke was related to long-term outcome, with significant differences among the groups of eventually deceased, partially improved, and completely recovered patients. Similar differences were described previously for cerebral blood flow measured early after stroke, when patients were retrospectively grouped according to their long-term neurological or social outcome.14,15 While global oxygen consumption was not related to neurological deficits,15 relative changes in glucose metabolism and the pattern of metabolic abnor-

![Fig 1. Bar graphs show mean±SD values of global, ipsilateral, and contralateral cerebral metabolic rate of glucose (CMRGlu) (in micromoles per 100 g per minute) in the three major outcome groups.](http://stroke.ahajournals.org/)

**TABLE 1. Mean±SD Values of Age and Metabolic Rates in Control Subjects and Patients, and Correlation Coefficients With Rehabilitation Index in Patients**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=51)</th>
<th>Patients (n=76)</th>
<th>Correlation With Rehabilitation Index (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.8±15.03</td>
<td>56.7±14.37</td>
<td>−.47 (.0001)</td>
</tr>
<tr>
<td>Global CMRg, μmol/100 g per min</td>
<td>34.1±4.28</td>
<td>30.2±4.90</td>
<td>.39 (0.005)</td>
</tr>
<tr>
<td>Gray matter ipsilateral CMRg, μmol/100 g per min</td>
<td>39.5±4.62</td>
<td>32.0±2.93</td>
<td>.42 (.0001)</td>
</tr>
<tr>
<td>Gray matter contralateral CMRg, μmol/100 g per min</td>
<td>34.1±6.06</td>
<td>31.9±6.06</td>
<td>.43 (.0001)</td>
</tr>
<tr>
<td>CMRg, asymmetry,* μmol/100 g per min</td>
<td>−0.5±0.84</td>
<td>2.2±2.42</td>
<td>.07 (NS)</td>
</tr>
</tbody>
</table>

CMRg indicates cerebral metabolic rate of glucose.

*Left minus right hemisphere in control subjects; contralateral minus ipsilateral in patients.
TABLE 2. Distribution of Clinical Prognostic Variables

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Deceased</th>
<th>Partially Recovered</th>
<th>Fully Recovered</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>13</td>
<td>19</td>
<td>7</td>
<td>.003</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>3</td>
<td>19</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>11</td>
<td>15</td>
<td>5</td>
<td>.005</td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>5</td>
<td>23</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>10</td>
<td>27</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>6</td>
<td>11</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Neurological deficit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monosymptomatic</td>
<td>17</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Disymptomatic</td>
<td>25</td>
<td>7</td>
<td>14</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Polysymptomatic</td>
<td>34</td>
<td>8</td>
<td>16</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

malities were significantly related to both types of clinical syndromes and the degree of eventual recovery after an average follow-up of 3 months. Infarct size may also be of prognostic relevance, but its planimetric measurement on CT was not possible in this study because scans were recorded on various scanners with different technical parameter settings.

In our study the analysis of an interaction of various factors on outcome was complicated by an uneven distribution of patients with respect to their rehabilitation index: a relatively high proportion either reached the maximal (complete recovery, n=22) or minimal (deceased, n=16) score. Hypertension and cardiac disease were unevenly distributed among these groups, and the presence of both was highly indicative of fatal outcome. Multiple regression analysis of the combined effect of various factors on prognosis could therefore only be performed in the group of partially recovered patients whose rehabilitation scores were normally distributed after logarithmic transformation. To improve discriminative power, especially with respect to quality of life in states of better rehabilitation, the Barthel Index, which has good reproducibility and high concordance with other tests but moderate sensitivity, was extended with 10 additional items modified from the functional life scale of Sarno et al. In these partially rehabilitated patients two subgroups evolved from the analysis: the 19 normotensive subjects, in whom age was the most important factor determining prognosis, but glucose metabolism was of insignificant influence; and the 19 hypertensive stroke victims, in whom glucose metabolism was the only factor significantly related to the rehabilitation score, while age was without effect.

This result permits two conclusions. As in experimental focal ischemia, where regional blood flow and metabolism are related to cellular loss in the tissue outside the gross infarction, metabolic studies by PET assess the condition of the tissue and its capability for functional improvement. Compensatory strategies, which were recently demonstrated by PET for regained motor function after ischemic stroke and which are the basis for continuing functional recovery following rehabilitation after stroke, depend on the preservation of effective neural networks. Reorganization of these neural networks helps to overcome a distinct neurological deficit, such as motor impairment or aphasia, and can be demonstrated in task-related activation studies. On the other hand, the results stress the importance of the functional capacity of the whole brain to cope with a focal defect. If this functional capacity is impaired by chronic brain damage, the rehabilitative state reached long after the ictus is limited. The data suggest that hypertension is a chronic condition leading to ischemic cellular losses in the brain.

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