Re-establishment of Cerebral Metabolism After Carotid Endarterectomy*

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Objectives: The purpose of this study was to evaluate the metabolic changes that occur in the human brain in patients with a symptomatic carotid artery stenosis.

Materials and Methods: N-acetyl-aspartate (NAA), choline, creatine and lactate were measured both before, and 4 days after, carotid endarterectomy, by magnetic resonance spectroscopic imaging (MRSI). Eight controls and 16 patients were examined. MRI and MRSI studies were performed on a Philips Gyroscan S15 whole body system operating at 1.5 Tesla. 1H spectra were selected from regions in the centrum semi-ovale outside areas showing white matter hyper intensities on MRI.

Results. All patients showed a decrease of the NAA/choline and NAA/creatine ratio in the symptomatic hemisphere compared to the contralateral hemisphere and also compared to the controls. Lactate was present in some patients (5/16). After endarterectomy, the NAA/choline and NAA/creatine ratios increased significantly compared to the ratios preoperative. Lactate was absent or more than 50% reduced after the operation. MRSI showed metabolic changes in areas of the brain that did not show any abnormalities on MRI.

Conclusions: There are marked changes in brain metabolism in the symptomatic hemisphere of patients with a severe carotid artery stenosis. These metabolic changes normalise four days after endarterectomy.

Key Words: 1H MRSI; Metabolism; Brain; Endarterectomy.

Introduction

The occurrence of a Transient Ischaemic Attack (TIA) is associated with an increased risk of stroke. Patients with a > 70% stenosis of the internal carotid artery (ICA), combined with hemispheric TIAS are at particular risk. A stroke rate of more than 40% has been reported for this specific group of patients. 1 Both the European Carotid Surgery Trial 2 and the North American Symptomatic Carotid Endarterectomy Trial 3 show a significant risk reduction for stroke, following a successful endarterectomy, in this group of patients. Therefore symptomatic patients with a > 70% stenosis of the ipsilateral carotid artery should receive surgery. 4

The success of the carotid artery endarterectomy can be explained by two mechanisms: removal of a source of micro-emboli from the extracranial vessels and by improvement of the flow in the internal carotid artery with a subsequent increase in cerebral blood flow. Transcranial Doppler (TCD) evaluation of the middle cerebral artery during and after carotid endarterectomy has shown a marked increase in Doppler flow velocity after clamp release. 5 It is expected that these changes in cerebral blood flow will cause changes in cerebral metabolism. Metabolites of the brain can be studied with Magnetic Resonance Spectroscopic Imaging (MRSI). This non-invasive technique can measure the relative concentrations of these metabolites. The metabolic changes that occur in a hypoperfused brain, due to severe carotid stenosis and the changes that occur after a carotid endarterectomy have not been studied by MRSI before.

The aim of this study is to evaluate the N-acetyl-aspartate (NAA)/choline ratio, the NAA/creatine ratio and the lactate content of the centrum semi-ovale in 16 patients with severe symptomatic carotid artery disease both before and 4 days after successful endarterectomy.
Patients and Methods

Patients

Eight control subjects and 16 patients were examined. The control group (five male, three female, ages 49–69 years, mean age 64 years) consisted of five volunteers and three subjects with small cerebellar tumours. None of the controls had ever experienced neurological symptoms that could be ascribed to carotid insufficiency or emboli.

The 16 patients (13 male, three female, ages 50–74 years, mean age 65 years) were all symptomatic and candidates for carotid endarterectomy. Twelve patients had suffered a transient ischaemic attack and four had suffered a stroke. Eleven of these patients had a unilateral carotid stenosis of more than 70%. Two had a stenosis of more than 70% and a contralateral occlusion of the internal carotid artery. The last three patients had a bilateral carotid stenosis of more than 70% and were operated on the symptomatic side. Quantification of the carotid pathology was based on intravascular Digital Subtraction Angiography (IaDSA). The time span between the last symptoms and the preoperative MRSI was less than 6 weeks in seven patients, 6-12 weeks in four and more than 12 weeks in five. All patients were operated on under general anaesthesia with peroperative EEG and TCD surveillance. All 16 operations were uncomplicated and there were no ischaemic events after the operation. The first MRSI examination was performed the day before the operation and the second MRSI on the fourth day after the operation.

MRI and MRSI

The MRI and MRSI studies were performed on a Philips Gyroscan $15 whole body system operating at 1.5 Tesla. First, Proton MR images were obtained: seven sagittal T1 weighted scout slices (slice thickness 5 mm, 1 mm slice gap, TR 450 ms, TE 30 ms), and 14 transaxial T2 weighted slices (slice thickness 7 mm, 1.6 mm slice gap, TR 2000 ms, TE 50 and 100 ms). The transaxial slices were generally not angulated. Six of the 16 patients showed a cerebral infarction on the MR images.

After MRI, the volume of interest (VOI) for 1H MRSI was selected in the transaxial images. For every subject a 15 mm thick transverse slice was selected within the centrum semi-ovale. The anterior-posterior and left-right dimensions of the VOI were chosen in such way that regions containing lipid were excluded.

For optimal MRS imaging the optimal 90 degree pulse length was determined and the gradients were tuned, followed by localised shimming of our VOI. The PRESS sequence was used for localised 1H MRSI acquisition and gradient phase encoding was applied in two dimensions. 16 × 16 Phase encoding steps were used over a field of view (FOV) of 200 × 200 mm, resulting in an in plane spatial resolution of 12.5 mm, and in a nominal voxelsize of 2.34 ml. For each phase encoding step two averages (with a repetition time of 2000 ms and an echo time of 272 ms), 512 time domain data points and a 1000 Hz spectral width were used. The total patient time including patient preparation, MRI and MRSI was 40 min.

For display purposes the spectroscopic images were interpolated to a 128 × 128 matrix. The display software (sunspecl, Philips Medical Systems, Best) provided a simultaneous display and spectral registration of the MR images and metabolite images. Regions, mainly containing white matter, were selected by mouse control of a cursor on either the MR or metabolite images. 1H spectra were selected from regions outside areas showing white matter hyper-intensities, infarctions, on MRI and, away from the edges and borders of the 1H PRESS (VOI) volume to avoid lipid contamination and chemical shift artifacts. In the individual spectra and for the individual metabolite images total choline, total creatine, N-acetyl aspartate and lactate peaks were identified by their chemical shifts. Individual peaks were quantified by peak height measurements. Reference spectra were obtained from the homologous region of the contralateral hemisphere. In the patient and control group, three spectra were selected in each hemisphere. In each hemisphere, one spectrum was selected in frontal region, one in the mesial region and one in the parietal region of the centrum semi-ovale.

Statistical Analysis

For statistical analysis, we used repeated measures of analysis of variance (ANOVA) to compare metabolite ratios by location and groups. Locations were grouped into frontal, mesial and parietal regions of the centrum semi-ovale. The subjects were grouped into normal controls (n = 8), patients with a stenosis in the internal carotid artery (ICA) before endarterectomy (n = 16) and the same patients after endarterectomy (n = 16). Analysis of differences in metabolite ratios between the two hemispheres within groups was performed using the unpaired two-tailed Student's t-test. For analysis of differences in metabolite ratios between
control subjects and patients we also used the unpaired two-tailed Student's t-test.

Results

MRSI

In the control group we did not find any asymmetry in the NAA/choline and NAA/creatine ratio and for the absolute peak heights of choline, creatine and NAA between the left and right hemispheres or between the frontal and parietal regions. Therefore the metabolite ratios of each hemisphere were averaged from all spectra selected in that particular hemisphere.

Figure 1 shows a MRSI data set of a patient with a stenosis of the right internal carotid artery: (A) the choline spectroscopic image, (B) the NAA spectroscopic image, (C) the lactate spectroscopic image and (D) the corresponding T2 weighted MRI, showing a watershed periventricular medial infarct. In all spectroscopic images, the high-pass filtered corresponding MRI is superposed. The rectangle indicates the VOI chosen. Fig. 2 shows 4 1H MR spectra (1-4) from voxels which were selected from the patient shown in Fig. 1.

Lactate

Lactate could not be traced in the eight control subjects. Although the VOIs in the patients were selected outside regions showing white or gray matter hyper-intensities on MRI, cerebral lactate was found in five of these 16 patients (31%) in the hemisphere on the side of the symptomatic stenosis. None of the patients showed lactate on the contralateral side. After endarterectomy in three of these five patients, lactate was no longer seen, whereas in the two other patients the lactate/NAA ratio was more than 50% reduced.

The NAA/Choline ratio

In the control group the NAA/choline ratio was 3.38 ± 0.29. In the patients the NAA/choline ratio was calculated in the hemisphere on the side of the symptomatic stenosis and on the contralateral side. Before endarterectomy the NAA/choline ratio on the side of the stenosis was 1.98 ± 0.43, and on the contralateral side 2.69 ± 0.63 (p < 0.001). In 15 of the 16 patients we observed an overall decrease in the NAA/choline ratio in the symptomatic cerebral hemisphere, compared to the ratio in the contralateral hemisphere.
In the other patient, the asymptomatic hemisphere showed a decrease in NAA/choline ratio, this was a patient with an occluded carotid artery on the asymptomatic side. After endarterectomy the NAA/choline ratio on the symptomatic side was significantly increased to 2.91 ± 0.56 (p < 0.001). The NAA/choline ratio on the contralateral side after endarterectomy was 3.10 ± 0.44. Fig. 3 shows the NAA/choline ratio of the symptomatic hemisphere of all patients before and after carotid endarterectomy. Before endarterectomy the NAA/choline ratio is significantly lower compared to control subjects (p < 0.001). After endarterectomy this NAA/choline ratio was increased in all patients but was still significantly lower compared to control subjects (p < 0.05).

**The NAA/ Creatine ratio**

In the control group the NAA/creatine ratio was 3.77 ± 0.47. In the patients the NAA/creatine ratio was calculated in the hemisphere on the side of the symptomatic stenosis and on the contralateral side. We found a small but significant asymmetry in NAA/creatine ratio (p < 0.05) between the hemisphere on the side of the symptomatic stenosis (3.21 ± 0.82) and the contralateral hemisphere, (4.34 ± 1.18). After endarterectomy this asymmetry disappeared and the NAA/creatine ratio in the operated, symptomatic hemisphere was 4.22 ± 1.04 vs. 4.03 ± 1.28 on the contralateral side.

**Discussion**

The most important findings of this study are: (1) in all 16 patients with symptomatic carotid artery disease the NAA/choline ratio in both hemispheres is decreased, compared to the ratios in the eight controls: (2) after a successful carotid endarterectomy the NAA/choline ratio in the symptomatic hemispheres increased significantly compared to the corresponding ratio before the operation. (3) the NAA/creatine ratio showed the same changes preoperatively compared to the controls and, postoperatively compared to the preoperative situation. However, the changes in NAA/creatine ratios were less pronounced than the changes in NAA/choline ratios. (4) In some patients we detected lactate in non-infarcted regions of the brain. (5) After the endarterectomy the lactate was considerably reduced, or no longer detectable in all these patients. Of the five patients with lactate, the time span between last symptoms and the carotid endarterectomy was less than 6 weeks in one patient, and 6–12 weeks in the other four patients.

A remarkable finding of this study was that we could demonstrate metabolic changes in regions of the brain that did not show any morphological damage on the T2 weighted MR images. NAA is found only in the brain and is a putative marker of vital neurons. The metabolic function of NAA is still unknown. Creatine and choline are more common metabolites that can be found in the brain both in neurons and in glia-cells. Many authors have investigated the local metabolic effects in infarcted areas of the human brain. MRSI studies of infarcted areas in the brain show a reduction of NAA content and an increase in lactate, compared to studies in the normal brain.

In our patient group we found the same changes, e.g. decreased NAA/choline and NAA/creatine ratios and increased lactate, suggesting hypoxic conditions. Since cerebral circulation is likely to be decreased in this hemisphere, these metabolite findings are not unexpected. However, in contrast to metabolite changes in infarcted regions, which are not reversible, the metabolite levels in the symptomatic hemisphere in our patient group returned to normal levels after endarterectomy. This suggests that hypoxic cerebral metabolite changes, in tissue that is not showing abnormalities on MRI, are reversible.

The increase of the NAA/choline and NAA/creatine ratios after endarterectomy can be explained

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Fig. 3. NAA/choline ratio of the symptomatic hemisphere of all patients before and after carotid endarterectomy. The shaded area represents the NAA/choline ratio ± 2 s.d. of the controls.
by an increase of NAA, a decrease in creatine or choline or a combination of both mechanisms. Based on our data we can only speculate on the cause of these changes. Although we were not able to measure the absolute concentrations of these metabolites the relative signal intensities of each metabolite suggests that a decrease in choline and creatine is more likely than an increase in NAA.

During, and after, the endarterectomy, there are marked changes in cerebral blood flow that can be evaluated with trans-cranial Doppler (TCD). Immediately after clamp release, a hyperaemic response starts. The hyperaemic response is more prolonged in a group of patients with an impaired cerebral vascular reserve. Seventy-two hours after the operation a >50% increase in middle cerebral artery blood flow velocity can be demonstrated in this group. This increase in cerebral bloodflow could be the mechanism that causes a decrease in choline and creatine by means of a wash-out effect after the endarterectomy.

In conclusion we have shown that there are marked changes in brain metabolism in the symptomatic hemisphere of patients with a severe carotid artery stenosis. These metabolic changes normalise 4 days after endarterectomy.

References

2 EUROPEAN CAROTID SURGERY TRIALISTS’ COLLABORATIVE GROUP: MRC European carotid surgery trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991; 337: 1235-1243.
20 GIDSON P, HENDRIKSEN O, SPEERLING B. Early time course of NAA, creatine and phosphocreatine and compounds containing choline in the brain after acute stroke, a proton magnetic resonance study. Stroke 1992; 23: 1566-1572.

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