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Original Article

The Effect of Stent Design on Plaque Protrusion after Carotid Artery Stenting

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Objective: The association between stent design and post-stent intravascular findings after carotid artery stenting (CAS) was evaluated.

Methods: Among the 79 patients who underwent CAS between March 2016 and June 2020 at our institution, we retrospectively analyzed 65 patients with full post-stent intravascular evaluation by both optical frequency domain imaging and angioscopy. All CAS procedures were performed under the flow reversal method, and the stent selection was determined by each operator's discretion, depending on the vessel anatomy or plaque characteristics. The patient's characteristics, plaque characteristics, ischemic complication, and post-stent intravascular findings (plaque protrusion, vessel wall apposition of stent) were compared between the closed-cell and open-cell stent groups.

Results: The closed-cell group (n = 34) had more high-risk plaques, such as symptomatic lesions or intraplaque hemorrhages, on MRI compared with the open-cell group (n = 31). There was no difference in the rate of ischemic complications between the groups. Although there was no difference in the frequency of plaque protrusion between the two, the maximum height of the protruded plaque was higher in the open-cell group (320 vs. 612 μm, p = 0.003) and incomplete apposition was higher in the closed-cell group (85.3 vs. 6.5%, p <0.0001).

Conclusion: The open-cell stent provided better apposition but had larger plaque protrusion. The need for a new hybrid stent that combines the merits of both open- and closed-cell stents was suggested.

Keywords carotid artery stenting, stent, plaque

Introduction

Carotid artery stenting (CAS) is a method of revascularization for symptomatic or asymptomatic internal carotid artery stenosis to prevent cerebral infarction and a minimally invasive alternative to carotid endarterectomy (CEA).

However, its superiority to CEA has not been demonstrated because the incidence of perioperative ischemic complications after CAS is higher than after CEA.[1–3)]

Distal embolism associated with plaque rupture has been suggested as one of the most probable causes of perioperative ischemic complications after CAS,[4,5)] and various strategies have been arranged to prevent it.

The plaques with intra-plaque hemorrhage is vulnerable and may rupture during the CAS procedure.[6)] If the risk of plaque rupture is considered to be high through preoperative evaluation of plaque characteristics by MRI, the surgical method may be better to be switched to CEA.[7)] However, CAS must be selected in high-risk patients for CEA such as elderly patients and those with high-position plaque. Perioperative antithrombotic therapy or the use of embolic protection device is effective to reduce the incidence of distal embolism, but it was observed even when using the proximal protection

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method, under which its incidence is reportedly the lowest.[8)]

There are various carotid artery stents of different designs. The open-cell stents have larger cell size and provide better vessel wall apposition than closed-cell stents. On the other hand, the incidence of perioperative ischemic complications is high,[9,10)] but the etiology remains to be clarified. In this study, we evaluated frequency, degree, and characteristics of intra-stent plaque protrusion after CAS and vessel wall apposition of stent using two intravascular imaging methods: optical frequency domain imaging (OFDI) and angioscopy, and compared the results between the two groups: open-cell and closed-cell stent groups.

Materials and Methods

Of the 85 patients who had undergone CAS at our hospital between March 2016 and June 2020, the subjects were 65 in whom both OFDI and angioscopy were performed after stenting, excluding 20 in whom sufficient assessment after stenting was impossible (n = 6, tortuous lesions; n = 2, blood contamination due to incomplete occlusion; n = 2, the use of distal protection; n = 7, carotid occlusion intolerance; and n = 3, physicians' discretion).

In all patients, preoperative evaluation of plaque characteristics using 3T MRI was performed before procedure. The intra-plaque signal intensity on the time-of-flight method and the plaque to sternocleidomastoid muscle signal intensity ratio on the magnetization-prepared rapid acquisition with gradient echo (MPRAGE) were measured. Patients with a signal intensity ratio of ≥1.3 were regarded as having significant intra-plaque hemorrhage.[11,12)]

Preoperative antiplatelet therapy with two or more drugs (aspirin, clopidogrel, and cilostazol) was performed for ≥1 week before surgery. Their antiplatelet effects were confirmed using a VerifyNow system (Werfen, Barcelona, Spain) in the morning on the day of surgery. When the effects were insufficient, some additional administration was conducted.

The CAS procedure was performed through the femoral artery using an Mo.Ma Ultra (Medtronic, Minneapolis, MN, USA), a proximal protection system, with the flow reversal method. After sheath insertion, a 5000 unit bolus infusion of heparin was administered, followed by maintenance-heparin infusion to achieve the activated coagulation time (ACT) ≥300. An additional dose of 1000 units was administered every hour until the end of the CAS procedure. The lesion was dilated with a percutaneous transluminal angioplasty (PTA) balloon measuring 3.5 to 4.5 mm. After the predilatation, one of the following stents was selected by each surgeon based on the plaque characteristics or vascular anatomy: Carotid Wallstent (Boston Scientific, Marlborough, MA, USA), PRECISE (Cordis, Santa Clara, CA, USA), or Protégé (Medtronic). Postdilation was added using a PTA balloon measuring 4.0 to 5.5 mm in reference to the distal vascular diameter only when ≥50% residual stenosis was present on intravascular ultrasound after stenting.

After stent implantation, intravascular assessment by OFDI (Lunawave/FastView; Terumo, Tokyo, Japan) and angioscopy (VISIBLE; iHeart, Tokyo, Japan) was performed under temporary proximal carotid occlusion.

Heparin was intravenously administered for 24 hours after CAS. Diffusion-weighted MRI after CAS was conducted during admission. The images were compared with the preoperative MRI findings to evaluate the presence of new ischemic lesions. Carotid ultrasonography was performed after 1, 3, and 6 months at the outpatient clinic. Patients with ≥50% intra-stent restenosis were regarded as having significant restenosis.

OFDI procedure

After stent insertion, an OFDI image wire was guided into the internal carotid artery distal to the site of stenting using a 0.014-inch guidewire. The external and common carotid artery balloons of the Mo.Ma Ultra system were dilated to block the blood flow. Subsequently, contrast medium diluted with physiological saline (1:1) was infused at a rate of 40 mL/5 sec using a motor-driven injector through a guiding catheter to rinse blood. After confirming the blood-free situation, 158 frame/sec images were accumulated for scanning of the vascular lumen while pulling back an OFDI wire at a rate of 20 mm/sec. The images were stored in a console for the following off-line quantitative analysis.

The maximum height (µm) of the plaque protruded from the inner surface of the stent, attenuation behind the protruded plaque,[4)] and the height (µm) and area (µm^2) of the gap between the stent and the inner wall of carotid artery were measured. Patients with a gap of ≥0.5 µm were regarded as showing incomplete apposition (**Fig. 1**).

Angioscopy

After OFDI, an Export aspiration catheter (Medtronic) was guided using a 0.014-inch guidewire, and an angioscopic

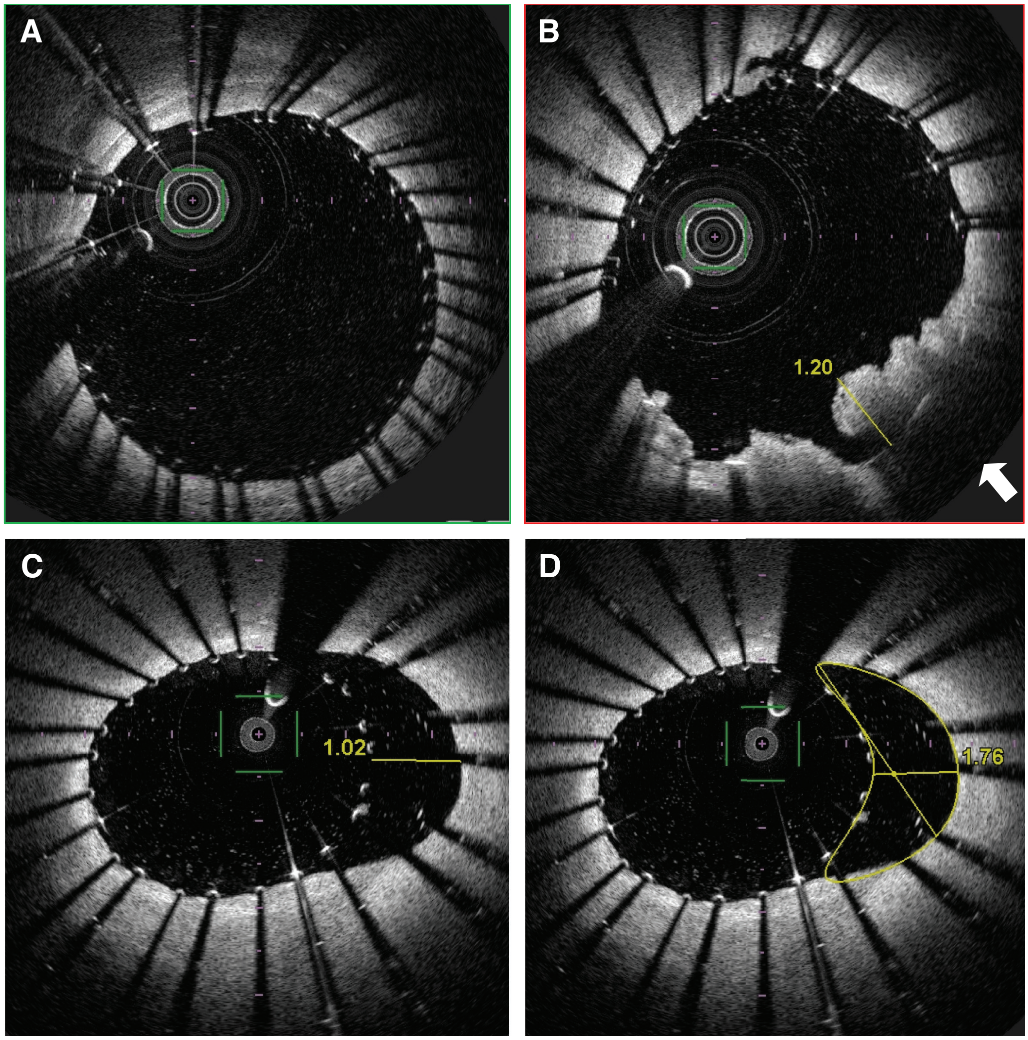

Fig. 1 Post-stent intravascular findings on OFDI. (**A**) Representative closed-cell stent case. OFDI showed no plaque protrusion and good apposition. (**B**) Representative open-cell stent case. OFDI showed plaque protrusion with attenuation (white arrow), and the height was 1200 µm. (**C** and **D**) Closed-cell stent case with incomplete apposition. Closed-cell stent case with incomplete apposition. The gap between the stent and the inner wall of the internal carotid artery was 1020 µm (**C**), and the gap area was 1760 µm^2 (**D**). OFDI: optical frequency domain imaging

catheter was inserted into its aspiration lumen and guided distal to the stent. The vascular lumen was examined while keeping the intra-stent lumen blood free by continuous and manual infusion of saline. The accumulated images were stored on a hard disc. An off-line qualitative analysis regarding the mobility of protruded plaques was performed (grade 1: no mobility, grade 2: blood flow-related mobility, and grade 3: marked mobility/rupture). Grade 3 patients were regarded as having significantly mobile plaque protrusion.

Statistical analysis

The patient background; clinical events, such as symptomatic cerebral infarction or asymptomatic ischemic lesions on MRI after CAS or restenosis after 6 months; and intravascular assessment findings after stenting (maximum height of protruded plaque, the height and area of a gap on OFDI, and mobility of the protruded plaque on angioscopy) were compared between the closed-cell (Carotid Wallstent) and open-cell (PRECISE and Protégé stent) stent groups. Concerning category variables, the Fisher's exact test or the chi-square test was used. Concerning continuous variables, the Wilcoxon's rank-sum test was used. For two-sided tests, a p-value of 0.05 was regarded as significant. JMP version 12 software (SAS Institute, Cary, NC, USA) was used. Prior to this study, its protocol was approved by the Ethics Review Board of our institution. Informed consent was obtained from all patients.

Table 1 Patients' characteristics

Variables	Closed-cell stent (n = 34)	Open-cell stent (n = 31)	p-value
Age	77.3 ± 1.23	74.5 ± 1.29	0.12
Female gender	5 (14.7%)	9 (29%)	0.23
Hypertension	29 (85.3%)	30 (96.8%)	0.36
Diabetes	13 (38.2%)	13 (41.9%)	1
Dyslipidemia	20 (58.8%)	23 (74.2%)	0.29
Coronary artery disease	13 (38.2%)	11 (36.7%)	0.79
Peripheral artery disease	9 (26.4%)	9 (31%)	1
Smoker	22 (64.7%)	21 (67.7%)	1
Left side	12 (35.3%)	16 (51.6%)	0.22
% stenosis	85.9 ± 1.66	82.80%	0.20
Symptomatic lesion	24 (70.6%)	14 (45.2%)	0.047
<2 weeks from stroke onset	3 (8.8%)	7 (21%)	0.4
High intensity signal on TOF	14 (41.2%)	5 (16.7%)	0.028
Signal intensity ratio on MPRAGE	1.94 ± 0.23	1.82 ± 0.23	0.72
SIR-MPRAGE >1.3	16 (47%)	16 (51.6%)	1

MPRAGE: magnetization-prepared rapid acquisition with gradient echo; SIR: signal intensity ratio (plaque to sternocleidomastoid muscle); TOF: time-of-flight

Results

The closed-cell stent group consisted of 34 patients (all patients: Carotid Wallstent). The open-cell stent group consisted of 31 patients (PRECISE stent: 26 patients and Protégé stent: 5 patients). There were no differences in the mean age, sex, or concomitant diseases as background factors between the two groups. However, in the closed-cell stent group, the rate of symptomatic lesions (70.6 vs. 45.2%, respectively, p = 0.04) and patients with a high intra-plaque signal intensity on time-of-flight imaging (41.2 vs. 16.7%, respectively, p = 0.03) were significantly higher than those in the open-cell stent group. The closed-cell stents had been inserted into higher-risk lesions (**Table 1**).

For intravascular assessment findings after CAS, there was no difference in the frequency of plaque protrusion between the two groups (73.5 vs. 83.9%, respectively, p = 0.38). There was also no difference in the frequency of attenuation suggestive of intra-plaque hemorrhage (36 vs. 65.4%, respectively, p = 0.051), but the height of protruded plaques was significantly higher in the open-cell stent group (320 vs. 612 µm, respectively, p = 0.003). Angioscopy showed that protruding plaques measuring >520 µm in height were mobile. In the presence of blood flow, plaques became violently mobile, being fragmented or scattered.[13]

On the other hand, the rate of patients with incomplete vessel wall apposition of stent was significantly higher in the closed-cell stent group (85.3 vs. 6.5%, respectively, p <0.0001).

Concerning postoperative clinical events, there were no differences in the appearance of a new high-signal-intensity area on diffusion-weighted MRI (52.9 vs. 61.3%, respectively, p = 0.62), incidence of symptomatic ischemic complications (2.9 vs. 3.2%, respectively, p = 1), or incidence of restenosis after 6 months (11.5 vs. 3.45%, respectively, p = 0.33) (**Table 2**).

Discussion

In this study, the closed-cell stent group comprised patients with higher-risk plaques more, but there was no difference in the incidence of clinical events after surgery. Detailed postoperative vascular assessment using OFDI and angioscopy did not show any difference in the frequency of plaque protrusion between the two groups. However, the height of protruded plaques was significantly higher in the open-cell stent group. The vessel wall apposition of stent was significantly better in the closed-cell stent group.

The merits of closed-cell stents include plaque-protrusion-reducing effects probably due to the small cell area. Bosiers et al. reported that the incidence of postoperative ischemic complications increased with an increase in the stent cell size.[9] The cell size of the PRECISE stent is about 5 times larger than that of the Carotid Wallstent; therefore, the plaque protrusion potential of open-cell stents can be readily imagined. The cell area of the Protégé stent is the largest among the stents used in this study. When comparing 26 patients with the PRECISE stent and 5 patients with the Protégé stent, there were no differences in the

Table 2 Post-stenting intravascular findings and clinical events

Variables	Closed-cell stent (n = 34)	Open-cell stent (n = 31)	p-value
Post-stenting intravascular findings			
PP	25 (73.5%)	26 (83.9%)	0.375
With attenuation	9/25 (36%)	17 /26 (65.4%)	0.051
Height of PP (μm)	320 ± 64	612 ± 68	0.003
Incomplete apposition	29 (85.3%)	2 (6.5%)	<0.0001
Gap height (μm)	0.89 ± 0.09	0.09 ± 0.09	<0.0001
Gap area (μm^2)	1.81 ± 0.157	0.16 ± 0.16	<0.0001
Mobile PP on angioscopy	5 (14.7%)	8 (25.8%)	0.356
Clinical events			
New high intensity area on DWI	18 (52.9%)	19 (61.3%)	0.62
Periprocedural ischemic complication	1 (2.9%)	1 (3.2%)	1
Restenosis	3 (11.5%)	1 (3.45%)	0.33

DWI: diffusion-weighted image; PP: plaque protrusion

frequency of plaque protrusion (84.6 vs. 80%, respectively), height (615 vs. 596 μm, respectively), or mobility (23.1 vs. 40%, respectively).

On the other hand, the merit of open-cell stents is their better vessel wall apposition of stent. These stents are very effective for high-angled lesions. Furthermore, as their long-term effects, the incidence of restenosis tends to be low. Müller et al. examined the long-term incidences of restenosis and ipsilateral stroke in closed-cell and open-cell stent groups among the patients enrolled in the International Carotid Stenting Study.[14] They reported that the incidence of moderate (50 to <70%) restenosis was significantly lower in the open-cell stent group, although there were no differences in the incidences of ≥70% (severe) restenosis or ipsilateral stroke between the two groups.

Furthermore, the demerit of closed-cell stents is straightening of vessels. When implanting a closed-cell stent into an angled lesion, the distal internal carotid artery may kink by accordion effect,[15] leading to carotid occlusion[15] or incomplete vascular wall apposition of the stent. A study suggested the involvement of such incomplete apposition in postoperative microembolism.[16]

Currently, stents that have various designs are available. In addition to closed-cell and open-cell stents, hybrid stents consisting of a combination of these have been successively developed and commoditized. In addition to the CASPER stent (Terumo) with a two-layer structure consisting of different mesh stents, which has been introduced in Japan, the CGuard stent (InspireMD, Tel Aviv, Israel), as a dual-layer stent consisting of a MicroNet-covered open-cell stent, is present. A single-arm study with the CGuard stent showed that this stent was also effective for markedly calcified lesions involving a >3/4 circumference, as indicated for non-calcified lesions.[17] A design to utilize the respective merits of closed-cell and open-cell stents and compensate for their demerits should be developed. The results of this study also suggest that a hybrid design in which an open-cell stent, of which the vessel wall apposition is superior, is placed on the outside and a closed-cell stent, of which the preventive effects on plaque protrusion are marked, is placed on the inside is appropriate.

Conclusion

The vessel wall apposition of a closed-cell stent was inferior, but the height of protruded plaque was significantly low. The vessel wall apposition of an open-cell stent was superior, but the frequency of plaque protrusion was high. The results suggest the necessity of a new hybrid stent in which the merits of the two stents are combined for improving the results of CAS.

Disclosure Statement

The authors declare no conflicts of interest.

References

1) Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010; 363: 11–23.
2) International Carotid Stenting Study investigators: Ederle J, Dobson J, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010; 375: 985–997.

3) Gargiulo G, Sannino A, Stabile E, et al. New cerebral lesions at magnetic resonance imaging after carotid artery stenting versus endarterectomy: an updated meta-analysis. *PLoS One* 2015; 10: e0129209.

4) Funatsu N, Enomoto Y, Egashira Y, et al. Tissue protrusion with attenuation is associated with ischemic brain lesions after carotid artery stenting. *Stroke* 2020; 51: 327–330.

5) Kotsugi M, Takayama K, Myouchin K, et al. Carotid artery stenting: investigation of plaque protrusion incidence and prognosis. *JACC Cardiovasc Interv* 2017; 10: 824–831.

6) Yoshimura S, Yamada K, Kawasaki M, et al. High-intensity signal on time-of-flight magnetic resonance angiography indicates carotid plaques at high risk for cerebral embolism during stenting. *Stroke* 2011; 42: 3132–3137.

7) Yoshimura S, Yamada K, Kawasaki M, et al. Selection of carotid artery stenting or endarterectomy based on magnetic resonance plaque imaging reduced periprocedural adverse events. *J Stroke Cerebrovasc Dis* 2013; 22: 1082–1087.

8) Stabile E, Sannino A, Schiattarella GG, et al. Cerebral embolic lesions detected with diffusion-weighted magnetic resonance imaging following carotid artery stenting: a meta-analysis of 8 studies comparing filter cerebral protection and proximal balloon occlusion. *JACC Cardiovasc Interv* 2014; 7: 1177–1183.

9) Bosiers M, de Donato G, Deloose K, et al. Does free cell area influence the outcome in carotid artery stenting? *Eur J Vasc Endovasc Surg* 2007; 33: 135–141; discussion 142–143.

10) Jansen O, Fiehler J, Hartmann M, et al. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. *Stroke* 2009; 40: 841–846.

11) Liu J, Balu N, Hippe DS, et al. Semi-automatic carotid intraplaque hemorrhage detection and quantification on Magnetization-Prepared Rapid Acquisition Gradient-Echo (MP-RAGE) with optimized threshold selection. *J Cardiovasc Magn Reson* 2016; 18: 41.

12) Saito A, Sasaki M, Ogasawara K, et al. Carotid plaque signal differences among four kinds of T1-weighted magnetic resonance imaging techniques: a histopathological correlation study. *Neuroradiology* 2012; 54: 1187–1194.

13) Enomoto Y, Egashira Y, Iwama T. What's happening in carotid stent? A case report of prominent plaque protrusion after carotid artery stenting observed on angioscopy. *Catheter Cardiovasc Interv* 2021; 97: E532–E535.

14) Müller MD, Gregson J, McCabe DJH, et al. Stent design, restenosis and recurrent stroke after carotid artery stenting in the international carotid stenting study. *Stroke* 2019; 50: 3013–3020.

15) Müller-Hülsbeck S, Schäfer PJ, Charalambous N, et al. Comparison of carotid stents: an in-vitro experiment focusing on stent design. *J Endovasc Ther* 2009; 16: 168–177.

16) Ito Y, Kato N, Nakai Y, et al. The relation between tortuosity of carotid artery and microembolization during carotid artery stenting using a closed-cell stent. *JNET J Neuroendovasc Ther* 2013; 7: 75–80. (in Japanese)

17) Mazurek A, Partyka L, Trystula M, et al. Highly-calcific carotid lesions endovascular management in symptomatic and increased-stroke-risk asymptomatic patients using the CGuard™ dual-layer carotid stent system: analysis from the PARADIGM study. *Catheter Cardiovasc Interv* 2019; 94: 149–156.