

# Triggering of Carotid Sinus Reflex during Deployment of the Flow-diverter Device

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## Abstract

The carotid sinus reflex (CSR) is a rare complication of the Pipeline Embolization Device (PED) deployment. No study has assessed the potential risk factors in a case series. The purpose of this study was to examine CSR triggering during PED deployment. Thirty-seven consecutive patients who underwent PED deployment were included. All procedures were performed under local anesthesia with mild sedation. We retrospectively analyzed patient characteristics, PED deployment time, and vital signs during the procedure. The vital signs included the pulse rate (PR) and systolic blood pressure (SBP) obtained at three timepoints (pre-deployment, during deployment, post-deployment). We examined the triggering of the CSR during PED deployment by comparing the vital signs at the three timepoints. Moreover, risk factors for CSR were analyzed with univariate analysis. The patients' average age was 66.3 years. The average size of the aneurysm was 18.0 mm. Six patients (16.2%) showed a decline in the SBP or PR defined as CSR. One patient had a transient cardiac arrest and two had severe transient bradycardia. Deployment into the ophthalmic segment of the internal carotid artery (C2 segment) aneurysm ( $p = 0.022$ ), prolonged PED deployment time more than 14.5 minutes ( $p = 0.005$ ), and an acute angle of the anterior genu less than 51.5 degrees ( $p = 0.005$ ) were risk factors in triggering CSR. CSR may be triggered during PED deployment under local anesthesia with mild sedation. Deployment to the C2 segment aneurysm, prolonged PED deployment time, and an acute angle of the anterior genu were associated with CSR triggering.

Keywords: aneurysm, bradycardia, cardiac arrest, complication, flow diverter

## Introduction

The deployment of the flow-diverter device, the Pipeline Embolization Device (PED; Medtronic, Minneapolis, MN, USA), is an increasingly common treatment for internal carotid artery (ICA) aneurysms, particularly when conventional stent-assisted coil embolization is difficult to use. Its safety and efficacy have been established in prospective or large-volume studies.<sup>1,2)</sup>

Ischemic stroke, perforator infarction, rupture of the aneurysm, and parenchymal hemorrhage were reported as common complications of PED deployment.<sup>3,4)</sup>

We previously reported a case complicated by cardiac arrest during PED deployment induced by triggering of the carotid sinus reflex (CSR).<sup>5)</sup> We have observed bradycardia and hypotension during PED deployment under local anesthesia with mild sedation and consider that the carotid sinus is stimulated by pushing the delivery catheter further in to achieve adequate PED expansion to the vessel wall.

The purpose of this study was to examine the relationship between the PED deployment and the potential triggering of the CSR by retrospectively analyzing patients' vital signs during the procedure.

## Methods

### Patient data collection

Thirty-seven consecutive patients who underwent PED deployment at our institution from September

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2017 to August 2019 were enrolled. We extracted the following data from the medical and intervention records: patient demographics (age and sex); laterality, size, and location (the segment of the ICA) of the aneurysm; anatomical geometry of the parental artery (angle of the anterior and posterior genu in the carotid siphon); the guiding catheter and the guiding sheath; PED deployment time; and pulse rate (PR) and systolic blood pressure (SBP) pre-deployment, during deployment, and post-deployment of the PED.

### Procedure of PED deployment

All procedures were performed after femoral puncture under local anesthesia with 1% lidocaine. Prior to puncture, pentazocine (15 mg) and hydroxyzine pamoate (25 mg) were administered intravenously. Mild sedation with dexmedetomidine hydrochloride 0.3 µg/kg/hour (after loading infusion of 6 µg/kg/hour for 5 minutes) was performed to maintain the Richmond Agitation Sedation Scale score at -2 during the procedure. Guiding catheters or sheaths were navigated into the ICA in all cases. Patients' vital signs during the procedure were continuously monitored (Life Scope, BSM-9101; Nihon Kohden, Tokyo, Japan) with blood pressure (BP) being measured using a non-invasive BP monitoring device every minute.

### Definition of the data

The angles of the anterior and posterior genua were measured with the vertex originating from the corresponding wall of the carotid siphon (anterior or posterior) and the vectors along the long axis of the ICA (Fig. 1).

The PED deployment time was defined as the period from the start of the PED opening to the end

of the PED deployment. SBP and PR were recorded at the start and end of the deployment procedure and referred to as pre- and post-deployment SBP and PR, respectively. SBP and PR during the PED deployment were defined as the lowest values during deployment. We defined the activation of the CSR as a fluctuation of SBP of >20 mmHg or fluctuation of PR of >20 beats per minute (bpm) during deployment compared with the pre- and post-SBP.

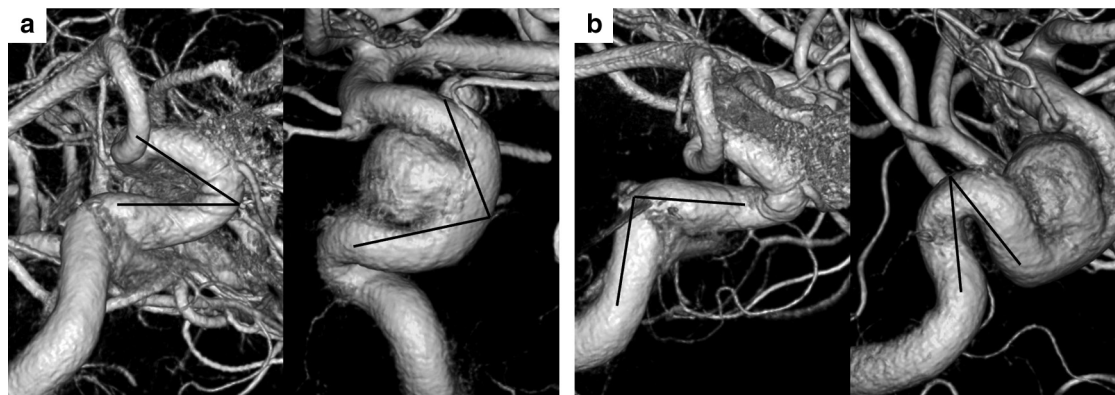
### Statistical analysis

By comparing the SBP and PR obtained at the three timepoints, we examined the possibility of CSR being triggered during PED deployment. Furthermore, we identified patients with and without CSR and analyzed potential risk factors for triggering CSR.

Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as numbers (percentages). We used univariate analysis to compare the variables between patients with and without CSR to identify potential risk factors for triggering CSR. Continuous variables between groups were compared using the Student's t-test. Categorical variables were compared using the chi-square test and Fisher's exact probability test. For continuous variables that showed statistically significant differences in the univariate analysis, receiver-operating characteristic (ROC) analysis were performed, and the cutoff values were calculated by the Youden index. Statistical significance was set at a p-value <0.05. Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

### Ethical approval

This study has been approved by the local ethics committee (IRB ID: 2019-0523). Informed consent



**Fig. 1** Measurement of anatomical geometry in the cavernous ICA by three-dimensional rotation angiography. a) The angle of the anterior genu. (35 and 90 degrees, respectively). b) The angle of the posterior genu. (86 and 35 degrees, respectively). ICA: internal carotid artery.

was obtained in the form of the opt-out on the website.

## Results

The patients' average age was 66.3 years, and 32 (86.5 %) patients were male. The aneurysm was on the right in 15 (40.5 %) patients, and the locations were as follows: ophthalmic segment of the ICA (C2) in 9 (24.3 %) patients, clinoid segment of the ICA (C3) in 5 (13.5 %) patients, and cavernous segment of the ICA (C4) in 23 (62.2 %) patients. The average aneurysm size was 18.0 mm. The guiding system entailed an 8-Fr guiding catheter in 31 (83.8 %) patients and a 6-Fr ultra-long sheath in 6 (16.2 %) patients. The Navien (Medtronic) was selected as the distal access catheter in all patients. Deployment was successfully completed in 36 patients. In 1 patient, deployment was abandoned, and stent-assisted coil embolization was performed instead, as it was difficult to achieve good adhesion of the PED to the vessel wall. The average time needed to deploy the PED was 15.9 minutes in all patients (Table 1).

The mean SBP was 116.2 mmHg pre-deployment, 100.5 mmHg during deployment, and 110.78 mmHg post-deployment, and the mean PR was 68.8, 63.5, and 66.2 bpm, respectively. The SBP decreased during the deployment of the PED ( $p = 0.005$  for the SBP during deployment vs. pre-deployment;  $p = 0.050$  for the SBP during deployment vs. post-deployment) However, the PR was not statistically different among the three timepoints (Fig. 2).

In our case series, 6 (16.2 %) patients met our criteria of a CSR (3 showed a decline of the SBP and PR, and 3 showed a decline of the SBP). In these patients, 1 had transient cardiac arrest, and 2 had severe transient bradycardia, but the normal hemodynamics were immediately restored by pulling down the catheter system to reduce the force toward the vessel wall. Statistically significant differences between patients with and without CSR were observed in the univariate analysis of potential risk factors for triggering of the CSR: deployment to the C2 segment aneurysm ( $p = 0.022$ ), acute angle of the anterior genu in the ICA siphon ( $p = 0.007$ ), and PED deployment time ( $p = 0.041$ ). The other factors were not statistically different between the two groups (Table 2). The ROC analysis for PED deployment time and area under curve for the angle of the anterior genu were 0.79 and 0.85, respectively. The cutoff values for the CSR risk factors were 14.5 minutes and 51.5 degrees (Fig. 3). When the PED deployment time and the angle of the anterior genu were classified into the two categorical variables by the cutoff values of

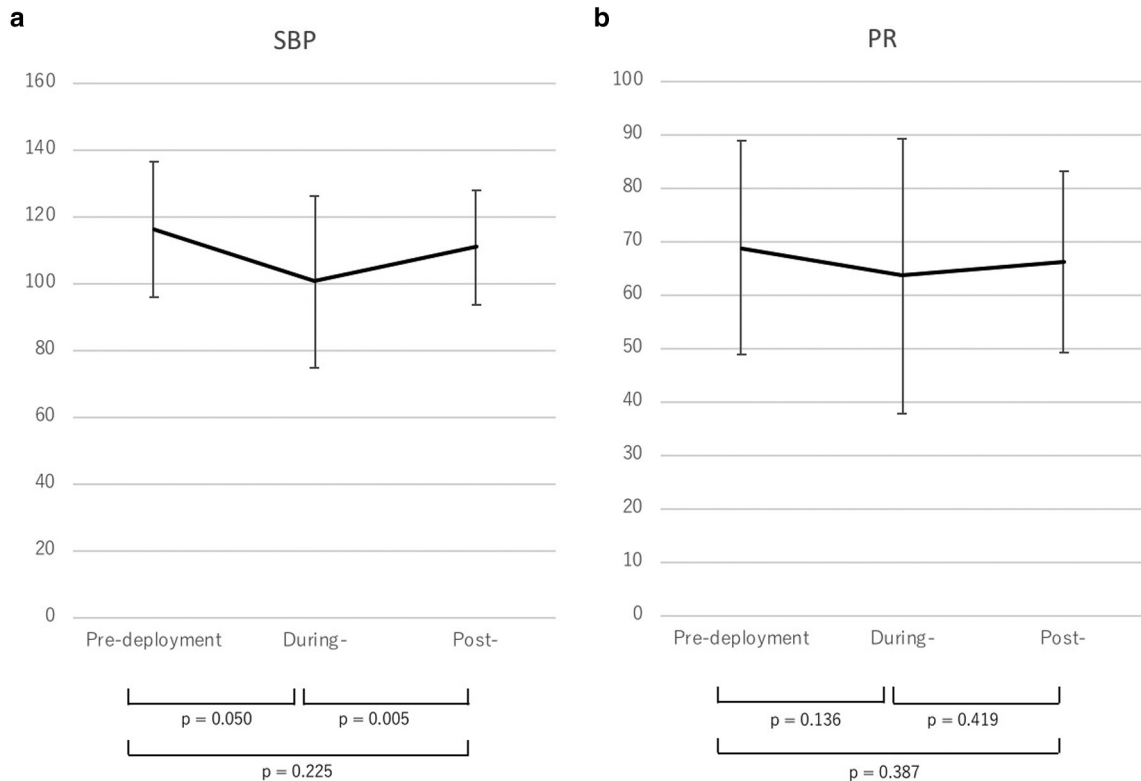
**Table 1 Patients characteristics**

n	37
Age	66.3 ± 12.2
Sex (male)	5 (13.5)
Laterality (right)	15 (40.5)
Aneurysm location	
C2	9 (24.3)
C3	5 (13.5)
C4	23 (62.2)
Angle of the ICA siphon	
Anterior genu	56.4 ± 18.7
Posterior genu	79.2 ± 26.6
Size of the aneurysm	18.0 ± 5.9
Guiding catheter and guiding sheath	
8F guiding catheter	31(83.8)
6F guiding sheath	6 (16.2)
Distal access catheter	
5F Navien	32 (86.5)
6F Navien	5 (13.5)
Size of the PED (mm)	
~3.75	5 (13.5)
4–4.75	23 (62.2)
5	9 (24.3)
Length of the PED (mm)	
~18	15 (40.5)
20–25	14 (37.8)
30–35	8 (21.6)
Successfulness of deployment	36 (97.3)
PED deployment time	15.9 ± 8.5
Blood pressure	
Pre deployment	116.2 ± 20.1
During	100.5 ± 25.8
Post deployment	110.8 ± 17.0
Pulse rate	
Pre deployment	68.8 ± 13.5
During	63.5 ± 16.1
Post deployment	66.2 ± 11.7

Continuous variables are presented as mean ± SD. Categorical variables are presented as n (%).

C2: ophthalmic segment of the internal carotid artery, C3: clinoid segment of the internal carotid artery, C4: cavernous segment of the internal carotid artery, F: French, ICA: internal carotid artery, n: number, PED: Pipeline Embolization Device.

14.5 minutes and 51.5 degrees, respectively, prolonged PED deployment time of more than 14.5 minutes and acute angle of the anterior genu of less than 51.5 degrees



**Fig. 2** Changes in the SBP and pulse rate pre-deployment, during deployment, and post-deployment of the PED in patients ( $n = 37$ ) with intracranial aneurysms. SBP during the procedure. The mean SBP values pre-deployment, during deployment, and post-deployment were 116.2, 100.5, and 110.8 mmHg, respectively. Lower SBP values were observed during PED deployment than before and after PED deployment ( $p = 0.005$  for SBP during deployment vs. pre-deployment;  $p = 0.05$  for SBP during deployment vs. post-deployment). PR during the procedure. The mean PR values pre-deployment, during deployment, and post-deployment were 68.8, 63.5, and 66.2 bpm, respectively. The PR was not statistically different among the three timepoints. bpm: beats per minute, PED: Pipeline Embolization Device, PR: pulse rate, SBP: systolic blood pressure.

were the risk factors for triggering the CSR (6/17 [35.3%] vs. 0/20 [0%];  $p = 0.005$  in both groups).

## Discussion

Our retrospective analysis of 37 patients at our institution who underwent PED deployment under local anesthesia with mild sedation to treat intracranial cerebral aneurysms showed that CSR occurred in 6 (16.2%) patients. Moreover, the risk factors for CSR in our case series were prolonged PED deployment time especially more than 14.5 minutes, deployment to the C2 segment aneurysm of the ICA, and an acute angle of the anterior genu of less than 52.5 degrees.

Flow-diverter device deployment was reported to have an overall complication rate of 17.0%, with PED deployment accounting for 16.0% of all complications, 14.8% of which were categorized as severe, according to a recent meta-analysis.<sup>3)</sup> Ischemic stroke,

perforator infarction, rupture of the aneurysm, and parenchymal hemorrhage are common complications. As PED deployment requires considerably more technical skills than conventional stents, rare unexpected complications have also been reported. Miyachi et al.<sup>6)</sup> described a case in which repeated attempts to deploy PEDs resulted in ties among the devices because of the complicated anatomical course with multiple turns to cross the aneurysm. Other complications described were a case of retinal hemorrhage after treating an ophthalmic segment aneurysm, a case of a delivery wire being trapped within the deployed PED and then broken during the attempted withdrawal, and five cases of spontaneous delayed migration or PED shortening.<sup>7-9)</sup> However, there is no report of CSR as a complication of PED deployment other than our previous case report.<sup>5)</sup> Therefore, this is the first study investigating the relationship between triggering of the CSR and PED deployment.

**Table 2 Comparison of the characteristics between patients with and without CSR**

	CSR	w/o CSR	p
n	6 (16.2)	31 (83.8)	
Age	63.2 ± 16.2	66.9 ± 13.0	0.480
Sex (male)	1 (16.7)	4 (12.9)	1.000
Laterality (right)	2 (33.3)	13 (41.9)	1.000
Location			
C2	4 (66.7)	5 (16.1)	0.022
C3	0 (0)	5 (16.1)	0.567
C4	2 (33.3)	21 (67.7)	0.173
Angle of the ICA siphon			
Anterior genu	38.0 ± 8.1	60.0 ± 18.1	0.007
Posterior genu	81.0 ± 23.5	80.2 ± 27.7	0.946
Size of the aneurysm	13.7 ± 4.6	18.8 ± 5.8	0.055
GC and GS			
8F GC	6 (100)	25 (80.6)	0.561
6F GS	0 (0)	6 (19.3)	0.561
DAC			
5F N	4 (66.7)	28 (90.3)	0.177
6F N	2 (33.3)	3 (9.7)	0.177
FD size	4.6 ± 0.3	4.3 ± 0.5	0.290
FD length	22.7 ± 7.0	22.2 ± 6.9	0.932
Pre SBP	108.5 ± 8.7	117.6 ± 21.5	0.322
Pre PR	68.0 ± 12.9	68.9 ± 13.7	0.881
PED deployment time	22.5 ± 9.1	14.6 ± 7.8	0.041

Continuous variables are presented as mean ± SD. Categorical variables are presented as n (%).

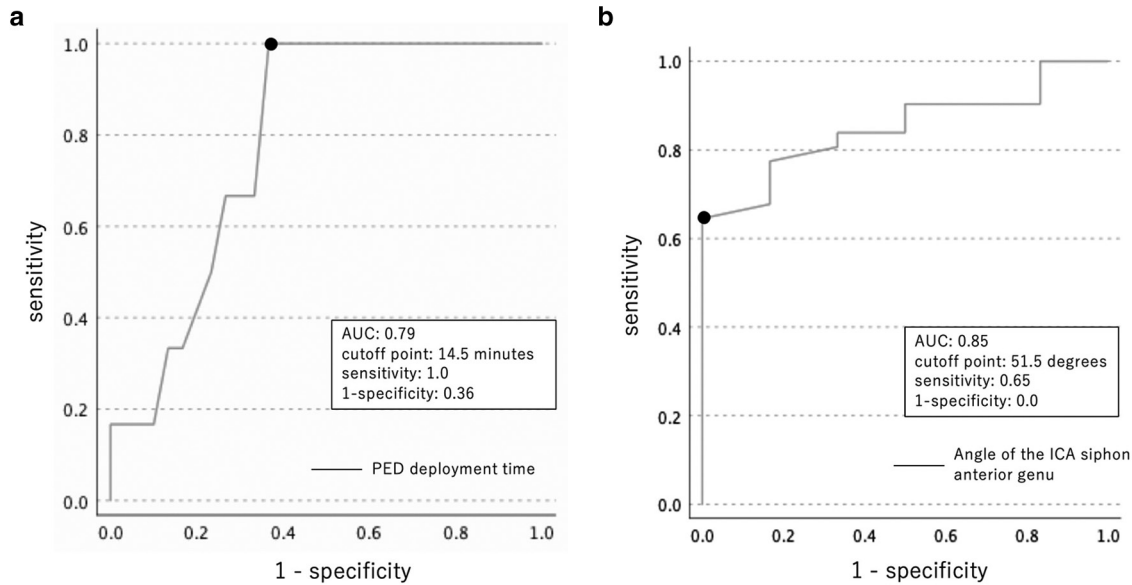
C2: ophthalmic segment of the internal carotid artery, C3: clinoid segment of the internal carotid artery, C4: cavernous segment of the internal carotid artery, CSR: carotid sinus reflex, DAC: distal access catheter, F: French, FD: flow diverter, GC: guiding catheter, GS: guiding sheath, ICA: internal carotid artery, n: number, N: Navien, pre PR: pre-deployment pulse rate, pre SBP: pre-deployment systolic blood pressure, w/o: without.

Triggering of the CSR commonly occurs during carotid artery stenting (CAS). Mylonas et al.<sup>10)</sup> reported that 39% of patients had hemodynamic instability during CAS. The definition of the CSR during CAS differs among studies, such as a decrease from the baseline SBP of >20–50 mmHg, an SBP of <80–90 mmHg, a decrease from the baseline PR of >20 bpm, and PR of <50–60 bpm.<sup>10)</sup> We defined the CSR as an SBP decrease of >20 mmHg or PR decrease of >20 bpm during deployment compared to the

pre- and post-deployment SBP. Our rationale behind this definition was that the SBP and PR during PED deployment performed under local anesthesia and intravenous sedation tend to be lower than the SBP during CAS, which is usually performed under local anesthesia. Moreover, as it is possible that dexmedetomidine could lower the SBP, we compared the SBP during deployment not only with the pre-deployment SBP but also with the post-deployment SBP. As a result, 16.2% of our patients met the criteria of a CSR.

Two distinct mechanisms that may trigger the CSR during CAS are described. One is the transient mechanical stretch of the carotid sinus baroreceptors during balloon inflation, which may be the cause of rapid and transient hemodynamic instability during the procedure. The other is continuous stretching caused by a self-expanding stent, which may be prolonged in some cases.<sup>11)</sup> During PED deployment, we suspect that the similar mechanism of transient stretching by balloon inflation in CAS is involved. The delivery system of the PED is pushed further in and may be bent laterally to the curved vessel wall to achieve adequate PED expansion. This action may stimulate the carotid sinus baroreceptors at the bifurcation of the carotid artery during the procedure. The CSR will, therefore, only be triggered temporarily during the procedure and is less likely to become a permanent clinical problem if appropriately managed during the procedure. However, it may still cause serious complications, such as cardiac arrest.

In the univariate analysis of our case series, PED deployment to the C2 segment, an acute angle of the anterior genu, and prolonged PED deployment time were risk factors for triggering the CSR. During the PED deployment, pushing the catheter inward might be necessary to achieve adequate opening of the PED and to increase the metal coverage ratio of the aneurysmal neck. Deployment into the C2 aneurysms is more of a challenge compared to C3/4 aneurysms, since the C2 aneurysms are located only in the distal portion of the anterior genu. Therefore, the force with which the catheter system is pushed inward and toward the proximal bend of the vessel wall becomes large in the deployment into the C2 aneurysms, to transmit the same radial force to the PED opening adequately. This difference may trigger the CSR due to stimulation of the baroreceptors. Considering the acute angle of the anterior genu, Lin et al. previously reported that cavernous ICA tortuosity, based on the geometry of the anterior and posterior genu angle, correlates with PED deployment complexity.<sup>12)</sup> In their report, fluoroscopy time was long and the frequency of encountering



**Fig. 3** ROC curve analysis: Prediction of the CSR risk factor. ROC analysis for the PED deployment time. AUC was 0.79. Cutoff value of the PED deployment time was 14.5 minutes, which was calculated by the Youden index (sensitivity was 1.0 and specificity was 0.64). ROC analysis for the angle of the ICA siphon anterior genu. AUC was 0.85. Cutoff value of the angle was 51.5 degrees (sensitivity was 0.65 and specificity was 1.0). AUC: area under curve, CSR: carotid sinus reflex, ICA: internal carotid artery, PED: Pipeline Embolization Device, ROC: receiver operating characteristic.

technical complexities increased, including PED twist, intraprocedural removal of PED, and balloon expansion in the deployed PED with incomplete adhesion when the cavernous ICA was so tortuous that the angles of the anterior and posterior genua were acute.<sup>12)</sup> In our study, regarding the anatomical geometry, an acute angle of the anterior genua was related to the CSR. Since it was an indication of difficulty in the deployment procedure, frequent push-pull movements of the catheter, and subsequent prolonged deployment time from the previous study, deployment to an acute angle of the anterior genua was likely to trigger the CSR. A prolonged PED deployment time more than 14.5 minutes also indicated a difficulty in deployment, but it was likely a confounding factor of the anatomical features that are difficult to deploy. The size and length of the PED are related to the difficulty in the deployment but were not found to be risk factors for triggering the CSR in our case series. In studies on the CSR in CAS, old age (especially ages >77 years) and a medical history of coronary artery disease and calcified plaques (particularly symptomatic calcified plaques) were reported as risk factors.<sup>10,11,13)</sup> We did not find any differences in these factors between patients with and without CSR.

Given that the flow-diverting treatment for intracranial aneurysms is increasingly performed,

awareness of the potential complications of this procedure and their adequate management is critical. When CSR is suspected, slightly pulling down the delivery catheter until the tension in the carotid sinus decreases has been recommended as the first step in the management of CSR.<sup>5)</sup> In our case series, the normal hemodynamics were immediately restored in all cases of severe CSR. The prophylactic use of atropine has been reported to be effective in preventing the triggering of the CSR during CAS.<sup>14)</sup> It may also be effective when there is a possibility of triggering the CSR during PED deployment. However, the most important factor in the management of CSR complications is to recognize the possibility that CSR can occur during the procedure and prevent it before it progresses into a serious complication. The operator should carefully monitor the vital signs during the procedure. Though the principle of the procedure for PED opening are push-pull maneuvers, excessive pushing maneuvers should be avoided not only for the prevention of the CSR but also as a general principle of the endovascular procedure. When it is difficult to achieve adequate partial apposition to the vessel wall, operators should not restrict themselves to only push-pull maneuvers but also make full use of useful deploying techniques such as “wagging” or post balloon expansion.<sup>15)</sup> Balloon expansion of the

PED was an effective option for deployment and was performed in about 20% of the cases in a previous multicenter retrospective study of the PED.<sup>16)</sup> Though the prolonged PED deployment time of more than 14.5 minutes was the result of the deployment procedure, C2 segment aneurysm and acute angle of the ICA anterior genu were easy to identify beforehand. Therefore, these should be noted as risk factors before the PED deployment. In high CSR risk cases, since general anesthesia is mainly used in PED deployment and similar associated complications have not been previously reported, it may be effective to choose general anesthesia for preventing the CSR. General anesthesia may suppress the autonomous nervous system and, therewith, the activity of the baroreceptors. On the other hand, it is well known that the damage to the carotid sinus baroreceptors during carotid artery endarterectomy under general anesthesia can trigger the CSR.<sup>17)</sup> Consequently, though incident rate and degree of the CSR were low and mild compared to local anesthesia, there was some possibility that CSR may be observed during PED deployment under general anesthesia. In our experience, the CSR during the procedure was properly managed even under local anesthesia by carefully observing the vital signs, avoiding excessive push-pull maneuvers during the usual deployment procedure, and reducing the tension by pulling down the catheter when CSR is suspected. However, general anesthesia should be considered for preventing the CSR in high CSR risk cases.

This study has some limitations. First, this study is limited by its small sample size and retrospective design. Second, the BP was measured only every minute using non-invasive BP cuffs. Therefore, there is a possibility that we underestimate the entire degree of the actual BP fluctuation during the procedure. However, the fluctuation itself is recorded. More details may be observed with continuous arterial BP monitoring. Third, since we performed the procedure under local anesthesia with mild sedation, we cannot comment on whether CSR occurs under general anesthesia. PED deployment is performed under general anesthesia in most institutions; however, the use of local anesthesia may increase in the future along with conventional stent-assisted coil embolization. Currently, the complications associated with the deployment of PED under local anesthesia are largely unknown; therefore, it is very important to recognize the CSR as a complication of PED deployment. Further well-designed and larger studies are necessary to fully understand the occurrence of the CSR during PED deployment.

## Conclusion

CSR may be triggered during PED deployment under local anesthesia with mild sedation. Prolonged PED deployment time, especially in cases of more than 14.5 minutes, deployment to the C2 segment aneurysm, and deployment to the acute angle of the anterior genu in the ICA siphon, especially in cases of less than 51.5 degrees, were associated with triggering the CSR in our case series. The most important is to recognize that the CSR can occur during the PED deployment procedure. When CSR is suspected, it is important to pull down the catheter system to reduce the tension to the vessel wall. In high CSR risk cases, which include the C2 segment aneurysm and the acute angle of the anterior genu, though the CSR could be properly managed even under local anesthesia, general anesthesia should be considered for preventing the CSR.

## Ethical Approval

We declare that this study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments. This study has been approved by the local ethics committee (IRB ID: 2019-0523). Informed consent was obtained in the form of the opt-out on the website.

## Conflicts of Interest Disclosure

All authors have no conflicts of interest to declare, which could inappropriately influence this study. All authors have submitted the Self-reported COI Disclosure Statement Forms online through the website for The Japan Neurosurgical Society members.

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