Anatomical Risk Factors for Ischemic Lesions Associated with Carotid Artery Stenting

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Summary

The purpose of this study was to investigate the anatomical risk factors for ischemic lesions detected by diffusion-weighted imaging (DWI) associated with carotid artery stenting (CAS).

DWI was performed within four days after CAS in 50 stenotic lesions between January 2008 and September 2013. We retrospectively analyzed the correlation between the anatomical factors and ischemic lesions associated with CAS.

Post-procedural DWI revealed new ischemic lesions after 24 (48%) of the 50 CAS procedures. All three patients with common carotid artery tortuosity, defined as the presence of severe angulation (less than 90 degrees) in the common carotid artery, developed new ischemic lesions. However, there were no significant differences between the patients with and without tortuosity, likely due to the small number of cases. Meanwhile, seven of eight patients with internal carotid artery tortuosity, defined as the presence of severe angulation (less than 90 degrees) in the cervical segment of the internal carotid artery, developed new ischemic lesions. A multivariate analysis showed internal carotid artery tortuosity (odds ratio: 11.84, 95% confidence interval: 1.193-117.4, $P=0.035$) to be an independent risk factor for the development of ischemic lesions associated with CAS.

Anatomical factors, particularly severe angulation of the internal carotid artery, have an impact on the risk of CAS. The indications for CAS should be carefully evaluated in patients with these factors.

Introduction

Recently, carotid artery stenting (CAS) has been presented as an alternative to carotid endarterectomy (CEA) for the treatment of carotid artery stenosis^{1,2}. The data published so far suggest that CAS has the same efficacy as CEA in terms of long-term stroke prevention, but it is associated with a higher periprocedural stroke rate^{2,3}.

Likewise, new ischemic lesions detected by diffusion-weighted imaging (DWI) occur more frequently after CAS than after CEA⁴⁻⁷. Although many new lesions seen on DWI after CAS are asymptomatic, the incidence of new DWI lesions is associated with the clinical outcome⁸. Moreover, the development of ischemic lesions after CAS may be associated with cognitive impairment, as was recently described⁹.

To improve the outcome after CAS, the identification of patients likely to be at high-risk for new lesions after CAS is necessary. There is growing evidence that CAS is associated with a higher periprocedural complication rate in octogenarians than in other age groups^{2,10,11}.

Other authors advocate the importance of anatomical characteristics as predictors of the complications associated with CAS¹¹⁻¹⁴. However, it remains unclear and controversial which factor is the most important.

The purpose of this study was to investigate the anatomical risk factors for ischemic lesions detected by DWI associated with CAS.

Materials and Methods

Study design and patient population

Between January 2008 and September 2013, 51 consecutive patients underwent 58 CAS procedures at our institution. Five CAS procedures performed via a trans-brachial or trans-radial approach, two where the patient could not be examined by post-procedural magnetic resonance imaging (MRI) within four days after the procedure due to systemic complications and one who underwent subclavian artery stenting during the same procedure were excluded. Therefore, 50 CAS procedures (45 patients) were retrospectively enrolled in this study. CAS was indicated by the presence of angiographically documented carotid artery stenosis of more than 50% in symptomatic patients or more than 60% in asymptomatic patients, according to the criteria established by the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial¹ and the Asymptomatic Carotid Atherosclerosis Study (ACAS)¹⁵. Carotid stenosis was considered to be symptomatic if the patients had experienced an ipsilateral ocular or cerebral (transient or permanent) ischemic event within the past six months. All patients underwent MRI before and after the procedure to detect all ischemic lesions, including new lesions after the procedure. The clinical, anatomical and procedural data were collected for each patient by reviewing their medical records, imaging data and surgical records. This study was approved by the Institutional Review Committee at our institution and all subjects gave informed consent.

Definitions

Ischemic lesions associated with CAS were defined as at least one high intensity signal on the DWI performed after CAS that was not present on the preprocedural MRI. No distinction was made between symptomatic and asymptomatic lesions, and all lesions in the ipsilateral territory and the other vascular territories were included. Contralateral lesions were defined as stenosis of more than 70% and occlusion of the common carotid artery (CCA) or internal carotid artery (ICA).

Imaging procedure

The postprocedural MRI was performed within four days after CAS (average, 1.29 days). No neurological events were found between the preprocedural MRI and the CAS procedure. We used four MRI scanners as follows: the Gyroscan NT 1.5T (Philips Medical Systems, Best, The Netherlands), Achieva 1.5T (Philips Medical Systems), Achieva 3.0T (Philips Medical Systems) and Ingenia 3.0T (Philips Medical Systems). New ischemic lesions were identified by a single neuroradiologist at our institution who did not participate in the procedure using the DWI with echo planar methods, and an MRI report was made at that time. We collected the data on ischemic lesions on the post-procedural MRI from these reports. The protocols used for DWI are summarized in Table 1.

Carotid artery stenting procedure

More than three days before the procedure, all patients received antiplatelet therapy with

Table 1 Magnetic resonance imaging scanners and protocols used for diffusion-weighted imaging with the echo planar method.

	TR (ms)	TE (ms)	ST (mm)	Matrix	b value (s/mm ²)
Gyroscan NT 1.5T (Philips Medical Systems, Best, The Netherlands)	3768.7	88.0	5.0	256×256	1000
Achieva 1.5T (Philips Medical Systems)	3500	67.1	5.0	256×256	1000
Achieva 3.0T (Philips Medical Systems)	5000	57.5	5.0	288×288	1000
Ingenia 3.0T (Philips Medical Systems)	6250	83.2	5.0	256×256	1000

TR: repetition time, TE: echo time, ST: slice thickness.

Figure 1 Angiographic images of the anatomical factors. A) Pseudo-occlusion. B) ECA occlusion and CCA stenosis. C-E) Tortuosity of the CCA and ICA (the severe angle is shown between reference lines). F) Type III arch. G) Bovine arch.

two of the following four drugs: aspirin (100 mg/day), ticlopidine (200-300 mg/day), clopidogrel (75 mg/day), or cilostazol (200 mg/day). All but two procedures were performed under local anesthesia, whereas two were performed under general anesthesia to eliminate body motion. Stenting was carried out through the femoral route with the use of stents and embolic protection devices (EPDs). After placement of an 8-9F sheath, each patient received intravenous heparin to achieve an activated coagulation time of 250-300 seconds. An 8-9F guide catheter was then advanced to the CCA. An EPD was used in all patients. We used an ANGIOGUARD XP (Cordis Endovascular, Miami Lakes, FL, USA) in 13 procedures (26.0%), PercuSurge GuardWire (Medtronic, Santa Rosa, CA, USA) in 27 (54.0%), FilterWire EZ (Boston Scientific, Natick, MA, USA) in ten (20.0%) and an Optimo (Tokai Medical

Products, Aichi, Japan) in 13 (26.0%) cases with distal protection (PercuSurge GuardWire in 12, ANGIOGUARD XP in one). All lesions were treated with self-expandable stents. In one procedure two stents had to be deployed to cover the lesion. A Precise stent (Cordis Endovascular, Miami Lakes, FL, USA) was used in 19 procedures (38.0%) and a Carotid Wallstent (Boston Scientific, Natick, MA, USA) was used in 31 (62.0%). Angioplasty balloons were used for predilation during 45 (90%) CAS procedures (3.0-4.5 mm in diameter) and post-dilatation in 43 (86%) CAS procedures (3.5-7.0 mm in diameter). When balloon protection was used (distal, or proximal and distal), an adequate amount of blood was aspirated through the catheter to collect debris before the balloon was deflated. Filter occlusion that required blood aspiration occurred in one procedure using the filter protection.

Evaluation of the angiogram

All angiographic images were retrospectively evaluated for the following anatomical properties by a single investigator (GI): the laterality of the lesion; pseudo-occlusion; external carotid artery (ECA) occlusion; CCA stenosis, defined as stenosis of more than 50% of the CCA, including the lesion itself located in the CCA; CCA tortuosity, defined as the presence of severe angulation (less than 90 degrees) in the CCA on the anteroposterior view; ICA tortuosity, defined as the presence of severe angulation (less than 90 degrees) in cervical segment of the ICA (bifurcation, first bend or second bend) on either the anteroposterior or lateral view; unfavorable arch anatomy, defined as a type III arch for right lesions or a bovine arch for left lesions (Figure 1). If an angiographic image of the aortic arch was not available, the preprocedural magnetic resonance angiography findings were investigated.

Statistical analysis

Continuous variables are expressed as mean values $\pm$ standard deviation, and comparisons of these variables between groups were performed using the Mann-Whitney U test. Categorical variables are expressed as counts and percentage frequencies, and were compared using the chi-square test and Fisher's exact test. A multivariate logistic regression test was used to identify the independent risk factors for ischemic lesions associated with CAS. The Kruskal-Wallis one-way analysis was used to compare multiple groups. Statistical significance was defined as a P value < 0.05 , and all of the analyses were carried out using the IBM SPSS statistics software program, version 22 (IBM, Armonk, New York, USA).

Results

The mean age of the patients who underwent the 50 CAS procedures was 71.6 ± 6.43 years, and the mean degree of stenosis was 80.0 ± 10.4 %. Twenty-two (44.0%) cases showed symptomatic lesions and ten showed contralateral lesions, including seven cases with occlusion of the contralateral ICA. Ten cases had a history of neck radiation, four had a history of CEA and one had a history of CAS. Concomitant disease states were recorded in many cases, in-

cluding 47 (94.0%) cases with hypertension, 19 (38.0%) with hyperlipidemia, 21 (42.0%) with diabetes mellitus and 14 (28.0%) with coronary artery disease. Twenty-eight (56.0%) cases showed vulnerable plaques and seven (14.0%) cases showed heavily calcified plaques, both of which were diagnosed by MRI, computed tomography and ultrasonography. The anatomical factors investigated by preprocedural angiography were as follows: the left side was affected in 30 (60.0%) cases; pseudo-occlusion in seven (14.0%), ECA occlusion in three (6.0%), CCA stenosis in seven (14.0%), CCA tortuosity in three (6.0%), ICA tortuosity in eight (16.0%) and there was unfavorable arch anatomy in six (12.0%) cases.

CAS was performed successfully for all lesions, although hemodynamic instability due to the carotid sinus reflex occurred in 21 (42.0%) cases. DWI after CAS revealed new ischemic lesions after 24 (48%) of the 50 CAS procedures, including two (4%) symptomatic lesions that led to permanent neurological deficits. There was no mortality associated with the procedure. The correlations between the clinical characteristics of patients and ischemic lesions associated with CAS are shown in Table 2. Only smoking status was significantly different between the two groups ($P = 0.049$). Age, sex, hypertension, hyperlipidemia, diabetes mellitus, coronary disease, prior neck radiation, prior CEA and prior CAS were not significantly different between the groups. The correlations between the anatomical or non-anatomical factors and ischemic lesions associated with CAS are shown in Table 3. Only ICA tortuosity was significantly ($P = 0.021$) different among the anatomical factors, whereas symptomatic lesions were significantly ($P = 0.050$) different among the non-anatomical factors. All cases with CCA tortuosity revealed new ischemic lesions, but there were no significant differences between the cases with and without tortuosity because of the small number of cases. Additionally, a multivariate analysis showed that only ICA tortuosity (odds ratio 11.84, 95% confidence interval 1.193-117.4) was an independent risk factor for ischemic lesions associated with CAS (Table 4). We experienced eight patients with ICA tortuosity, among whom postprocedural MRI showed new ischemic lesions in seven patients. Severe angulation of the ICA was detected at both first and second bends in four cases, the first bend only in three cases and the second bend only in one case;

Table 2 Correlation between clinical characteristics and ischemic lesions associated with carotid artery stenting.

	All cases (n = 50)	Ischemic lesions		P value
		Yes (n = 24)	No (n = 26)	
Age, years	71.6 ± 6.43	73.3 ± 6.27	70.0 ± 6.30	0.078
Female	8 (16.0)	4 (16.7)	4 (15.4)	1.000
Hypertension	47 (94.0)	23 (95.8)	24 (92.3)	1.000
Hyperlipidemia	19 (38.0)	8 (33.3)	11 (42.3)	0.514
Diabetes mellitus	21 (42.0)	9 (37.5)	12 (46.2)	0.536
Coronary artery disease	14 (28.0)	8 (33.3)	6 (23.1)	0.420
Smoking	30 (60.0)	11 (45.8)	19 (73.1)	0.049
Prior neck radiation	10 (20.0)	5 (20.8)	5 (19.2)	1.000
Prior CEA	4 (8.0)	0 (0)	4 (15.4)	0.111
Prior CAS	1 (2.0)	0 (0)	1 (3.8)	1.000

Data are presented as the n (%) or means ± SD. CEA: carotid endarterectomy, CAS: carotid artery stenting.

Table 3 Correlation between anatomical or non-anatomical factors and ischemic lesions associated with carotid artery stenting.

	All cases (n = 50)	Ischemic lesions		P value
		Yes (n = 24)	No (n = 26)	
Non-anatomical factors:				
Age ≥ 80 years	7 (14.0)	5 (20.8)	2 (7.7)	0.239
Degree of stenosis, %	80.0 ± 10.4	81.2 ± 11.1	78.8 ± 9.86	0.527
Symptomatic lesion	22 (44.0)	14 (58.3)	8 (30.8)	0.050*
Contralateral lesion	10 (20.0)	6 (25.0)	4 (15.4)	0.490
Vulnerable plaque	28 (56.0)	13 (54.2)	15 (57.7)	0.802
Heavily calcified plaque	7 (14.0)	4 (16.7)	3 (11.5)	0.697
Filter type EPD	23 (46.0)	11 (45.8)	12 (46.2)	0.982
Proximal protection	13 (26.0)	4 (16.7)	9 (34.6)	0.148
Precise stent	19 (38.0)	12 (50.0)	7 (26.9)	0.093
Carotid sinus reflex	21 (42.0)	13 (54.2)	8 (30.8)	0.094
Filter occlusion	1 (2.0)	1 (4.2)	0 (0)	0.480
Anatomical factors:				
Left side	30 (60.0)	16 (66.7)	14 (53.8)	0.355
Pseudo occlusion	7 (14.0)	5 (20.8)	2 (7.7)	0.239
ECA occlusion	3 (6.0)	2 (8.3)	1 (3.8)	0.602
CCA stenosis	7 (14.0)	3 (12.5)	4 (15.4)	1.000
CCA tortuosity	3 (6.0)	3 (12.5)	0 (0)	0.103
ICA tortuosity	8 (16.0)	7 (29.2)	1 (3.8)	0.021
Unfavorable arch anatomy	6 (12.0)	3 (12.5)	3 (11.5)	1.000
Data are presented as the n (%) or means ± SD. EPD: embolic protection device, ECA: external carotid artery, CCA: common carotid artery, ICA: internal carotid artery. * The P value was actually < 0.05.				

Table 4 Results of the multivariate logistic regression analysis of risk factors for ischemic lesions associated with carotid artery stenting.

	Odds ratio	95% CI	P value
Smoking	0.505	0.134 - 1.905	0.313
Symptomatic lesion	3.483	0.930 - 13.05	0.064
ICA tortuosity	11.84	1.193 - 117.4	0.035

CI: confidence interval.

there were no cases of severe angulation of the carotid bifurcation. A summary of these cases is shown in Table 5.

The frequency of the detection of new ischemic lesions was not significantly different among the various scanners used ($P=0.202$) (Gyrosan NT 1.5T, 13 of 20 (65.0%); Achieva 1.5T, four of 14 (28.6%); Achieva 3.0T, six of 13 (46.2%); Ingenia 3.0T, one of three (33.3%)).

Discussion

The present study demonstrated that ICA tortuosity is an independent risk factor for ischemic lesions associated with CAS. Vessel tortuosity increases the technical difficulty of per-

forming CAS. This increase in unfavorable anatomy may be associated with ischemic complications. From this point of view, octogenarians are thought to be at higher risk for complications during CAS than other age groups because elderly patients theoretically have a higher incidence of unfavorable anatomy^{16,17}. However, a recent study showed that the incidence of periprocedural complications was increased in patients with unfavorable aortic arch anatomy but not in octogenarians¹³. This suggests that unfavorable anatomical factors may be more important than the age of patients.

Several authors have referred to the risk factors for the ischemic lesions detected by DWI after CAS. A history of coronary artery disease⁷, hemodynamic instability due to the carotid

Table 5 Summary of the patients with ICA tortuosity.

Case	Age	Sex	Location of lesion	Location of ICA tortuosity	EPD	Stent	Stent-induced kinking	Number of ischemic lesions
1	68	M	ICA proximal	2 nd bend	PercuSurge GuardWire	Precise	+	4
2	68	M	ICA proximal	1 st + 2 nd bend	Angioguard XP	Precise	-	1
3	76	M	ICA proximal	1 st bend	Angioguard XP	Precise	-	2
4	72	M	ICA proximal	1 st + 2 nd bend	Angioguard XP	Precise	+	1
5	73	M	ICA proximal	1 st bend	Filterwire EZ	Carotid Wall	-	7
6	71	F	CCA	1 st + 2 nd bend	PercuSurge GuardWire	Carotid Wall	-	1
7	81	F	ICA proximal	1 st bend	PercuSurge GuardWire	Carotid Wall	+	3
8	79	M	ICA proximal	1 st + 2 nd bend	Filterwire EZ	Carotid Wall	+	0

ICA proximal means the area between the carotid bifurcation and first bend of ICA.

sinus reflex^{18,19}, performing an arch aortogram prior to CAS⁶, advanced age²⁰, the presence of ulcerated stenosis²⁰ and a lesion length more than 1 cm²⁰ were all described as risk factors. However, it remains unclear which factor is the most important, and few clinical studies have addressed the anatomical risk factors for ischemic lesions associated with CAS²¹.

A scoring system of anatomical suitability for CAS based on an objective expert consensus was published in 2009²². Twelve anatomical factors were ranked in ascending order from the most straightforward (low bifurcation) to the most difficult (tortuous CCA) with a mean difficulty score chosen by experts. The rankings reported in that article were as follows: low bifurcation, occluded or severely diseased ECA, bovine arch, 99% stenosis (flow beyond), diseased CCA (> 50%), angulated distal ICA, severe arch atheroma, a type III arch, circumferential calcification of the ICA, an angulated ICA origin, severe arch origin disease and a tortuous CCA. After low bifurcation and a tortuous CCA were excluded, the scoring system was developed to categorize the expected difficulty of CAS and to aid in case selection. In a retrospective clinical study using this scoring system reported by Werner et al.²³, the classification correlated well with the periprocedural neurological outcome. We investigated nine of the above factors, although we classified calcification as a non-anatomical factor. We also distinguished plaque morphology from the anatomical factors.

Various anatomical factors associated with periprocedural complications during CAS were described in previous reports. For example, Naggara et al.¹² assessed the relationships between anatomical and technical factors and the 30-day risk of stroke or death after CAS in the Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, and performed a systematic review of the literature. The risk of stroke and death was higher in patients with increased ICA-CCA angulation, left-sided CAS and when the target ICA stenosis was >10 mm, whereas the risk was not related to the stent or EPD type. Werner et al.²³ reported that the presence of a bovine arch, tortuous CCA and angulated distal ICA were associated with higher risks of stroke and transit ischemic attack. Faggioli et al.¹⁴ evaluated the impact of arch angulation and proximal and distal tortuosity in a series of CAS procedures. They used

a tortuosity index defined as the sum of all angles diverging from the ideal straight axis, and showed that the proximal tortuosity index was an independent predictor of both neurological complications and technical failure. Conversely, Ito et al.²⁴ demonstrated that the angles at the carotid bifurcation and the first bend of the ICA were significantly associated with the incidence of microembolization. Thus, vascular tortuosity is an important factor for predicting the development of periprocedural ischemic complications after CAS, as we described above.

There may be some reasons why ICA tortuosity is associated with ischemic lesions. When the lesion was located proximally at the ICA and the site of tortuosity was located at the first bend of the ICA, stent deployment directly influenced the severe angulation of the ICA. The extension of the ICA angulation may increase the amount of debris associated with CAS, as described by Sorimachi et al.²⁶. To reduce the changes in ICA angulation, they recommended the use of shorter devices (stents or angioplasty balloons) when the ICA angulation is pronounced.

On the other hand, when the site of vessel tortuosity was far from the stenotic lesion, the stent did not cover the tortuous lesion. However, the EPDs were always influenced by the change in angulation of the tortuous vessels during the procedure, despite the distance between the stenotic and tortuous lesions. The instability of the EPDs during the procedure caused by the straightened nature of the ICA may result in inadequate protection, consequently leading to embolic complications. Therefore, we believe that the presence of tortuosity both near and far from the stenotic lesion is a risk factor for ischemic events.

With respect to reducing the incidence of ischemic complications associated with EPDs, the use of proximal protection without insertion of an EPD into the ICA is theoretically useful for treating patients with ICA tortuosity. Although the use of proximal protection was not found to be a significant factor affecting the incidence of ischemic lesions in the present study, Asakura et al.²⁵ reported the usefulness of protection by reverse carotid arterial flow during CAS. In this article, both the CCA and ECA were continuously occluded using balloons before the insertion of a guidewire through the stenotic lesion until the end of the procedure. The rate of appearance of new ischemic lesions detected by DWI was not sig-

nificantly different between conventional angiography and the CAS procedure using this protection system.

From another point of view, the condition after stent deployment, such as incomplete attachment of the stent and stent-induced kinking, may be associated with the development of ischemic lesions after CAS. Four of the eight patients treated in the present study exhibited stent-induced kinking after stent deployment. Ischemic lesions were detected after CAS in three of these cases. Stent-induced kinking may occur more frequently in cases involving ICA tortuosity, although we were unable to demonstrate an increase in the frequency of ischemic lesions in patients with stent-induced kinking. Onizuka et al.²⁷ stated that the existence of incomplete stent apposition had no adverse morphological or clinical effects. In addition, although stent-induced kinking was observed in eight of 15 patients in this article, no ischemic lesions were detected in any of the 15 patients. A sufficiently large sample size is necessary to confirm the correlation between the postprocedural condition and the ischemic complications in CAS.

Considering the risk of CAS, the entire access route from the puncture site to the objective lesion should be considered. This is because ICA and/or vessel tortuosity throughout the access route may increase the incidence of thromboembolic complications due to endothelial damage caused by the interventional devices. In such high-risk cases, selecting CEA as an alternative to CAS or changing the access route should be considered. Regarding the periprocedural management of CAS in patients with severe vessel tortuosity, the administration of antiplatelet and anticoagulant therapy should be intensified. Therefore, evaluating the

degree of vessel tortuosity associated with the lesion and access route is important to determine the treatment strategy in patients with carotid artery stenosis.

The principal limitations of the present study are its retrospective nature and small sample size. Nevertheless, a statistically significant outcome was observed among patients with ICA tortuosity. The patients with CCA tortuosity represented a similar trend, but the data did not reach statistical significance due to the small number of cases. Another limitation of the present study is that we did not evaluate the risk factors for stroke and death as described in previous reports. We also did not investigate the changes in cognitive function after CAS. Further studies are needed to determine the anatomical risk factors for neurological morbidity, including cognitive impairment, and mortality associated with CAS.

Conclusions

The present study showed that the most important anatomical factor to predict the development of ischemic lesions associated with CAS was ICA tortuosity. This result may aid in a better selection of patients for CAS. We should therefore evaluate preprocedural angiography findings from an anatomical point of view.

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