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Focal Ischemia of the Brain After Neuroprotected Carotid Artery Stenting

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OBJECTIVES This study sought to assess the incidence of cerebral ischemia in nonselected patients undergoing neuroprotected carotid angioplasty and stenting (CAS) without preceding multiple-vessel diagnostic angiography.

BACKGROUND Protection devices to prevent distal embolization during CAS are presently under clinical investigation. Diffusion-weighted magnetic resonance imaging (MRI) visualizes recent ischemia of the brain and may aid in assessing the efficacy of protection devices.

METHODS Elective CAS was performed in 42 consecutive patients (15 female, 27 male; mean age, 67 ± 9 years) using six different types of cerebral protection systems. All patients underwent MRI of the brain before and after a total of 44 interventions.

RESULTS Placement and retrieval of the devices and stent deployment was achieved in all procedures. New ischemic foci were seen on postinterventional MRI in 10 cases (22.7%). One patient had sustained a major stroke, whereas no adverse neurological sequelae were associated with the other nine procedures. In the latter, one to three foci (maximum area 43.0 mm^2) were detected in cerebral regions subtended by the ipsilateral carotid artery in eight cases and by the contralateral carotid artery in one case. In the stroke patient, 12 ischemic foci (maximum area 84.5 mm^2) were exclusively located in the contralateral hemisphere. Follow-up MRI at 4.1 months (median, n = 7) identified residuals of cerebral ischemia only in this patient.

CONCLUSIONS Neuroprotected CAS is associated in about 25% of cases with predominantly silent cerebral ischemia. Our findings suggest manipulation of endoluminal equipment in the supraaortic vessels to be a major risk factor for cerebral embolism during neuroprotected CAS. (J Am Coll Cardiol 2003;42:1007–13) © 2003 by the American College of Cardiology Foundation

Diffusion-weighted magnetic resonance imaging (MRI) has been shown to be a highly sensitive tool for the detection of cerebral ischemia, visualizing recently ischemic regions as hyperintense areas within minutes of onset (1,2). The technique has been used as an adjunct to diagnostic cerebral angiography (3) as well as "unprotected" carotid artery stenting preceded by three- or four-vessel cerebral angiography (4). In both settings, clinically silent cerebral ischemia was detected with an incidence of 26% and 37%, respectively.

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Ever since the inception of endovascular treatment of carotid artery stenoses, interventionists have been concerned about the risk of stroke secondary to procedure-related distal embolization (5). However, following the recent advent of neuroprotective devices to prevent embolic complications, carotid angioplasty and stenting (CAS) has gained considerable momentum as an alternative to carotid endarterectomy. The most extensively studied of these devices has been the PercuSurge GuardWire (Medtronic AVE, Santa Rosa, California) (6,7). Despite distal occlusion of the target artery via an inflatable balloon, severe neurological sequelae have been observed in interventions performed with the device in place (7,8). Technological efforts presently focus on filter-based protection devices; a feasibility study of three of these devices has recently been published (9). In 16 selected patients undergoing CAS preceded by three- or four-vessel cerebral angiography and using the AngioGuard filter device (J & J Cordis, Miami Lakes, Florida) for cerebral protection, clinically silent ischemia has been detected by diffusion-weighted MRI in 25% (10).

The present study sought to prospectively assess the incidence of cerebral ischemia, by way of serial diffusion-weighted MRI, in an unselected, consecutive cohort of patients subjected to CAS without preceding diagnostic angiography and with a variety of devices, other than the GuardWire, utilized for embolic protection.

METHODS

Patients. Between February 14, 2001, and December 31, 2001, 50 consecutive patients underwent elective CAS at our institution. Forty-two patients who underwent a total of 44 interventions (corresponding to 44 vessels/hemispheres treated) consented to pre- and postinterventional diffusion-weighted MRI of the brain. All patients were informed about the investigational nature of CAS in general and the use of neuroprotective devices in particular and gave their written consent. Patient and lesion characteristics are summarized in Table 1.

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Abbreviations and Acronyms

CAS = carotid angioplasty and stenting
CI = confidence interval
MRI = magnetic resonance imaging

Protection devices. Six different cerebral protection systems were used in this study, selected by availability. They were the second- and third-generation MedNova NeuroShield (Abbott Vascular, Redwood City, California; n = 14), the FilterWire (Boston Scientific, Maple Grove, Minnesota; n = 14), the TRAP (ev3, Plymouth, Minnesota; n = 11), the AngioGuard (J & J Cordis; n = 2), and the Distal Protection Device (Medtronic AVE; n = 2). These systems have in common that, before angioplasty, a self-expanding basket-type filter of varying pore size (80 to 130 μm) is deployed distal to the lesion to maintain cerebral perfusion and capture any debris liberated during the intervention. In one patient, an "endovascular clamping" device with two balloons attached to a single guiding catheter was used (MO.MA, Invatec s.r.l., Roncadelle, Italy). The balloons can be inflated separately to occlude the external and common carotid artery and thereby block antegrade flow across the targeted internal carotid artery lesion. Close to the proximal balloon, the exit port of the guiding catheter enables the advancement of angioplasty equipment and the aspiration of debris.

CAS procedure. Patients received clopidogrel (75 mg/day) and aspirin (100 mg/day) at least three days preintervention. In patients not premedicated, a loading dose of clopidogrel (300 mg) and a bolus of intravenous aspirin (500 mg) were administered before the intervention. A 100-cm 5F Vitek catheter (Cook Inc., Bloomington, Indiana) introduced into the target lesion-related common carotid artery was used for brachiocephalic angiography. Subsequently, a 0.035-inch guidewire was introduced through the lumen of the Vitek catheter into the external carotid artery.

Table 1. Patient and Lesion Characteristics

Patient characteristics (n = 42)	
Age (yrs)	67 ± 9
Males	27 (64%)
Hypertension	34 (81%)
Diabetes	12 (29%)
Hyperlipidemia	31 (74%)
Smoking, current or ex	23 (55%)
Bilateral disease	13 (31%)
Target lesion (n = 44)	
Left internal carotid artery	23 (52%)
Left common carotid artery	1 (2%)
Right internal carotid artery	20 (45%)
Lesion characteristics (n = 44)	
Lesion-related symptoms ≤6 months	13 (30%)
De novo	43 (98%)
Diameter stenosis (%)	88 ± 9
Lesion length (mm)	13.6 ± 4.9
Ulcerated	19 (43%)
Calcified	12 (27%)

For patients in whom a filter-based protection system was to be employed, the Vitek catheter was exchanged for a long 7F introducer sheath (Cook Inc.). With the sheath placed in the common carotid artery and the 0.035-inch guidewire withdrawn, a bolus of 70 to 100 IU/kg of heparin was administered and an angiogram taken in anteroposterior and lateral views to document cerebral blood flow. After advancement of the introducer sheath towards the carotid bifurcation, a magnified "worst view" angiogram of the lesion was taken. Subsequently, the filter systems were deployed by way of delivery catheters that ranged in crossing profile between 3.5F (1.16 mm [TRAP]) and 5.5F (1.82 mm [AngioGuard]).

In the remaining patient, the Vitek catheter was withdrawn and the 11F MO.MA system advanced over the 0.035-inch guidewire. With the distal tip in the external carotid artery, both balloons were then inflated.

After placement of the protection devices, the lesions were predilated, supplied with self-expanding stents (predominantly Wallstents, Boston Scientific), and postdilated (Bypass Speedy, Boston Scientific). The procedures were completed by retrieval of the protection systems. Retrieved filters were flushed with saline solution and their contents visually assessed. In case of the MO.MA device, 20 ml of aspirate was withdrawn after pre- and postdilation, filtered through a 40-μm mesh and rinsed with saline solution. Patients were discharged on a regimen of clopidogrel (75 mg/day for one month) and aspirin (100 mg/day).

MRI. Magnetic resonance imaging scans were obtained within 24 h before and after the intervention, utilizing a 1.5-T whole-body system (Intera, Philips Medical Systems, Andover, Massachusetts). Identical single-shot echo-planar sequences were used at both diagnostic sessions, with the trace of the diffusion tensor sampled in three orthogonal acquisitions. All images were reviewed by an experienced radiologist (J.C.S.). Hyperintense foci on MRI were described by their number, location in the brain, and size. Areas covered by hyperintense foci were calculated using the formula for an ellipse: $\pi/4 \times$(long axis)$\times$(short axis). Patients with hyperintense foci on postinterventional MRI were asked to undergo follow-up MRI (including postcontrast T1 sequences) three to six months after the intervention.

Neurological examination. An independent neurologist established the indication for intervention. The neurological examination included a calculation of the National Institutes of Health Stroke Scale and was repeated after intervention and before discharge.

Statistics. Continuous variables are presented by their mean ± 1 SD. Comparisons were made utilizing Mann-Whitney's *U* test. A p value <0.05 was considered statistically significant. Exact 95% confidence intervals (CIs) based on the binomial distribution were calculated for proportions (11).

RESULTS

All protection devices could be used as intended and procedures were completed successfully in all patients within 57 ± 23 min. A mean of 184 ± 66 ml of contrast agent had been administered. One (female) patient, the 31st in our series, gradually developed dysarthria and amnesic aphasia within 2 h of an intervention that utilized the TRAP device; symptoms had not completely resolved at 30 days and the event was classified as a major stroke. Another female patient (Patient #21 in our series) sustained a transient ischemic attack (scotoma of ipsilateral eye) for 3.5 h after the 10th of 14 interventions that utilized the NeuroShield device.

Before intervention, no patient showed signs of recent cerebral ischemia on MRI. After intervention, MRI exhibited no changes between pre- and postinterventional scans in 34 cases, including the patient with a transient ischemic attack.

Hyperintense foci were detected on postinterventional MRI in nine patients and 10 hemispheres (22.7% [Table 2]; 95% CI 11.5% to 37.8%). They were observed in three patients with bilateral disease (23.1%, 95% CI 5.0% to 53.8%) and six patients with unilateral disease (20.7%, 95% CI 7.8% to 39.7%). With respect to the symptomatic status of the lesions treated, positive MRI findings were noted after three (23.1%) of 13 interventions at symptomatic lesions (95% CI 5.0% to 53.8%) and 7 (22.6%) of 31 interventions at asymptomatic lesions (95% CI 9.6% to 41.1%). In these 10 procedures, session duration and the amount of contrast agent administered were not statistically different from in the other 34 procedures. The mean baseline diameter stenosis of the targeted lesion was 91 ± 7% and 86 ± 10% in procedures with positive and negative MRI findings, respectively ($p = 0.124$); also, no statistically significant difference was found in the mean crossing profile of the filter devices used (1.23 ± 0.11 mm vs. 1.32 ± 0.17 mm, respectively; $p = 0.058$).

Eight patients who had undergone nine of these procedures (Patient #5 [Table 2] had bilateral disease and was treated in two sessions on both left and right carotid artery) did not experience any periprocedural neurological complications. The foci were small in number (median 1, range 1 to 3) and had a mean size of 6.9 × 2.7 mm. In the two patients with three foci each, these were located in adjacent tomographic layers (Fig. 1). Cerebral regions containing ischemic foci were supplied by the targeted (ipsilateral) carotid artery in eight cases yet by the contralateral circulation in Patient #4. Follow-up MRI scans were obtained in six of nine cases within a median of 4.2 months and revealed no persistent ischemic lesions.

In Patient #6 (Table 2), who sustained a major stroke, 12 hyperintense foci distributed over five adjacent tomographic layers were seen on the postinterventional MRI scan (Fig. 2). The largest focus covered an area of 84.5 mm^2, which was almost twice as large as the largest focus (43.0 mm^2) observed in any of the other positive MRI findings (Table 2). Of note, all foci in this patient were located in the contralateral hemisphere. On follow-up MRI at 3.7 months, five (42%) of the 12 foci persisted, namely, the two largest and three of the smaller foci.

DISCUSSION

Utilizing diffusion-weighted MRI, this study showed that focal ischemic lesions in the brain are seen in about 23% of patients undergoing neuroprotected CAS exclusively, without extensive preinterventional diagnostic cerebral angiography. Neuroprotection was provided by a variety of systems chosen by availability. The incidence of positive MRI findings was not dependent on the presence of bilateral carotid disease nor on the symptomatic status of the lesion treated. Of the 10 cases with cerebral ischemic lesions, nine were not associated with overt periprocedural neurological symptoms, and follow-up MRI showed that the lesions were reversible. In eight of these nine cases, basket-type filters had been placed distal to the target lesion and ischemic foci were all found in the cerebral region supplied by the targeted carotid artery. In contrast, the one patient in whom the balloon-based MO.MA system was employed exhibited focal ischemia in the contralateral cerebellum.

One major periprocedural neurological complication, namely, a major stroke, was encountered in our series. In this patient, postinterventional MRI exhibited a markedly higher number of ischemic foci (12 vs. a median of 1 [maximum 3] in procedures not associated with neurological complications), the largest of which was nearly twice as large as the largest focus on the other positive MRI findings. Interestingly, in this patient, too, ischemic foci were all contained in the contralateral hemisphere, whereas the cerebral region supplied by the targeted carotid artery remained free of ischemic lesions. Follow-up MRI revealed persistence of 42% of the ischemic foci at 3.7 months.

The transient ischemic attack, namely, scotoma of the ipsilateral eye, experienced by one of our patients had no correlate on MRI, probably because retinal ischemia cannot be visualized by this technique.

In concordance with previous studies (2,3,12), our findings suggest embolism as the underlying mechanism of cerebral ischemia. Several scenarios are conceivable.

1) Manipulation of catheters, guidewires, and sheaths within the supraaortic vasculature before deployment of the protection device may have resulted in small pieces of vessel wall to be scraped off. Such pieces would have had free access to the cerebral circulation. This mechanism is apparently corroborated by the fact that in two of our patients ischemic lesions were located in the contralateral hemisphere. In the MO.MA case, introduction of the bulky 11F system may have released a particle from the aortic wall that ended up in an artery supplying the

Table 2. Findings in Patients With Hyperintense Areas on MRI

Patient	#1	#2	#3	#4	#5	#5*	#6	#7	#8	#9
Location of target lesion	left ICA	right ICA	right ICA	left ICA	left ICA	right ICA	right ICA	left ICA	right ICA	right ICA
Lesion history	symptomatic	asymptomatic	asymptomatic	asymptomatic	symptomatic	asymptomatic	asymptomatic	asymptomatic	symptomatic	symptomatic
Protection device	TRAP	TRAP	FilterWire	MO.MA	NeuroShield 2	TRAP	TRAP	NeuroShield 3	NeuroShield 3	FilterWire
Hyperintense foci										
Location	left posterior midbrain	right upper midbrain	right occipital lobe	right cerebellum	left posterior midbrain	right occipital lobe	left frontal lobe and midbrain	left paraventricular midbrain	right head of caudate nucleus	right upper midbrain
Number	1	3	1	1	3	2	12	1	1	1
Size (mm)	7.8 × 2.2	9.3 × 3.2 6.8 × 1.7 6.2 × 1.8	5.2 × 2.1	4.8 × 2.1	6.7 × 2.5 7.1 × 2.2 2.3 × 1.8	11.9 × 4.6 6.9 × 1.7	15.6 × 6.9 6.0 × 5.1 5.9 × 3.2 3.1 × 2.3 2.6 × 2.1 2.2 × 1.9 2.1 × 2.0 3.2 × 1.2 2.1 × 1.7 2.0 × 1.5 2.4 × 1.2 1.6 × 1.5	8.6 × 4.7	7.3 × 4.4	6.1 × 2.3
Area (mm^2)†	13.5	23.4	8.6	7.9	13.2	43.0	84.5	31.7	25.2	11.0
Clinical symptoms	none	none	none	none	none	none	dysarthria/amnesic aphasia	none	none	none
Repeat MRI										
Elapsed months	6.7	—	4.6	4.3	2.8	4.1	3.7	—	—	1.1
Hyperintense foci	none	—	none	none	none	none	5	—	—	none

*Second intervention; †maximum area where number >1.

ICA = internal carotid artery; MRI = magnetic resonance imaging; NeuroShield 2 = second-generation (fixed-wire) MedNova device; NeuroShield 3 = third generation (bare-wire) MedNova device.

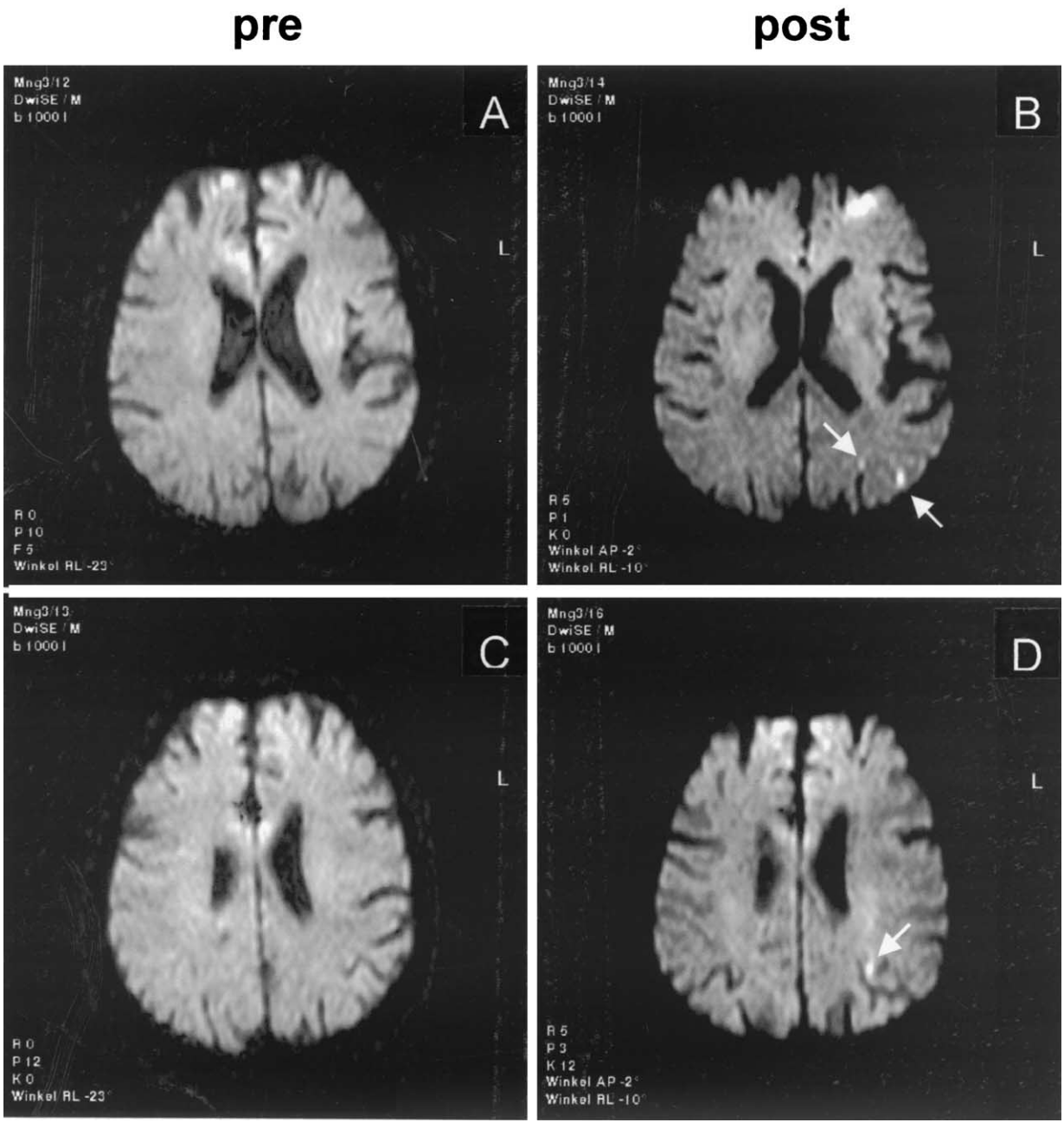

Figure 1. Magnetic resonance imaging scans showing three ischemic lesions (**arrows** in **panels B** and **D**) in adjacent tomographic layers of the left posterior midbrain in Patient #5 (Table 2, first intervention). Corresponding preinterventional MRI scans in **panels A** and **C**.

contralateral cerebellum. In the patient who sustained a stroke, access to the right common carotid artery was extremely difficult and a considerable amount of time was spent with attempts to cannulate this vessel using a variety of endoluminal devices. Most likely, particulate matter released during introduction and/or withdrawal of these devices had entered the patient's brain by way of the contralateral cervical vasculature.

2) Particulate matter liberated during the intervention may have passed through the filter pores (~100 μm in diameter) and occluded one or more ipsilateral arteries in the terminal vascular bed of the brain. This mechanism would likely be related to the composition of the stenotic plaque and the amount of debris liberated during predilation, stenting, and/or postdilation.
3) Withdrawal of the protection device may have liberated particles from the device itself (in case of filter systems), the lesion site, or from vessel walls.

The incidence of cerebral ischemia found in this study was on the same order of magnitude as that reported in previous studies involving either diagnostic cerebral angiography alone (3) or unprotected and protected CAS preceded by multiple-vessel cerebral angiography (4,10). In the latter,

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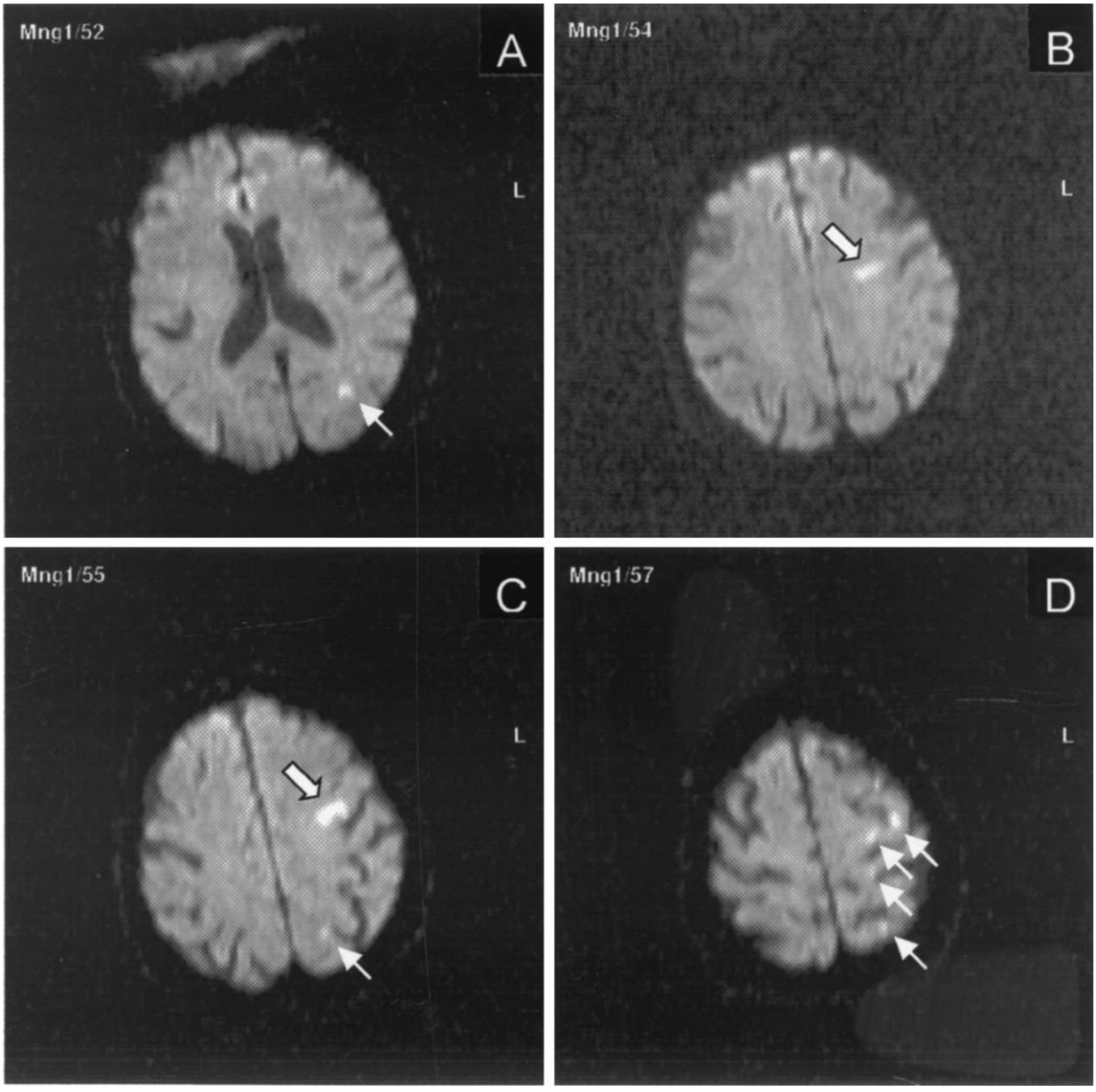

Figure 2. Postinterventional magnetic resonance imaging scans in Patient #6 (Table 2) showing ischemic lesions **(arrows)** in several tomographic layers. The **open arrows** in **panels B** and **C** both denote the largest lesion found in this patient, which extends over two adjacent layers, 5 mm apart.

no distinction could be made as to whether the diagnostic or the therapeutic part of the intervention was "responsible" for cerebral embolism; in the former, patients were not systemically anticoagulated and may therefore not be strictly comparable with the patients of our study. However, anticoagulation would not prevent the liberation from vessel walls, and subsequent entry into the cerebral circulation, of atherosclerotic matter, which has been found to constitute the debris collected or aspirated from carotid artery lesion sites (8,9).

Clinical relevance. Clinically, the ischemic lesions detected in our patients remained silent in nine out of 10 cases and were not related to the targeted carotid artery in the remaining patient who sustained a major neurological complication. Transcranial Doppler studies have shown that increased counts of microembolic signals are observed during wire crossing of the lesion, predilation, stenting, and postdilation (13,14). Although it is not known how these findings relate to cerebral ischemia on diffusion-weighted MRI, one may assume that microembolic particles possibly released during predilation, stenting, and/or postdilation would increase the incidence of cerebral ischemia over that observed during diagnostic angiography (3). As this was not the case, neuroprotection in our study had apparently been effective. With filter devices, lesion crossing as a possible source of cerebral embolism remains an issue. This may be related to the degree of stenosis and the crossing profile of the filter device used. We observed no statistically significant differences in the mean degree of stenosis or in the mean crossing profile between procedures associated with

positive and those with negative MRI findings, but this is not conclusive evidence.

Our study therefore suggests that cerebral ischemia was related to the manipulation of endoluminal equipment in the supraaortic vasculature before the deployment of the neuroprotective device. This is primarily supported by the fact that in two patients cerebral ischemia occurred in the contralateral hemisphere. Preinterventional transesophageal echocardiographic or MRI scanning of the aortic arch may have aided in assessing the embolic risk of the intervention.

In an MRI study on patients undergoing carotid endarterectomy, Barth et al. (12) reported an incidence of silent cerebral ischemia of only 4.2% (2 out of 48 patients). This significantly lower incidence points to an increased risk of periprocedural cerebral embolism during CAS as opposed to carotid endarterectomy. In consideration of the fact that inevitable interventional maneuvers before actual lesion treatment may lead to serious neurological complications, it appears imperative: 1) for the interventionist to be extremely wary of adverse vessel anatomy, and 2) for the medical industry to develop less traumatic endoluminal materials to be used in supraaortic vessels.

The "true" clinical significance of cerebral ischemia that is not associated with overt neurological symptoms is not known. Impairment of cognitive function as demonstrated in patients after cardiac surgery (15) may also be present in patients with "silent" cerebral ischemia after CAS and warrants further investigation.

Study limitations. The number of patients in this study was too small to infer general conclusions on the clinical efficacy of the neuroprotective devices investigated. The study lacked a control group of patients. Histological analysis of filter contents has not been performed; therefore, no relation of its amount and composition with the incidence, number, and size of ischemic cerebral lesions could be established. Transcranial Doppler monitoring has not been performed. To possibly determine the actual interventional maneuver "responsible" for cerebral ischemia, monitoring of the vascular access routes to both hemispheres would be mandatory. However, although continuous Doppler monitoring is possible, continuous peri-interventional MRI scanning of the brain is not. Thus, the value of peri-interventional transcranial Doppler to elucidate postinterventional MRI findings appears limited. A shorter follow-up time would have been desirable for a more precise assessment of the persistence of the ischemic lesions.

Rationale. This study was not designed as a comparative study aimed at detecting differences in efficacy between neuroprotective devices. Rather, it is an observational study on the incidence of procedure-related cerebral ischemia in consecutive patients undergoing CAS and consenting to pre- and postinterventional MRI.

Conclusions. Neuroprotected CAS is associated with a 23% incidence of focal, predominantly clinically silent, cerebral ischemia on diffusion-weighted MRI. This incidence is not different from that reported for diagnostic cerebral angiography. Cerebral ischemia mostly occurs in the ipsilateral hemisphere, but the finding, in 2 of 10 patients, of contralateral cerebral ischemia is cause for concern—particularly because a major neurological complication not related to the targeted carotid artery was encountered in one study patient. Our results suggest manipulation of endoluminal equipment in the supraaortic vasculature to be a major risk factor for cerebral embolism during neuroprotected CAS. Conclusive evidence as to the actual mechanism of cerebral embolism could not be provided and warrants further studies to elucidate the safety of CAS, even when neuroprotection is employed.

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