Long-Term Hemodynamic Effects of Carotid Endarterectomy

Manon Kluytmans, MSc; Jeroen van der Grond, PhD; Bert C. Eikelboom, MD, PhD; Max A. Viergever, DSc

Background and Purpose—The presence and importance of hemodynamic factors to the beneficial effect of carotid endarterectomy (CEA) in patients with severe stenosis of the internal carotid artery (ICA) is unclear. The purpose of this study was to investigate possible hemodynamic changes caused by a severe ICA stenosis and the subsequent changes after CEA.

Methods—Hemodynamic parameters were acquired with dynamic susceptibility contrast MRI. Regional cerebral blood volume (rCBV), mean transit time (MTT), time of appearance, and time to peak were determined in 19 patients with severe stenosis (>70%) of the ICA before and after CEA and in 33 control subjects. Four patients had an occlusion of the contralateral ICA. Corresponding T2-weighted MRI and inversion recovery MRI scans were used for segmentation of gray and white matter regions.

Results—In the hemisphere ipsilateral to the stenosed ICA, no significant differences were found for the rCBV or MTT between patients and control subjects. Also, no significant alterations in these two parameters were observed after CEA. In the hemisphere contralateral to the stenosed ICA, hemodynamic changes were observed only in patients with an ICA occlusion contralateral to the stenosed ICA. In these patients, rCBV, MTT, time of appearance, and time to peak were all increased in the contralateral hemisphere. After CEA, all hemodynamic parameters fell in the normal range.

Conclusions—Although CEA does improve the cerebral circulation in patients with a severe stenosis and a contralateral ICA occlusion, the hemodynamic effects of CEA in patients with severe stenosis without a contralateral ICA occlusion are negligible. (Stroke. 1998;29:1567-1572.)

Key Words: carotid endarterectomy ■ hemodynamics ■ magnetic resonance imaging ■ perfusion

In symptomatic patients, carotid endarterectomy (CEA) of severe stenosis (>70%) of the internal carotid artery (ICA) has proven to be highly beneficial in the secondary prevention of stroke. Two possible favorable effects of surgery have been recognized. First, CEA removes the atheromatous plaque, which is a possible source of cerebral emboli. Another more hypothetical explanation of the beneficial effect of CEA is the restoration of the cerebral perfusion pressure. Although the importance of the latter is questionable, many studies have shown improved hemodynamics after CEA. Reduction of the cerebral autoregulation, vasomotor reactivity, cerebral perfusion, and decreased cerebral blood flow do suggest that at least in some patient groups CEA may improve the hemodynamic status of the brain. However, other studies were not able to show hemodynamic abnormalities in patients with severe stenosis of the ICA. Possible confounding aspects in these studies are the timing of the observations after CEA, differences in the composition of the patient population, and the analysis of different pathophysiological regions or vessels in the brain. In this respect, the role of a contralateral ICA lesion, the presence of cerebral infarctions, and differences in gray and white matter perfusion seem to have been underestimated.

Recently, many studies have been published concerning dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI). DSC-MRI is a perfusion-weighted MRI technique capable of measuring a variety of hemodynamic parameters in patients with acute stroke as well as in patients with occlusive disease of the ICA. The technique is based on the analysis of a bolus passage of contrast material and is well suited for application in routine clinical practice. DSC-MRI yields relative values for regional cerebral blood volume (rCBV), mean transit time (MTT), time of appearance (TA), and time to peak (TP). In patients with severe occlusive disease, reduced regional cerebral blood flow (rCBF), increased rCBV, and MTT have been found. At present, no studies have been published investigating the hemodynamic effects of CEA with DSC-MRI.

The purpose of this study was to investigate the hemodynamic effects of CEA in patients with severe stenosis of the...
the ICA, by means of DSC-MRI. The hemodynamic effects in white and gray matter are considered separately.

Subjects and Methods

Subjects

Between August 1996 and September 1997, 19 patients with severe stenosis of the ICA (14 men and 5 women, age 49 to 81 [68±9] years) and 33 control subjects (20 men, 13 women, age 40 to 81 [55±11] years) were included in this study. All patients underwent DSC-MRI before CEA and received a follow-up DSC-MRI examination 8 weeks to 6 months (mean 12.7 weeks, median 12 weeks) after CEA. All patients underwent duplex sonography and intra-arterial digital subtraction angiography. However, quantification of the carotid artery stenosis was based on duplex sonography and intra-arterial digital subtraction angiography.

Of the 19 patients, 17 were operated on because of symptomatic stenosis defined as ischemic episodes of the ipsilateral hemisphere in the last 6 months before operation; transient ischemic attacks (TIAs) in 8 patients, nondisabling (minor) stroke in 3 patients, or transient (amaurosis fugax) or chronic ocular ischemia in 2 patients. Four patients had a contralateral ICA occlusion. The symptoms affected the side of the brain ipsilateral to the carotid occlusion: 3 patients had TIAs, in 1 combined with amaurosis fugax, and the fourth had a minor stroke.

Two of the 19 patients were asymptomatic: 1 never had any neurological symptoms, whereas the other had a minor stroke more than 6 months before surgery.

Patients were divided into 2 groups. Group 1 (n=15) consisted of patients with a severe ICA stenosis. Group 2 (n=4) consisted of patients with a severe ICA stenosis and an occlusion of the ICA on the contralateral side. In group 1, the mean percent stenosis was 83% (range 70% to 95%) on the CEAside and 27% (range 0% to 70%) in the contralateral ICA. In group 2, the mean percent stenosis on the CEAside was 75% (range 70% to 80%), whereas on the contralateral side all ICAs were occluded.

Thirty-three control subjects (20 men, 13 women; age 55.3±11.4 years, range 40 to 81) were selected from an age-matched group (n=52) of patients who underwent MRI to exclude the presence of an acoustic neurinoma. Subjects with a tumor or any other intracranial abnormality on the MRI scans (n=19) were excluded. None of the control subjects had a history of neurological deficits.

Magnetic Resonance Imaging

The MRI and DSC-MRI studies were performed on a Gyroscan ACS-NT (Philips) whole-body system operating at 1.5 T.

IR and T2-Weighted MRI Protocols

Inversion recovery (IR) and T2-weighted (T2-w) images were obtained for 5 slices. Four slices were positioned in the centrum semiovale, and the fifth slice was positioned through the cerebellum (IR: inversion recovery turbo spin-echo (IR-TSE) sequence; TSE factor=5; field of view (FOV)=230 mm; reduced field of view (RFOV)=70%; flip angle=90 degrees; repetition time [TR]=2200 ms; echo time [TE]=14 ms; IR delay=300; slice thickness=8 mm; slice gap=2 mm; matrix=256×256; scan percentage=70%; reconstruction=256×256; total scan duration=1 minute, 13 seconds) (T2-w: TSE sequence; TSE factor=6; FOV=230 mm; RFOV=80%; flip angle=90 degrees; TR=2000 ms; TE=100 ms; slice thickness=8 mm; slice gap=2 mm; matrix=256×256; scan percentage=60%; reconstruction=256×256; total scan duration=0 minutes, 42 seconds).

DSC-MRI Protocol

Five slices identical to those used in the IR and T2-w MRI protocols were imaged with the use of a T2-weighted gradient echo sequence (DSC-MRI: fast field echo [FFE] echo planar imaging [EPI] sequence; number of echoes per excitation [EPI factor]=9; FOV=230 mm; RFOV=70%; flip angle=30 degrees; TR=260 ms; TE=30 ms; slice thickness=10 mm; matrix=90×128; scan percentage=70%; reconstruction=256×256 and/or 128×128; dynamic scan=50; dummy scan=5; time resolution=1.5 seconds; total scan duration=1 minute, 19 seconds). Nine seconds after the start of acquisition, a contrast bolus of 30 mL gadopentetate dimeglumine (Gd-DTPA2-), Magnevist, Shering AG) was injected over 6 seconds by means of an MR-compatible injection pump (5 mL/s) (Spectris MR injector, Medrad). The infusion line was prefilled with gadopentetate dimeglumine and the Gd-DTPA2- injection was immediately followed by a saline flush (10 mL saline: 5 mL at 5 mL/s followed by 5 mL at 2 mL/s).

Image Analysis

Perfusion maps were constructed off-line on a clinical workstation. For each voxel in the dynamic data sets, time-intensity curves were converted into time-concentration curves, which were subsequently fitted by a gamma-variate function. Curve fitting was performed with the use of the downhill simplex method in multidimensions.30 MTT, TA, and TP maps were expressed in time units (s), whereas rCBV was expressed in arbitrary units. Regions of interest (ROIs) were defined by segmentation of IR images corresponding to the 5 perfusion slices, for white matter and gray matter of both hemispheres, and of the total cerebellum. Lesions were excluded on T2-w images. Segmentation was performed on a UNIX workstation (HP 9000/750) with the use of an image analysis package (ANALYZE, Mayo Foundation). rCBV, MTT, TA, and TP data were averaged over the relevant ROIs of the 4 cerebral slices. To allow interpatient comparison and control-patient comparison of perfusion parameters, data were normalized over the cerebellum. In each hemisphere (white matter and gray matter), the hemodynamic parameters (rCBV, MTT, TA, and TP) were divided by the corresponding values for the entire cerebellum. The Figure shows the perfusion maps of a single slice from a patient with a 70% stenosis of the right ICA and an occlusion of the left ICA, before and after CEA.

Statistical Analysis

Patients were divided into 2 groups. Group 1 consisted of 15 patients with a severe ICA stenosis without, or with a less severe, stenosis of the contralateral ICA. Group 2 consisted of 4 patients with a severe ICA stenosis and an occlusion of the ICA on the contralateral side. All data are expressed as mean±standard deviation. In both groups, hemodynamic parameters were studied in white matter and in gray matter of the hemisphere ipsilateral to the stenosis (side of CEA), and in the contralateral hemisphere. Data between patients and control subjects and between symptomatic and asymptomatic sides were compared with the nonparametric Mann-Whitney U method for independent samples. Hemodynamic parameters of patients before and after CEA were compared with the paired-samples t test. A value of P<0.05 was considered statistically significant.

Results

Control Subjects

To allow comparison of perfusion parameters between patients and control subjects, data were normalized over the cerebellum. In each hemisphere (white matter and gray matter), the parameters (rCBV, MTT, TA, and TP) were divided by the corresponding values for the entire cerebellum. Because we did not find any difference between the left and right hemispheres in control subjects, the hemodynamic parameters of both hemispheres were pooled (see Table 1).

Patients, Group 1

Before CEA, no differences in rCBV or MTT were found either in white matter or in gray matter between patients with severe stenosis without contralateral ICA occlusion and

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TABLE 1. Normalized Hemodynamic Parameters of Patients and Control Subjects: Control Subjects (n=33)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>White Matter</th>
<th>Gray Matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV</td>
<td>0.40±0.07</td>
<td>1.00±0.22</td>
</tr>
<tr>
<td>MTT</td>
<td>1.01±0.07</td>
<td>0.99±0.05</td>
</tr>
<tr>
<td>TA</td>
<td>1.01±0.03</td>
<td>0.96±0.02</td>
</tr>
<tr>
<td>TP</td>
<td>1.00±0.03</td>
<td>0.97±0.03</td>
</tr>
</tbody>
</table>

Perfusion maps before and after carotid endarterectomy of a single slice from a patient with a 70% stenosis of the right ICA and an occlusion of the left ICA before CEA (left column) and perfusion maps of best corresponding slice after CEA (right column). Top to bottom: rCBV, MTT, TA, and TP maps. High signal intensity corresponds to large rCBV, long MTT, delayed TA, and delayed TP, respectively. Images before and after CEA are equally scaled. Little difference between the 2 hemispheres can be seen in the rCBV maps, although rCBV appears to be slightly increased in the left hemisphere before surgery (top row). MTT is increased before surgery in the left hemisphere compared with the right hemisphere; after surgery this hemispheric difference is diminished (second row). TA and TP show similar enhancement patterns. Before surgery, regions of delayed contrast arrival (third row) and peak times (bottom row) can be seen in white matter; these phenomena are diminished after CEA.

control subjects (see Table 2). Two of the time parameters were slightly delayed. In the ipsilateral hemisphere, TA was significantly increased in white matter (P<0.05). In gray matter, both TA and TP were significantly delayed (P<0.01 and 0.05, respectively). In the contralateral hemisphere, only TA in gray matter was delayed (P<0.05). No asymmetries in perfusion parameters were found in white matter and gray matter when the side of CEA was compared with the contralateral side. After CEA, we did not observe significant alterations in any of the perfusion parameters. Parameters that were not significantly different from control values remained in the normal range, whereas the time-parameters that were increased remained increased after operation. No differences were found when symptomatic patients (n=13) were compared with asymptomatic patients (n=2).

TABLE 2. Normalized Hemodynamic Parameters of Patients and Control Subjects: Patients With Severe ICA Stenosis and Less Severe or No Contralateral Stenosis (Group 1, n=15)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Side of CEA Before CEA</th>
<th>Side of CEA After CEA</th>
<th>Contralateral Side Before CEA</th>
<th>Contralateral Side After CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV</td>
<td>0.44±0.11</td>
<td>0.42±0.08</td>
<td>0.41±0.10</td>
<td>0.43±0.08</td>
</tr>
<tr>
<td>MTT</td>
<td>1.05±0.14</td>
<td>1.03±0.09</td>
<td>1.00±0.10</td>
<td>1.02±0.06</td>
</tr>
<tr>
<td>TA</td>
<td>1.04±0.05†</td>
<td>1.04±0.05†</td>
<td>1.03±0.05</td>
<td>1.04±0.05</td>
</tr>
<tr>
<td>TP</td>
<td>1.03±0.06</td>
<td>1.02±0.05</td>
<td>1.01±0.05</td>
<td>1.02±0.05</td>
</tr>
</tbody>
</table>

Patients vs control subjects: † P<0.05, ‡ P<0.01.

Patients, Group 2

On the side of CEA, similar hemodynamic differences were found as were observed in group 1 (Table 2). Compared with control subjects, no differences were observed for rCBV, whereas TA and TP in white matter and TA in gray matter were larger. Although all hemodynamic parameters tended to improve on the CEA side after CEA (more than in group 1), this improvement was statistically significant only for TA in white matter (P<0.05). After CEA, both in white matter and

TABLE 3. Normalized Hemodynamic Parameters of Patients and Control Subjects: Patients With Severe ICA Stenosis and Contralateral ICA Occlusion (Group 2, n=4)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Side of CEA Before CEA</th>
<th>Side of CEA After CEA</th>
<th>Contralateral Side Before CEA</th>
<th>Contralateral Side After CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV</td>
<td>0.43±0.02</td>
<td>0.40±0.07</td>
<td>0.50±0.04‡</td>
<td>0.39±0.07*</td>
</tr>
<tr>
<td>MTT</td>
<td>0.99±0.04</td>
<td>0.97±0.05</td>
<td>1.15±0.07‡</td>
<td>1.06±0.07</td>
</tr>
<tr>
<td>TA</td>
<td>1.08±0.05‡</td>
<td>1.02±0.02*</td>
<td>1.08±0.07</td>
<td>1.01±0.04*</td>
</tr>
<tr>
<td>TP</td>
<td>1.06±0.05†</td>
<td>1.00±0.02</td>
<td>1.08±0.07</td>
<td>1.01±0.03</td>
</tr>
</tbody>
</table>

Patients vs control subjects: † P<0.05, ‡ P<0.01. After CEA vs before CEA * P<0.05.
in gray matter, all hemodynamic parameters fell in the normal range.

In the contralateral hemisphere, rCBV, MTT, TA, and TP were all increased in white matter compared with that in control subjects, whereas in gray matter MTT, TA, and TP were increased. Again, all hemodynamic parameters tended to improve on the CEA side after CEA, and this improvement was statistically significant for rCBV and TA in white matter ($P<0.05$). After CEA, all hemodynamic parameters fell in the normal range in white matter as well as in gray matter.

Before CEA we found statistically significant ($P<0.05$) hemispheric asymmetries on the contralateral side for rCBV and MTT in white matter. After CEA, no hemispheric asymmetries were found.

When data were analyzed by sex, no differences between men and women were found in any of the perfusion parameters before or after CEA in all 3 patient groups.

**Discussion**

The most important finding of this study is that hemodynamic parameters in patients with a severe stenosis are only barely different from control values and do not change after CEA. However, in patients with an occlusion of the contralateral ICA, hemodynamic parameters are seriously impaired. In this patient group, all hemodynamic parameters improved after CEA, especially on the contralateral side. The observed hemodynamic alterations were more pronounced in white matter than in gray matter.

Contradictory results have been published on the effect of CEA on alterations in hemodynamic parameters. Some studies did not report significant hemodynamic changes after CEA, whereas other studies did find significant changes. Other studies report that significant hemodynamic changes after CEA may occur in some but not all patients. In our study we observed only minor hemodynamic changes on the side of CEA independent of the presence or absence of severe lesions in the contralateral ICA.

The finding of unchanged rCBV and MTT (rCBV/MTT is proportional with rCBF) after CEA appears to be contradictory to previous findings with MR angiography (MRA) that flow through the ipsilateral ICA increases after CEA. However, these measurements were performed shortly after surgery and may therefore show a temporary effect caused by transient hyperperfusion, which may occur after CEA. An MRA study 3 months after CEA also showed an increased flow through the ICA but showed in addition a decreased flow through the basilar artery, suggesting that CEA diminishes dependency on collateral flow rather than increases total flow.

When autoregulation plays an important part in maintaining the rCBF at a normal level, it is expected that MTT and rCBV are both increased and normalize after CEA. However, in our study, no changes in rCBV and MTT were observed after CEA.

Furthermore, we observed an increased TA and TP in both white and gray matter before CEA. Delayed timing parameters may suggest the participation of collateral pathways in the cerebral blood supply. However, although TA and TP were slightly delayed, both did not return to normal level after CEA. It is not unlikely that the observed increase in TA and TP is caused by other reasons than the presence of an ICA stenosis but may still be related to vascular or cerebral changes specific for this patient group.

Our data show that patients with a severe stenosis of the ICA are not hemodynamically impaired on that side, which indicates that hemodynamic changes are not likely to contribute to the patients’ clinical symptoms. Although several studies showed impaired reserve capacity that improved after CEA in these patients, other studies failed to show decreased reserve capacity or showed impaired reactivity and subsequent improvement after CEA only in a small subgroup of patients. Because we found no indication of vasodilatory compensation (no increased rCBV), we speculate that the beneficial effect of CEA in patients with a unilateral severe stenosis of the ICA is caused by removal of the embolic source rather than by restoration of the cerebral blood flow.

Patients who have a contralateral ICA occlusion in addition to an ipsilateral ICA stenosis have a higher risk of stroke, and in this population CEA has also been shown to be beneficial in the long term. In 2 out of 4 patients, symptoms (TIA)s on the side of occlusion (contralateral to the ICA stenosis) were uncovered after the ICA occlusion had been diagnosed. In these 2 patients, low cerebral perfusion may have played an important role in the patients’ symptoms. However, it cannot be excluded that the symptoms occurred by an embolic material through the collateral pathways. In the other 2 patients the cause of the symptoms remains speculative. Our results show that in contrast to the CEA side, the occluded side is significantly impaired. Similar abnormalities were described in previous DSC-MRI studies for larger groups of patients with ICA occlusions. In addition, our data show that white matter is especially impaired. The observed increase in rCBV and MTT in the white matter on the occluded side shows that vasodilation is an important mechanism to maintain a normal cerebral blood flow. The improvement in hemodynamic parameters after CEA might explain why, despite the higher perioperative morbidity rates, patients with a symptomatic contralateral ICA occlusion had a better long-term prognosis than medically treated persons. In this respect, the finding that in patients with severe contralateral ICA lesions the increment in mean volume flow rate in the operated ICA is larger than in patients with less severe contralateral ICA lesions is interesting.

The results of our study emphasize that when studying hemodynamic consequences of carotid artery disease, it does not suffice to study the ipsilateral artery and hemisphere only. Also, the contralateral artery and hemisphere should be considered because, in particular when flow through the ICA is diminished, the contralateral artery can contribute significantly to the blood supply of the ipsilateral hemisphere—or vice versa, if the contralateral ICA is occluded, the ipsilateral ICA does have a large impact on the contralateral hemisphere.

**Limitations**

A limitation of the technique used is that the obtained hemodynamic values are relative and not quantitative. Al-
though it is possible to obtain quantitative rCBV and MTT data by deconvolution of the time-concentration curves with a simultaneously measured arterial input function, this technique is less suited for patients with severe ICA lesions. The reliability of the method depends on the measurement accuracy of the arterial input function. In the normal situation, the middle cerebral artery is supplied directly by the ICA, and input function can be calculated by measuring the passage of the contrast bolus through the ICAs. However, when one ICA is occluded or severely obstructed, the ipsilateral hemisphere will be supplied by the ICA on the contralateral side by cross-flow through the anterior communicating artery, by the basilar artery through the ipsilateral posterior communicating artery, by the ophthalmic artery, or by leptomeningeal vessels. As a result, the contribution of the different pathways is not known. Moreover, the input function of different parts of the brain will not necessarily be similar, and estimations of the arterial input function in small vessels are not reliable with the current techniques.

To enable a comparison of patients and control subjects, data were normalized over the cerebellum. The use of the cerebellum as a reference assumes that cerebellar perfusion is normal. Although the posterior circulation appeared normal on MRA in all patients, it cannot be excluded that flow and flow-related variables in the cerebellum did change, depending on the severity of ICA lesions. However, because no significant perfusion asymmetries in the cerebellum were found that might have been caused by cerebellar diaschisis, we assumed that any disturbance in cerebellar perfusion is small compared with the changes in cerebral perfusion.

Conclusions

Our data show that patients with ipsilateral ICA stenosis >70% without a severe contralateral ICA lesion are not hemodynamically impaired. We hypothesize that in these patients the beneficial effect of CEA is mainly caused by removal of the plaque as a source of embolism. However, from a hemodynamic point of view, CEA is especially advantageous in patients with an occlusion of the contralateral ICA.

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