Incidence of New Brain Lesions After Carotid Stenting With and Without Cerebral Protection

Andreas Kastrup, MD; Thomas Nägele, MD; Klaus Gröschel, MD; Friederike Schmidt, MD; Eva Vogler, MD; Jörg Schulz, MD; Ulrike Ernemann, MD

Background and Purpose—Diffusion-weighted imaging (DWI) may be a useful tool to evaluate the efficacy of cerebral protection devices in preventing thromboembolic complications during carotid angioplasty and stenting (CAS). The goals of this study were (1) to compare the frequency, number, and size of new DWI lesions after unprotected and protected CAS; and (2) to determine the clinical significance of these lesions.

Methods—DWI was performed immediately before and within 48 hours after unprotected or protected CAS. Clinical outcome measures were stroke and death within 30 days.

Results—The proportion of patients with any new ipsilateral DWI lesion (49% versus 67%; P<0.05) as well as the number of new ipsilateral DWI lesions (median=0; interquartile range [IQR]=0 to 3 versus median=1; IQR=0 to 4; P<0.05) were significantly lower after protected (n=139) than unprotected (n=67) CAS. The great majority of these lesions were asymptomatic and less than 10 mm in diameter. Although there were no significant differences in clinical outcome between patients treated and not treated with protection devices (7.5% versus 4.3%, not significant), the number of new DWI lesions was significantly higher in patients who developed a stroke (median=7.5; IQR=1.5 to 17) than in patients who did not (median=0; IQR=1 to 3.25; P<0.01).

Conclusions—The use of cerebral protection devices significantly reduces the incidence of new DWI lesions after CAS of which the majority are asymptomatic and less than 10 mm in diameter. The frequent occurrence of these lesions and their close correlation with the clinical outcome indicates that DWI could become a sensitive surrogate end point in future randomized trials of unprotected versus protected CAS. (Stroke. 2006;37:2312-2316.)

Key Words: angioplasty ■ embolism ■ magnetic resonance imaging ■ protective device ■ stent

Carotid endarterectomy is currently widely performed for severe carotid artery stenosis. However, the benefit of carotid endarterectomy is highly dependent on a low risk of procedural neurological complications and is eliminated when the combined 30-day stroke and death rates exceed approximately 5% to 7% for symptomatic and 3% or even lower for asymptomatic patients, respectively.1,2 Because higher morbidity and mortality rates have been reported when carotid endarterectomy is used in everyday clinical practice,3 carotid angioplasty and stenting (CAS) might become an attractive alternative treatment strategy. Although evidence is accumulating that CAS can be performed with acceptable complication rates,4,5 fear of distal embolization of plaque fragments to the brain has generated great concern regarding the safety of this technique. Therefore, recent efforts have focused on the development of cerebral protection devices aimed at preventing the passage of embolic material into the cerebral vasculature. Although the concept of cerebral protection during CAS is appealing and has indirectly been supported by several case series and stent registries,4,5 no randomized study has yet been conducted to investigate the clinical efficacy of this approach. Moreover, the use of cerebral protection devices increases the intervention time, the complexity and cost of the procedure, and may also have a negative influence on embolization rates themselves.6,7

Because clinical events after CAS are relatively uncommon, additional surrogate markers for clinical stroke that occur at a greater frequency would have considerable use to evaluate the efficacy of protection devices. Against the background of a high incidence of clinically silent emboli occurring during CAS detected by diffusion-weighted imaging (DWI),8-14 this imaging modality could become a useful tool in this scenario. In fact, DWI is currently the most sensitive tool to detect early cerebral ischemia15 and offers the possibility of making even small and thus asymptomatic lesions visible shortly after their emergence.16 Although
several DWI studies have documented a high incidence of silent ischemia after either unprotected or protected CAS,8–14 until now, only one small study published recently has directly compared the frequency of new DWI lesions between protected and unprotected CAS.15 Moreover, the clinical significance of these lesions has not yet been established in a larger patient population. Therefore, the goals of the present study were (1) to compare the frequency, number, and size of new DWI lesions after unprotected and protected CAS; and (2) to determine the clinical significance of these lesions.

Methods

Study Population
From April 1999 to October 2005, consecutive patients with high-grade carotid stenosis (≥70% in symptomatic patients and ≥90% in asymptomatic patients assessed with ultrasound) were treated with CAS after a prospective protocol at our institution. The severity of carotid stenosis was evaluated by measuring the peak systolic velocity with angle correction at the narrowest point of stenosis. A stenosis was classified ≥70% if the peak systolic velocity was greater than 210 cm/s and ≥90% if it was >300 cm/s, respectively. A carotid stenosis was considered symptomatic if the patient had experienced an ipsilateral ocular or cerebral (permanent or transient) ischemic event within the past 6 months. Those patients without contraindications for magnetic resonance imaging (MRI) received preinterventional and postinterventional DWI scans of the brain. All patients were informed of the investigative nature of CAS and gave their written consent. Our Institutional Ethics Review Board had approved our CAS protocol.

Carotid Stent Protocol
All patients were treated with carotid angioplasty with stenting according to a standardized protocol described in detail recently.18 Initially, all CAS procedures had been performed without cerebral protection devices. When cerebral protection devices became available, the choice of which type of device to use, if any, depended on the personal preference of the interventional neuroradiologist performing the procedure.

MRI
In all patients, MRI scans were obtained immediately before and within 48 hours after the intervention. MRI was performed by echoplanar imaging using a 1.5-T MRI system (Siemens Magnetom Vision or Sonata; Siemens). Multislice diffusion-weighted single-shot echoplanar images were acquired in all patients while using the following parameters: repetition time (TR)=0.8 ms; echo time (TE)=123 ms; acquisition time 4 seconds; and b=1100 s/mm². Diffusion sensitivity was in the slice selection direction and hence perpendicular to the imaging plane. The number of measurements was five, the first run was omitted, and the remaining four were added to create an average image with improved signal-to-noise ratio. The conventional MRI sequences included T2-weighted fluid-attenuated inversion recovery turbo spin echo images (TR=9000 ms; inversion time=2200 ms; TE=119 ms). A magnetic resonance angiography was performed in all subjects before CAS using either a 90-mm Hg measured on repeated occasions), diabetes mellitus (HbA1c >6.5% or fasting blood glucose >120 mg/dL), hyperlipidemia (fasting serum cholesterol levels >220 mg/dL), smoking (current or within the previous year), previous transient ischemic attacks and strokes, coronary artery disease (angina, myocardial infarction, percutaneous transluminal angioplasty, or surgery), and the presence of contralateral carotid disease (assessed with ultrasound).

Definitions of Clinical Outcome Measures
The clinical outcome measures were minor/major stroke or death within 30 days19 and were defined as follows:

Minor Stroke
Any new neurological deficit (either ocular or cerebral) that persisted for more than 24 hours and that either resolved completely within 30 days or increased the National Institutes of Health Stroke Scale <3 points.

Major Stroke
Any new neurological deficit that persisted after 30 days or increased the National Institutes of Health Stroke Scale by >3 points.

Statistical Analysis
Continuous values were expressed as mean±SD and nominal variables as count and percentages. Median values and the interquartile range were computed as appropriate. For comparisons of categorical data, 2-tailed χ² statistics with Yates correction and univariate Fisher exact test were used. The Fisher exact test was used when the predicted contingency table cell values were <5. Analyses of continuous variables between the cohorts were performed with an unpaired Student t test. Because the imaging data were not distributed normally, differences between both groups were tested by using the Mann–Whitney U statistic. A value of P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (version 12; SPSS Inc).
Results

Demographic Results
From April 1999 to October 2005, a total of 353 consecutive patients had been treated with CAS at our institution. Within this series, 206 patients (152 male and 54 female; mean age = 69 ± 9 years; range = 42 to 89 years) comprised the study population for this analysis. The remaining 147 patients were excluded because they had declined or were unable (eg, as a result of claustrophobia) to participate in this substudy (56%) or had had contraindications for MRI examinations (44%).

The demographic and clinical characteristics of patients treated with and without cerebral protection devices were similar and are summarized in Table 1. In both groups, the demographic and clinical characteristics were also comparable between those patients treated before and those treated after protection devices had become available.

### TABLE 1. Baseline Characteristics of Patients According to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Unprotected CAS</th>
<th>Protected CAS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>67</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Mean age, years</td>
<td>69 ± 9</td>
<td>68 ± 9</td>
<td>1.0</td>
</tr>
<tr>
<td>Male</td>
<td>51 (76)</td>
<td>101 (73)</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>16 (24)</td>
<td>38 (27)</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (66)</td>
<td>73 (53)</td>
<td>0.1</td>
</tr>
<tr>
<td>No</td>
<td>23 (34)</td>
<td>66 (47)</td>
<td></td>
</tr>
<tr>
<td>Type of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (12)</td>
<td>27 (19)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hemispherical transient ischemic attack</td>
<td>26 (39)</td>
<td>36 (26)</td>
<td>0.07</td>
</tr>
<tr>
<td>Retinal transient ischemic attack</td>
<td>10 (15)</td>
<td>10 (7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>54 (81)</td>
<td>112 (81)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>33 (49)</td>
<td>77 (55)</td>
<td>0.6</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>26 (39)</td>
<td>44 (32)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (28)</td>
<td>42 (30)</td>
<td>0.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (18)</td>
<td>28 (20)</td>
<td>0.8</td>
</tr>
<tr>
<td>Radiologic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>33 (49)</td>
<td>87 (63)</td>
<td>0.07</td>
</tr>
<tr>
<td>Right</td>
<td>34 (51)</td>
<td>52 (37)</td>
<td></td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>88 ± 8</td>
<td>86 ± 8</td>
<td>0.4</td>
</tr>
<tr>
<td>Contralateral disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral internal carotid artery occlusion</td>
<td>11 (16)</td>
<td>30 (22)</td>
<td>0.5</td>
</tr>
<tr>
<td>Contralateral internal carotid artery stenosis (≥50%)</td>
<td>25 (37)</td>
<td>38 (27)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data are mean values ± SD or n (%).

MRI Lesion Load and Protection Devices
Twenty-three patients were treated without cerebral protection devices before these had become available, 44 patients were treated without cerebral protection devices after these had become available, and in 139 patients, filter-type embolic protection devices were used during the CAS procedures. According to physician preference and commercial availability, four different cerebral protection devices were used in this study: Neuroshield, n = 31 (MedNova); Angioguard, n = 11 (Cordis J&J); Emboshield, n = 61 (Abbott); and Filterwire, n = 36 (Boston Scientific).

There was overall agreement between both reviewers as to the number (κ = 0.94 for interobserver agreement, 95% CI = 0.91 to 0.97), size (κ = 0.93 for interobserver agreement, 95% CI = 0.87 to 0.99), and location (κ = 0.82 for interobserver agreement, 95% CI = 0.72 to 0.91) of new DWI lesions. Before the procedure, DWI revealed ipsilateral cerebral lesions in 15 (22%) of the patients treated without and in 22 (16%) of the patients treated with cerebral protection devices (not significant). The proportion of patients with any new ipsilateral DWI lesion in the group of unprotected CAS was 61% in those patients treated before protection devices had become available and 70% after these had become available (not significant). Moreover, the number of new ipsilateral DWI lesions was comparable between these two groups (median = 1; interquartile range [IQR] = 0 to 6 versus median = 1.5; IQR = 0 to 4; not significant) so that they were combined for further analysis.

The proportion of patients with any new ipsilateral DWI lesion(s) after unprotected CAS was significantly lower than after unprotected CAS (49% versus 67%; P < 0.05). In addition, the total number of new ipsilateral DWI lesions was significantly lower after protected CAS than after unprotected CAS (median = 0; IQR = 0 to 3; versus median = 1; IQR = 0 to 4; P < 0.05), and in both groups, the vast majority of new DWI lesions had a diameter of < 10 mm (Table 2).

No statistical correlations were found between the incidence or number of any new ipsilateral DWI lesion and the type of protection device used, the degree of stenosis, or the presence of a contralateral stenosis. A total of 14 (21%) patients treated without and 24 (17%) of the patients treated...
with cerebral protection devices developed new DWI lesions outside the vascular territory of the target lesion (P=0.1).

MRI Lesion Load and Stroke Outcomes
The neurological complications within 30 days for patients with and without cerebral protection are summarized in Table 3. All minor or major strokes occurred in the territory of the treated artery and within 24 hours after CAS. There were no significant differences in the overall clinical complication rates between patients treated with versus those treated with protection (7.5% versus 4.3%, not significant). However, in patients who had developed a minor or major stroke, the number of new DWI lesions (median=7.5; IQR = 1.5 to 17) was significantly higher than the number of new DWI lesions in patients without neurological deficits (median=1; IQR = 1 to 3.0; P<0.01). Both patients with major stroke had multiple DWI lesions larger than 20 mm in diameter, whereas all patients with minor stroke had had multiple (range=2 to 15) new DWI lesions smaller than 10 mm in diameter.

Discussion
Our study is the largest to date directly comparing the number, size, and location of new DWI lesions with respect to unprotected and protected CAS. We demonstrated that the application of a filter systems during CAS significantly reduced the proportion of patients with any new ipsilateral DWI lesion. Moreover, patients treated with cerebral protection had significantly fewer new DWI lesions than unprotected patients, conferring with results of a recent small study.17

Also consistent with investigation by others was our finding that the majority of new DWI lesions were smaller than 10 mm and were asymptomatic.8-14 It must be kept in mind that these lesions do not necessarily represent irreversible brain damage.10 On the other hand, in our study, patients who developed a stroke had significantly more new DWI lesions than those who did not, indicating a strong association between DWI lesions and ischemic injury. To the best of our knowledge, a similar finding has not been reported before.

To date, no randomized trial has shown that cerebral protection devices reduce the incidence of stroke associated with CAS. Using our data at least 1500 patients would have to be randomized to detect a statistically significant difference in stroke and death rates between patients treated with unprotected versus protected CAS.

However, because DWI lesions are frequent and more common in those who develop stroke after CAS, it appears that DWI could be a sensitive surrogate end point for ischemic injury if the risk of stroke associated with these lesions could be quantified. Using our data and the proportion of patients with any new DWI lesion as the outcome measure, only 120 patients would have to be randomized to detect a statistically significant difference between patients treated or not treated with filter devices. Such a randomized study would be useful to overcome the limitations of this observational study, which was subject to some selection bias and operator improvements through experience and was not completely blind with respect to the assessment of the DWI lesions.

Finally, the high incidence of new brain lesions within the vascular territory of the treated carotid artery found in the group of protected patients with CAS documents that dislodgement of a large number of embolic particles to the brain is not prevented by the use of currently available filter devices. It is possible that (1) many emboli are too small to be captured by the filter devices; (2) various protection devices do not completely cover the internal carotid artery allowing emboli to pass by; or (3) the manipulation of catheters and guide wires within the internal carotid artery might have produced DWI lesions before deployment of the protection devices.20 Aside from its use to quantitatively evaluate ischemic injury after CAS, DWI could also be used to improve and develop new protection devices.

Conclusions
New cerebral lesions detected with diffusion-weighted MRI are frequent after both unprotected and protected carotid angioplasty and stenting, the majority of which are clinically silent. The use of cerebral protection devices significantly reduces the number of these lesions. The frequent occurrence of these lesions as well as their close correlation with the clinical outcome stresses the potential use of DWI to quantitatively evaluate ischemic injury after carotid angioplasty and stenting.

Disclosures
None.

References

TABLE 3. Periprocedural Complications Within 30 Days After CAS According to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Unprotected CAS (n=67)</th>
<th>Protected CAS (n=139)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor stroke</td>
<td>4/67 (6%)†</td>
<td>4/139 (2.9%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Major stroke</td>
<td>1/67 (1.5%)</td>
<td>1/139 (0.7%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Death†</td>
<td>0/67 (0%)</td>
<td>1/139 (0.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>5/67 (7.5%)</td>
<td>6/139 (4.3%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*P values are from χ² analysis; †all minor or major strokes occurred ipsilateral to the treated artery; ‡nonstroke-related death secondary to pneumonia 3 weeks after the procedure.

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