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Late Cerebral Embolization After Emboli-Protected Carotid Artery Stenting Assessed by Sequential Diffusion-Weighted Magnetic Resonance Imaging

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Objectives This study sought to assess the timing of cerebral ischemia after emboli-protected carotid artery stenting (CAS).

Background Predominantly clinically silent cerebral ischemia has been observed in up to 50% of patients undergoing emboli-protected CAS. The timing and location of cerebral ischemia has not been sufficiently elucidated.

Methods In 58 patients (69.6 ± 8.3 years) who underwent 59 procedures, diffusion-weighted magnetic resonance imaging (DWMRI) was performed before the intervention and at 2 time points (t_1 and t_2) after the intervention.

Results No patient showed recent cerebral injury before CAS. At $t_1 = 3.5 \pm 1.8$ h, new ischemic foci, all located in the ipsilateral hemisphere, were observed in 12 of 59 DWMRI studies (20.3%, 95% confidence interval: 11.0% to 32.8%). At $t_2 = 18.0 \pm 3.1$ h, 7 more DWMRI scans showed recent ischemic foci, and 3 scans in patients with positive scans at t_1 showed additional foci, for a total of 10 scans (17.0%, 95% confidence interval: 8.4% to 29.0%) documenting late cerebral ischemia. In 4 of these (40%), ischemic foci were located contralaterally. Cerebral ischemia was not associated with overt neurological sequelae out to 30 days in any patient.

Conclusions The incidence of late cerebral ischemia occurring between 3.5 and 18 h after emboli-protected CAS was 17%. It may occur with equal likelihood in either hemisphere. Preventive measures to possibly reduce the incidence of cerebral embolization should focus not only on the target lesion, but also on the access vasculature. Patients should be monitored and DWMRI delayed for at least 18 h after the intervention. (J Am Coll Cardiol Intv 2008;1:571–7) © 2008 by the American College of Cardiology Foundation

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Emboli-protected carotid artery stenting (CAS) is being increasingly used as a less invasive alternative to carotid endarterectomy for the treatment of patients with high-grade symptomatic and asymptomatic carotid artery stenosis. However, despite the introduction of embolic protection devices, the cumulative 30-day stroke and death rate of this procedure is still in the range of 6% to 12% (1–4) depending on the risk profile of the patients. Diffusion-weighted magnetic resonance imaging (DWMRI) is a highly sensitive tool for the detection of cerebral ischemia. Ischemic regions can be identified as hyperintense areas within minutes of onset, as has been shown experimentally and in vivo (5,6). The DWMRI studies have been performed before and after protected carotid artery stent procedures, revealing new post-procedural ischemia of the brain in 20% to 50% of patients. In the vast majority of patients, these lesions remain clinically silent (7–12).

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In terms of patient care after the procedure, it is important to know whether the occurrence of cerebral ischemia is restricted to the duration of the procedure itself or is an ongoing process lasting for several hours. Therefore, the purpose of the present study was to assess the time course of cerebral ischemia after emboli-protected CAS by way of sequential DWMRI.

Abbreviations and Acronyms

CAS = carotid artery stenting

CI = confidence interval

DWMRI = diffusion-weighted magnetic resonance imaging

Methods

Patients. Between April 2006 and June 2007, 58 consecutive patients without contraindications for DWMRI who had either a symptomatic carotid artery stenosis of at least 60% or an asymptomatic stenosis of at least 80% underwent a total of 59 elective emboli-protected CAS procedures at our institution. Eight procedures were performed for a lesion that had given rise to neurological symptoms within the previous 6 months, and 51 procedures (86%) were performed for an asymptomatic lesion. Written informed consent was obtained from all patients. Pertinent patient and lesion characteristics are summarized in Table 1.

Magnetic resonance angiography. Magnetic resonance angiography of the aortic arch, the supra-aortic arteries, and the intracerebral arteries was performed before the procedure to assess vessel anatomy and pathology as well as target lesion morphology.

CAS procedure. The CAS procedure as performed at our institution has been described in detail previously (8). In short, patients were either pre-medicated with clopidogrel (75 mg/day) and aspirin (100 mg/day) for at least 3 days or given a loading dose of clopidogrel (600 mg) immediately before the intervention. In all patients, a bolus of 70 IU/kg to 100 IU/kg heparin was administered at the start of the procedure. Glycoprotein IIb/IIIa antagonists were not used. A long sheath (Shuttle-SL, Cook Medical Inc., Bloomington, Indiana) was introduced into the common carotid artery by way of the femoral artery. Fluoroscopic visualization of the target carotid artery, and in patients with bilateral carotid disease on magnetic resonance angiography, also of the contralateral carotid artery, was then performed. In the majority of interventions, a filter device (mostly [n = 44] the Emboshield BareWire Embolic Protection System, Abbott Vascular, Abbott Park, Illinois) was subsequently placed distal to the target lesion. In 3 patients who had >20-mm lesions with a >90% stenosis, a distal occlusive balloon system (GuardWire, Medtronic Inc., Minneapolis, Minnesota) was used instead, and a proximal flow-blockage system (Mo.Ma, Invatec s.r.l., Roncadelle, Italy) was used in 1 patient with a severely tortuous vessel distal to the target lesion. Once embolic protection was established, lesions were pre-dilated (only if the stenosis was severely calcified or caused >90% lumen narrowing) and stenting was carried out. The Acculink Carotid Stent System (Abbott Vascular) was predominantly (n = 54) used. Post-dilation with a slightly undersized balloon (nominal diameter 0.5 to 1.0 mm less than the reference vessel diameter) was performed on all stented lesions. Carotid and intracerebral angiography concluded the procedure. Patients were discharged on an oral regimen of clopidogrel (75 mg/day for 4 weeks) and aspirin (100 mg/day indefinitely).

Magnetic resonance imaging. The DWMRI scans of the brain using a 1.5-T whole-body system (Magnetom Sonata, Siemens, Erlangen, Germany) were obtained within 24 h before CAS and at 2 time points after CAS: within 6 h (t_1) and between 18 h and 24 h (t_2). The DWMRI protocol consisted of a diffusion-weighted echo-planar imaging sequence (b = 1,000 mm^2/s, TR 2,900 ms, TE 84 ms) in axial scan direction, with diffusion gradients simultaneously applied on all 3 axes. All images were reviewed by 1 experienced radiologist (J.Sa.). In all cases in which ischemic foci were seen for the first time during t_2, a repeat review of the t_1 scans was performed to verify absence of ischemic foci during t_1.

Hyperintense foci on DWMRI were described by their number, location in the brain, and size. Location of foci was defined as ipsilateral if they were found in the territory subtended by the culprit carotid artery, and otherwise as nonipsilateral. For size determination, hyperintense foci were marked manually, whereupon the area was calculated automatically by the system. Areas were then presented as mean area per patient, maximum area (area of the largest spot), and total area (sum of all identified foci).

Neurological examination. An independent neurologist established the indication for intervention. The neurological

Table 1. Baseline Patient, Lesion, and Procedure Characteristics

Patients (N = 58)	
Age, yrs	69.6 ± 8.3
Age ≥75 yrs, n (%)	16 (27)
Men, n (%)	39 (67)
Diabetes mellitus, n (%)	17 (29)
Hypertension, n (%)	53 (91)
Hyperlipidemia, n (%)	42 (72)
Previous/current smoking, n (%)	32 (55)
Bilateral carotid disease, n (%)	16 (28)
Target lesion (N = 59)	
Left internal carotid artery, n (%)	27 (46)
Right internal carotid artery, n (%)	32 (54)
De novo, n (%)	57 (97)
Eccentric, n (%)	54 (92)
Ulcerated, n (%)	26 (44)
Calcified, n (%)	33 (56)
Lesion-related neurological symptoms within previous 6 months, n (%)	8 (14)
Diameter stenosis, %*	80 ± 10
Lesion length, mm	15 ± 6
Procedures (N = 59)	
Procedure duration, min	28 ± 12
Type of embolic protection device used	
Distal filter, n (%)	55 (93)
Distal balloon, n (%)	3 (5)
Proximal balloon, n (%)	1 (2)
Dwell time of embolic protection device, min	4.8 ± 1.5
Type of stent implanted	
Open cell	57 (97)
Closed cell	1 (2)

*Visual estimate.

examination included a calculation of the National Institutes of Health Stroke Scale and was repeated immediately after the intervention and before discharge.

Statistics. Continuous variables are presented by their mean ± 1 SD or, where appropriate, by their median and interquartile range. Nominal variables are presented as counts and percentages. Exact 95% confidence intervals (CIs) were calculated based on the binomial distribution. Group differences between continuous variables were compared using the Mann-Whitney *U* test. Comparisons between nominal variables were performed using the Fisher exact text. These analyses used the StatView 4.5 software package (Abacus Concepts, Inc., Berkeley, California). A 2-tailed p value < 0.05 was considered statistically significant.

Results

All procedures were successfully completed within 28 ± 12 min. Embolic protection devices were used as intended in all procedures; they were in effect for a mean of 4.8 min. A de novo lesion was treated in the majority (97%) of cases; 3 interventions (2 with stenting, 1 with balloon angioplasty only) were performed for in-stent restenoses. No patient experienced neurological symptoms periprocedurally out to 30 days. Pertinent procedural details are given in Table 1.

DWMRI findings. Before intervention, no patient showed signs of recent cerebral ischemia on DWMRI. The first follow-up DWMRI study took place 3.5 ± 1.8 h after the intervention (t_1) and revealed new cerebral ischemic foci in 12 of 59 studies (20.3%, 95% CI: 11.0% to 32.8%). At the time (t_2) of the second follow-up DWMRI study, at 18.0 ± 3.1 h, 7 more studies (11.9%, 95% CI: 4.9% to 22.9%) revealed new cerebral ischemia. Moreover, 3 studies (5.1%, 95% CI: 1.1% to 14.2%) showed additional foci in patients who already had a positive DWMRI scan at t_1. Thus, a total of 10 studies (17.0%, 95% CI: 8.4% to 29.0%) revealed new or additional foci at t_2, and the overall incidence of new cerebral ischemia at a mean of 18 h after emboli-protected CAS was 32.2% (19 studies, 95% CI: 20.6% to 45.6%) (Fig. 1).

The incidence of new cerebral ischemia in selected patient and lesion subgroups is given in Table 2. Except for diabetic patients, in whom a tendency toward an increased incidence was observed (50% vs. 24% in nondiabetics, p = 0.072), no other patient or lesion characteristic seemed to impact the incidence of new cerebral ischemia.

All ischemic foci detected at t_1 were located in the ipsilateral hemisphere. In contrast, of the late (new or additional) ischemic foci that were first seen at t_2, these were located exclusively ipsilaterally in only 6 of 10 DWMRI studies. Three studies detected ischemic foci solely in the contralateral hemisphere, and 1 study showed 1 ischemic focus each in both the ipsilateral and the contralateral hemisphere, for a total of 4 of 10 studies (40%, 95% CI: 12.2% to 73.8%) revealing contralateral cerebral ischemia at t_2. Of the late contralateral foci, 3 (75%) occurred in patients with bilateral carotid disease. The affected con-

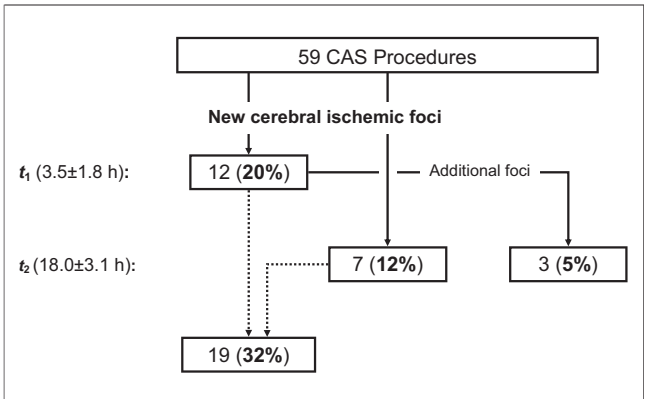

Figure 1. Cerebral Ischemia on Sequential DWMRI

Flowchart showing new cerebral ischemic foci at time points t_1 and t_2 after CAS, as well as additional foci at t_2 in 3 patients who already had cerebral ischemic foci at t_1. CAS = carotid artery stenting; DWMRI = diffusion-weighted magnetic resonance imaging.

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Table 2. Cerebral Ischemia on DWMRI in Selected Patient and Lesion Subgroups

	No. of CAS Procedures	New Cerebral Ischemia	p Value	Late Cerebral Ischemia	p Value
Total	59	19 (32)		10 (17)	
Patient subgroups					
Men	40	13 (33)	>0.999	7 (18)	>0.999
Women	19	6 (32)		3 (16)	
Age <75 yrs	43	12 (28)	0.348	6 (14)	0.436
Age ≥75 yrs	16	7 (44)		4 (25)	
Nondiabetic	41	10 (24)	0.072	5 (12)	0.256
Diabetic	18	9 (50)		5 (28)	
Normal lipids	16	6 (38)	0.755	2 (13)	0.713
Hyperlipidemia	43	13 (30)		8 (19)	
Nonsmoker	26	11 (42)	0.169	6 (23)	0.311
Smoker	33	8 (24)		4 (13)	
Unilateral disease	43	13 (30)	0.755	7 (16)	>0.999
Bilateral disease	16	6 (38)		3 (19)	
Lesion subgroups					
Noncalcified	26	10 (39)	0.410	6 (23)	0.311
Calcified	33	9 (27)		4 (13)	
Nonulcerated	33	10 (30)	0.784	6 (18)	>0.999
Ulcerated	26	9 (35)		4 (15)	
Asymptomatic	51	15 (29)	0.417	9 (18)	>0.999
Symptomatic	8	4 (50)		1 (13)	

Values are n (%).

CAS = carotid artery stenting; DWMRI = diffusion-weighted magnetic resonance imaging; late = new plus additional ischemic foci detected at t_2; new = cumulative incidence of new ischemic foci detected at t_1 and t_2.

tralateral hemisphere was the left and right hemisphere in 2 cases each. In the latter, the left common carotid artery originated in close proximity to the origin of the brachiocephalic artery in 1 patient, whereas in the other, it originated directly from the brachiocephalic artery (Fig. 2). With respect to the occurrence of late foci, no patient or lesion characteristic was found to exert an influence (Table 2).

The number of ischemic foci in all 31 studies with positive DWMRI scans ranged from 1 to 5, with the area covered by an ischemic focus ranging from 3 mm^2 to 94 mm^2. Descriptive statistics of ischemic foci seen at t_1 and t_2 are given in Table 3. Multiple foci were significantly more often observed in patients ≥75 years than in patients <75 years (5 of 16 [31%] vs. 3 of 43 [7%], respectively, p = 0.0278) and tended to occur more frequently in patients with symptomatic lesions (3 of 8 [38%] vs. 5 of 51 [10%] in patients with asymptomatic lesions, p = 0.0678). The symptomatic lesion status was also the only variable to impact the size of ischemic foci: in patients with a symptomatic lesion, the mean area of the ischemic foci was significantly larger than in patients with an asymptomatic lesion (48 mm^2 vs. 31 mm^2, respectively, p = 0.0205).

Discussion

As a diagnostic tool capable of visualizing ischemia of the brain within minutes of onset, DWMRI has been used to assess procedure-related cerebral ischemia after both carotid endarterectomy (9,13,14) and carotid angioplasty and stenting with and without embolic protection (7–12). Follow-up DWMRI has usually been performed once within 12 to 48 h of the intervention and has yielded incidences of new focal cerebral ischemia between 4% (13) and 17% (14) for carotid endarterectomy and between 23% (8) and 49% (12) for emboli-protected CAS. In the present study, post-procedural DWMRI was performed twice: at a mean of 3.5 h and again at a mean of 18 h after the intervention, yielding overall incidences of new cerebral ischemia of 20% and 32%, respectively. In the first post-procedural DWMRI, ischemic foci were exclusively found in the territory subtended by the targeted carotid artery, whereas in the second post-procedural DWMRI, 40% of ischemic lesions were located in the contralateral hemisphere.

Our results indicate that the embolic process after emboli-protected CAS is not restricted to the intervention itself but may still occur within an average time frame of 3.5 to 18 h after the intervention. Thus, this study confirms the phenomenon of late embolization first reported in a recent investigation (15).

Mechanisms of new and late cerebral ischemia. The finding of exclusively ipsilateral ischemic lesions at the first follow-up DWMRI study suggests that these early lesions originate from emboli released in the course of the actual

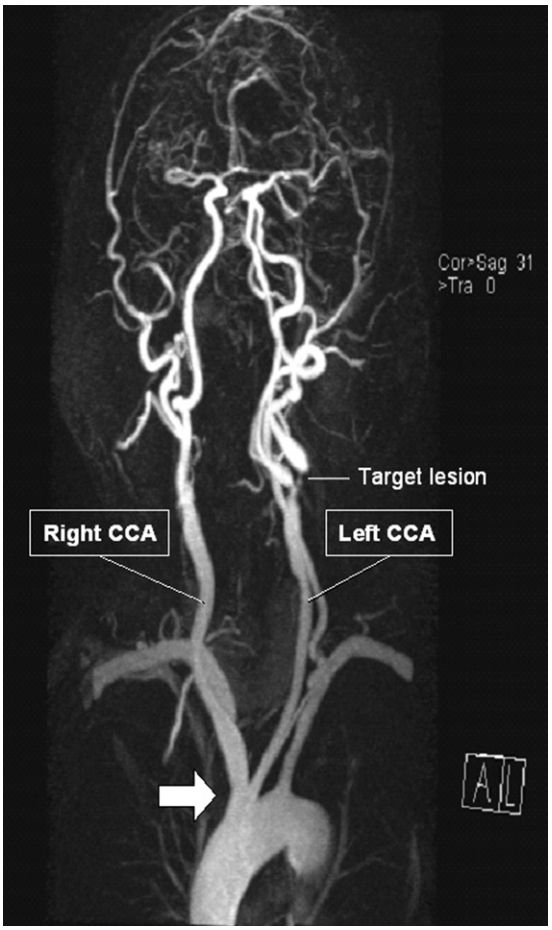

Figure 2. Magnetic Resonance Angiography

Left common carotid artery (CCA) originating from brachiocephalic artery **(arrow)**. A = anterior; L = left.

intervention or shortly thereafter. The most likely mechanism is the liberation of atherosclerotic particulate matter during one (or more) of several stages of the intervention: sheath placement in the common carotid artery, maneuvering through the carotid lesion, and placement of the distal embolic protection device, passage of particles through the filter pores or past a malapposed filter during stenting, incomplete aspiration of debris after stenting in the presence of a balloon occlusive protection system, withdrawal of the embolic protection device after stenting, and protrusion with subsequent release of atherosclerotic matter through the stent meshes.

Both ipsilateral and contralateral ischemic foci were observed at the second follow-up DWMRI study. Although it is conceivable that late ipsilateral foci have originated from the stented site, the approximate incidence ratio of 50:50 between late ipsilateral and late contralateral foci points to a different mechanism for late cerebral ischemia. Thrombus apposition to wall segments close to or at the origin of the brachiocephalic artery injured during the advancement of endoluminal equipment into the left common carotid artery may have given rise to thromboembolic matter to be carried downstream with equal likelihood into either hemisphere, particularly in cases in which the left common carotid artery originates in close proximity to the brachiocephalic artery. Although it is noteworthy that 3 of the 4 late contralateral foci were observed in patients with bilateral carotid disease, this increased incidence seems to be a chance finding because the overall incidences of new cerebral foci was not different between patients with unilateral disease and patients with bilateral disease (Table 2), thus making an influence of the selective introduction of a diagnostic catheter for fluoroscopic visualization of the respective carotid artery unlikely.

Impact of patient/lesion characteristics on late cerebral ischemia. We were not able to identify any patient or lesion characteristic predisposing to the occurrence of late cerebral ischemia, which may thus be a phenomenon inherent, with a likelihood ranging from 5% to 23%, to any emboli-protected CAS procedure and to any patient undergoing the intervention. Elderly patients and patients with a previously symptomatic carotid lesion had (or tended to have) more often multiple ischemic lesions covering larger brain areas in the latter patients, and diabetic patients tended toward an increased overall incidence of post-CAS cerebral ischemia. These findings are probably related to advanced atherosclerosis in elderly, symptomatic, and diabetic patients, which, however, did not impact the incidence of late brain injury.

Cerebral ischemia and overt neurological sequelae. Within 30 days of the carotid intervention, neither we nor Rapp et al. (15) observed neurological symptoms associated with cerebral ischemia on DWMRI. To date, all studies of DWMRI after emboli-protected CAS have consistently reported a paucity of overt neurological complications in the presence of focal ischemic brain injury (7–12). Apparently, the lesion location in the brain (eloquent vs. noneloquent brain regions [16]) as well as the embolic load determine whether cerebral ischemia causes overt neurological deficits

Table 3. Analysis of Ischemic Foci on DWMRI

	Time of Post-Procedural DWMRI	
	t_1	t_2
Time after CAS, h	3.5 ± 1.8	18.0 ± 3.1
Number of studies exhibiting ischemic foci	12	19
Number of ischemic foci*	1 (0–1)	1 (1–3)
Mean area,* mm^2	29 (20–48)	37 (26–46)
Maximum area,* mm^2	29 (20–59)	38 (26–58)
Total area,* mm^2	29 (20–66)	42 (26–152)

*Median and interquartile range.
Abbreviations as in Table 2.

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or not. In a previous study, we found that the 1 patient of 10 with post-CAS brain ischemia who sustained a major stroke had both a markedly higher number of ischemic foci (12, as opposed to a median of 1, range 1 to 3, in the 9 patients without neurological symptoms) and the largest area covered by an ischemic focus (85 mm^2, as opposed to 43 mm^2, the largest ischemic area found in a patient without neurological symptoms) (8). These findings were recently supported by Kastrup et al. (12), who observed that patients who experienced a minor or major stroke after CAS, as compared with patients without neurological deficits, had a significantly higher number of new DWMRI lesions (median 7.5 vs. median 1) and that patients with a major stroke had multiple ischemic lesions larger than 20 mm in diameter, whereas patients with a minor stroke had multiple ischemic lesions <10 mm in diameter.

Despite the lack of overt neurological sequelae of cerebral ischemia observed in this study, our findings seem to be supported by the Carotid RX Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) study of 3,500 patients, in which 38% of all strokes occurred later than 24 h after the intervention (17).

Little is known about the extent by which focal cerebral ischemia affects cognitive function. In a recent study, a deterioration of cognitive function after emboli-protected CAS was observed at discharge in 18 of 22 patients with cerebral ischemia on post-CAS DWMRI (18). A decline in cognitive function has also been found in elderly patients with silent brain infarcts (19).

Clinical implications. Our findings indicate that the use of embolic protection devices (distal filters in particular) during CAS does not completely prevent particulate matter from entering the ipsilateral cerebral vascular territory. Moreover, the unprotected nonipsilateral cerebral vasculature may be invaded post-CAS by emboli presumably originating from trauma to the aortic arch and/or the proximal part of the brachiocephalic artery. To possibly reduce the incidence of cerebral embolization, preventive measures therefore need not only focus on the target lesion, but also on the access vasculature. Because the occurrence of both ipsilateral and nonipsilateral cerebral ischemia is not restricted to the actual intervention but continues for several hours, it seems advisable to monitor the patients for at least 18 to 24 h after intervention and delay follow-up DWMRI until discharge, to possibly capture the full extent of procedure-related cerebral ischemia. It is not known whether embolization occurs even later than 24 h after the intervention.

Further study is needed to: 1) clarify whether stronger or prolonged heparinization reduces the incidence of late cerebral ischemia; and 2) elucidate the clinical impact of silent cerebral ischemia on neuropsychological function.

Study limitations. The number of patients in this study is fairly low, giving rise to wide confidence intervals of proportions and precluding logistic regression analyses to determine predictive factors for new and late cerebral ischemia.

Conclusions

This study showed that emboli-protected CAS may give rise to clinically silent late embolization into the cerebral vasculature in 8% to 29% of patients, with a time lag averaging 3.5 to 18 h after the intervention. Late embolization occurred in both the ipsilateral and contralateral hemisphere, whereas early embolization was only observed in the ipsilateral hemisphere. Preventive measures to possibly reduce the incidence of cerebral embolization should focus not only on the target lesion, but also on the access vasculature. To capture the full extent of CAS-related cerebral injury, patients should be monitored and DWMRI delayed for at least 18 h after the intervention.

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Key Words: carotid artery disease ■ cerebral ischemia ■ magnetic resonance imaging ■ stents.