Silent Cerebral Ischemia Detected With Diffusion-Weighted Imaging in Patients Treated With Protected and Unprotected Carotid Artery Stenting

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Background and Purpose—Percutaneous transluminal angioplasty with stent (CAS) is an alternative method to endarterectomy in the revascularization of carotid artery stenosis. Protected CAS is currently used to prevent distal embolization. Diffusion-weighted MRI (DWI) is the most sensitive tool to evaluate silent cerebral ischemia. The purpose of this research was to assess the incidence of cerebral embolic lesions during CAS and to evaluate whether cerebral protection devices can reduce the number of silent cerebral ischemia with respect to unprotected CAS.

Methods—Fifty-two patients with high-grade internal stenosis underwent CAS; 30 patients (group a) were treated with a cerebral protection device, and 22 (group b) were treated without it. All of the patients were evaluated preoperatively and postoperatively with fluid-attenuated inversion recovery and DWI sequences to depict the number of new embolic silent cerebral lesions.

Results—Embolic silent cerebral lesions occurred in 30% of CAS. Cerebral protection devices reduce the number of new lesions significantly reducing the consistent lesions ipsilateral to the treated vessel. Inconsistent lesions do not differ in both groups of patients. Clinical, radiological, and procedural variables do not correlate with the appearance of new cerebral lesions.

Conclusions—Embolic cerebral lesions detected with DWI are more frequent with unprotected CAS, although they are present also with the use of cerebral protection devices. Probably a part of silent cerebral lesions arise from the procedural maneuver in the aortic arch. (Stroke. 2005;36:2389-2393.)

Key Words: angioplasty and stenting ■ carotid stenosis ■ embolism ■ endovascular treatment ■ magnetic resonance

Carotid endarterectomy (CEA) is a proven standard treatment in carotid artery stenosis and is considered the most effective method to prevent stroke occurrence in patients with symptomatic and asymptomatic high-grade carotid artery stenosis.1,2 On the basis of new experiences, percutaneous transluminal angioplasty with stent (CAS) has gradually been established as an alternative method to CEA with encouraging results.3,4 The risk of embolization that derives from plaque fragments mobilization is a well-known complication of endovascular therapies,5 and cerebral protection devices are developed and currently used widespread in the CAS procedure to limit cerebral embolism.6 The role of cerebral protection during the endovascular procedure of revascularization is still under study and clinical investigation, but it is feasible, effective, and seems to reduce the procedural neurological event rate.7 Recently, a review of the literature8 states that major and minor strokes are significantly reduced if the CAS procedure is made with a cerebral protection device with respect to unprotected procedures, and, therefore, protected CAS seems to decrease thromboembolic complications. Moreover, in high-surgical risk patients, protected CAS was not inferior to CEA in reducing the cumulative incidence of major cardiovascular events within 1 year.9 Diffusion-weighted MRI (DWI) is sensitive to early brain ischemia,10 is widely available, and can be used to assess the safety and efficacy of neurovascular intervention.11 Based on the lesional pattern, DWI findings after endovascular diagnostic and interventional procedures are supposed to indicate the occurrence of cerebral microemboli12 that are usually asymptomatic and named silent cerebral ischemia.

Stent implantation in the carotid artery is associated with new areas of cerebral ischemia, detected by using diffusion-weighted magnetic resonance images during both the protected13 and unprotected endovascular procedures.14
The aim of our study is 2-fold: (1) to assess the incidence of silent cerebral ischemic insults detectable with DWI after the stenting procedure; and (2) to evaluate the role of cerebral protection during the stenting procedure as an effective method to reduce the number of silent cerebral ischemic events.

Methods

Patient Selection and Data Collection

From December 2003 to October 2004, we prospectively enrolled 52 consecutive unselected patients (42 men and 10 women; mean age, 73 years; range, 55 to 84 years) with internal carotid artery stenosis superior to 70% according to North American Symptomatic Carotid Endarterectomy Trial criteria who underwent CAS at our institution. In the first 22 patients (42.3%), the procedure was performed without cerebral protection (group a). After March 2004, protection devices were routinely used in the remaining 30 patients (57.7%; group a).

All of the patients gave their written informed consent for diagnostic and interventional procedures. Cerebral protection device placement was not randomized and depended on the period of arrival to our observation. All of the patients underwent magnetic resonance examination before (range, 1 to 24 hours; mean time, 4 hours) and within 7 days after the procedure (range, 2 to 7 days; mean time, 4 days). All of the patients were preoperatively and postoperatively examined by a neurologist; the baseline modified Rankin scale score was included in examination.15 Clinical, radiological, and procedural data were collected and do not significantly differ in both groups of patients. Clinical variables included symptomatic status of patients and the presence of comorbidity. Radiological variables were established by evaluation of preprocedural MRI and diagnostic digital subtraction angiography (DSA). They included the number of stroke areas, white matter and basal ganglia lesions load measured according to the age-related white matter changes (ARWMC) rating scale,16 grade of stenosis, presence of ulcerated plaques. Moreover, the presence of intracranial compensation circles from the treated side to the contralateral one was assessed with diagnostic DSA. Procedural variables included predilation and procedural duration.

CAS Procedure

All of the procedures were performed with local anesthesia and percutaneous transfemoral access F8. Patients were premedicated with aspirin (100 mg/die) and ticlopidine (500 mg/die) ≥3 days preintervention.

The patients received intraarterial administration of 70 IU/kg of heparin to achieve an activated clotting time ≥200 to 250 s. By using a 100-cm long guiding catheter (Multipurpose Boston Scientific), the filter guide wire was introduced crossing the stenosis and the cerebral protection device, a self-expanding basket type filter (Filter Wire EZ Boston Scientific), was deployed in the cervical portion of internal carotid artery. A self-expandable stent (Carotid Wallstent Boston Scientific in 42 patients; Precise Rx J & J Cordis in 10 patients) was mounted on the protection device guide wire and placed and deployed across the stenosis. The stent was diluted to reach an adequate vessel recanalization by using an appropriate size angioplasty balloon (Ultrastiff SV Boston Scientific; 5.5 to 6 mm×20 mm). One mg of atropine sulfate was intravenously administered during angioplasty balloon insufflations to prevent carotid sinus stimulation and bradycardia. Then, the cerebral protection device, when used, was removed. Predilation with a 3-mm PTA balloon catheter was performed before stent placement in tight stenoses with a residual lumen smaller than the diameter of the stent delivery catheter. A permanent daily medication with acetylsalicylic acid (100 mg) and a prevention therapy with 500 mg/die of ticlopidine were started for 1 month after endovascular recanalization.

Before the interventional procedure, all of the patients were submitted to diagnostic DSA by selective injection of both common carotid arteries and vertebral arteries of ≥1 side. Intracranial vessel evaluation of the treated side was repeated after the endovascular procedure. In the case of unprotected CAS, the procedure differed exclusively for the use of guide wire instead of filter guide wire to encompass the stenosis.

Magnetic Resonance Protocol

Magnetic resonance examination was performed with a 1.5-T system (Magnetom Symphony Siemens Medical System) equipped with a standard head coil. The magnetic resonance protocol included a preprocedure and postprocedure evaluation: a fluid-attenuated inversion recovery (FLAIR) sequence in the oblique-axial plane was performed (repetition time 10 000 ms, echo time 144 ms, inversion time 2500 ms, field of view 24 cm, thickness 4 mm, gap 1 mm, number of excitations 1, matrix 192×256, and acquisition time 4’16”). DWIs were obtained with a spin-echo/echo-planar imaging sequence (repetition time 4300, echo time 100, field of view 24, thickness 4 mm, gap 1 mm, number of excitations 3, matrix 128×128, and acquisition time 1’15”). Images were achieved with 2 levels of diffusion sensitization gradients (b=0, 1000 s/mm²) in the 3 principal gradient directions (x, y, and z) and anisotropically displayed. Magnetic resonance protocol was repeated within 7 days after endovascular procedure in all of the patients.

Image Analysis

The postprocedural set of magnetic resonance images was evaluated by 2 radiologists in a blinded fashion with respect to the use of cerebral protection to assess the number of new brain ischemic lesions, considering FLAIR and DWI images independently. In the case of disagreement between the 2 readers, a consensus opinion was reached. Compared with the baseline DWI, a new hyperintense DWI lesion in the postprocedure examination was considered a new cerebral ischemic event. New lesions were considered consistent if homolateral to the treated vessels and inconsistent if they occurred in the vascular territory of the untreated carotid artery or vertebrobasilar arteries.

Statistical Analysis

The consistent and inconsistent lesions load per patient in groups a and b were compared with a nonparametric 2-tailed Mann–Whitney test. The level of significance was set to 0.05.

A comparison between the number of DWI lesions and clinical nominal variables in all of the treated patients was obtained with Kruskal–Wallis ANOVA, whereas correlation with radiological and procedural continuous variables was made with a Spearman rank correlation test. Finally, lesion load of inconsistent lesions was compared with the presence of intracranial circles compensation with the Mann–Whitney test.

Results

Based on clinical data, 23 patients were symptomatic and 29 asymptomatic. One of all patients (belonging to b group) developed a major stroke (1.9% of complications). In this patient, magnetic resonance images revealed an infarction in the left frontoopercular area. Postprocedural neurological examination did not reveal changes in the clinical conditions of the remaining patients. Clinical radiological and procedural data are summarized in the Table.

In the postprocedural magnetic resonance examination, 16 patients (30%) submitted to CAS procedure developed new focal brain hyperintensities on DWI images (Figure). The number of lesions was 65 with a mean lesion load of 1.25/s/ patient. The mean diameter of the lesions was 5.5 mm. Fifty-one lesions were at the cortical-subcortical junction, whereas 14 were in the deep white matter. All of the DWI lesions corresponded with high-signal lesions on FLAIR images indicating a structural change of the brain tissue after
the endovascular procedure. There were 31 consistent lesions, whereas there were 34 inconsistent lesions.

Microembolic lesions detectable with DWI appeared in 26% of the patients in group a with a mean lesion load of 0.53 per patient, whereas in group b they appeared in 36% of patients with a mean lesion load of 2.22/patient. DWI lesions were lower in group a (16 lesions) compared with group b (49 lesions). Consistent lesions were significantly lower ($P=0.03$) in group a (2 lesions) compared with group b (29 lesions), whereas the inconsistent lesions did not differ in both groups of patients (14 and 20 lesions, respectively, in group a and b with a $P=0.41$). The number of lesions did not correlate with clinical, radiological, or procedural variables.

**Discussion**

New DWI focal lesions are detectable in 30% of patients submitted to CAS. This result is in line with previous reports that reveal a number of silent ischemic lesions after CAS ranging from 22% to 54%. The mean diameter, the subcortical location, and the prevalent distribution in the vascular territory supplied by the treated vessel of the lesions are indicative of their embolic origin; DWI lesions were clinically silent in all but 1 of the patients.

Transcranial Doppler monitoring during stent implantation had clearly demonstrated that the embolization is present in most patients treated with CAS and is related to guide wire, catheter manipulation, stent placement, postdilation, and balloon deflation. Nevertheless, there is no relationship between the number of emboli revealed with Doppler monitoring and neurologic complications, because the majority of emboli are not particulate but include air bubbles that probably do not induce structural brain damage. This could explain why no correlation was found between the total number of microembolic signals measured with transcranial Doppler during the procedure and DWI-detected lesions.

Therefore, DWI can be considered one of the most robust methods to monitor the effects of endovascular therapies. In our study group, the presence of high-signal areas on both DWI and FLAIR images indicates subclinical infarcts. In other series, only a percentage of DWI lesions is visible on conventional images, and some of these can be reversible. Transient DWI lesions not associated with correspondent hyperintensities on FLAIR or T2 images have been reported in animals and humans; they could be attributable to acute bioenergetic compromise with early restoration of blood flow and probably are not related to brain definitive parenchymal damage. In our study protocol, the detection of transient DWI lesions not corresponding to definitive brain damage is probably reduced because of the timing of postprocedural DWI acquisition (mean, 4 days).

Silent cerebral lesions after CAS have also been reported with protected devices procedures ranging from 23% to 43%. We can suppose that particulate plaque debris can be spread during the filter passage through the stenosis or during predilatation, when necessary, to bypass the stenosis. Moreover, we have to consider that some atherosclerotic particles may pass through the filter pores or among the filter basket and the vessel wall especially when, as we did, an autoexpandable filter with a fixed size is used. We also cannot exclude that the withdrawal of the filter protection system may squeeze captured atherosclerotic materials from the filter basket into the treated vessel.

The total number of lesions in our study group is not related exclusively to the CAS procedure, because all of the patients underwent diagnostic DSA before interventional maneuvers and emboli may source from guiding catheter placement, guide wire introduction, or retrieval before cerebral protection deployment.

Because silent cerebral lesions at DWI, after diagnostic DSA, range between 6% and 26%, the number of the emboli directly related to CAS is less conspicuous than that we report. Certainly, diagnostic DSA is mandatory for CAS.

**Table 1.** Clinical, Radiological, and Procedural Variables in Both Groups of Patients

<table>
<thead>
<tr>
<th>Data</th>
<th>Characteristics</th>
<th>Group a (n=30)</th>
<th>Group b (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td>Symptomatic</td>
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<td>12</td>
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<tr>
<td></td>
<td>Hypertension</td>
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<td>17</td>
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<tr>
<td></td>
<td>Diabetes</td>
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<td>7</td>
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<tr>
<td></td>
<td>Coronary artery disease</td>
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<td>8</td>
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<tr>
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<td>Heart failure</td>
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<tr>
<td></td>
<td>Cardiac arrhythmia</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
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<td>1</td>
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<tr>
<td></td>
<td>COBP</td>
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<td>0</td>
</tr>
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<td></td>
<td>Extracerebral neoplasms</td>
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<td>2</td>
</tr>
<tr>
<td>Radiological data</td>
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<td>11</td>
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<tr>
<td></td>
<td>WM-ARWMC</td>
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<tr>
<td></td>
<td>BG-ARWMC</td>
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<tr>
<td></td>
<td>Grade of stenosis (%)</td>
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<td>Compensation circles</td>
<td>16</td>
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<tr>
<td></td>
<td>Ucerated plaques</td>
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<tr>
<td>Procedural data</td>
<td>Predilation</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Duration of procedure (min)</td>
<td>42±12</td>
<td>48±12</td>
</tr>
</tbody>
</table>

COBP indicates chronic obstructive bronchopneumopathy; WM, white matter; BG, basal ganglia.

Preprocedural (a) and postprocedural (b) axial DWI of the brain. After protected CAS, an ipsilateral hyperintense lesion related to silent cerebral embolism is appreciable at the cortical-subcortical junction of right parietal lobe.
planning, and then the global number of lesions has to be considered in the assessment of CAS safety.

A cerebral protection filter seems to reduce the number of silent ischemic lesions in patients undergoing endovascular recanalization of carotid arteries. In particular, in group A, we observed a decrease of consistent lesions. This result is in line with the assumption of an effective protective function of the filters. On the other hand, the number of inconsistent lesions does not differ in the 2 groups, indicating that other sources of emboli than those arising from treated vessels can contribute to total lesion load. One hypothesis to explain the inconsistent lesion appearance is that emboli source from the treated vessel and proceed through intracranial compensation supply reaching the cortical hemisphere. This interpretation is not supported by the lack of reduction of inconsistent lesions in patients treated with cerebral protection devices. Moreover, this conflicts with the observation that the number of inconsistent lesions does not correlate with the presence of intracranial compensation circles. Finally, inconsistent DWI lesions are reported after CAS but not after CEA, indicating that maneuvers on the aortic arch and unaffected vessels play a predominant role in the occurrence of inconsistent silent cerebral ischemia. The incidence of inconsistent silent cerebral lesions points out the need for the development of less traumatic endoluminal devices.

The clinical meaning of silent cerebral ischemia is not fully understood. A recent study reports that a definite infarction after endarterectomy correlates with the number and volume of postoperative DWI lesions suggesting that a clinically evident stroke could represent the tip of the iceberg of embolic ischemic events. Nevertheless, the role of microembolic DWI lesions in stroke onset during revascularization and the consequential potential benefit in using cerebral protection devices is currently under judgment and will be the challenge of additional larger randomized studies.

Until now, silent brain infarcts were associated with a decline in global cognitive function and particulate embolization during cardiovascular interventions or CEA seems to be correlated with neuropsychometric deterioration. Subcortical infarcts end up with cognitive deficits on neuropsychometric testing after both endarterectomy and carotid artery stenting. Theoretically, cerebral protection could play a role in reducing the effects of microembol on cognitive functions after endovascular procedures.

Symptomatic status of patients, as well comorbidity, is not related to the incidence of silent ischemic lesions detectable with DWI. Also, radiological variables do not influence the DWI lesion occurrence. Surprisingly, procedural variables do not correlate with the number of new DWI lesions. We suppose that the low variance of the time duration procedure in our study group does not allow us to find a statistically significant correlation between the variables.

The main limitation of our work is the absence of neuropsychological monitoring with appropriate tests to evaluate an eventual cognitive impairment related to the embolic lesions. An additional limitation is the chronological enrolment of patients that may have introduced a bias because of the learning curve in the assessment of lesions in the second (protected CAS) group of patients. With Pearson’s correlation test, we do not reveal any significant linear correlation between the number of new DWI lesions and the time at which CAS was performed, indicating that there is no significant reduction of lesion load over time in both groups of patients. Therefore, we may presume that the effect of this bias is minimal.

Conclusions

Using DWI, the incidence of microembolic lesions after CAS was 30%. CAS with cerebral protection devices may reduce the number of silent ischemic lesions detectable with DWI. Because the protective function of filters is limited to treated vessels, and a certain number of embolic events are obviously directed to the treated vessels probably source from endovascular maneuvers, improvement of angiographic materials may increase the safety of endovascular procedures.

References


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