Cerebral Hemodynamics in Asymptomatic and Symptomatic Patients With High-Grade Carotid Stenosis Undergoing Carotid Endarterectomy

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Background and Purpose—Asymptomatic patients with carotid stenosis benefit less from carotid endarterectomy (CEA) than symptomatic patients because the risk of embolic events is lower, but it is not known whether the hemodynamic effect of CEA is different between the groups. We evaluated hemodynamics of symptomatic and asymptomatic patient groups before and after CEA.

Methods—Forty-six independent patients with a unilateral high-grade carotid stenosis, 23 asymptomatic and 23 symptomatic, underwent dynamic susceptibility contrast MRI (DSC-MRI) and transcranial Doppler ultrasound (TCD) evaluation before CEA and 3 and 100 days afterward. Quantitative perfusion parameters were calculated separately in selected regions of white and gray matter and watershed regions in each hemisphere, and mean transit time (MTT) maps were assessed visually by 2 independent observers. Vasomotor reactivity was determined with breath-holding index and flow impedance with pulsatility index ipsilaterally.

Results—In contrast to the asymptomatic carotid stenosis group, symptomatic carotid stenosis patients had preoperatively increased MTT and lower cerebral blood flow values in the ipsilateral hemisphere, more in white matter and watershed regions than in gray matter. Visually detected perfusion deficits were associated with symptomatic status. The interhemispheric asymmetries were abolished by CEA. The improving trend over time was greater in the symptomatic carotid stenosis group and was best seen in MTT. On TCD, pulsatility index was lower in symptomatic carotid stenosis patients preoperatively, with no postoperative difference, whereas the breath-holding index improved only in the symptomatic carotid stenosis group after CEA.

Conclusions—Patients with asymptomatic and symptomatic carotid stenosis differ significantly by means of DSC-MRI and TCD before and in response to CEA. (Stroke. 2003;34:1655-1661.)

Key Words: carotid stenosis ■ hemodynamics ■ magnetic resonance imaging, perfusion-weighted ■ ultrasonography, Doppler, transcranial

Carotid stenosis (CS) or occlusion may compromise cerebral hemodynamics. Hemodynamic factors have long been associated with the symptomatic status of stenosis, although their role is controversial.1 The degree of carotid stenosis correlates poorly with cerebral perfusion pressure, and several studies have been unable to detect any significant cerebral hemodynamic abnormality in a majority of patients with a high-grade CS.2–4 Several other reports indicate the importance of cerebral hemodynamics in association with the risk of stroke in patients with CS or occlusion.5–8

Carotid endarterectomy (CEA) improves the outcome of patients with symptomatic high-grade CS,2 but its role in asymptomatic CS is less beneficial.10 It may also improve the hemodynamic state, as suggested by postoperative improvement in cerebrovascular reactivity and cerebral blood flow (CBF).7,11–14 Several studies including both symptomatic and asymptomatic subjects with CS have detected hemodynamic improvement after CEA.12–15 but some findings suggest differences in hemodynamics between these populations.5,16

Dynamic susceptibility contrast MRI (DSC-MRI) utilizes rapid collection of the MR signal during the passage of a paramagnetic contrast agent bolus through the brain.17,18 The acquired data yield information on the tissue perfusion in form of the cerebral blood volume (CBV), CBF, and mean transit time (MTT) of the bolus.19–22 The methodology seems to reasonably allow for quantitative assessment of brain perfusion,22 and some reports suggest its applicability in carotid occlusive disease.23–26 Transcranial Doppler ultrasound (TCD) allows for assessment of cerebrovascular reactivity, and the breath-holding index (BHI) is a widely used screening method.5–8
Aims of the Study
We performed DSC-MRI on symptomatic and asymptomatic patient populations with a high-grade CS before and after CEA. We investigated MTT, CBV, and CBF and compared the results with data on cerebrovascular reactivity obtained by TCD. We sought to determine (1) the hemodynamic changes induced by CS and CEA over time, (2) whether there are hemodynamic differences between asymptomatic and symptomatic CS groups, and (3) whether there are differences between gray and white matter or watershed regions in the occurrence of hemodynamic change.

Subjects and Methods
Characteristics
This study was approved by the ethics committees of the departments of neurology and radiology and was performed according to the principles of the Declaration of Helsinki and the institutional guidelines during 1997–2000. All subjects gave written informed consent. We recruited 46 in-group consecutive patients with either symptomatic (n=23) or asymptomatic (n=23) high-grade CS referred to the departments of neurology and cardiovascular and thoracic surgery who fulfilled the study criteria: subjects had to be independent in daily life (modified Rankin Scale score ≤2), without potential cardiogenic origin of emboli, with no history of previous ipsilateral CEA or radiotherapy, and with a surgically accessible unilateral CS measuring ≥70% on digital subtraction angiography according to criteria of the North American Symptomatic Carotid Endarterectomy Trial. The subjects underwent a thorough clinical assessment and questioning by an experienced neurologist. None of the patients had significant stenoses in intracranial vasculature on angiography. Ipsilateral silent lacunar infarcts were detected in 2 patients in the asymptomatic group. In the symptomatic group, relevant minor infarcts were detected in 11 patients. Demographic and risk factor profiles are given in Table 1. Blood samples were collected preoperatively (on the morning of CEA), on the same day postoperatively, and at 3 months.

Imaging Techniques
All MR images were acquired on a Siemens Magnetom Vision whole-body clinical scanner (Siemens Medical Systems; 1.5 T) with a standard head coil. In addition to axial DSC-MRI, conventional T2- and proton-density–weighted images were obtained. No adverse effects occurred. The first imaging was performed in the evening on the preoperative day, and it was repeated 3 days and 100 days after CEA.

DSC-MRI was performed with a gradient-echo, echo-planar imaging sequence with repetition time of 1.2 ms, echo time of 42.1 ms, flip angle of 90°, and gradient strength of 25 mT/m covering five 5-mm-thick slices (interslice gap, 1.5 mm; field of view, 230×230 mm²; matrix size, 128×128). The centermost slice was leveled with corpus callosum and anatomic landmarks to keep the slicing constant. The slices were imaged 1 per second a total of 60 times. After collection of 7 baseline images, gadopentetate dimeguline (GD-DTPA) (Magnevist, Schering AG; 0.15 mmol/kg) was injected into the antecubital vein via an 18-gauge catheter at a speed of 5 mL/s with the use of an MR-compatible power injector (Spectris, Medrad), followed by a 10-mL flush of saline. The DSC-MRI data were analyzed as described in detail previously.

Region of Interest and Visual Analysis
In each hemisphere, 10 distinct neuroanatomic structures were selected for the analysis (normal-appearing frontal, parietal, temporal, and occipital gray and white matter and the watershed regions between the territories of middle cerebral artery and anterior and posterior cerebral artery [Figure 1a]). T2 images were used to identify the anatomic structures, and then the regions of interest (ROIs) were drawn manually on the CBF maps and transferred to the equivalent absolute CBV and MTT maps (Figure 1b).

Statistical Analysis
Interhemispheric and regional variations as well as comparison between asymptomatic and symptomatic patient groups were studied with repeated-measures ANOVA (or ANCOVA) with symptomatology as the between-subjects variable. The variance homogeneity was studied with the use of the box M test, and sphericity was evaluated with Greenhouse-Geisser ε values. Pairwise comparisons were made with Student’s t test, with correction for multiple comparisons. The χ² test or Fisher exact test was applied to univariate dichotomous variables. Correlations were studied with Spearman rank correlation. The values are given as means and 95% CIs or SDs. A 2-tailed value of P<0.05 was considered significant.

| TABLE 1. Clinical Profiles of the Patient Subgroups at Baseline (±SD) |
|------------------------|------------------------|--------|
| Symptomatic | Asymptomatic | P |
| **Age** | 63.2 (±9.1) | 65.0 (±6.6) | 0.53 |
| Degree of carotid stenosis | 80% (±10.9) | 77% (±7.8) | 0.33 |
| Cerebrovascular events | | | |
| Stroke | 10 (43%) | 0 | |
| TIA | 13 (57%) | 0 | |
| Sex (F/M) | 6/17 | 11/12 | 0.22 |
| Arterial hypertension | 16 (70%) | 14 (61%) | 0.56 |
| Coronary heart disease | 9 (39%) | 12 (52%) | 0.39 |
| Diabetes | 8 (35%) | 4 (17%) | 0.44 |
| Peripheral arterial disease | 7 (30%) | 9 (39%) | 0.59 |
| Smoking | | | |
| Never | 4 | 3 | |
| Former | 13 | 15 | |
| Current | 6 | 5 | 0.78 |
| Blood viscosity (Fibrinogen Hct)² | 0.28 (±0.08) | 0.24 (±0.07) | 0.04* |
| Total cholesterol | 5.3 (±1.1) | 5.3 (±1.1) | 0.90 |
| Triglycerides | 1.6 (±0.8) | 1.7 (±0.9) | 0.64 |
| On anticoagulation | 10 (43%) | 4 (17%) | 0.10 |
| On antiaggregation | 12 (52%) | 16 (70%) | 0.58 |

*Postoperatively, 0.30 (±0.11) versus 0.27 (±0.08). $P=0.27$; for overall groupwise difference 0.11 (main effect of symptomatic state, repeated-measures ANOVA).
Results

Interhemispheric Within-Group Differences
In the symptomatic CS group, the preoperative ipsilateral hemispheric MTT values were intrindividually higher than contralateral values in watershed regions and white matter (P < 0.001 for each, paired t test) and marginally higher in gray matter (P = 0.05, paired t test) (Table 2, Figure 2). There was no such difference in the asymptomatic CS group. Correspondingly, the preoperative ipsilateral CBF values were lower in watershed regions and white matter (P < 0.001 for each) and marginally lower in gray matter (P = 0.05, paired t test) in the symptomatic CS group only. There were no differences in the asymptomatic CS group, notwithstanding the preoperative CBF values in gray matter, for which the ipsilateral value was also lower in the asymptomatic CS group (P < 0.05) (Table 2). For CBV values, there were no significant interhemispheric differences in either group at any stage (Figure 2). The evolution of the interhemispheric ratios is depicted in Figure 2, showing the abolition of interhemispheric asymmetry by CEA and the significance of group × time interaction. In watershed regions, there was no difference between the anterior and posterior territories (data not shown).

Between-Group Differences
Patients with symptomatic CS displayed longer ipsilateral MTT before CEA, which was most pronounced in watershed regions and white matter and improved on subsequent measurements, whereas in the asymptomatic CS group the improvement was marginal or transient (Table 2). For CBF, there was a trend for slightly lower preoperative values in the symptomatic CS group. The CBV values remained homogeneous between the groups. None of the parameters showed significant groupwise differences after correction for multiple comparisons. The probability values in the study of the 2-way interaction (group × time) for each hemisphere are shown in Table 2. Results of between-group analyses were not altered by having blood viscosity or degree of stenosis as covariate. A total of 14 patients had a visible perfusion deficit in the ipsilateral carotid territory (Figure 1b), with a perfect inter-observer agreement (k = 1.0). Of the patients with a visualized hypoperfusion, 12 were in the symptomatic CS group (P = 0.003, Fisher test). In the population with a visualized deficit, the MTT values were 5.5 seconds (95% CI, 4.9 to 6.2 seconds) for ipsilateral gray matter, 7.5 seconds (95% CI, 6.7 to 8.3 seconds) for white matter, and 7.2 seconds (95% CI, 6.2 to 8.2 seconds) for watershed regions. The respective values for the subpopulation without a deficit were 4.1 seconds (95% CI, 3.7 to 4.6 seconds; P < 0.001), 5.4 seconds (95% CI, 4.9 to 6.0 seconds; P < 0.001), and 5.5 seconds (95% CI, 5.0 to 6.1 seconds; P = 0.002, t test). The interhemispheric MTT ratio in visually hypoperfused subjects was 1.28 (95% CI, 1.13 to 1.42) for gray matter, 1.46 (95% CI, 1.32 to 1.60) for white matter, and 1.39 (95% CI, 1.21 to 1.56) for watershed regions. In subjects without deficit, the respective values were 1.02 seconds (95% CI, 0.98 to 1.06 seconds), 1.06 seconds (95% CI, 1.01 to 1.11 seconds), and 1.09 seconds (95% CI, 1.04 to 1.15 seconds) (P < 0.0001 for all comparisons, t test). The patients with a visible deficit represented a higher grade of stenosis (85% [95% CI, 81% to 90%] versus 76% [95% CI, 73% to 79%]; P = 0.001, t test). The lowest degree of stenosis with a visually detected perfusion deficit was 71% (2 subjects). In the postoperative maps, no hypoperfusion was seen.

Figure 1. a, Preoperative CBV maps of a 73-year-old man with a left-sided high-grade CS, showing all ROIs: frontal gray (1) and white matter (2), temporal gray (3) and white matter (4), and occipital gray (6) and white matter (5) (A); anterior (7) and posterior watershed regions (8) (B); and parietal gray (9) and white matter (10) (C). b, Perfusion maps of slice B from panel a. Preoperative (preop), postoperative (postop), and chronic stage images of MTT (A), CBV (B), and CBF (C) are shown.
TABLE 2. Quantitative Perfusion Parameters at Different Time Points With 95% CIs

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The P values given for the interaction of symptom status and time point of measurement (repeated-measures ANOVA).

SCS indicates symptomatic carotid stenosis; ACS, asymptomatic carotid stenosis; GM, gray matter; WM, white matter; WsR, watershed regions; MTT, mean transit time; CBV, cerebral blood volume; CBF, cerebral blood flow.
The ipsilateral PI was initially significantly lower in the symptomatic than in the asymptomatic CS group, undergoing a similar pattern of improvement with no significant postoperative difference (Figure 3). The change in PI after CEA correlated with the improvement of the interhemispheric ratios of perfusion parameters. The association was significant for all parameters in white matter (MTT, \( R = -0.64, P < 0.0001 \); CBF, \( R = 0.42, P = 0.01 \); CBV, \( R = -0.46, P = 0.006 \)) and for 2 parameters in watershed regions (MTT, \( R = -0.55, P < 0.001 \); CBF, \( R = 0.46, P < 0.01 \); CBV, \( R = -0.10, P = 0.59 \)). In gray matter the associations were not significant (MTT, \( R = -0.29, P = 0.09 \); watershed regions, \( R = 0.06, P = 0.74 \); CBV, \( R = -0.23, P = 0.18 \)).
The BHI was comparable in the 2 groups at baseline, but only the symptomatic CS group improved postoperatively (group × time interaction; \( P = 0.02 \), ANOVA) (Figure 3). The change in BHI after CEA was associated with improvement in interhemispheric ratios in MTT (white matter, \( R = -0.53 \), \( P = 0.001 \); watershed regions, \( R = -0.34 \), \( P = 0.04 \); gray matter, \( R = -0.48 \), \( P < 0.005 \)). Improvement of CBF was associated positively with change in BHI only in watershed regions (\( R = 0.46 \), \( P < 0.01 \)).

**Discussion**

The main finding of this study was the subtle hemodynamic preoperative impairment of the symptomatic CS patient group and its more pronounced response to CEA in comparison to the asymptomatic CS group, elicited with both DSC-MRI and TCD modalities. The data are in accord with previous studies on hemodynamics in CS or occlusion\(^{6,13,16}\) but underscore the cerebral hemodynamic state as a correlate of the symptomatic state.

In perfusion imaging, the most substantial change linked to the hemodynamic effect of the stenosis was found in the MTT parameter, supporting previous findings.\(^{24,30}\) The initial hypoperfusion was severe enough to be visually detected in more than half of the symptomatic CS group and was significantly associated with symptomatic status. The threshold of visual detection of perfusion deficit on MTT can be approximated as an ipsilateral prolongation of \( > 15\% \) to \( 20\% \). The prevalence of perfusion deficit in the symptomatic CS group is a reminder of the potentially confounding role of chronic hypoperfusion in the setting of acute ischemia because it may be attributed erroneously to acute thrombosis and be regarded as tissue at risk.\(^{31,32}\) In such cases, MR angiography demonstrating a tight CS without intracranial arterial occlusions should arouse suspicion for a chronic state of hypoperfusion.

The chronic-stage values approached baseline values in asymptomatic CS patients particularly. This may explain why little long-term change has been detected previously.\(^{12,14}\) In MTT, there was some improvement even in the contralateral hemisphere, which contributed to the significance of the group × time interaction (Table 2). Our findings also corroborate the greater hemodynamic impairment of white matter in comparison to gray matter.\(^{14}\) The data did not support particular vulnerability of watershed areas or an asymmetrical impact on anterior and posterior border zones.\(^{12}\) Variation in CBV was notably low. CBV should not be sensitive to delay and dispersion of the bolus,\(^{33}\) and in this analysis only very subtle differences between the asymptomatic and symptomatic CS groups were seen. CBV is unlikely to be the most sensitive indicator of hemodynamic reserve.\(^{7,24,34}\)

On TCD, there was little difference among the asymptomatic and symptomatic CS groups in preoperative reactivity, but improvement was observed only in the symptomatic patients. PI is proposed to reflect cerebrovascular impedance, influenced by several properties of the vasculature and by cardiac function,\(^{27}\) but it is often applied as an indiscriminate index of resistance.\(^{28}\) It has been associated with symptomatic status, but its predictive value has been poor.\(^{7,38}\) CS is known to decrease PI by reducing inflow, and the retained pulsatility is thought to indicate lower impedance of collateral vessels. Increase of PI after CEA has been confirmed previously.\(^{39}\) The preoperative difference in PI between asymptomatic and symptomatic CS groups is in accord with previous findings,\(^{35}\) and the greater improvement of pulsatility in symptomatic CS supports the notion of a more severe initial hemodynamic impairment. As well, the correlation between the improvement in interhemispheric asymmetry of MR parameters and BHI underscores the effect of CEA in the symptomatic CS group.

DSC-MRI has not fulfilled the criteria of strict quantification or accuracy, essentially because of the simplified assumptions made of the underlying microvascular structure.\(^{20,37}\) The premises of the calculation may lead to a systematic error, although the values would be expected to be reasonably in proportion to the actual blood flow. Partial refinement may be possible by correction algorithms,\(^{25}\) which could also be used for partial volume effects arising from the fairly low resolution of images.\(^{38}\) We refrained from correction because of the comparative study design without emphasis on quantification.

The absolute dependence on arterial input function may be a crucial prerequisite for quantification, especially in the presence of CS. Delay or dispersion in the bolus passage inevitably introduces error, although some preliminary data suggest that reasonable quantification results in carotid occlusive disease.\(^{24,33}\) We chose to select an arterial input function from the contralateral hemisphere, using the feeding branch of the middle cerebral artery distal to the circle of Willis to measure the arterial input function as close to the ROI as reasonable, after the input of main collaterals. The choice may risk a greater partial volume effect. Finally, the variation in the fraction of cardiac output reaching the brain is a potential confounding factor, although this is not very likely in this study with major cardiac diseases as exclusion criteria.

In conclusion, the results corroborate that in homogeneous patient groups with unilateral high-grade CS, the preoperative hemodynamic adaptation is inferior in symptomatic CS patients in comparison to asymptomatic CS patients; this may be detected particularly as an abnormal interhemispheric ratio of MTT in DSC-MRI, often producing a visible perfusion deficit in higher-grade stenoses. The asymptomatic CS group represented a more stable hemodynamic constitution, and their long-term hemodynamic response to endarterectomy was negligible. The better hemodynamic adaptation may partly account for the lesser benefit from surgery in asymptomatic patients. Although not guiding treatment of CS, the findings serve as a reminder not to overlook the hemodynamic concept in viewing the determinants for symptomatic CS, and they encourage future trials to take advantage of more functional and dynamic methods for an improved evaluation and risk assessment in carotid disease.

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