Hemodynamic and Metabolic Changes in Transient Ischemic Attack Patients
A Magnetic Resonance Angiography and 1H-Magnetic Resonance Spectroscopy Study Performed Within 3 Days of Onset of a Transient Ischemic Attack

Robertus H.C. Bisschops, MD; L. J. Kappelle, MD, PhD; Willem P.T.M. Mali, MD, PhD; Jeroen van der Grond, PhD

Background and Purpose—We investigated whether patients with transient ischemic attack (TIA) have systemic low flow to the brain or an abnormal intracranial flow distribution caused by an abnormal anatomy of the circle of Willis. Furthermore, we investigated whether metabolic changes were present in the brain.

Methods—Forty-four patients with clinically diagnosed TIA were prospectively included in our study. Clinical and neurological data were compiled. MR imaging; quantitative flow measurements of the internal carotid, middle cerebral, and basilar arteries; MR angiography of the circle of Willis; and 1H-MR spectroscopy were performed in all patients within 3 days of onset of symptoms.

Results—Compared with control subjects, TIA patients did not have altered flow volume in any of the arteries and had normal flow distribution through the circle of Willis. In TIA patients, the N-acetylaspartate (NAA)/choline ratio in noninfarcted regions was significantly decreased in the symptomatic hemisphere (1.73±0.16) compared with the asymptomatic hemisphere (1.84±0.19, P<0.05) and control subjects (1.90±0.17, P<0.001). In the symptomatic hemisphere, the lactate/NAA ratio was significantly increased (0.04±0.08) compared with control subjects (0.00±0.01, P<0.05). Patients with a history of prior TIA had a significantly decreased NAA/choline ratio in both the symptomatic (P<0.05) and asymptomatic (P<0.05) hemispheres compared with TIA patients without a prior TIA.

Conclusions—TIA patients have neurological deficits that are transient; however, metabolic damage to the brain is present up to 3 days after the onset of the symptoms. These metabolic changes are not restricted to the symptomatic hemisphere or to areas close to ischemic lesions. (Stroke. 2002;33:110-115.)

Key Words: ischemic attack, transient ▪ magnetic resonance angiography ▪ magnetic resonance spectroscopy

A cerebral ischemic event caused by vascular disease with focal neurological deficit that clears completely in <24 hours is called a transient ischemic attack (TIA). Patients with TIA have an annual risk of death from all vascular causes, nonfatal stroke, or nonfatal myocardial infarction of 7% to 12%.1–4 Arteriosclerosis of the cerebrovascular arteries causes transient ischemia in about half of all cases, whereas intracranial small-vessel disease and embolism from the heart account for ≈25% and ≈20%, respectively.5 In addition to these risk factors, it has been described that in patients with TIA without severe carotid artery lesions, cerebral perfusion was decreased in the affected hemisphere. This decreased perfusion status of the brain not only was present shortly after the onset of symptoms but also was found to exist up to 90 days after the onset of symptoms.6–10

It is still unclear why patients with TIA have reduced regional cerebral blood flow (CBF). Also, the effect of chronically reduced CBF on brain metabolism in these patients is unknown.

In this study, our aim was to investigate whether patients with TIA have systemic low flow to the brain or any altered intracranial flow distribution caused by an abnormal anatomy of the circle of Willis. Furthermore, we investigated whether metabolic changes were present in the brain.

Subjects and Methods

Subjects
Forty-four consecutive patients with clinically diagnosed TIAs were prospectively included in this study. All patients had an MR imaging (MRI), an MR angiography (MRA), and an 1H-MR spectroscopy...
Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
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<tbody>
<tr>
<td>Age (mean), y (range)</td>
<td>57 (29–81)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>26 (59)</td>
</tr>
<tr>
<td>History of prior TIA, n (%)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>17 (38)</td>
</tr>
<tr>
<td>ICA stenosis (≥99%), n (%)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Non-htIA, n (%)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Acute ischemic lesions on MRI, n (%)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>White matter lesions on MRI scan, n (%)</td>
<td>23 (52)</td>
</tr>
<tr>
<td>MR examination within 24 h after TIA, n (%)</td>
<td>22 (50)</td>
</tr>
</tbody>
</table>

(1H-MRS) within 3 days of the onset of transient neurological deficits. The baseline characteristics of the 44 patients are shown in Table 1. Hemispheric TIAIs (htTIA) were defined as symptoms of presumed ischemic cerebrovascular origin lasting <24 hours. Five patients with nonhemispheric TIAIs (non-htTIA) were also included (2 with brainstem and 3 with cerebellar symptoms). The following clinical data were compiled for all patients: age, sex, symptom(s) of TIA (side, motor and/or sensory deficit and dysphasia), duration of symptoms, history of previous clinical TIA(s) or minor stroke(s), and presence of vascular risk factors, including hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg), diabetes mellitus (fasting serum glucose >7.0 mmol/L), hypercholesterolemia (total cholesterol >6.5 mmol/L), and history of tobacco use. All patients underwent duplex ultrasound of both carotid arteries. Patients with occlusion of the internal carotid artery (ICA) on duplex ultrasound were excluded from the study. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of subtypes of ischemic stroke,11 we assigned all TIA patients to 1 of the following 4 groups: (1) large-artery atherosclerosis (n=6, 14%), (2) cardioembolism (n=6, 14%), (3) small-vessel occlusion (n=10, 22%), and (4) other or undetermined origin (n=22, 50%).

The Human Research Committee at our hospital approved the study protocol. All patients and control subjects gave informed consent to participate in the study.

Control Subjects

The control group consisted of 57 subjects (mean age, 58 years; range, 28 to 77 years; 33 men, 24 women) who were treated in the Department of Neurology for diseases other than intracranial diseases and who had no history of ischemic neurological deficits. These control subjects underwent the same MRI, MRA, and 1H-MRS investigations as the patients. The MRI of the brain and MRA of the intracranial arteries of these control subjects did not show any abnormalities.

MRI Methods

All MRI, MRA, and 1H-MRS investigations were performed on a Philips Gyroscan ACS-NT 15 whole-body system operating at 1.5 T (Philips Medical Systems). The MRI examinations consisted of a sagittal T1-weighted spin-echo sequence [repetition time (TR)/echo time (TE), 545/15 ms], a transaxial double-echo T2-weighted spin-echo sequence (TR/TE, 2000/20 and 2000/100 ms), fluid-attenuating inversion recovery (TR/TE, 6160/100 ms), and a diffusion-weighted imaging (DWI; TR/TE, 1691/40 ms) scan. Quantitative flow measurements were performed in the ICAs, basilar artery (BA), and middle cerebral arteries (MCAs). Two-dimensional phase-contrast flow measurements through the ICAs and BA were performed perpendicular to the arteries (slice thickness, 5 mm; field of view, 250×250 mm; TR, 16 ms; TE, 9 ms; flip angle, 7.5°; velocity sensitivity, 1000 mm/s; and 8 averages). These measurements were followed by 2 separate 2-dimensional phase-contrast quantitative flow measurements for the left and right MCAs (slice thickness, 5 mm; field of view, 250×250 mm; TR, 17 ms; TE, 10 ms; flip angle, 8°; velocity sensitivity, 700 mm/s; and 24 averages). All volume flow data were obtained by integration of manually drawn regions of interest that enclosed the vessel lumen as closely as possible. The total blood flow to the brain was calculated by summing the flow through both ICAs and the flow through the BA. To visualize the circle of Willis, 50 slices were obtained with a 3-dimensional MRA time-of-flight technique (TR/TE, 316/6.9 ms). These images were reconstructed in 3 directions with a maximum intensity projection algorithm. The anterior part of the circle of Willis was graded complete if the left and right A1 segments of the anterior cerebral artery and the anterior communicating artery (ACoA) were present. The posterior part of the circle of Willis was graded complete if the left and right P1 segments of posterior cerebral artery and both posterior communicating artery (PCoA) were present. The direction of blood flow in the circle of Willis was measured with 2 2-dimensional phase-contrast acquisitions: 1 was phase encoded in the anterior-posterior direction, and 1 was in the left-right direction (TR/TE, 169/9.1 ms; velocity sensitivity, 40 cm/s).

Two collateral flow pathways were studied: cross flow through the ACoA and posterior-to-anterior flow through the ipsilateral PCoA. The presence of collateral flow through these pathways was independently evaluated by 2 authors (R.B., J. van der G.), and discrepancies were reevaluated in a consensus reading.

The 1H-MRS investigations were performed with a single-voxel technique. Two volumes of interest (VOI) of equal size were selected in the noninfarcted centrum semiovale of each subject: 1 in the symptomatic hemisphere and 1 in the asymptomatic hemisphere. These VOIs were chosen from the T2-weighted transaxial MRI and the DWI. The white matter in the centrum semiovale is particularly vulnerable to hypoperfusion because this area is a so-called border zone, located in the distal part of the deep and superficial branches of the MCA. This area is likely to be one of the first to suffer ischemic damage when blood flow decreases.12 The dimensions of the selected VOIs were kept equal in both hemispheres and were typically 40 mm in the anterior-posterior direction, 15 mm in the left-right direction, and 10 mm in the caudocranial direction. Special care was taken to position these VOIs away from gray/white matter hyperintensities, and the VOI size was reduced when necessary. After VOI selection, the 90° degree pulse length was determined. To minimize eddy currents and to maximize the water echo signal, localized spectroscopy was first performed without water suppression for adjustments of the gradients (gradient tuning). This was followed by localized automatic shimming of the VOI, resulting typically 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. A double spin-echo point-resolved spectroscopy sequence was used for VOI localization.13 14 Each measurement was performed with a TR of 2000 ms, a TE of 144 ms, 2048 time domain data points, 4000-Hz spectral width, and 128 signals acquired. After zero filling to 4096 data points, gaussian multiplication of 5 Hz, exponential multiplication of ~4 Hz (line broadening), Fourier transformation, and linear baseline correction, N-acetylaspartate (NAA; referenced at 2.0 ppm), total choline, total creatine, and lactate peaks were identified by their chemical shifts. To distinguish lactate resonances from lipid resonances at a TE of 144 ms, lactate was defined as an inverted resonance at 1.33 ppm with a signal-to-noise ratio >2. To suppress lipid signal possibly arising from the outside the VOI, additional outer volume suppression slabs were (automatically) positioned. Signal intensities were determined by peak height measurements. Because we were unable to calculate absolute metabolic concentrations, the metabolic data were expressed as ratios between the peak intensities of NAA, choline, creatine, and lactate. Total study time...
per patient was ~30 minutes: 8 minutes for MRI, 10 minutes for MRA, and 12 minutes for 1H-MRS.

Statistical Analyses

Differences in flow measurements in the intracranial arteries between patients and control subjects were tested with ANOVA by use of post hoc Scheffé’s tests. Differences in the circle of Willis anatomy between patients and control subjects were analyzed for the anterior and posterior parts of the circle of Willis separately with a χ² test. The metabolic ratios between the symptomatic and asymptomatic hemispheres in patients and control subjects were tested with ANOVA, by use of post hoc Scheffé’s tests. Differences between non-hTIA patients and hTIA patients were tested with the Wilcoxon 2-sample test. Differences in metabolic signal ratios between (1) TIA patients with or without acute infarctions on DWI, (2) TIA patients with or without white matter lesions, and (3) TIA patients with a complete or incomplete circle of Willis were tested by use of an independent-sample T test. Differences in metabolic ratios between the 4 groups according to the TOAST classification were tested with ANOVA and post hoc Scheffé’s tests. In all tests, P<0.05 was noted as significant.

Results

Volume flow in the ICAs, BA, and MCAs and total flow (ICAs + BA) of patients and control subjects are shown in Table 2. Compared with control subjects, TIA patients did not have significantly altered flow in any of the arteries measured. Furthermore, patients with TIA did not show any differences in volume flow between the symptomatic and asymptomatic ICA and MCA. In the patient group, no difference in volume flow was found in any of the arteries when hTIA patients were compared with non-hTIA patients.

The completeness of the circle of Willis on MRA in the 44 TIA patients did not significantly differ from that of normal control subjects (Table 3).

<table>
<thead>
<tr>
<th>TABLE 3. Completeness of the Circle of Willis</th>
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<tbody>
<tr>
<td>Circle of Willis</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Anterior</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Incomplete</td>
</tr>
<tr>
<td>Posterior</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Incomplete</td>
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</table>

Results of the MRS studies in patients and control subjects are shown in Tables 4 through 6. Typical MRS spectra of an hTIA patient, a non-hTIA patient, and a control patient are shown in the Figure. In patients with TIA, the NAA/choline ratio in the symptomatic hemisphere was significantly decreased (1.73±0.16) compared with the asymptomatic hemisphere (1.84±0.19, P<0.05) and control subjects (1.90±0.17, P<0.001). In accordance with the decrease in NAA/choline ratio and a more or less stable NAA/creatine ratio, the choline/creatine ratio was significant increased in the symptomatic hemisphere (1.16±0.10) compared with the asymptomatic hemisphere (1.08±0.10, P<0.05) and control subjects (1.08±0.15, P<0.05). In the symptomatic hemisphere, the lactate/NAA ratio was slightly increased (0.04±0.08) compared with the asymptomatic hemisphere (0.01±0.02) and control subjects (0.00±0.01, P<0.05). In a comparison of patients with hTIA and non-hTIA patients, the NAA/choline ratio in the symptomatic hemisphere of the hTIA patients was significantly decreased (1.70±0.14 versus 1.92±0.13, P<0.05), whereas the lactate/NAA ratio was increased (0.04±0.08 versus 0.00±0.01, P<0.05).

None of the independent clinical risk factors tested (hypertension, diabetes mellitus, hypercholesterolemia, and smoking) were correlated with the metabolic ratios in the symptomatic or asymptomatic hemisphere. There was no significant difference
in metabolic signal ratios between the 4 groups according to the TOAST classification. However, patients with a history of a prior TIA had a significantly decreased NAA/choline ratio in both the symptomatic (1.58±0.11, P<0.05) and asymptomatic (1.61±0.26, P<0.05) hemispheres compared with patients who suffered from TIA only once.

Twenty-one patients (47%) had an acute ischemic lesion on DWI. The NAA/choline, NAA/creatine, choline/creatine, and lactate/NAA ratios of patients with acute ischemic lesion on DWI did not differ significantly from patients without acute ischemic lesions on DWI for either the symptomatic or the asymptomatic hemisphere. In addition, there was no significant difference in metabolic signal ratios for the symptomatic and asymptomatic hemispheres between patients with (52%) and without white matter lesions.

The duration of the TIA and the time between onset of the TIA and the MR study did not significantly contribute to a change in the NAA/choline or lactate/choline ratios.

### Discussion

This study shows that patients with clinically diagnosed TIA do not have diminished CBF, an altered circle of Willis configuration, or an altered intracranial distribution of flow to the brain. However, patients with TIA demonstrated a decreased NAA/choline ratio in noninfarcted white matter in the symptomatic hemisphere compared with control subjects.

In our study, we did not find any indication of reduced blood flow to the brain in TIA patients compared with our control subjects or control subjects described in previous publications. Several studies with single-photon emission computer tomography (SPECT) have demonstrated “reduced” CBF in TIA patients. One difference between these SPECT studies and our study is that SPECT semiquantitatively measures the regional CBF, whereas we measured quantitative volume flow to the brain. Therefore, it is possible that our quantitative blood flow measurements are not sensitive enough to detect the small differences in blood flow to the brain in TIA patients. A second reason could be that SPECT studies measure a reduced effective oxygen extraction in TIA patients, whereas the total amount of blood delivered to the brain remains unchanged. Another explanation could be differences in the patient groups studied. In our population, 6 patients (14%) had severe ICA stenosis; in SPECT studies, this varies from 10% to 75%, and in some studies, it is unclear which percentage of patients have ICA stenosis. A high prevalence of patients with severe ICA stenosis could lead to decreased flow to the brain.

The anatomy of the circle of Willis, ie, the presence or absence of the ACoA or ipsilateral PCoA, in our patient population is not statistically different from a previously published normal population. The circle of Willis is a potential collateral pathway through which adequate distribution of CBF can be maintained in case of impaired or decreased flow. Its ability to redistribute blood flow depends on its morphology, the presence and size of its component vessels. A small or absent PCoA or ACoA is suggested to be a risk factor for ischemic cerebral infarction in patients with ICA occlusion. Therefore, the presence or absence and size of the vessels of the circle of Willis could be risk factors for TIA or an explanation for regional hypoperfusion. Nevertheless, we could not demonstrate any noticeable abnormality in circle morphology.

The 1H-MRS findings in the TIA population showed a decrease in the NAA/choline ratio and an increase in the choline/creatine and lactate/ NAA ratios in the symptomatic hemisphere. The difference in ratios is caused mainly by an increase in choline, which could reflect membrane breakdown, which could reflect ischemic brain injury in TIA patients. Several proton MRS studies in ischemic stroke patients reported reduced NAA and an increase in lactate in the infarcted area, whereas our results show mainly a rise in choline in the noninfarcted white matter. Compared with the metabolic damage seen in infarcted regions in stroke patients, we found relatively small but significant metabolic alterations in TIA patients. These relatively small changes could be explained by the facts that (1) the VOI is located in the noninfarcted white matter on the basis of the T2W and DWI, (2) all TIA patients do not have neurological deficits at the time of the MR scan, and (3) often a TIA is the first manifestation of cerebrovascular disease, which implies that the brain is relatively unaffected.

In a recent study with 5 patients, cerebral metabolism was assessed with 1H-MRS after a TIA. This study revealed an increase in lactate in the affected hemisphere. This increase was explained by an increase in anaerobic glycolysis. Our findings are in accordance with these results.

Patients with a history of a prior TIA demonstrated a significant decrease in NAA/choline in the ipsilateral and contralateral hemispheres compared with patients who suffered from TIA only once. From our study, it remains unclear whether decreased NAA/choline ratios are causative for symptoms or are secondary to the occurrence of TIAS. However, when a decreased NAA/choline ratio is secondary to TIA, it remains unclear why the asymptomatic hemisphere is also affected. It is possible that a long-lasting load of microemboli causes ischemic damage. It is also interesting that we found a significant NAA/choline decrease and increased lactate/NAA ratio in hTIA patients compared with

### Table 6. Metabolic Ratios in the Symptomatic and Asymptomatic Hemispheres in Patients Without or With a History of Prior TIA

<table>
<thead>
<tr>
<th></th>
<th>No History of Prior TIA</th>
<th>History of Prior TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/choline</td>
<td>1.76±0.15</td>
<td>1.58±0.11*</td>
</tr>
<tr>
<td>NAA/creatine</td>
<td>2.01±0.16</td>
<td>1.88±0.17</td>
</tr>
<tr>
<td>Choline/creatine</td>
<td>1.14±0.09</td>
<td>1.20±0.14</td>
</tr>
<tr>
<td>Lactate/NAA</td>
<td>0.04±0.08</td>
<td>0.02±0.04</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/choline</td>
<td>1.88±0.16</td>
<td>1.61±0.26*</td>
</tr>
<tr>
<td>NAA/creatine</td>
<td>2.00±0.19</td>
<td>1.77±0.13*</td>
</tr>
<tr>
<td>Choline/creatine</td>
<td>1.06±0.10</td>
<td>1.11±0.09</td>
</tr>
<tr>
<td>Lactate/NAA</td>
<td>0.01±0.02</td>
<td>0.02±0.02</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 between patients with and without a history of prior TIA.
non-hTIA patients. This may reflect a possible difference in pathogenesis between the 2 types of TIA.

In our population, 47% had an acute ischemic lesion on DWI. This finding is consistent with results of other MRI studies. Several studies have shown that many patients meeting the clinical criteria for TIA demonstrate neuroanatomically relevant infarcts on standard neuroimaging, 12% to 48% using CT or 31% to 48% using MRI. These infarcts are seen not only in the region appropriate for the symptoms of TIA but also in other unrelated parts of the brain. It has also been shown that TIA patients with ischemic brain lesions have a different prognosis from patients without lesions. Patients with acute ischemic lesions in our study did not have significantly different metabolic ratios than patients without these acute lesions. In addition, in 52% of the cases, white matter lesions did not influence the spectroscopic findings. This inconsistency in MRI and MRS is remarkable. The presence of ischemic brain lesions on brain imaging is an independent risk factor for stroke in patients with TIA; however, we did not find metabolic differences in patients with or without ischemic lesions. As mentioned, patients with recurrent TIAs have a decreased NAA/choline ratio, so compared with infarction, previous TIAs on MRI seem more harmful to the brain in respect to metabolic changes observed. Unfortunately, we do not have the clinical follow-up of these patients, and we are unable to investigate whether spectroscopic findings have a prognostic value in TIA patients.

Conclusions
No evidence was found that low flow to the brain of an incomplete circle of Willis is related to the clinical symptoms in TIA patients. Although patients with hTIA have neurological deficits that are transient, metabolic damage to the brain is present up to 3 days after the onset of symptoms. These metabolic changes are not restricted to the symptomatic hemisphere or to areas close to ischemic lesions. In contrast, no metabolic changes are observed at all in patients with non-hTIA.

References


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