Risk of Stroke, Transient Ischemic Attack, and Vessel Occlusion Before Endarterectomy in Patients With Symptomatic Severe Carotid Stenosis

Till Blaser, MD; Katrin Hofmann, MD; Thomas Buerger, MD; Olaf Effenberger, MD; Claus-Werner Wallesch, MD; Michael Goertler, MD

Background and Purpose—We aimed to identify and determine the clinical relevance of parameters predictive of stroke recurrence and vessel occlusion before carotid endarterectomy.

Methods—One hundred forty-three consecutive patients (105 men; mean age, 66.1±8 years) with symptomatic severe carotid artery stenosis were prospectively followed up until carotid endarterectomy. Patients had suffered an ischemic vascular event in the ipsilateral anterior circulation 9.6 days (median; range, 0 to 92 days) before presentation and assessment of stenosis. Admission examination included medical history, neurological status, extracranial and transcranial Doppler/duplex sonography, CT/MRI, ECG, and routine laboratory examination. All patients were reevaluated in the same way the day before surgery (without CT/MRI) and at recurrence of an ischemic event (including CT/MRI).

Results—The end point of follow-up after 19.0 days (median; range, 0 to 118) was carotid endarterectomy in 120 patients, ipsilateral recurrent ischemia in 15 patients (7 transient events and 8 disabling strokes, with carotid occlusion in 4), and (asymptomatic) carotid occlusion in 8 patients. An exhausted cerebrovascular reactivity as determined by a Doppler CO2 test in the middle cerebral artery ipsilateral to the stenosis was the only independent predictive parameter for disabling stroke (odds ratio [OR], 9.7; 95% confidence interval [CI], 2.1 to 44.1; P=0.003). Stroke rate in patients with exhausted reactivity was 27% per month compared with 5.2% in those with normal reactivity. Progression of stenosis toward occlusion was observed in 12 patients and correlated with decreased poststenotic peak systolic velocity (OR, 0.75; 95% CI, 0.62 to 0.90; P=0.002), poststenotic arterial narrowing (OR, 22.7; 95% CI, 3.6 to 141.6; P=0.001), and very severe stenosis (OR, 13.6; 95% CI, 2.2 to 83.7; P=0.005). In patients without hemodynamic compromise, occlusion was not associated with increased stroke risk.

Conclusions—Patients with recently symptomatic high-grade carotid artery stenosis and ipsilateral hemodynamic compromise are at high risk for early disabling stroke. Assessment of the hemodynamic status is recommended after diagnosis of severe carotid stenosis in symptomatic patients to further investigate and evaluate whether these patients may benefit from early endarterectomy. (Stroke. 2002;33:1057-1062.)

Key Words: carotid artery occlusion ■ carotid endarterectomy ■ carotid stenosis ■ cerebrovascular circulation ■ stroke, ischemic ■ ultrasonography, Doppler, transcranial
We prospectively followed up consecutive patients scheduled for carotid endarterectomy as a consequence of a recently symptomatic high-grade carotid artery stenosis until surgery. We attempted to identify parameters predictive of stroke recurrence and vessel occlusion before endarterectomy and to determine their clinical relevance.

**Subjects and Methods**

Eligible patients were selected from a series of 211 consecutive patients referred to the Department of Neurology or the Department of Surgery/Vascular Surgery (University of Magdeburg, Germany) with an ischemic vascular event in the anterior circulation within the last 3 months and an ipsilateral severe carotid stenosis diagnosed or confirmed at presentation. Patients were excluded from this study if endarterectomy was not thought to be the adequate therapy, ie, according to the modified Rankin Scale (n=16), high operative risk because of severe cardiac disease (n=15), expected additional ipsilateral high-grade intracranial stenosis (n=9), and concurrent stroke pathology (prosthetic cardiac valve; n=1). Eight patients refused the recommended endarterectomy. Twelve patients referred from distant hospitals or physicians to the cerebrovascular outpatient service for reference sonography were lost to follow-up.

One hundred forty-three patients (105 men, 38 women; mean age, 66.1±8 years) were scheduled for carotid endarterectomy for their recently symptomatic high-grade carotid stenosis and were included in the study. Twenty-seven patients had suffered amaurosis fugax, 1 had a retinal infarction, 37 experienced a transient ischemic attack (TIA), and 78 had an ischemic stroke 9.6 days (median; range, 0 to 92 days) before presentation and assessment of stenosis. All patients were seen at the Department of Neurology and underwent a standardized admission and follow-up procedure. Findings were documented in the local stroke database.

At admission, a detailed medical history, including cardiovascular risk factors, was taken. In patients who had experienced an ischemic event with persisting neurological deficit, the disability was rated according to the modified Rankin Scale, which was repeated after 7 days in case of acute stroke. Patients were considered eligible for endarterectomy if neurological signs had completely resolved or caused only slight to moderate disability (scored 3 or less on the modified Rankin Scale and could walk without assistance). This was discrepant to large endarterectomy trials that included patients with a maximally slight disability (scoring 2 or less on the modified Rankin Scale).1 2 The rationale for also operating on 12 patients with a maximally slight disability (scoring 2 or less on the modified Rankin Scale) was that these patients presented with hemiparesis of the upper extremity as the only relevant clinical deficit, and severe disability was that these patients presented with hemiparesis of the upper extremity as the only relevant clinical deficit, and severe disability was rated as severe enough for surgery, ie, localization of the carotid bifurcation in relation to thyroid cartilage, visible length of the extracranial ICA and presence of arterial kinking, length and localization of the stenotic plaque, and presence and degree of an extracranial or intracranial tandem stenosis. If complete extracranial and intracranial examination was not possible, eg, in case of an insufficient acoustic temporal bone window, patients underwent additional vascular investigations, ie, MR or digital subtraction angiography. To determine cerebrovascular reactivity, a transcranial Doppler CO₂ test in the middle cerebral artery (MCA) distal to the symptomatic stenosis was performed by breathing a mixture of 5% CO₂ in 95% oxygen and subsequent hyperventilation to induce hypocapnia and hypopnoea.13 Exhausted reactivity was defined as <5% flow velocity increase per 1 vol% end-expiratory CO₂ increase and <10% decrease per 1 vol% CO₂ decrease.14

CT or MRI was performed in all patients and was repeated after 24 to 48 hours if hemispheric signs persisted for >24 hours and the initial scan failed to demonstrate a corresponding infarction. Infarct type and size were categorized as subcortical with <1.5-cm maximal diameter, subcortical or cortical/subcortical with <3.0-cm diameter, and cortical/subcortical >3.0-cm diameter. Thus, small infarcts included lacunar and terminal zone infarction; medium-sized infarcts strio-subcortical, watershed, and predominantly solitary territorial infarction; and large infarcts multiple/extensive territorial infarction.15 17

Patients underwent additional Holter monitoring and transosophageal echocardiography if 12-lead ECG, clinical examination, or medical history at admission revealed findings suggestive of clinically relevant cardiac disease.

At admission, 93 patients already received antithrombotic medication for secondary prevention, which was acetylsalicylic acid (ASA) 100 to 300 mg/d in 64 patients, ticlopidine 500 mg/d or clopidogrel 75 mg/d in 14 (added-on ASA in 6), activated partial thromboplastin time–relevant intravenous heparin in 15 (added-on ASA in 2), and non–activated partial thromboplastin time–relevant subcutaneous heparin in 1. In the remaining 50 patients, prevention was started after admission examinations with ASA in 17 patients, clopidogrel in 15 (added-on ASA in 11), intravenous heparin in 10 (added-on ASA in 6), and subcutaneous heparin in 8.

All patients, regardless of outpatient or inpatient status, were prospectively followed up until surgery. They were reevaluated the day before endarterectomy and at recurrence of an ischemic event. Evaluation before surgery included recent medical history, clinical and routine laboratory examination, ECG, and Doppler/duplex sonography of brain-supplying arteries. Patients with a recurrent event also underwent CT or MRI. Ischemic recurrence was defined as the occurrence of neurological symptoms or clinical signs corresponding to the distribution area of the initially symptomatic stenosis that appeared after the initial deficit had completely resolved, as a sudden deterioration of initial symptoms, or as occurrence of new focal symptoms. Results of laboratory and technical examinations were required to be compatible with the diagnosis. The end point of follow-up for the 143 patients was carotid endarterectomy, recurrent ipsilateral ischemia, or carotid occlusion.

Statistical analysis was performed with SPSS, version 10.0. Baseline clinical and diagnostic findings were compared by the χ² test and nonparametric tests for independent samples. The clinical relevance of parameters for the prediction of stroke and vessel occlusion was estimated by Cox regression analysis with forward stepwise entry (P<0.05) and removal selection (P>0.10) based on the likelihood ratios at the first block. Independence of the selected parameters was investigated by forced entry of further variables at the second block. Significance was set at a value of P<0.05.

**Results**

The end point of follow-up after a median duration of 19.0 days (range, 0 to 118 days) in the 143 patients was carotid endarterectomy in 120, an ipsilateral recurrent ischemic event in 15 (with carotid occlusion in 4), and (asymptomatic) carotid occlusion in 8. Of the 15 recurrent ischemic events, 7 were transient (6 TIA, 1 remittent stroke) and 8 were...
persistent strokes that caused a moderate disability (scored 3 on the modified Rankin Scale) in 4 and a severe disability (scored 4 or 5) in another 4 patients, resulting in a rate of 7.5% per month for disabling stroke. Eleven patients with TIA/remittent stroke (n=6), moderately disabling stroke (n=4), or severely disabling stroke (n=1, already admitted for surgery and operated on 2 hours after symptom onset) and a still-open artery underwent carotid endarterectomy 13.0 days (median; range, 0 to 62 days) after the event. In 3 patients with a severely disabling stroke and 1 patient with TIA, subsequent duplex sonography revealed a carotid occlusion.

Patients’ characteristics, risk factors, cardiovascular diseases, neurological status, and CT/MRI and cerebrovascular findings are reported in the Table. Patients who suffered a disabling stroke during follow-up had a higher proportion of very severe stenosis, lower poststenotic peak systolic velocity, and more often an exhausted CO2 reactivity. Compared with those without a recurrent ischemic event, these patients also were older and less often had suffered recurrent symptoms before admission and diagnosis of their carotid artery stenosis, but both were without statistical significance. Transient ischemic events were associated with previous transient event at entry, either hemispheric (TIA) or ocular (amaurosis fugax). Other variables listed in the Table revealed no differences between patients with and without stroke and TIA at follow-up.

The forward stepwise Cox regression procedure was used to search for clinically relevant predictors of recurrent disabling stroke. Of all the parameters listed in the Table, the first and only variable entered in the regression model was an exhausted CO2 reactivity ipsilateral to the symptomatic stenosis (odds ratio [OR], 9.7; 95% confidence interval [CI], 2.1 to 44.1; P=0.003). This was independent from all other vascular findings as assessed by sonography (adjusted OR, 6.8; 95% CI, 1.3 to 36.5; P=0.026) and remained significant after correction for age; sex; risk factors; cardiovascular findings; size of infarction on CT/MRI; time since symptoms; and type, severity, and recurrence of symptoms that had led to admission (adjusted OR, 54.1; 95% CI, 2.3 to 1267.1; P=0.013). The rate for disabling stroke was 27% per month if CO2 reactivity was exhausted compared with 5.2% per month if it was not (P=0.003, Kaplan-Meier survival analysis; Figure 1). At entry, an exhausted CO2 reactivity was associated with a higher degree of stenosis, lower poststenotic flow velocity, and a single symptomatic event before admission (P<0.01 for all) but not with type and severity of the initial event, size of infarction, poststenotic arterial narrowing, or contralateral high-grade stenosis/occlusion.

Patients who developed an occlusion of their symptomatic carotid artery stenosis during follow-up more often had very severe (95%) stenosis, poststenotic arterial narrowing, and lower peak systolic velocity of the poststenotic ICA (the Table). As solitary vascular parameters, very high (95%) degree of stenosis (adjusted OR, 13.6; 95% CI, 2.2 to 83.7; P=0.005), low poststenotic peak systolic velocity (adjusted OR, 0.75; 95% CI, 0.62 to 0.90; P=0.002), and arterial narrowing of the poststenotic ICA (adjusted OR, 22.7; 95% CI, 3.6 to 141.6; P=0.001) predicted vessel occlusion also after correction for patient characteristics, risk factors, and clinical and CT/MRI findings as listed in the Table. Because of their high association with each other (P<0.001) (Figure 2), poststenotic peak systolic velocity remained the only independent predictor after all sonographic parameters were included in the regression analysis (adjusted OR, 0.82; 95% CI, 0.72 to 0.94; P=0.003). Poststenotic peak systolic velocity (OR, 0.83; 95% CI, 0.74 to 0.93; P=0.001) and degree of stenosis (OR, 0.77; 95% CI, 0.59 to 1.00; P=0.055) also were the only variables selected by forward stepwise Cox regression procedure from all clinical and sonographic parameters listed in the Table to predict subsequent vessel occlusion (Figure 3).

Progression of the initially symptomatic stenosis to occlusion was observed in 12 patients and was associated with a disabling stroke in 3, whereas 5 of 131 patients with a still-open artery had suffered a stroke (P<0.05). In 110 patients without hemodynamic impairment, 8 stenoses progressed to occlusion, which was accompanied by a severe stroke in 1 compared with 3 strokes in 102 open arteries (P=0.26). In 13 patients with exhausted CO2 reactivity, both patients with occlusion suffered a disabling stroke, as well as 2 of 11 with persisting stenosis (P=0.077). Twenty patients, including 2 with subsequent occlusion of their stenosis, had an insufficient temporal bone window that disallowed transcranial examination.

Discussion

Our study revealed hemodynamic compromise as assessed by an exhausted Doppler CO2 reactivity in patients with high-grade carotid artery stenosis and recent ischemic event without severe disability and without large infarction on CT/MRI as the most relevant parameter to predict early stroke recurrence before endarterectomy. This relationship was independent after controlling for other potential markers of an increased risk, including cardiovascular risk factors, type and severity of the ischemic event, time since the event, size of infarction on CT/MRI, degree of stenosis, poststenotic reduction of flow velocity or vessel diameter, and contralateral severe stenosis or occlusion. Correlation between an impaired cerebrovascular reactivity as assessed by reduced or absent response of blood flow velocity to vasodilatory stimulation with CO2 and an increased stroke risk has already been reported in patients with carotid occlusion and severe asymptomatic stenosis.14,18–20 Considerably higher absolute stroke rates in our patients, found to be as high as 27% per month for the first 3 months in patients with hemodynamic compromise and 5.2% in those without, may be explained by the different study populations. In contrast to ours, these other studies included asymptomatic patients14,18,19 and started follow-up in symptomatic patients at least 3 months after the index event18,20; both factors are associated with a lower risk of a subsequent stroke.20,21 In addition, arterial embolism, a major cause of stroke besides hemodynamic compromise in patients with large arterial vessel disease, is expected more frequently behind a stenosed than an occluded artery as demonstrated by a higher event rate in patients without hemodynamic impairment and carotid stenosis compared with those with normal cerebrovascular reactivity and carotid
occlusion. However, selection of an exhausted CO₂ reactivity as the only independent predictor of early subsequent stroke in our patients suggests hemodynamic compromise rather than embolism as the most likely cause.

In contrast to stroke recurrence, which was not correlated with any of the extracranial vascular parameters, progression of severe stenosis to occlusion was predicted by very severe stenosis, highly diminished poststenotic flow velocity, and poststenotic arterial narrowing, independently from hemodynamic status and clinical and CT/MRI findings. Of 12 patients with subsequent occlusion of carotid artery stenosis, 3 suffered an ipsilateral stroke, which was similar to the 20% to 25% rate observed by others. Although occlusion was associated with stroke recurrence in the entire study population, this effect was caused predominantly by patients with hemodynamic compromise because we found no association in those with normal cerebrovascular reactivity.

Our data suggest that occlusion of a recently symptomatic severe carotid artery stenosis is correlated with findings of low poststenotic blood flow, ie, highly reduced peak systolic velocity and arterial narrowing. However, neither extracranial vascular findings associated with reduced blood flow distal to severe carotid artery stenosis nor subsequent vessel occlusion seems to be an independent predictor of an early recurrent stroke, which is related primarily to patients’ intracranial hemodynamic status. This is corroborated by recent studies that failed to demonstrate a correlation between high risk of stroke and reduced ICA lumen diameter or stringlike lumen distal to a severe symptomatic carotid stenosis.

Baseline Characteristics of 143 Patients With Symptomatic Severe Carotid Artery Stenosis in Relation to Recurrent Stroke, TIA, and Vessel Occlusion Before Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Recurrence of Ischemic Event</th>
<th>Carotid Artery Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>128 (100)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>92 (72)</td>
</tr>
<tr>
<td>Age, (mean±SD), y</td>
<td>65.6±8</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>79 (62)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>37 (29)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>61 (48)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>32 (25)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>40 (31)</td>
</tr>
<tr>
<td>Hemispheric (nonocular) symptoms, n (%)</td>
<td>103 (81)</td>
</tr>
<tr>
<td>Persistent (nontransient) symptoms, n (%)</td>
<td>73 (57)</td>
</tr>
<tr>
<td>Recurrent symptoms, n (%)</td>
<td>43 (34)</td>
</tr>
<tr>
<td>Median time since last symptoms (range), d</td>
<td>9.6 (0–92)</td>
</tr>
<tr>
<td>CT/MRI infarction, n (%)</td>
<td>None</td>
</tr>
<tr>
<td>Subcortical &lt;1.5 cm in diameter</td>
<td>44 (34)</td>
</tr>
<tr>
<td>Cortical/subcortical &lt;3.0 cm in diameter</td>
<td>32 (25)</td>
</tr>
<tr>
<td>Degree of stenosis, n (%)</td>
<td>80%</td>
</tr>
<tr>
<td>85%</td>
<td>26 (20)</td>
</tr>
<tr>
<td>90%</td>
<td>43 (34)</td>
</tr>
<tr>
<td>95%</td>
<td>49 (38)</td>
</tr>
<tr>
<td>Mean poststenotic PSV (range), cm/s</td>
<td>38 (8–120)</td>
</tr>
<tr>
<td>Mean poststenotic PI (range)</td>
<td>1.0 (0.5–2.0)</td>
</tr>
<tr>
<td>Poststenotic arterial narrowing, n (%)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Exhausted CO₂ reactivity (ipsilaterally),* n (%)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Contralateral high-grade stenosis/occlusion, n (%)</td>
<td>19 (15)</td>
</tr>
</tbody>
</table>

PSV indicates peak systolic velocity; PI, pulsatility index.

* n=123.
† P<0.001; † P<0.01; ‡ P<0.05.
our patients with exhausted cerebrovascular reactivity, 4 were disabling strokes (scored 3 or more on the modified Rankin Scale), 3 of them occurring within 1 month of the index event, which was transient or nondisabling in all cases. Kleiser and Widder\textsuperscript{14} reported 6 ischemic events, 5 of which were strokes, in patients with carotid occlusion and exhausted CO\textsubscript{2} reactivity, 4 of them within 2 to 3 months of follow-up. These data suggest that early disabling stroke is the predominant type of ischemic recurrence in patients with hemodynamic compromise. Selection of NASCET patients within a maximum time of 4 months and ECST patients within a mean time of 2 months (maximum, 6 months) after an index event and with maximal minor nondisabling stroke (scored 2 or less on the modified Rankin Scale)\textsuperscript{1,2} therefore might have excluded a considerable number of patients with exhausted cerebrovascular reactivity and high risk for subsequent disabling stroke. This is corroborated by the finding of an intracranial collateral circulation in 96\% of NASCET patients with near occlusion in whom the intracranial circulation was visualized by angiography.\textsuperscript{23} In included patients, most thought to be without hemodynamic compromise as a consequence of selection criteria, a proposed explanation for the decreased risk of stroke in the presence of extracranial vascular findings associated with severe poststenotic blood flow reduction was that poststenotic flow might be too low to dislodge emboli from the stenotic plaque and carry them to the brain.\textsuperscript{22} This would also be consistent with the high number of asymptomatic occlusions found in corresponding patients in our study.

There was a remarkable difference in factors predicting disabling stroke in contrast to those associated with transient ischemic events, particularly the absence of a correlation between transient ischemic events and exhausted CO\textsubscript{2} reactivity. However, the number of ischemic events in our study was small, and embolism as another potential cause was not investigated. Therefore, we are unable to give a sufficient explanation for this finding on the basis of our data, particularly with respect to the potential interaction between hemodynamic and embolic stroke pathology.\textsuperscript{25}

In view of the established impairment of cerebral autoregulation and decreased reactivity of cerebral blood flow (velocity) on hypercapnia during and shortly after ischemia,\textsuperscript{26} concern may arise about the validity of hemodynamic testing in our patients, which was performed early after an ischemic event. However, the Doppler CO\textsubscript{2} test as performed in our study is a global assessment of the cerebrovascular reactivity downstream of the insonated MCA to evaluate whether morphologically intact brain tissue with normal function is hemodynamically compromised, ie, at increased risk for misery perfusion. Focal ischemia with decreased or lost reactivity will influence test results only if a considerable amount of brain tissue in relation to the whole MCA-supplied brain territory is affected. In all our patients, however, large brain infarction had been excluded by CT/MRI.

In summary, in patients with a recently symptomatic high-grade carotid artery stenosis and without severe disability and large infarction on CT/MRI, exhausted cerebrovascular reactivity as assessed by the Doppler CO\textsubscript{2} test is highly
predictive of early recurrence of disabling stroke. Reduced blood flow in the poststenotic carotid artery as assessed by low peak systolic velocity or arterial narrowing is associated with progression toward occlusion but not with an increased risk of subsequent stroke if cerebrovascular reactivity is presumed. Assessment of the hemodynamic status is recommended in all patients with symptomatic high-grade carotid artery stenosis to further investigate and evaluate whether patients with hemodynamic compromise and high risk for early disabling stroke may benefit from early endarterectomy.

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References
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