Cognitive Impairment Is Related to Cerebral Lactate in Patients With Carotid Artery Occlusion and Ipsilateral Transient Ischemic Attacks

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Background and Purpose—Patients with carotid artery occlusion (CAO) and ipsilateral transient ischemic attack (TIA) can have lasting cognitive impairment, despite the recovery of focal neurological deficits. We sought to assess whether cognitive impairment in these patients is associated with hemodynamic compromise and/or impaired cerebral metabolism.

Methods—In 39 consecutive patients with a TIA associated with an angiographically proven occlusion of the carotid artery, we examined (1) cognitive functioning, (2) cerebrovascular reserve capacity of the middle cerebral artery ipsilateral to the CAO as measured by transcranial Doppler ultrasound, and (3) metabolic ratios as measured by 1H-MR spectroscopy in the centrum semiovale ipsilateral to the symptomatic CAO. Findings were compared with those in healthy control subjects.

Results—As a group, patients were cognitively impaired. Mean CO₂ reactivity and the mean ratio of N-acetyl aspartate to creatine were decreased. In approximately one third of patients, lactate was present in noninfarcted regions. The presence of lactate proved to be a stronger correlate of cognitive impairment than MRI-detected lesions (β = 0.41 versus β = 0.15). Cognitive impairment did not correlate with CO₂ reactivity or the ratio of N-acetyl aspartate to creatine.

Conclusions—This exploratory study in patients with CAO and ipsilateral TIA showed that 1H-MR spectroscopy–detected lactate in noninfarcted regions is a better indicator of cognitive impairment than MRI-detected lesions. Cognitive impairment did not correlate with CO₂ reactivity.

Key Words: carotid artery occlusion cerebral ischemia, transient cerebral metabolism cognitive disorders hemodynamics

Patients with obstructive disease of the carotid artery who have suffered a transient ischemic attack (TIA) can have lasting cognitive impairment, despite the recovery of focal neurological deficits. This holds true even for patients without ischemic lesions on MRI or history of stroke. The cause of this cognitive impairment has not been elucidated yet. Thromboembolism and chronic cerebral hypoperfusion have been suggested to play a role.

The association between hemodynamic compromise and cognitive impairment has not been examined in patients with TIA, but correlations have been reported in patients with acute stroke, vascular dementia, or cerebral microangiopathy. One indication of hemodynamic compromise is exhausted cerebral autoregulation of the cerebral blood flow (CBF), as can be demonstrated by the inability to respond to vasodilatory stimuli. Additionally, cerebral metabolic changes found on 1H-MR spectroscopy (1H-MRS) in combination with low blood flow have been suggested to indicate compromised CBF.

The purpose of the present study was to assess whether cognitive impairment in patients with carotid artery occlusion and ipsilateral TIA is associated with a poor hemodynamic or metabolic state of the brain, as measured by transcranial Doppler (TCD) CO₂ reactivity and metabolic measurements by 1H-MRS.

Subjects and Methods

Patients
Thirty-nine consecutive patients with symptoms of transient (lasting <24 hours) ischemia associated with angiographically proven occlusion of the internal carotid artery (ICA) were investigated at the...
University Medical Center Utrecht (the Netherlands). In all patients, symptoms had occurred at most 6 months before inclusion in the study. Patients experiencing stroke within 6 months before the study and those with a modified Rankin score of ≥3 were excluded.

Of the 39 patients, 22 had suffered symptoms of cerebral ischemia, and 17 had experienced only transient monocular blindness. Cerebral symptoms had consisted of facial or limb weakness (21 patients), sensory disturbances (12 patients), and cortical deficits such as homonymous hemianopia and dysphasia (10 patients). The symptomatic ICA occlusion was on the left side in 23 and on the right side in 16 patients. Thirteen patients also had a contralateral ICA occlusion (n=6) or a contralateral stenosis of at least 70% (n=7) (according to the North American Symptomatic Carotid Endarterectomy Trial criteria). Volume blood flow in the middle cerebral artery ipsilateral to the symptomatic ICA occlusion, as measured with MR angiography, was decreased in patients (mean ± SD, 80 ± 28 mL/min). Thirteen patients had a history of a minor ischemic stroke that had occurred 7 months to 17 years previously (median, 3 years).

All patients underwent neuropsychological assessment, MR investigations, and TCD ultrasonography as described below. The median time intervals between the last ischemic event and neuropsychological, MR, and TCD investigations were 54, 50, and 47 days, respectively (range, 2 days to 6 months). In each patient, all investigations were done within a few days.

Control Subjects
Spouses and occasionally siblings of the patients were asked to cooperate with the neuropsychological assessment, thus providing a healthy control group. Excluded were persons with neurological or psychiatric diseases.

The control group for the MR investigations (MRI, 1H-MRS) consisted of subjects who were treated in the neurology or urology department for something other than intracranial disease. No control subjects had a history of ischemic neurological deficits, and none showed abnormalities on MRI scans of the brain. The TCD control group consisted of subjects who were investigated before implantation of an internal cardioverting defibrillator. These subjects all had a normal cardiac output function and no history of ischemic neurologic deficits.

Neuropsychological Assessment
The tests and the parameters used for data analysis are listed below. Patients were screened for the presence of dysphasia, agnosia, or apraxia. Signs of these disorders in executing the tests, in making conversation, or in moving around were recorded and, if present, explored further by means of a picture-naming and writing task in case of dysphasia and a drawing task in case of unilateral neglect.

General Intelligence
Nonverbal intelligence was assessed with the Standard Progressive Matrices. We used a time limit of 20 minutes and scored the number of correct answers (maximum, 60). In addition, we performed the vocabulary subtest of the Wechsler Adult Intelligence Scale–Revised, which is relatively insensitive to brain damage and yields an indication of premorbid verbal intelligence. The maximum score is 70.

Learning and Memory
From the Wechsler Memory Scale Form 1, we used the raw score (maximum = 97). The Verbal Learning and Memory Test is the recently developed Dutch version of the California Verbal Learning Test. The reproductions of a list of 16 orally presented nouns were summed over 5 trials (maximum, 80). On the Visual Retention Test part C, administration A, we scored the number of errors.

Executive Function
From the Trail Making Test, we used the number of errors (parts A and B) and the increase in execution time from part A to part B. From the Modified Card Sorting Test, we scored the number of errors.

In word production according to lexical rules (UNKA test), a production time of 60 seconds per phoneme was used, and the total number of correct words was counted.

Reaction Speed
In one of the “go–no go” conditions of the Vienna reaction apparatus, combinations of stimuli (“light–light”) were presented among irrelevant signals that had to be ignored. The median reaction time (in milliseconds) was calculated and used as a parameter.

Mood
The VROPSOM is the Dutch version of the Depression Adjective Check Lists, which screen for the presence of depressive affect. The score was the sum of dysphoric items ticked and euphoric items not ticked.

We obtained an overall measure of cognitive impairment (cognitive impairment score) by converting raw scores on all cognitive tasks except vocabulary to standardized z scores (mean of normative data minus patient’s score divided by the SD of normative data) and summing these z scores. A higher impairment score indicates worse cognitive functioning. The normative data consisted of psychologically established norms, adjusted for age, sex, and education or estimated premorbid intelligence. In the absence of adequate norms (Trail Making Test, reaction speed task), the performances of the male and female control groups were used.

MRI Studies
MR studies (MRI, 1H-MRS) were performed on a 1.5-T whole-body system (AC5/NT-15 model, Philips Medical Systems). MRI investigations consisted of a sagittal T1-weighted spin-echo sequence (repetition time [TR], 545 ms; echo time [TE], 15 ms; slice thickness, 4 mm with a 0.6-mm interslice gap; field of view [FOV], 225 mm: matrix, 256×256) and a transaxial T2-weighted spin-echo sequence (TR, 2000 ms; TE, 20 and 100 ms; slice thickness, 7 mm with a 1.5-mm interslice gap; FOV, 225 mm; matrix, 256×256). All MRI scans were reviewed independently by 2 investigators (C.J.M.K., L.J.K.) for the presence of infarcts or white matter lesions. White matter lesions were graded according to the method of Van Swieten et al.

1H-MRS
1H-MRS was performed with a single voxel technique (TR, 2000 ms; TE, 136 ms; 2000-Hz spectral width; 2048 time domain data points; 64 signals acquired). In each subject, a volume of interest (VOI) (typically 70×35×15) was selected in the centrum semiovale of the hemisphere ipsilateral to the symptomatic ICA occlusion, thus containing primarily white matter. The anterior-posterior and left-right dimensions of the VOIs were chosen so that regions containing subcutaneous lipid were excluded. Areas of gray or white matter hyperintensities were excluded from the VOI with a margin of 2 cm, thus reducing the VOI in size.

After selection of a VOI, the 90° pulse length was determined. To minimize eddy currents and to maximize the water echo signal, spectroscopy was first performed without water suppression for adjustment of the gradients. Subsequently, localized automatic shimming of the VOI was performed, resulting in a water resonance line width of ≤6 Hz (full width at half-maximum).

Water suppression was performed by selective excitation (60-Hz bandwidth), followed by a spoiler gradient. After zero filling of the time domain data points to 4096 data points, gaussian multiplication of 5 Hz, exponential multiplication of −4 Hz, Fourier transformation, and baseline correction, the N-acetyl aspartate (NAA; referenced at 2.01 ppm), total creatine, and lactate peaks were identified by their chemical shifts. To distinguish lactate resonances from lipid resonances at a TE of 136 ms, lactate was defined as an inverted resonance at 1.33 ppm with a signal-to-noise ratio >2 and a clearly identifiable 7-Hz J coupling.

Because it was not possible to calculate absolute concentrations, data were expressed as ratio of peak intensities of NAA and creatine and as the presence or absence of lactate.
TCD CO2 Reactivity
The TCD sonography was performed with a Multi-Dop X device (DWL). CO2 reactivity was measured in the middle cerebral artery ipsilateral to the symptomatic ICA occlusion with a 2-MHz Doppler probe with the subject in the supine position. The TCD probe was fitted in a light metal frame, which was firmly fixed with 2 ear pieces and an adjustable nose saddle. After a 2-minute baseline period, subjects inhaled a gas mixture of 5% CO2 and 95% O2 (carbogene) for the next 2 minutes. The carbogene was inhaled through a mouthpiece connected to a respiratory balloon, and use of a nose clip ensured proper inhalation. The CO2 content of the breathing gas was monitored continuously with an infrared gas analyser. A spectral TCD recording of 5 seconds was made after 1 minute during the baseline period and after 1.5 minutes of carbogene inhalation. CO2 reactivity was expressed as the relative change in minute during the baseline period and after 1.5 minutes of carbogene inhalation. CO2 reactivity was calculated according to the equation $\left(\frac{\text{BFV}_{\text{CO2 baseline}}}{\text{BFV}_{\text{baseline}}} - 1\right) \times 100\%$. The mean of the maximal BFV values during the spectral TCD recordings was used in this calculation.

Data Analysis
Patients were compared with control subjects on demographics [age, analysis of variance (ANOVA); sex, chi-squared test; education, Mann-Whitney U test] and on their performances on cognitive tasks and the checklist for depressive affect (ANOVA). We corrected for the difference in sex distribution between the 2 groups by entering sex as an independent variable in the model.

Subsequently, CO2 reactivity and the NAA-to-creatine ratio, both ipsilateral to the symptomatic ICA occlusion, were compared between patients and control subjects (Student’s t test and Mann-Whitney U test, respectively). In patients, associations of CO2 reactivity and the NAA-to-creatine ratio with the cognitive impairment score were examined (Pearson’s correlation). Patients with and without lacate were compared on the cognitive impairment score (Student’s t test). Furthermore, we examined whether the pattern of performances across the cognitive tasks discriminated between patients with and those without lacate (discriminant analysis, stepwise).

Two-tailed values of $P<0.05$ were considered to reflect a statistically significant result. If the probability value was between 0.05 and 0.10, a tendency toward significance was presumed and reported. All statistical analyses were performed with SPSS for Windows, version 8.0.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol, and informed consent was obtained from all patients and control subjects.

Results
The patient and control groups did not differ in age, level of education, or proportion of men, except for a lower proportion of men in the control group for neuropsychological examination, for which we corrected in the statistical analysis (Table 1). Fourteen patients had no lesions according to MRI scanning. Twenty-two patients had cerebral infarcts, and 3 had mild (grade 1) ischemic white matter lesions in 1 or both hemispheres. Twelve patients had border-zone infarcts, 8 had territorial infarcts, and 11 had lacunar infarcts. Nine patients showed 2 types of infarction. Apart from 2 patients with remaining mild word-finding difficulty and 1 with remaining mild hemispatial neglect, no patient had full-blown dysphasia, agnosia, or apraxia.

As a group, patients were cognitively impaired. The mean cognitive impairment score in patients deviated significantly from the norm score, ie, from 0, and from that of control subjects (Table 2). The absence of a significant difference between patients and controls on the vocabulary task is supportive of a good match between the 2 groups in level of premorbid cognitive functioning. Patients and control subjects did not differ in depressive effect, according to the VROPSOM checklist (Table 2). Also, the proportion of persons with VROPSOM scores in the clinical range of depressed mood did not differ between patients and control subjects (8% and 7%, respectively; Fisher’s exact test, $P=1.000$). Thus, the worse cognitive performances in patients compared with control subjects could not be explained by depressed mood.

Mean CO2 reactivity and mean NAA-to-creatine ratio in the hemisphere ipsilateral to the ICA occlusion were significantly lower in patients than in control subjects (Table 3). In 5 patients, 1H-MRS could not be obtained for

### TABLE 1. Demographic Characteristics of Patients and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=39)</th>
<th>NPA (n=46)</th>
<th>MR (n=28)</th>
<th>TCD (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD, range)</td>
<td>62 (8.7, 44–78)</td>
<td>59 (8.3, 40–77)</td>
<td>59 (10.5, 40–73)</td>
<td>59 (10.5, 40–78)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>32/7</td>
<td>18/28*</td>
<td>22/6</td>
<td>24/5</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower, n</td>
<td>34</td>
<td>35</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Middle-higher, n</td>
<td>5</td>
<td>11</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*Patients versus controls, $P<0.001$.

NPA indicates neuropsychological assessment; MR, magnetic resonance imaging; TCD, transcerebral Doppler sonography.

### TABLE 2. Cognition and Depressive Affect in Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=39)</th>
<th>Controls (n=46)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary (raw score)</td>
<td>36.6 (9.1)</td>
<td>38.4 (8.0)</td>
<td>0.690</td>
</tr>
<tr>
<td>Cognitive impairment score</td>
<td>5.6 (5.9)</td>
<td>-0.1 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depressive affect*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VROPSOM (total dysphoric)</td>
<td>10.3 (5.8)</td>
<td>11.0 (5.2)</td>
<td>0.467</td>
</tr>
</tbody>
</table>

*The test(s) and their parameters are described in the Subjects and Methods section.
technical reasons. In 12 of the 34 patients with 1H-MRS data, lactate was present in the hemisphere ipsilateral to the symptomatic ICA occlusion. Figure 1 provides an example of a spectrum with lactate and 1 without lactate.

As a group, patients with lactate had a significantly higher cognitive impairment score, indicating more severe cognitive impairment, than those without lactate (95% confidence interval for mean difference, 1.3 to 8.4) (Figure 2). Also, more patients with lactate had an MRI-detected ischemic lesion in the ipsilateral hemisphere (75% of patients with lactate versus 41% of patients without lactate) (P=0.057). To determine whether it was the presence of lactate or the presence of cerebral ischemic lesions that accounted for the worse cognitive performances, we entered both variables in a linear regression analysis. The presence of lactate was related to cognitive impairment (b=4.7; SE=2.0; P=0.023), whereas the presence of ischemic lesions was not (b=1.7; SE=1.9; P=0.382).

The cognitive impairment score did not correlate with the ipsilateral CO2 reactivity or with the ipsilateral NAA-to-creatine ratio (Figure 3). Patients with lactate had a lower mean CO2 reactivity than those without (7.2±14.4 versus 19.5±16.6, P=0.046).

Because white matter lesions have been related to cognitive impairment and in particular to a decreased psychomotor speed, we checked whether the 12 patients with lactate in the centrum semiovale had specific impairments in psychomotor speed compared with patients without lactate. This was not the case. Of all cognitive tasks, the modified card-sorting task proved to be most useful in discriminating patients with from those without lactate (discrimination analysis, P<0.001). Psychomotor speed forms no component of this task.

Discussion

In patients with carotid artery occlusion and ipsilateral TIA, the presence of lactate in noninfarcted regions of the ipsilateral centrum semiovale was associated with more severe cognitive impairment. No correlations were found between cognitive functioning and CO2 reactivity or NAA-to-creatine ratio.

The origin of lactate in noninfarcted brain areas of patients with carotid artery occlusion has not been elucidated yet. It has been suggested that anaerobic glycolysis caused by chronic hypoperfusion produces lactate in these patients. An alternative explanation is that microembolic infarcts invisible on MRI led to metabolic changes. In the present study, patients with lactate had worse CO2 reactivity than those without lactate, suggesting that hemodynamic compromise was more prominent in patients with lactate. Perhaps the finding of more severe cognitive impairment in patients with lactate reflects the impact of hemodynamic impairment on cognitive functioning. However, CO2 reactivity did not correlate with cognitive impairment. Thus, we could not demonstrate a direct relation between hemodynamic compromise and cognitive impairment.

In the literature, no data are available on the relationship between cerebral hemodynamics and cognitive impairment in patients with symptomatic carotid occlusion, but correlations have been reported in groups of patients with related diseases. In stroke patients, cognitive impairment correlated better with volume of hypoperfused tissue as measured by MR perfusion imaging than with volume of infarction as measured by diffusion-weighted imaging, both within 24 hours of stroke onset or progression and after reperfusion therapy. In patients with cerebral microangiopathy, cognitive impairment correlated with impaired regional cerebral perfusion (measured by single photon emission CT) and glucose metabolism (measured by PET), even in the absence of brain atrophy.7
No correlations were found between cognitive impairment and number or severity of lacunar infarcts and deep white matter lesions. In patients with subcortical lacunar infarction, the degree of glucose hypometabolism (as measured by PET and corrected for atrophic changes in the brain) correlated with the degree of cognitive impairment, whereas the number of subcortical strokes related only weakly to both of these factors. Thus, impaired metabolic measures and regional hypoperfusion have been reported to be stronger correlates of cognitive impairment than MRI-detected morphological alterations in patients with vascular diseases.

An explanation for the discrepancy in findings between the present study and other studies might be that our measure of hemodynamic compromise was not sensitive enough. In contrast to the studies mentioned earlier, we did not examine regional CBF; rather, we measured TCD CO2 reactivity in the middle cerebral artery, which may be too crude. Another explanation might be that in all patients, the hemodynamic state of the brain was already impaired to such an extent that further discrimination among patients was not possible. Cognitive impairment and CO2 reactivity might have been related if we had examined patients with less impaired cerebral hemodynamics. Finally, in patients with lacinate in noninfarced regions, the damage to the brain may be greater than in patients without lacate and more extensive than can be detected by MRI. This may result in more severe cognitive impairment as a direct result of the ischemic episodes and may not necessarily be related to a supposedly chronic state of impaired blood flow toward the brain.

We conclude that in patients with carotid artery occlusion who have suffered a TIA, 1H-MRS–detected lactate in noninfarcted regions is a better indicator of cognitive impairment than MRI-detected lesions. Cognitive impairment did not correlate with CO2 reactivity.

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References


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