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**ORIGINAL
RESEARCH**

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Cerebral Ischemia after Filter-Protected Carotid Artery Stenting Is Common and Cannot Be Predicted by the Presence of Substantial Amount of Debris Captured by the Filter Device

PURPOSE: Protected carotid artery stent placement is currently under clinical evaluation as a potential alternative to carotid endarterectomy. The current study was undertaken to determine the incidence of new ischemic lesions found on diffusion-weighted MR imaging (DWI) in nonselected patients after protected carotid artery stent placement using a filter device and to determine the potential relationship between these new ischemic lesions and the presence or absence of a clear amount of debris captured by the neuroprotection filter device.

MATERIALS AND METHODS: A nonrandomized cohort of 52 patients (40 men, 12 women) presenting with carotid occlusive disease underwent protected carotid artery stent placement using a filter device. DWI obtained 1 day before stent placement was compared with that obtained 1 day after stent placement. In addition, the macroscopic and microscopic analysis of debris captured by the filter device during the carotid stent placement procedure was assessed.

RESULTS: Neuroprotected carotid stent placement was technically successful in all 53 procedures but was complicated by a transient ischemic attack in 3 patients (5.6%). In 22 patients (41.5%), new ischemic lesions were found on DWI, and in 21 filter devices (39.6%), a substantial amount of atheromatous plaque and/or fibrin was found. No clear relationship between the presence of debris captured by the filter device and new lesions detected by DWI was found ($P = .087$; odds ratio 3.067).

CONCLUSION: Neuroprotected carotid artery stent placement will not avoid silent cerebral ischemia. Systematic microscopic analysis of debris captured by the filter device has no predictive value for potential cerebral ischemia after carotid artery stent placement.

In recent years, carotid artery stent placement (CAS) has gained a lot of enthusiasm as a potentially valuable minimally invasive alternative to carotid endarterectomy (CEA).¹ However, CAS has a major drawback: cerebral embolization and infarction during or immediately after the stent placement procedure, which potentially can result in symptoms of stroke.² To minimize these problems, neuroprotection devices have been designed and are currently under clinical evaluation.^{3,4} However, CAS under cerebroprotection is also not free of inducing cerebral ischemia,³ and the mechanisms of these phenomena have not yet been examined *in vivo*. Although these ischemic lesions, detected by diffusion-weighted MR imaging (DWI), are silent in the vast majority of cases, they potentially have clinical relevance as a result of progressive impairment of the cognitive function.⁵ The purpose of our study was to assess the incidence of new ischemic cerebral lesions after protected CAS using a polyurethane-membraned filter device and to determine the potential relationship between these new ischemic lesions and the presence of debris, consisting of atherosclerotic plaque and fibrinous material captured by the neuroprotection filter device, to obtain a better understanding of the mechanisms of cerebral ischemia and its relation to the use of a neuroprotection filter in CAS.

Patients and Techniques

Study Design

This is a unicenter, prospective cohort study performed in the vascular center of our institution from January 2003 until April 2005 to investigate whether CAS with use of a neuroprotective filter device would prevent ischemic cerebral lesions being detected by MR imaging. Therefore, DWI was performed the day before and the day after the CAS procedure. In addition, microscopic analysis of the debris captured by the filter device was performed.

Study Population

Fifty-two patients (40 men and 12 women) with a mean age of 72.7 years (range, 55–89 years) were included in the study. Patients' informed consent was obtained and the study protocol was in accordance to the guidelines of the local institutional ethical committee. Fifty-three carotid artery stenoses were treated: 1 patient underwent CAS bilaterally, with an interval of 13 months between the procedures. Indication for CAS was an asymptomatic carotid artery stenosis of greater than 80% ($n = 36$; 68%) or a symptomatic carotid artery stenosis of more than 70% ($n = 17$; 32%); all patients were surgically high-risk patients as a result of either a "hostile" neck ($n = 8$; 15%) or cardiopulmonary insufficiency ($n = 45$; 85%). Symptoms experienced by the 17 patients were transient ischemic attack (TIA) ($n = 9$), minor stroke ($n = 1$), major stroke ($n = 2$), and tinnitus ($n = 1$). Assessment of the neurologic status before and 1 day after the procedure was made by an independent neurologist. The degree of stenosis was assessed by duplex ultrasound scanning and confirmed by digital subtraction angiography before the stent placement procedure. The carotid artery stenosis was located on the right ($n = 32$; 60.3%) or left side ($n = 21$; 39.6%). In 4 cases (7.5%), the common carotid artery

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(CCA) was stenosed; in the remaining 49 cases (92.5%), the lesion was located at the carotid bifurcation.

Stent Placement Procedure

All stent placement procedures were performed under local anesthesia by a team of 2 experienced interventionalists (G.M. and K.D.) in a dedicated angiography suite (Angiostar; Siemens, Erlangen, Germany). The day before the procedure, the patients were orally administered 75 mg of clopidogrel (Plavix). Vascular access was made under local anesthesia by femoral approach by using an 8F sheath (Terumo Europe, Leuven, Belgium). After administration of 5000 IU of heparin, selective catheterization of the CCA was made, and DSA was always performed to confirm the degree of carotid artery stenosis and to evaluate the carotid anatomy to decide whether CAS was technically feasible. After exchange for a stiff guidewire, an 8F guiding-catheter (Soft Tip; Boston Scientific, Natick, Mass) was placed in the CCA. We always performed protected predilation with a 3-mm diameter balloon (Ultrasoft; Boston Scientific) and postdilation with a 5–7-mm diameter balloon (Ultrasoft, or Viatrac; Guidant, Santa Clara, Calif). Both dilation procedures were done after injection of 0.125 mg of atropine. Finally, a closure device (Angio-Seal; St. Jude Medical, Minnetonka, Minn) was used to obtain hemostasis in the groin. In all cases, neuroprotection was performed by a commercially available filter device and the stents implanted were dedicated carotid stents. In 6 patients, the protected CAS was performed with use of a carotid Wallstent and a FilterWire EZ (Boston Scientific). In 20 patients, the AngioGuard filter device was used in combination with a Precise stent (Cordis, Miami Lakes, Fla), and in the remaining 27 cases, the AccUNET neuroprotection filter was used, and an AccuLink stent (Guidant) was implanted. All 3 neuroprotection devices (the AngioGuard, the Filterwire, and the AccUNET filter) have a nitinol skeleton and a polyurethane filter. The pore diameter of the filters are 100, 110, and 115 μm , respectively. Finally, the crossing profile of the above mentioned devices are 3.2, 3.2, and 3.5F, respectively.

Pathologic Filter Analysis

Filter devices were entirely fixed in a 4% buffered formalin solution. Material within the devices was collected, if necessary, with the aid of a needle or after centrifugation, and embedded in paraffin. Four-micrometer sections were cut in a semiserial way and stained with hematoxylin and eosin, and phosphotungstic acid hematoxylin for fibrin, and examined with a light microscope.

MR Imaging

All patients having undergone a CAS procedure during the study period were examined by DWI within 24 hours before and after the procedure; subsequently, no stented patient was excluded from the study. Brain MR imaging included axial T2-weighted turbo spin-echo and turbo fluid-attenuated inversion recovery sequences and were interpreted by 2 experienced neuroradiologists (P.D. and G.W.), both blinded to the result of the CAS procedure. A coronal T2* gradient-echo sequence was obtained as well as axial DWI using a single-shot, multisection echo-planar sequence. Diffusion encoding involved 1 scan without DWI ($b = 0$), 3 DWI scans with $b = 500 \text{ s/mm}^2$, and 3 DWI scans with $b = 1000 \text{ s/mm}^2$ (orthogonal gradient orientations). The apparent diffusion coefficient maps were available.

Statistical Analysis

The Fisher exact test was used to analyze a potential relationship between the presence of a substantial amount of debris in the filter device and new lesions detected on the post CAS DWI. A P value of $<.05$ was considered statistically significant.

Results

Technical and Clinical Results

In all 53 protected CAS procedures, the filter device could be placed and at the end of the procedure retrieved successfully, and the carotid stent was placed correctly. In no case was more than a single stent needed to completely cover the stenotic segment. Three TIAs occurred in the immediate posttreatment interval. Two of them occurred at the end of the CAS procedure, and the other became clinically apparent 20 minutes after sheath removal. Complete neurologic recovery occurred after 10 seconds, 10 minutes, and 20 hours, respectively. Two of the 3 patients with a CAS-related TIA were asymptomatic before the procedure; one patient was initially symptomatic.

DWI Findings

In 22 patients (41.5%), new lesions were detected by DWI. The new ischemic lesions were located in the cerebral hemisphere, ipsilateral to the stented carotid artery ($n = 12$; 54.5%), in the contralateral hemisphere ($n = 3$; 13.6%), in both ipsilateral and contralateral hemispheres ($n = 5$; 22.7%), and in the ipsilateral cerebellar hemisphere ($n = 2$; 9%). No new ischemic lesion was detected by DWI in the contralateral cerebellar hemisphere. In all 3 patients presenting with a TIA immediately after the CAS procedure, a new ischemic lesion was also detected by DWI in the ipsilateral hemisphere.

Microscopic Analysis of Captured Debris

In 21 of 53 collected filter devices (39.6%), a substantial amount of debris was found. It consisted of atherosclerotic plaque material in a combination of fibrinous material. In the remaining 32 collected filters, only a few red blood cells were at the wall of the filter and these were considered as empty. In 12 of 21 patients (57.14%) presenting with a substantial amount of debris in the collected filter, a new ischemic lesion was detected on post-CAS DWI. In the remaining 9 patients (42.8%) presenting with captured debris in the filter, no new lesions were detected on post-CAS DWI. In 10 of 32 patients (31.5%) and despite an empty filter, a new ischemic cerebral lesion was detected. Finally, in 2 of 3 patients presenting with a TIA after the stent placement procedure, a clear amount of atherosclerotic debris was found in the filter; in the remaining patient with a complicated CAS, the filter was empty. Statistical analysis using the Fisher exact test revealed a P value of .087 and an odds ratio of 3.067 (range 0.85–11.17) showing no clear relationship between the capture of debris in the filter device and the presence of new ischemic cerebral lesions detected by DWI.

Discussion

DWI of the brain is considered a useful surrogate end point for ischemic stroke in the evaluation of new devices and new invasive treatment modalities of cerebrovascular disorders.⁶ Jae-

ger et al⁷ described this imaging technique to evaluate the safety and efficacy of nonprotected CAS and found new ischemic lesions in 29% of cases ($n = 70$). Using an identical imaging technique, the same group⁸ demonstrated new ischemic lesions in 25% of patients ($n = 16$) using the AngioGuard cerebroprotection filter device. Schlüter et al⁹ also found new ischemic lesions in 25% of patients ($n = 42$) after protected CAS, and Flach et al¹⁰ described new brain lesions in 43% of stented patients ($n = 21$). Different types of cerebroprotection devices were used in both studies, but a distal filter device was preferred in most cases. Our data are quite similar to these published data: we demonstrated new ischemic cerebral lesions in 41.5% of cases exclusively using 3 similar types of distal filter devices. These neuroprotection devices used in the present study nearly have an identical construction and method of deployment and retrieval. In accordance with Schlüter et al⁹ and Flach et al,¹⁰ we found clinical (minor) stroke in only 5.6% of patients, which is clearly less than the new ischemic lesions (40%) detected by DWI. These percentages of new ischemic lesions after filter-protected CAS are substantially higher than the number of new lesions detected after diagnostic angiographic studies of the carotid arteries or after CEA; Britt et al¹¹ found less than 9% new lesions after selective carotid angiography. Barth et al¹² found new ischemic cerebral foci in 4%, Flach et al¹⁰ in 9%, and Feiwell et al¹³ in 4% of cases after CEA. Although neurologic events during or immediately after protected CAS are substantially less frequent (5.6% in the presented study) than new ischemic lesions detected by DWI (41.5% in the present study), distal filter devices clearly seem to be not as effective as a surgical clamp in avoiding (silent) ischemic brain lesions.¹²⁻¹⁴ On the other hand, the real clinical value of new asymptomatic ischemic lesions found by DWI remains to be determined. Some reports suggest progressive impairment of cognitive function in case of progressively increased number of ischemic cerebral lesions, but these observations were made in elderly patients, followed-up during several years, who did not undergo protected CAS or other carotid revascularization treatments, as demonstrated by Vermeer et al⁵ and Fearn et al.¹⁵ The location of the new ischemic lesions is not always the ipsilateral (stented) hemisphere; in 77.2% of cases, the new ischemic lesions were located in the ipsilateral hemisphere and are most probably related to the transluminal manipulations in the carotid arteries. We were surprised to also find new ischemic lesions in the contralateral hemisphere in 26.3% and in the ipsilateral cerebellar hemisphere in 9% of cases. Guidewire catheter or guiding-catheter manipulations in the aortic arch could have been responsible for these lesions.

The second part of the present study deals with the presence or absence of debris captured by the filter device. A substantial amount of debris, revealed by microscopic analysis of the retrieved filter, was found in 39.6% of cases, which is less than that in the study by Sprouse et al.¹⁶ These authors noted a clear amount of debris in 60% of cases after visual analysis of the retrieved filter device. The present study did not reveal a clear correlation between the presence of captured debris in the filter and new ischemic lesions on postprocedural DWI; in 57% of cases with a substantial amount of captured debris in the filter, we also found new lesions on DWI. Conversely, in 43% of cases

with a clear amount of plaque material captured by the filter, the postprocedural MR imaging findings were unchanged. The last scenario illustrates the effective working mechanism of a filter device, but the first suggests that filter devices are insufficient to protect the brain during CAS. Of course, these new ischemic lesions can occur during guidewire or catheter manipulation in the carotid arteries before filter deployment or after filter retrieval, but it might also occur when the filter is already deployed. Small particulate debris can pass through the pores of the filter when smaller than 100 μm , and the filter itself can damage the surrounding vessel wall which can subsequently result in dislodgement of vessel wall fragments and clot as a result of an adverse movement of an activated protection device, as demonstrated by Muller-Hulsbeck et al¹⁷ in a porcine carotid model. Vos et al¹⁸ concluded that protected CAS yielded more microemboli than unprotected CAS, essentially based on intracranial Doppler analysis during CAS, but also potentially provoking emboli to the brain. These findings are probably also of clinical importance: 2 of 3 patients presenting with a TIA immediately after CAS had a clear amount of debris captured by the filter and presented also with symptomatic new ischemic brain lesions on DWI. Based on these data, we may conclude that the presence of a certain amount of debris captured by the filter still potentially can be associated with new ischemic brain lesions and, consequently, distal neuroprotection filters are not a guarantee of total brain protection during CAS. In addition, an empty filter is also no guarantee of absence of ischemic lesions. In 31.5% of cases, we found an empty filter but new ischemic lesions were depicted on post-CAS DWI. These new ischemic lesions could be the result of catheter and guidewire manipulations in the carotid arteries, but could also be the result of damage of the vessel wall and dislodgement of clot by the filter, again as demonstrated by Muller-Hulsbeck et al¹⁷ in an ex vivo model. We suggest that the 1 patient with TIA immediately after CAS and an empty filter possibly became symptomatic for one of these reasons. Eventually, we demonstrated the absence of a clear relationship between the capture of debris by the filter device and the potential risk of cerebral ischemia. Consequently, analysis of the filter debris immediately after retrieval will not give the interventionalist reliable information on potential clinical or silent cerebral ischemia.

Conclusion

Protected CAS using a distal filter device seems to be a clinically safe interventional treatment technique with acceptable procedural adverse event rate. Despite these encouraging immediate clinical results, caution should be used concerning the efficacy of the currently available distal filter devices in view of the relatively high number of new silent ischemic lesions, demonstrated by postprocedural DWI and the fact that filter devices in place are potentially unable to capture all debris and, furthermore, potentially can provoke cerebral emboli. In our series, the presence or absence of any debris in the filter will not predict potential clinical or silent cerebral ischemia. Further technical refinements and new design of filter devices without these potentially embolizing characteristics is war-

ranted to guarantee a maximum of neuroprotection during CAS.

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