Cerebral Hemodynamics and Metabolism in Patients With Symptomatic Occlusion of the Internal Carotid Artery

D.R. Rutgers, MD; M.J.P. van Osch, MSc; L.J. Kappelle, MD, PhD; W.P.T.M. Mali, MD, PhD; J. van der Grond, PhD

Background and Purpose—The goals of this study were to investigate (1) whether the concentrations of choline, creatine, and N-acetyl aspartate (NAA) in cerebral white matter are changed in patients with symptomatic occlusion of the internal carotid artery (ICA) and (2) whether possible changes in metabolite concentration are related to regional cerebral perfusion or cerebral vasoreactivity.

Methods—In 19 patients (mean ± SD age, 60 ± 9 years), white matter metabolite concentrations were measured with proton MR spectroscopic imaging on average 4 ± 2 months after symptoms occurred. In selected voxels, corresponding cerebral blood flow and volume, mean transit time, and time-to-bolus peak were determined with dynamic susceptibility contrast MRI. Cerebral CO₂ reactivity was determined with transcranial Doppler sonography.

Results—No significant changes in choline and creatine concentrations were observed. NAA concentration was significantly reduced in the hemisphere on the side of the symptomatic ICA (9.1 ± 1.7 mmol/L) compared with the contralateral hemisphere (10.5 ± 1.7 mmol/L, P < 0.005) and control subjects (10.5 ± 0.9 mmol/L, P < 0.01). Although no significant interhemispheric difference in NAA concentration was found in patients who presented with retinal ischemia, patients with cerebral ischemia had a significantly lower NAA concentration in the symptomatic hemisphere (9.0 ± 1.7 mmol/L) compared with the asymptomatic hemisphere (10.4 ± 1.6 mmol/L, P < 0.05). In all patients, NAA concentration was not significantly correlated with quantitative cerebral perfusion parameters or CO₂ reactivity.

Conclusions—Patients with symptomatic ICA occlusion may show chronic neuronal damage in cerebral white matter as evidenced by reduced NAA concentration. This seems to be related to previous symptomatology rather than to the cerebral hemodynamic status in a chronic stage. (Stroke. 2003;34:648-652.)

Key Words: carotid artery diseases • choline • creatine • hemodynamics • N-acetyl aspartate • occlusion

Patients with a symptomatic occlusion of the internal carotid artery (ICA) are at risk of future stroke.1–3 High-risk patients may be identified by MR spectroscopy (MRS) because a reduced ratio of the metabolite N-acetyl aspartate (NAA) to the metabolite choline in noninfarcted cerebral white matter predisposes to recurrent cerebral ischemia.4 The pathophysiological cause of a decreased ratio of NAA to choline is unclear, but it may be suggested that metabolic alterations are related to chronically reduced cerebral perfusion or cerebral vasoreactivity.5,6 Interpretation of spectroscopic findings in patients with ICA occlusion is difficult because metabolites have often been reported as ratios.4–7 For example, a reduction in the ratio of NAA to choline may be explained by a decrease in NAA or an increase in choline. This distinction is important because different pathophysiological mechanisms are involved. An NAA decrease probably indicates neuronal loss because NAA is found almost exclusively in neurons.8,9 An increase in choline, ie, choline-containing compounds that are involved in cellular membrane synthesis and breakdown,10 may indicate gliosis or increased myelin breakdown.11,12 Measurement of metabolite concentrations rather than ratios may show which metabolites are changed in carotid artery occlusion.

In the present study, we investigated whether the concentrations of choline, creatine, and NAA in cerebral white matter are changed in patients with symptomatic ICA occlusion. In addition, we studied whether possible changes in metabolite concentrations are related to regional cerebral perfusion and cerebral vasoreactivity.

Methods

Patients and Control Subjects

Nineteen patients (mean ± SD age, 60 ± 9 years; 16 men, 3 women) with an angiographically (n = 17) or ultrasonographically (n = 2) proven symptomatic ICA occlusion who had not been examined in previous studies were investigated in the present study. They were referred to the Department of Neurology at our hospital because of

Received July 22, 2002; final revision received September 18, 2002; accepted October 7, 2002.

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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000058158.41581.41
transient (lasting <24 hours) or minor disabling (modified Rankin score, \( \geq 5 \)) neurological deficits in the supply territory of an occluded ICA. The neurological deficits occurred on average 4±2 months before investigation. Sixteen patients had symptoms of cerebral ischemia (transient ischemic attack, \( n=6 \); minor stroke, \( n=10 \)), and 3 patients had symptoms of retinal ischemia (transient monocular blindness, \( n=2 \); retinal infarction, \( n=1 \)). Three patients had a bilateral ICA occlusion as shown by angiography. All patients received best medical treatment.

Reference metabolite concentrations were assessed in 24 control subjects (age, 56±9 years; 21 men, 3 women). They were referred to our hospital because of peripheral vascular disease or stable angina pectoris. Reference perfusion values were measured in 9 control subjects (age, 65±10 years; 4 men, 5 women). They were referred to the patient become accustomed to scanner noise, a bolus of 30 mL gadolinium-DTPA contrast agent (Magnevist, Schering) was injected at a rate of 5 mL/s with a Spectris power injector (Medrad). The injection of contrast agent was followed by a 10-mL saline flush with 5 mL at 5 mL/s and 5 mL at 2 mL/s. The arterial input function (AIF) of the contrast bolus entering the brain was obtained from a slice through the nonoccluded ICA and/or the vertebral arteries with only TE1. Partial volume correction was performed for quantitative determination of the AIF. Tissue response functions were calculated in the voxels selected in the MRSI investigation. The passage curves were deconvolved with the AIF, after which cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were derived. Time-to-bolus peak (TBP) was obtained from the original passage curves. Perfusion values from the selected voxels in each hemisphere were averaged to obtain mean hemispheric perfusion values. In control subjects, white matter perfusion was measured with the same method as in patients. Perfusion parameters of both hemispheres were averaged because no asymmetrical perfusion was observed.

**DSC-MRI Technique**

DSC-MRI was used to measure quantitative cerebral perfusion. Localization, thickness, and field of view of the DSC-MRI slice were the same as for the MRSI slice. T2* weighting was applied with a dynamic gradient echo pulse sequence (TR/TE1/TE2, 70/9/24 ms; flip angle, 15°; echoplanar imaging factor, 5; dynamic TR, 1.1 seconds; 90 dynamic scans; pixel size, 2.8 mm²). After 5 dummy scans that were made to obtain magnetization equilibrium and to let the patient become accustomed to the scanner noise, a bolus of 30 mL gadolinium-DTPA contrast agent (Magnevist, Schering) was injected at a rate of 5 mL/s with a Spectris power injector (Medrad). The injection of contrast agent was followed by a 10-mL saline flush with 5 mL at 5 mL/s and 5 mL at 2 mL/s. The arterial input function (AIF) of the contrast bolus entering the brain was obtained from a slice through the nonoccluded ICA and/or the vertebral arteries with only TE1. Partial volume correction was performed for quantitative determination of the AIF. Tissue response functions were calculated in the voxels selected in the MRSI investigation. The passage curves were deconvolved with the AIF, after which cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were derived. Time-to-bolus peak (TBP) was obtained from the original passage curves. Perfusion values from the selected voxels in each hemisphere were averaged to obtain mean hemispheric perfusion values. In control subjects, white matter perfusion was measured with the same method as in patients. Perfusion parameters of both hemispheres were averaged because no asymmetrical perfusion was observed.

**Transcranial Doppler Sonography**

Measurements were performed in the middle cerebral arteries with a 2-MHz Doppler probe (Multi-Dop X device, DWL). After a 2-minute baseline period, patients inhaled a gas mixture of 5% CO2 and 95% O2 (carbogene) for the next 2 minutes to assess cerebral vasoreactivity to CO2 administration. The carbogene was inhaled through a mouthpiece connected to a respiratory balloon, while a nose clip ensured proper inhalation. In 7 of the 38 investigated hemispheres (3 symptomatic side, 4 asymptomatic side), the middle cerebral artery could not be insonated because of an insufficient temporal window. The CO2 content of the breathing gas was continuously monitored with an infrared gas analyzer (Mijnhardt). CO2 reactivity was expressed as the relative change in blood flow velocity in the middle cerebral artery per change in end-tidal CO2 (in mm Hg) after 1.5 minutes of carbogene breathing compared with the baseline velocity.

**Statistical Analysis**

Mean metabolite concentrations, perfusion parameters, and CO2 reactivity were calculated for the hemisphere on the side of the symptomatic ICA occlusion and the asymptomatic hemisphere. Student’s paired \( t \) test was used to compare parameters between both hemispheres in patients. To compare patients with control subjects, Student’s independent \( t \) test with a Bonferroni correction for multiple comparisons was used. The \( t \) tests were preceded by an \( F \) test to determine equality of variances. If the \( F \) test was statistically significant, the results for unequal variances were used. Pearson’s correlation was calculated between metabolite concentrations and hemodynamic measures. A value of \( P<0.05 \) was considered statistically significant.

**Results**

Figure 1 shows typical findings in a patient with a left-sided symptomatic ICA occlusion. The T2-weighted image (left) shows the localization of 5 MRSI voxels from which proton
symptomatic ICA occlusion, 2 voxels were selected, whereas in the asymptomatic hemisphere, 3 voxels were selected. The corresponding CBF image is shown on the right.

Metabolite concentrations are shown in Table 1. The concentrations of choline and creatine did not differ significantly between the hemisphere on the side of the symptomatic ICA occlusion and the contralateral, asymptomatic hemisphere. Also, no differences in choline and creatine concentrations were found between patients and control subjects. The NAA concentration in the hemisphere on the side of the symptomatic ICA occlusion was significantly reduced compared with the asymptomatic hemisphere (P<0.001) and the control subjects (P<0.01). In both hemispheres, no significant difference was found between anteriors and posteriorly located voxels. In patients who presented with cerebral ischemia, there was a significant difference in NAA concentration between the symptomatic hemisphere (9.0±1.7 mmol/L) and the asymptomatic hemisphere (10.4±1.6 mmol/L, P<0.01), whereas in patients with retinal ischemia, no significant interhemispheric difference in NAA concentration was found (9.6±1.7 versus 10.4±1.4 mmol/L, respectively).

Regional cerebral perfusion and cerebral CO₂ reactivity are shown in Table 2. CBF was significantly reduced in the hemisphere on the side of the symptomatic ICA occlusion compared with the asymptomatic hemisphere (P<0.05). CBF did not differ significantly between hemispheres. MTT and TBP were significantly increased on the side of the symptomatic ICA occlusion compared with the asymptomatic side (P<0.001) and control subjects (P<0.01, P<0.05, respectively). No correlation was found between perfusion parameters and time from occurrence of symptoms. CO₂ reactivity was significantly reduced on the symptomatic side compared with the asymptomatic hemisphere (P<0.001) and control subjects (P<0.001).

Figures 2 and 3 show scatterplots of NAA concentration versus CBF and CBV. Both for CBF (r = −0.17, P = 0.30) and CBV (r = −0.26, P = 0.12), no significant correlation was found with NAA concentration. Also, MTT (r = −0.07, P = 0.69) and TBP (r = −0.26, P = 0.11) were not significantly correlated with NAA concentration. Figure 4 shows a scatterplot of NAA concentration versus CO₂ reactivity. No significant correlation (r = 0.22, P = 0.21) was found between these parameters.

Discussion

This study has 2 major findings. First, patients with symptomatic ICA occlusion show no change in choline and creatine concentrations in cerebral white matter in the hemisphere on the side of the symptomatic ICA occlusion compared with the asymptomatic side and control subjects. Second, NAA concentration is reduced on the symptomatic side but is not correlated regional cerebral perfusion or cerebral vasoreactivity.

We found that the main spectroscopic alteration in patients with a symptomatic ICA occlusion was a reduction in the NAA concentration in the hemisphere on the side of the symptomatic ICA occlusion.

**TABLE 1. Metabolite Concentration in Patients With a Symptomatic ICA Occlusion and Control Subjects**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Symptomatic Side, Mean±SD</th>
<th>Asymptomatic Side, Mean±SD</th>
<th>Control Subjects, Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline (mM)</td>
<td>1.4±0.4</td>
<td>1.5±0.5</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>Creatine (mM)</td>
<td>6.4±1.2</td>
<td>6.6±1.3</td>
<td>6.0±1.3</td>
</tr>
<tr>
<td>N-acetyl aspartate</td>
<td>9.1±1.7*†</td>
<td>10.5±1.7</td>
<td>10.5±0.9</td>
</tr>
</tbody>
</table>

Symptomatic side refers to the hemisphere on the side of the symptomatic ICA occlusion, asymptomatic side to the contralateral hemisphere.

*P<0.005 vs asymptomatic side; †P<0.01 vs control subjects.

**TABLE 2. Regional Quantitative Perfusion and CO₂ Reactivity in Patients With a Symptomatic ICA Occlusion and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Side, Mean±SD</th>
<th>Asymptomatic Side, Mean±SD</th>
<th>Control Subjects, Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF (mL/100 mL/min)</td>
<td>33.1±11.9*</td>
<td>37.4±12.1</td>
<td>35.9±9.7</td>
</tr>
<tr>
<td>CBV (mL/100 mL)</td>
<td>4.5±1.4</td>
<td>4.1±1.3</td>
<td>3.5±1.2</td>
</tr>
<tr>
<td>MTT, s</td>
<td>8.8±2.2†‡</td>
<td>6.7±1.8</td>
<td>6.1±2.5</td>
</tr>
<tr>
<td>TBP, s</td>
<td>5.6±2.0†§</td>
<td>3.3±1.5</td>
<td>3.8±1.0</td>
</tr>
<tr>
<td>CO₂ reactivity (%)</td>
<td>1.3±1.7†</td>
<td>3.9±2.0</td>
<td>4.2±1.1</td>
</tr>
</tbody>
</table>

Symptomatic side refers to the hemisphere on the side of the symptomatic ICA occlusion, asymptomatic side to the contralateral hemisphere.

CBF indicates cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TBP, time to bolus peak.

*P<0.05, †P<0.001 vs asymptomatic side; §P<0.05, ‡P<0.01, ||P<0.001 vs control subjects.
symptomatic ICA. Because NAA is generally considered a neuronal marker, this suggests that neurons were lost or dysfunctional in this hemisphere. In the hemisphere on the side of the asymptomatic ICA, the NAA concentration agrees well with previously published multicenter data that range from 10.0 to 11.0 mmol/L. From a clinical point of view, measurement of NAA concentration may be relevant because NAA concentration is associated with cognitive function. Possibly, the reduction in the NAA concentration is related to impaired cognition, which can be found in patients with a symptomatic ICA occlusion.

Our patients showed no correlation between NAA concentration and cerebral perfusion. This implies that the NAA concentration does not represent the current perfusion status. Also, we found no correlation between NAA concentration and cerebral vasoreactivity. Cerebral vasoreactivity represents the reserve capacity of cerebral arterioles to dilate. Reduction in cerebral vasoreactivity indicates an impaired cerebral hemodynamic status in which arterioles are dilated as a result of autoregulatory vasodilatation. This situation is related to the recurrence of stroke. The low vasoreactivity in the hemisphere ipsilateral to the symptomatic ICA occlusion in our patients indicated that this hemisphere was hemodynamically impaired. Lythgoe et al have previously investigated the relation between NAA concentration and cerebrovascular reactivity in patients with severe carotid artery disease. They found no association between these parameters. In contrast to our study, their patients showed no decrease in NAA concentration. This may be explained by differences in patient selection because most of their patients had been asymptomatic for 2 years and did not have an ICA occlusion. Other studies have used ratios to investigate the relation between metabolism and cerebral hemodynamics. Visser et al found a positive correlation between the ratio of NAA to choline and cerebral vasoreactivity in patients with severe ICA stenosis. However, they included asymptomatic patients, which may have influenced the observed correlation. Tsuchida et al found a positive correlation between regional CBF and the ratio of NAA to creatine. They also found an increase in choline in the symptomatic hemisphere. As opposed to their study, we found no significant correlation between cerebral hemodynamics and NAA concentration and no choline increase in the symptomatic hemisphere. A possible explanation for these discrepancies is that Tsuchida et al examined patients in an earlier stage after symptoms occurred. Hypothetically, CBF and cerebral metabolism are correlated in this stage, whereas in a more chronic stage, they may dissociate because of normalization of CBF. It should be emphasized that with severe reductions in cerebral blood supply such as in acute ischemic stroke, tissue damage will probably occur. In these circumstances, an association between metabolite concentration and cerebral perfusion is likely to be present.

Cerebral metabolism is known to differ between patients with and patients without cerebral ischemia. Therefore, it may be suggested that the reduction in NAA concentration in patients with symptomatic ICA occlusion is related to the occurrence of previous cerebral ischemia. This is supported by the present results that showed no significant NAA reduction in patients with retinal ischemia at presentation, as opposed to patients with cerebral ischemia. There may be several explanations for the NAA reduction in patients who presented with cerebral ischemia. For example, they may have had multiple small emboli to the brain at the time that the symptoms occurred, causing microscopic damage to the semiovale center. Alternatively, the NAA concentration could have been affected by a severe impairment of cerebral blood supply at the time that the cerebral symptoms arose.

Although DSC-MRI has recently emerged as a useful method to study cerebral perfusion, the quantitative nature of DSC-MRI can be compromised by a delay of the AIF or by additional dispersion of the AIF between the position of AIF measurement and the tissue under investigation. However, we accounted for the possible delay effects by the deconvolution technique used. Dispersion effects would result in an erroneous decrease in CBF, which was not observed in the present study. We therefore conclude that delay and/or dispersion effects on the AIF do not play an important role in this study. Although the present study

**Figure 2.** NAA concentration vs CBF ($r = -0.17, P = 0.30$).

**Figure 3.** NAA concentration vs CBV ($r = -0.26, P = 0.12$).

**Figure 4.** NAA concentration vs CO$_2$ reactivity ($r = 0.22, P = 0.21$).
showed no correlation between NAA concentration and cerebral perfusion or cerebral vasoreactivity, a limited number of patients was included. We cannot exclude that with a high number of patients, a correlation between NAA concentration and cerebral hemodynamics may be discerned. However, our results suggest that such a possible correlation will be relatively small compared with the effect of previous symptoms on NAA concentration.

In conclusion, MRS may be used clinically to identify patients with symptomatic ICA occlusion who are at risk of future stroke.4 The present study shows that the principal metabolic alteration in these patients is a NAA reduction in the hemisphere on the side of the symptomatic ICA occlusion. However, in terms of regional cerebral perfusion and cerebral vasoreactivity, this reduced NAA concentration is not related to cerebral hemodynamics in a chronic stage.

Acknowledgments

Dr Rutgers is supported by the Netherlands Organization for Scientific Research (NWO), grant 920–03–091. Dr van Osch is supported by the Netherlands Ministry of Economic Affairs, IOP Beeldverwerking, grant IBV97010. Drs R.H.C. Bisschops, R.C.J.M. Donders, and C.J.M. Klijn helped enlist patients and control subjects.

References

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*Stroke.* 2003;34:648-652; originally published online February 13, 2003; doi: 10.1161/01.STR.0000058158.41581.41

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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