Carotid artery stenting using overlapped double closed-cell stents for unstable plaque

Abstract

Purpose: Stent design is one of the risk factors associated with periprocedural ischemic complications during carotid artery stenting (CAS). Closed-cell stents have a lower rate of ischemic complications than open-cell stents, and it has been reported that this is because closed-cell stents have a smaller free cell area, restricting plaque protrusion (PP). Reducing the free cell area of stents may thus reduce the incidence of ischemic complications. We examine whether CAS for carotid artery stenosis with unstable plaque using overlapped double closed cell stents undergo without plaque protrusion (PP).

Methods: A total of 35 consecutive patients with carotid artery stenosis with unstable plaque diagnosed by magnetic resonance plaque imaging (29 men; [mean 75.8 years]; symptomatic stenosis, 20 lesions; mean stenosis rate, 83.5%) were prospectively analyzed. All CAS procedures were performed by conservative post-dilatation after stent-in-stent placement of two Carotid Wallstents using an embolic protection device. The technical success rate, incidence of PP, ischemic stroke within 30 days, and new ipsilateral ischemic lesions on diffusion-weighted imaging (DWI) within 48 h after CAS and follow-up results (ipsilateral stroke rate and restenosis rate) were prospectively assessed.

Results: The technical success rate was 100% (35/35). No PP and stroke occurred in any patients. New ischemic lesions were observed on DWI in 10 patients (28.6%). During the follow-up period (mean 11.6 months), no ipsilateral strokes occurred. Asymptomatic restenosis (53%) occurred in 1 patient (2.9%); asymptomatic occlusion occurred in 1 patient (2.9%).

Conclusion: CAS using overlapped double stents for unstable plaque may be useful for preventing PP and ischemic complications.

Keywords

Carotid artery stenting, plaque protrusion, overlapped double closed-cell stents

Introduction

The reported risk factors associated with periprocedural ischemic complications during carotid artery stenting (CAS) include the use of a protection device, the operator's skill, patient age, plaque characteristics, and stent design.[1,2,3,4,5,6] With respect to stent design, it has been reported that closed-cell stents have a smaller free cell area than open-cell stents, which restricts plaque protrusion (PP) and reduces the incidence of periprocedural ischemic complications.[7]

Today, micromesh stents, which have a smaller free cell area than conventional stents, are already in clinical use, and studies have found that they reduce the incidence of periprocedural ischemic complications compared with conventional stents.[8,9,10,11,12] This may be because the free cell area is small, restricting PP. However, no method for reducing the free cell area using conventional stents has yet been reported. We considered that using double stents would decrease the free cell area, and that this might be effective in reducing the incidence of ischemic complications by avoiding PP. Therefore, we investigated whether CAS for carotid artery stenosis with unstable plaque using overlapped double closed-cell stents could be performed without PP.

Methods

Among 104 patients (107 stenoses) who underwent CAS under intravascular ultrasound (IVUS) at our hospital or an affiliated institution between December 2014 and August 2018, 35 consecutive patients with carotid atherosclerotic stenosis with unstable plaque (symptomatic cases, n=20[TIA, n=8; minor stroke, n=12]; asymptomatic cases, n=15) with a mean stenosis rate (North American Symptomatic Carotid Endarterectomy Trial [NASCET] method) of 83.5% (range 51-99%), were prospectively analyzed. The mean age of the patients was 75.8 years (range58-88 years). The study was approved by each hospital research ethics committee. All patients provided written informed consent before participation in this study.

CAS procedure

Antiplatelet therapy consisting of oral administration of two drugs, aspirin (100 mg) and clopidogrel (75 mg) or cilostazol (200 mg), was started at least 7 days before the procedure. All CAS procedures were performed under local anesthesia using an embolic protection device (EPD). Basically CAS was performed using both MoMa Ultra and Filterwire EZ (Boston Scientific, Natick, MA, USA), except for ischemia-intolerant cases or anatomical inappropriate cases. In such cases CAS was performed using the Filterwire EZ alone.

CAS was performed using a double-stent technique. The double-stent technique was defined as the procedure of conservative post-dilatation after stent-in-stent placement of two overlapped Carotid Wallstents (Boston Scientific Corp) while using an EPD. Pre- dilation was performed in all cases when

the stenosis rate was more than 80%. Conservative postdilation means that postdilation was performed using a PTA balloon with a diameter no greater than approximately 80% of the normal luminal diameter somewhat distal to the stenosis, as determined by IVUS. The first stent was placed at a location between the internal carotid artery (ICA) and the common carotid artery (CCA) and then the for second stent, when 6mm Carotid Wallstent was used, we tried to place it at location ICA only or between ICA and carotid bifurcation to achieve as less stent malapposition as possible (Figure 1). However, when 8mm Carotid Wallstent was used, we placed it at a location between the ICA and the CCA.

IVUS

A Volcano Visions PV 0.014P IVUS catheter (Volcano Corp., Rancho Cordova, CA, USA) was used. ChromaFlo IVUS, which can be used with this system, colorizes the flow and displays the results immediately. The addition of colorized flow assists the IVUS operator to more readily recognize the true lumen.

Magnetic resonance imaging (MRI) technique

MR plaque imaging

MRI for plaque characterization was performed using 1.5 or 3-T scanners (NT Intera 1.5 T POWER; Philips Medical Systems, Best, the Netherlands or ACHIEVA 3.0T Quasar; Philips Medical Systems, Best, the Netherlands). A 2D T1-weighted fast spin-echo sequence was performed using a black blood, double inversion, recovery preparation pulse and a fat-saturation pulse. The signal intensities of the carotid plaque were evaluated at the most severely stenotic level. Unstable plaque was defined as having a signal intensity more than 1.25 of the average relative overall signal intensity compared to that in the sternocleidomastoid muscles.

Diffusion-weighted imaging (DWI)

DWI was performed using scanners with field strengths of 1.5 or 3 T, and the same imaging parameters were used for both MRI scanners. The imaging protocol included the same DWI sequences (b = 0, 1,000 s/mm2; section thickness 5.0 mm; gap 1 mm); apparent diffusion coefficient maps were obtained in all cases. The protocol specified MRI scans to take place within 72 h before CAS and within 48h after CAS. Two board-certified neuroradiologists independently and blindly analyzed all scans, and they evaluated the number of lesions measuring ≤10 mm and >10 mm separately on the ipsilateral side.

Endpoints

The primary endpoints of this study were the technical success rate, incidence of PP during the procedure, rate of stroke within 30 postoperative days, and the frequency of the appearance of new ipsilateral high-

intensity areas and the number of lesions on DWI scans performed within 48 h after the procedure. Technical success was defined by a minimum lesion diameter after post-dilatation of ≥ 3mm on IVUS or residual stenosis of <30% on digital subtraction angiography (DSA).

PP was defined as observation of plaque inside the stent lumen after post-dilatation on IVUS. Stroke was defined as an ischemic neurologic deficit that persisted for more than 24 h. It was classified as major or minor using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) (major: NIHSS score >5 or mRS score >2; minor: NIHSS score ≦4 and mRS score ≦2).

The secondary endpoints were the ipsilateral stroke rate and the restenosis rate (above 50% stenosis on US) at least 1 month after CAS.

Results

Full baseline and procedural characteristics are summarized in Table 1.

The technical success rate was 100%. PP was observed in 0 cases (0%), and stroke was observed in 0 cases (0%) within 30 postoperative days. New ipsilateral ischemic lesions were observed in 10 (28.6 %) cases. The mean number of ischemic lesions was 2.9 (range 1–6): the median number of lesions was 2.5. All ischemic lesions were ≤10 mm and asymptomatic.

The following EPDs were used: Filterwire EZ (Boston Scientific), n. 21(ischemia-intolerant cases, 13 [37.1%]); and Filterwire EZ and MoMa Ultra (ev3 Covidien, Irvine, CA), n. 14. The following stents were used: 8mm x 21mm and 6mm x 22mm Carotid Wallstents (Boston Scientific Corp), n=13; 8mm x 29mm and 6mm x 22mm Carotid Wallstents, n. 20; and 8mm x 29mm and 8mm x 21mm Carotid Wallstents, n=2. Because the diameter of the common carotid was ≤ 8 mm and that of the internal carotid was ≤ 6 mm in all but two patients, an 8-mm stent was chosen for use as the first stent and a 6-mm stent was selected as the second stent. On the other hand, the stenosis in both of the cases in which were used 8mm x 29mm and 8mm x 21mm Carotid Wallstents was located at the CCA, the diameter of which was ≤ 8mm.

During the follow-up period (mean 11.6 months, range 1.0–39.9 months), no ipsilateral strokes occurred. Restenosis was observed in one case (2.9%); % diameter stenosis was 53%, and the patient was asymptomatic, so this patient continues to be carefully followed-up. Asymptomatic occlusion was observed in one case (2.9%); this case was underwent CAS for symptomatic left carotid pseudo occlusion. This patient discharged without any complication. However the patient hasn't been going to a hospital regularly. Follow-up ultrasound was performed 12 month later, asymptomatic in-stent occlusion occurred.

Discussion

According to a study by Kotsugi et al[8], the frequency of PP in CAS to treat carotid artery stenosis was 2.6%; PP is strongly associated with periprocedural cerebral infarction, and procedures to prevent PP

during CAS are required. That study stated that the risk factors for PP are unstable plaque and the use of an open-cell stent, and it may be conjectured that the mechanism whereby PP occurs is that the use of a stent with a strong dilating force or the performance of post-dilatation destroys the fibrous cap, causing soft plaque to move into the stent via the stent strut.

Numerous studies have reported that unstable plaque is a risk factor for periprocedural ischemic complications in CAS. Casserly et al[13] conjectured that the slow-flow phenomenon, which occurs in 9.3% of cases when a filter-type EPD is used, may be due to clogging by plaque. If slow-flow occurs, the incidence of periprocedural ischemic complications increases significantly (9.5% vs. 2.9%, $p = 0.03$). They stated that risk factors for slow-flow include clinically symptomatic carotid lesions and the use of large-diameter stents, and they suggest that PP by unstable plaque may be involved. Sakamoto et al[6] used 1.5-T MR plaque imaging for the preoperative evaluation of 31 patients who underwent CAS with a filter-type EPD. They found that slow-flow occurred in 57% of those with unstable plaque and 12% of those with stable plaque, significantly higher among those with unstable plaque, and that post-procedural DWI showed new ischemic lesions in 5/10 (50%) of those patients who showed slow-flow. This suggests that unstable plaque may be associated with PP and ischemic complications.

With respect to the diagnosis of unstable plaque on MR plaque imaging, Yoshida et al[14] compared pathological tissue from CEA and pre-procedural MR plaque imaging using 1.5-T MRI. They defined the ratio between plaque and the sternocleidomastoid muscle on T1-weighted imaging as the relative overall plaque signal intensity (roSI), and they found that unstable plaque had a higher signal intensity on T1-weighted imaging than stable plaque. They reported that a cutoff point of roSI = 1.25 had 79.4% sensitivity and 84.4% specificity for the diagnosis of unstable plaque. On the basis of that publication, unstable plaque was defined as plaque with a ratio of signal intensity compared to sternocleidomastoid muscle on T1-weighted imaging of 1.25 or more in the present study. Narumi et al[15], on the other hand, carried out 1.5-T MR plaque imaging without electrocardiogram (ECG) synchronization of continuous lesions in 40 patients with CEA, and they investigated plaque characteristics by comparing the results with pathological tissue from CEA. They found that the ratio between plaque and the sternocleidomastoid muscle on T1-weighted imaging was 0.54–1.17 if fibrous tissue was present, 1.16–1.53 for lipid/necrosis, and 1.40–2.29 for hemorrhage, showing that plaque was unstable if this ratio was 1.25 or less. Thus, 1.5-T MR plaque imaging without ECG synchronization may enable more accurate diagnosis of unstable plaque.

Differences in the incidence of periprocedural ischemic complications in CAS as a result of stent design have previously been reported. Bosiers et al[2] reported that the frequency of cerebral infarction, death, and TIA within 30 days after CAS was 5.9% for open-cell type stents [Precise (Cordis, Miami Lakes, FL, USA), Exponent (Medtronic, Vascular, Santa Rosa, CA, USA), Protégé (ev3, Plymouth, MN, USA), and Acculink (Guidant, Santa Clara, CA, USA)], significantly higher than the rate of 1.2% for closed-cell type stents [Carotid Wallstent], and X-act (Abbott Vascular Devices, Redwood City, CA,

USA), NexStent (Endotex, Cupertino, CA, USA)], and suggested that the incidence is higher because of the larger free cell area of open-cell stents. On the basis of that paper, we also considered that the higher incidence of periprocedural ischemic complications in CAS when open-cell stents with a large free cell area are used suggested that PP may be associated with periprocedural ischemic complications in CAS.

Micromesh stents, which have an even smaller free cell area than conventional stents, have recently been developed. Wissgott C et al.[8] reported the first clinical results using micromesh stent (CASPER/ Roadsaver) (Terumo, Tokyo, Japan) and concluded that micromesh stent showed promising results in their small clinical study, with no ischemic events. Micromesh stents such as Roadsaver (Terumo) (closed-cell design; cell size, 375–500 μm) or C-guard (inspireMD, Boston, MA, USA) (open-cell design, 150–180 μm) are now in clinical use, and the incidence of periprocedural ischemic complications is reportedly decreasing. Bosiers et al. [10] reported only one case of a minor stroke event (1.0%) in the CLEAR-ROAD study of 100 CAS cases using the Roadsaver (Terumo). Musialek et al.[11] reported one case of a minor stroke event from among 106 cases (0.9%) in the PARADIGM study using C-guard stents (inspireMD). Recently, Wissgott et al.[12] also reported that there were no cases of stroke within 30 days among 30 cases using C-guard stents (inspireMD) and no cases of stroke were observed during the 6-month follow-up period.

As an explanation, Schofer et al. [9] stated that the structural characteristics of the C-guard (inspireMD) stent reduced ischemic complications that can be confirmed on postoperative MRI. Yamada et al.[16] investigated 46 consecutive patients who underwent CAS for carotid artery stenosis with unstable plaque and who were analyzed by optical frequency domain imaging. A comparison between a micromesh stent (Roadsaver stent) (n = 9) and regular stents [Carotid Wallstent (n = 20), Precise (n = 16), and Protégé (n =1)] found that the incidence of PP was significantly lower in patients treated with a micromesh stent (44% vs. 88%; p = 0.022), and that the PP area was much smaller in the Roadsaver stent group (mean PP area 0.013 ± 0.034 mm2 vs. 0.057 ± 0.09 mm2; p = 0.006). Umemoto et al.[17] also reported that an optical coherence tomography (OCT) analysis revealed that the incidence of PP in patients treated with CGuard stent (10.8%) was significantly lower than in that in patients treated with RoadSaver stent(20.7 %). These reports suggest that use of a micromesh stent reduces ischemic complications by reducing the incidence of PP. Moreover Umemoto et al.[17] indicated that the use of much smaller free cell micromesh stent reduced the incidence of PP even if the micromesh stent was used.

Sakamoto et al[18] it is considered important to have knowledge regarding the state of the stent cells of different sizes of Carotid Wallstent. The aim of this study was to examine the state of stent cells of different sizes. Placed 6-mm, 8-mm, and 10-mm diameter Carotid Wallstents inside a tube with a 6-mm lumen and measured the stent cell area. They found that the mean area was 2.70 ± 0.09 mm^2 for the 6-mm diameter Carotid Wallstent, 3.22 ± 0.08 mm^2 for the 8-mm diameter Carotid Wallstent, and 4.41 ± 0.12 mm^2 for the 10-mm diameter Carotid Wallstent, indicating that a stent with a diameter close to that of the target vessel must be chosen in order to make the stent cell mesh finer. Therefore, a 6-mm Carotid

Wallstent inside an 8-mm Carotid Wallstent was used for all but 2 of the patients in the present study. It was thought that performing CAS using two overlapping Carotid Wallstents would produce an effect similar to that of a micromesh stent. Experiments were carried out using a silicone tube to test whether the use of two overlapping Carotid Wallstents would have the same effect as that of a micromesh stent. The results of the silicone tube experiment showed that the theoretical minimum and maximum free cell areas were 0.1102 mm^2 and 0.4408 mm^2, respectively (Figure 2), meaning that the free cell area was theoretically equivalent to or better than that of a micromesh stent.

Our double-stent technique differs from conventional CAS in the following three points. (1) The potential for the second stent to catch on the first stent during its introduction (2) The difficulty of positioning the second stent for placement (3) The potentially higher risk of luminal narrowing due to stent-in-stent placement, and of restenosis because of a larger amount of metal. With respect to (1), in 1 patient (2.9%) the second stent caught on the proximal edge of the first stent, making stent introduction difficult, but this was resolved by turning the patient's neck. Care is required when introducing the second stent. With respect to (2), because the lumen diameter of the distal healthy at the stenotic site was ≤6 mm and stenosis was located on the ICA in all patients but two cases, a 6 mm × 21 mm stent was used as the second stent in all cases in which the stenosis was located in the ICA. The key to positioning was not to attempt to place the distal edge of the second stent inside the first stent, but rather to place it so that the proximal edge of that stent was approximately one vertebral body from the site of minimum stenosis, to take account of shortening. As a result, optimal positioning and placement without malapposition were achieved in all cases. In some cases, the distal side of the second stent was positioned distal to the distal side of the first stent. With respect to (3), post-dilation was performed after stent placement in all cases and was confirmed by IVUS. The stenotic site was seen to be dilated by ≥ 3 mm in all patients, a similar level of dilation to that achieved by regular stenting. Follow-up ultrasound revealed 1 case of restenosis and 1 case of asymptomatic stent occlusion. The restenosis rate was thus 5.7% (2/35), similar to the 8.3%[19] reported for CAS using Carotid Wallstents. González et al[20] reported a stent occlusion rate of 2.6% in CAS for pseudo-occlusion. In our study as well, the one case of occlusion involved pseudo-occlusion. As restenosis after CAS usually occurred within 6 months, if this patient had undergone followed-up ultrasound within 6 months, restenosis might have discovered before carotid occlusion occurred.

It has been already reported that new ischemic lesions, even without a corresponding focal deficit, might lead to long-term clinical consequences, including cognitive decline and dementia[21]. Gensicke H et al.[22] also reported that new ischemic lesions are associated with an increased risk of recurrent cerebrovascular events after CAS. Thus, it is essential to reduce ischemic lesions as much as possible is essential in CAS. Several investigators who used DWI to detect clinically silent embolic lesions after conventional CAS reported that the incidence of new DWI lesions was 35.7–51%,[6,7,23]. Although all cases in our study had unstable plaque which is associated with a high risk of new DWI lesions, the incidence of the new ipsilateral

ischemic lesions was 28.6 %. However recent studies with C-Guard reported that new ipsilateral ischemic lesions occurred in 31%-37.0% of cases [9, 24]. Our results seemed be similar to or superior to those reported in the C-guard studies, although baseline characteristics of the patients were different. Overlapped double closed-cell stents might be an alternative to micromesh stent. Although the present study included only 35 patients, all were successfully treated, and none developed symptomatic ischemic complications, despite the fact that they all had unstable plaque lesions that were a high risk for PP. The DWI-positive rate and restenosis rate were also low. This may have been because the double stent had the same effect in restricting the occurrence of PP and preventing ischemic complications as that of a micromesh stent.

There are some limitations in the present study. First, this study had a small number of patients, and the mean length of follow-up was only 11.6 months. Second, PP was evaluated by IVUS alone in present study. If PP is evaluated by OCT which has much higher resolution than IVUS, OCT may provide more detail than clinically relevant. Thus, further investigations with a larger number of cases or with OCT may be needed to draw more definitive conclusions.

Conclusion

CAS using overlapped double stents for unstable plaque may be useful for preventing PP and ischemic complications.

Declaration of Conflicting Interests

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Table 1. Demographics and baseline characteristics	
Baseline and Procedural Characteristics (n=35)	
Age, years	75.8 ± 7
Male	29 (82.9)
Hypertension	31 (88.6)
Hyperlipidemia	25 (71.4)
Diabetes mellitus	12 (34.3)
Cigarette smoking, current	25 (71.4)
Previous myocardial infarction	6 (17.1)
Previous TIA	8 (22.9)
Femoral access	31 (88.6)

Brachial access	4 (11.4)
Target vessel	
Stenosis % (average)	83.5 ± 13.1
Right ICA	20 (57.1)
Left ICA	12 (34.3)
Right CCA	3 (8.6)
Lesion length, mm	17.7 ± 4.73
Protection used	
Distal filter protection alone	21 (60)
Proximal balloon protection and distal filter protection	14 (40)
Pre-dilation	28 (80)
Post-dilation	35 (100)
Post-dilation diameter, mm	4.01 ± 0.30
Procedure success	35 (100)
1st stent diameter×length, mm	
8×29	21 (60.0)
8×21	14 (40.0)
2nd stent diameter×length, mm	
6×22	33 (94.3)
8×21	2 (5.7)
Values are the mean ± SD, %, or n (%).TIA, transient ischemic attack ICA = internal carotid artery; CCA, common carotid artery	

Legends

Figure 1. Carotid artery stenting by the double-stent method using a MoMa Ultra and a Filterwire EZ stent to treat internal carotid artery stenosis with unstable plaque.

A. MR plaque imaging (T1W1)

A high-intensity signal area is evident at the origin of the left internal carotid artery, suggesting the presence of unstable plaque (arrow).

B. MR plaque imaging (T1W1)

Relative signal intensity was then measured for the plaque components relative to the sternocleidomastoid muscle on T1-weighted images., the relative signal intensity on T1-weighted images was at 2.4, suggesting the presence of unstable plaque (arrow).

C. Left common carotid artery angiogram (Lateral view). There is 81% stenosis of the origin of the left internal carotid artery by the NASCET criteria.

D. A Carotid Wallstent 8 mm × 29 mm is guided to cover the stenotic site, with proximal protection provided by a MoMa Ultra and filter protection by a Filterwire EZ.

E. First stent (Carotid Wallstent 8 mm × 29 mm) was placed.

F. Second stent (Carotid Wallstent 6 mm × 22 mm) guided inside the first stent.

G. Second stent (Carotid Wallstent 6 mm × 22 mm) was placed as a stent-in-stent.

H. Post-dilation was performed with a balloon catheter (4 mm × 40 mm).

I. Final angiography shows good vascular dilation at the stenotic site, with no obvious plaque protrusion.

J. Intravascular ultrasound (IVUS) (minimum lumen diameter at the lesion site). IVUS is performed after stent placement, and the absence of plaque protrusion is confirmed.

K. MRI diffusion-weighted imaging on the following day after CAS does not show any new high-intensity signal areas compared with before the procedure.

L. Left common carotid angiogram (Lateral view). Follow-up digital subtraction angiography 6 months after CAS does not show any restenosis.

Figure 2. Double Carotid Wallstent experiment using a silicone tube

A. An 8 mm × 29 mm Carotid Wallstent (CWS) was placed in a transparent tube with a 6-mm lumen (below). A 6 mm × 22 mm CWS is placed within the stent (above).

B. Enlargement of A. The cell size in the lower picture has been subdivided in the upper picture, reducing

the free cell size.

C. Diagram of the placement of the 6 mm × 22 mm CWS and 8 mm × 29 mm CWS.

The theoretical calculated value for the doubled CWSs is:

Simple minus area: CWS 8 mm – area of one side; 1.34 – (0.119 × 2 = 0.238) = 1.102 mm^2. The free cell area of the CWS 8 mm × 29 mm is divided into four areas:. If the expansion ratio is 4:2.5:2.5:1, the areas are 0.4408 mm^2, 0.2755 mm^2, 0.2755 mm^2, and 0.1102 mm^2, respectively.