Pathophysiology of the flow impairment during carotid artery stenting with embolus protection filter

Kentaro Hayashi M.D., Nobutaka Horie M.D., Minoru Morikawa M.D.*, Susumu Yamaguchi M.D., Shuji Fukuda M.D., Yoichi Morofuji M.D., Tsuyoshi Izumo M.D., Izumi Nagata M.D.

Department of Neurosurgery and Radiology*, Nagasaki University School of Medicine, JAPAN

Kentaro Hayashi

Department of Neurosurgery
Nagasaki University School of Medicine
Sakamoto 1-7-1, Nagasaki city, Nagasaki 852-8501, Japan
Tel: +81-95-819-7375
Fax: +81-95-819-7378
E-mail: kenkuni@nagasaki-u.ac.jp
Abstract

Objective: Carotid artery stenting (CAS) is a well-accepted treatment for atherosclerotic stenosis of carotid arteries. Since the occurrence of distal embolization with CAS is still a major concern, embolus protection device is usually employed during the procedure. We examined the two types of embolus protection filters (Angioguard XP; AG, Filterwire EZ; FW) and evaluated each function. Thus, the filter was examined postoperatively and the cause of intraoperative flow impairment was evaluated.

Materials and Methods: CAS was performed for 54 patients with carotid artery stenosis (55 lesions, AG; 25, FW; 27, others; 3). After completing CAS, filter membrane was stained with hematoxylin-eosin (HE) solution and removed from filter strut. Mounting onto a glass slide, filter was evaluated under microscope. The area occupied with debris was measured and the relation with intraoperative flow impairment was evaluated. Furthermore, relation of perioperative ischemic complication and the intraoperative flow impairment was statistically analyzed.

Results: Microscopical observation of the slide revealed that the pore density of FW was 1.5 times higher than that of AG, and filter area of FW was 2.5 times wider than that of AG. HE stain facilitated the characterization of the debris composition. The occupied area with debris was significantly more in AG (0.241 ± 0.13 cm²) than in FW (0.129 ± 0.093 cm²). Thus, fibrin was precipitated more in AG significantly. The flow impairment occurred 6 cases of AG (24.0%) and 4 cases of FW (14.8%). It was induced by the filter obstruction in AG and by the vasospasm in FW. Three cases (12.0%) treated with AG
were complicated with cerebral infarction and all of them were related to the flow impairment. A case of FW (3.7%) was complicated with cerebral infarction in presence of the preserved flow throughout the intervention.

**Conclusion:** Filter function is different according to each design. The cause of the flow impairment was filter obstruction in AG and vasospasm in FW. The filter obstruction tends to result in cerebral infarction.

**Key words:** carotid artery stenting, protection filter, debris, cerebral infarction
Introduction

Carotid artery stenting (CAS) in high-surgical-risk patients is considered as an effective alternative to carotid endarterectomy (CEA). Embolism is known to be associated with a high neurological complication rate and are also recognized as a potential cause of periprocedural stroke during CAS. Currently, to avoid embolization, the distal trapping technique using balloon or filter device has been developed [14, 16, 18]. One of the advantages of filter device is maintain the blood flow during the procedure. However, the flow is occasionally impaired and it affects the perioperative stroke [2, 9]. Loghmanpour et al. compared the characteristics and outcomes of filter devices and reported that lower porosity, lower number of pores, and lower pore density were significant for minimizing peri-postprocedure adverse event [11]. We have developed a technique for microscopical filter observation and identified the characteristics of the debris [3, 4]. In this study, observing the filter, the cause of flow impairment was evaluated in Angioguard XP (AG) (Cordis Corporation, Miami Lakes, FL, USA) and Filterwire EZ (FW) (Boston Scientific, Natick, MA, USA). Moreover, the relation of flow impairment and perioperative stroke was studied.

Materials and Methods

From January 2008 to December 2012, Carotid artery stenting was performed for 54 patients (55 sides) with high grade internal carotid artery (ICA) stenosis. From January
2008 to December 2010, only a pair of AG and Precise stent (Cordis Corporation, Miami Lakes, FL, USA) was available in Japan and AG was used for 25 cases. In January 2011, FW and Carotid Wallstent (Boston Scientific, Natick, MA, USA) were introduced to Japan and FW was used for 27 cases. In Japan, CAS was recommended for the case with high risk on CEA [17]. Therefore, CEA was first choice especially in the vulnerable plaque. During same period, CEA was performed for 54 cases. For the three cases of CEA high risk and vulnerable plaque, PercuSurge guardwire system (Medtronic, Santa Rosa, CA, USA) was employed and stent was placed. In 25 cases of AG, Precise stent was used for all cases. In 27 cases of FW, Carotid Wallstent was used for 24 cases and Precise stent was used for 3 cases, which had tortuous ICA lesion.

The procedure of CAS was as follows. The anticoagulant and antithrombotic protocol comprised administration of 200 mg of aspirin and 75 mg of clopidogrel at least 4 days before the procedure. Intra-arterial heparin bolus at the beginning of the procedure (70-100 IU/kg body weight) maintained an activated coagulation time of 300 s. All procedure were performed via the femoral approach using an 8 Fr guiding catheter. Embolus protection filter was employed to prevent distal embolism during stenting. The size of AG (5,6,7,8 mm) was selected for 1 mm larger than ICA diameter as company’s recommendation. FW is one size and fit for 3.5 mm to 5.5 mm ICA diameter. Following predilation (nominal balloon diameter 4 mm, inflation pressure 4-6 atm), Precise stent or Wallstent was positioned covering stenotic portion and deployed. After stent deployment, postdilation was performed with a balloon matched to the distal reference vessel diameter in order to achieve optimal stenting result (nominal balloon diameter 5 mm, inflation
pressure 6-8 atm).

We have reported a technique for microscopical filter observation [7, 9]. After brief washing with distilled water, the filter was placed Mayer’s hematoxylin solution for 1 minutes, and then placed in eosin for another 1 minute with brief wash in between procedures. Subsequently, the filter membrane was cut off from the strut and mounted onto a glass slide using paramount. Finally, the hematoxylin & eosin (HE)-stained debris on the filter could be visualized using light microscopy. The structure of the filter was observed and the pore density and the area of the filter was measured (Fig. 1). Moreover, the percentage of the occupied area with debirs was measured. The actual area was considered as amount of the debris. The subtype of debris was classified atheroma fragment or fibrin precipitation (Fig. 2). Microspical image was save as JPEG file and imported to Adobe Photoshop CS6 (Adobe, San Jose, CA, USA) for quantitative analysis.

Intraoperative flow status was defined as normal flow, slow flow and flow arrest. Slow flow indicates the flow of ICA is apparently delay comparing with external carotid artery (ECA) in the carotid angiography. Flow arrest indicates no visualization of ICA in the carotid angiography. Thus, the timing of flow impairment such as immediately after filter placement and after postdilation was evaluated. Postoperatively, all patients were neurologically examined with neurologist and evaluated with CT and MRI.

The plaque characteristic was preoperatively evaluated using high resolution MRI, CT angiography and ultrasonography, and divided into stable, unstable, and vulnerable according to those findings. The plaque, which showed high intensity lesion in
MRI T1 weighted image and hypoechoic lesion in ultrasonography was considered as unstable. It is histologically lipid-rich plaque or intraplaque hemorrhage [5]. Vulnerable indicated quite unstable such as extremely high intensity lesion in MRI T1 weighted image or mobile lesion in ultrasonography. The plaque, which showed iso or low intensity in MRI T1 weighted image and hyperechoic lesion in ultrasonography was considered as stable. It is histologically fibrous tissue [5]. An increase in Hunsfield units from the early phase on multidetector CT angiography indicates plaque stability with more fibrous tissue and less lipid-rich necrotic core, intraplaque hemorrhage, and neovascularization [6]. In addition, the volume of plaque was measured using high resolution MRI as follows [8].

Total plaque volume (mm³)

= \sum \{ \text{plaque areas on each slices (mm}^2\text{)} \times \text{thickness of each slices (2.5~3.0mm)} \} \}

All data were expressed as mean ± SD. Factors related to flow impairment and complication was firstly analyzed with univariate manner and possible factors are calculated with logistic regression analysis. It was statistically analyzed with JMP10.0 (SAS institute Inc, Cary, NC, USA). Statistical significance was accepted at p < 0.05.

Results

The basic structure of both filters was polyurethane membrane with numerous pore made
by laser. The size of pore was 100 μm in AG and 110 μm in FW. Microscopical observation of the slide revealed that the pore density of AG and FW was 26/mm² and 40/mm² respectively. The filter area of AG and FW was 0.59 cm² and 1.48 cm² respectively. The pore density of FW was 1.5 times higher than that of AG, and filter area of FW was 2.5 times wider than that of AG.

HE stain facilitated the characterization of the debris composition. The mean percentage of occupied area with debris of AG and FW was 40.9 ± 22.1% and 8.7 ± 6.1% respectively. It was significantly more in AG. The actual area was 0.241 ± 0.13 cm² in AG and 0.129 ± 0.093 cm² in FW. The atheroma fragment was 0.124 ± 0.053 cm² in AG and 0.102 ± 0.073 cm² in FW. The fibrin precipitation was 0.117 ± 0.091 cm² in AG and 0.027 ± 0.027 cm² in FW. Fibrin was attached significantly more in AG.

Flow impairment while the filter was in place was observed in 10 (19.2%) cases. Among 10 cases, 6 cases (24.0%) were treated with AG (flow arrest 3 and slow flow 3) and 4 cases (14.8%) were treated with FW (flow arrest 2 and slow flow 2). Flow impairment occurred after postdilation in all AG cases. In cases of FW, it occurred immediately after filter placement in 2 cases and after postdilation in 2 cases. In all cases, flow was restored after retrieval of the filter.

Regarding with flow impairment and occupied area of AG, occupied area was significantly more in the flow impairment cases (70.32 ± 14.19%, 0.415 ± 0.084 cm²) than in normal flow cases (30.34 ± 12.68%, 0.179 ± 0.075 cm²). Moreover, the fibrin precipitation was significantly more in flow impairment cases (0.228 ± 0.086 cm²) comparing with normal flow cases (0.077 ± 0.053 cm²). On the other hand, in the FW,
occupied area of the flow impairment cases (10.65 ± 5.37%, 0.158 ± 0.080 cm²) and normal flow cases (8.29 ± 6.32%, 0.124 ± 0.097 cm²) were not different (Fig. 3). Taken together, flow impairment was induced by the filter obstruction in AG and by the vasospasm in FW.

Three cases treated with AG (12.0%) were complicated with cerebral infarction and all of them were related to the flow impairment. A case of FW (3.7%) was complicated with cerebral infarction in presence of the preserved flow throughout the intervention. In AG group, flow impairment and the larger filter occupied area were related to the cerebral infarction. On the other hand, flow impairment or filter occupied area were not related to the cerebral infarction in FW group.

Among 25 cases of AG treatment, 11 cases (44.0%) were considered as stable plaque and 14 cases (56.0%) were unstable plaque. Among 27 cases of FW treatment, 13 cases (48.1%) were considered as stable plaque and 14 cases (51.9%) were unstable plaque. The mean plaque volume was 1326 ± 323 mm³ in the AG group and 1366 ± 413 mm³ in the FW group. Taken together, the background such as plaque characteristic and volume was not statistically different between AG group and FW group.

Illustrative case

Case 1

A 74-year-old man was referred to our hospital because of symptomatic right ICA stenosis. Since ischemic attack repeated despite medical treatment, CAS was planned. A
8 Fr guiding catheter was introduced to the right common carotid artery (CCA). Carotid angiogram showed high grade stenosis (Fig. 4A). A 5 mm AG was placed at the subcranial portion of the right ICA. Balloon angioplasty was performed and Precise stent 10 mm X 40 mm was placed from ICA to CCA. Following stenting and postdilation, angiogram revealed flow arrest (Fig. 4B). Then, AG was retrieved with capture catheter. The flow was restarted upon retrieving the filter (Fig. 4C). Postoperatively, the patient was suffered from mild left hemiparesis and MRI diffusion weighted image showed multiple high intensity lesions in the right cerebral hemisphere (Fig. 4D). Filter observation study showed 78.4% of the area was occupied with debris and fibrin (Fig. 4E). The occupied area was 0.463 cm$^2$ and the fibrin precipitation was 0.185 cm$^2$. The cause of the flow impairment was filter obstruction.

Case 2

A 60-year-old man who had a history of angina pectoris was referred to our hospital for the treatment of asymptomatic ICA stenosis. Since he needed dual antiplatelet agents for coronary artery stent, CAS was planned. A 8 Fr guiding catheter was introduced to the right CCA. Carotid angiogram shows high grade stenosis (Fig. 5A). A FW was placed subcranial portion of the right ICA without difficulty. Immediately after filter placement, angiogram revealed the flow arrest (Fig. 5B). Since the patient was neurologically intact, the procedure was continued. Stenosis was dilated with 4 mm balloon and Wallstent 8 mm X 30 mm was placed from ICA to CCA. Since the dilatation was not sufficient, postdilation was performed with 5 mm balloon. Following filter retrieval, the blood flow
was recovered with residual vasospasm at the filter placed portion (Fig. 5C). Postoperative course was uneventful and MRI diffusion-weighted image showed no abnormal lesion (Fig. 5D). The filter membrane was examined, and the occupied area was measured as 17.8% (Fig. 5E). The occupied area was 0.178 cm$^2$ and the fibrin precipitation was 0.089 cm$^2$. Filter obstruction was denied and it was considered that the cause of flow impairment was vasospasm.

**Discussion**

Although methods for filter observation have been reported, they contain technical difficulty and have not been widely spread [1, 12]. We developed a debris observation method staining with HE [3, 4]. The method was simple and required no special instrument. The debris was observed on the filter and the finding was consistent with preoperative imaging studies [4]. In this study, we revealed the function of the AG and FW, and evaluated the cause of the intraoperative flow impairment.

At first we observed the filter itself and revealed the function. Microscopical observation of the slide revealed that the pore density of FW was 1.5 times higher than that of AG, and filter area of FW was 2.5 times wider than that of AG. Multiply the density and the area, the filter function of FW is 3.75 times superior than that of AG. According to each company’s reports the volume of the filter is 20 $\mu$ l in AG and 80 $\mu$ l in FW. Thus, the actual pore number is 1100 in AG, and 2576 in FW. Taken together, FW is superior in terms of the filter function.
We observed captured debris on the filter and evaluated the amount measuring the occupied area of the filter. The material was divided atheroma debris and fibrin. Because the former is fragment of the atheroma and later is a reaction to the filter, that is precipitation. The amount of atheroma fragment was not different in AG and FW. However, the fibrin was significantly more in AG. Capturing debris, the filter function becomes less and the turbulence of the blood flow may induce fibrin adhesion, that is vicious cycle.

Flow impairment occurred more frequently with AG (6/25; 24%) than with FW (4/27; 14.8%). In term of intraoperative flow impairment and the etiology, the cases with flow impairment, the filter area was occupied significantly more in AG. In cases of flow impairment with AG, approximately 70% of filter area was occupied with debris. Against that, even in the flow impairment cases with FW, only 10% of the area was occupied. As shown in Fig. 5C, residual vasospasm was identified in the FW placed portion, the cause of the flow impairment is vasospasm. Regarding with timing of vasospasm, there are two type, i.e. immediately after filter placement and after postdilation. Later may be due to the stress of insertion or removal of the devices such as stent and balloon catheter. Size of AG can be selected depending on the size of ICA and the attachment area for the ICA is relatively wider (Fig. 6A). However, FW is only one size and the attachment for the ICA is linear (Fig. 6C). Therefore, stress to the ICA is more in FW and results in vasospasm.

According to the post-marketing surveillance on FW in Japan, the flow arrest occurred in two cases (1.6%) out of 126 cases and vasospasm occurred one case (0.8%). Roffi et al. [15] reported the flow impairment in the ICA occurred more frequently with
AG (22/68, 32.3%) than with FW (2/32, 6.2%). With respect to the degree of flow impairment, slow flow occurred in 9 (13.2%) AG patients, in 2 (6.2%) FW patients. Flow arrest occurred in 13 (19.1%) patients treated under AG protection; no patients protected with FW experienced this event. These tendencies are consistent with our study.

Finally, we evaluated the relation of the flow impairment and perioperative stroke. Cerebral infarction occurred in 3 cases of AG group and all of them were complicated with intraoperative flow impairment. In case of AG, filter tends to be obstruct due to its poor function and flow stagnation results in fibrin precipitation. Then, flow containing debris may be through between filter and ICA wall (Fig. 6A, B). Those flow results in cerebral embolism. On the other hand, cerebral infarction occurred in a case of FW group and it was not complicated with intraoperative flow impairment. The cause of flow impairment is vasospasm. More careful handling is required for the CAS under FW. The filter tend to be patent and attach for the ICA wall, the debris is captured by the filter (Fig. 6C, D). Therefore, it is not complicated with cerebral embolism.

The effect of embolus protection device (EPD) has been controversial [7, 10, 11]. According to the Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study, the perioperative complication of the CAS with EPD was 7.9% and that of without EPD was 25% [13]. On the other hand, the result of Stent-Protected Angioplasty versus Carotid Endarterectomy Trial (SPACE) indicated that perioperative complication of the CAS with EPD or without EPD were not different (with EPD; 7.28%, without EPD; 6.73%) [19]. It is clear that filter captures debris. However,
negative effect the filter such as fibrin precipitation or vasospasm may be accompanied. Therefore, the effect of EPD has not been established.

Regarding with stent type, closed cell stent and open cell stent have each advantage and disadvantage. However, the affect of stent for the perioperative stroke has not been clear [7, 11]. We prefer to use a pair of filter and stent made by the same company. In 25 cases of AG, Precise stent (open-cell type) was used for all cases. In 27 cases of FW, Carotid Wallstent (closed-cell type) was used for 24 cases and Precise stent was used for 3 cases. As shown in Fig. 3B, the amount of atheroma, which come from plaque was not significantly different between AG and FW group. Therefore, the type of stent may not affect distal embolization so much. We usually use 4mm balloon for predilation, and 5mm balloon for postdilation. We prefer to dilate vessel adjusting the pressure of the balloon. Because minimum dilatation may be better to prevent plaque rupture or plaque protrusion.

The limitation of this study includes retrospective nature of the data analysis. For the CEA high risk case with vulnerable plaque, PercuSurge guardwire system was used since filter obstruction tends to occur in vulnerable plaque and may result in stroke [2, 17]. The amount of debris was evaluated with area since the thickness of the debris was not able to measured on the slide.

**Conclusion**

Filter function is different according to each design. The cause of the flow impairment
was filter obstruction in AG and vasospasm in FW. The filter obstruction tends to result in cerebral infarction.

**Disclosure**
None.

**Acknowledgement**
no

**Source of Funding**
No

**Conflict of Interest – None**

**References**


**Figure legends**

Fig. 1 Photograph and hypermagnification of the filter membrane (A-C; Angioguard XP, D-F: Filterwire EZ)

A: Gross inspection of Angioguard XP; AG
B: The filter membrane is removed and mounted onto glass slide.
C: Microscopical observation of the membrane. The pore density is 26/mm$^2$.
D: Gross inspection of Filterwire EZ; FW
E: The filter membrane is removed and mounted onto glass slide.
F: Microscopical observation of the membrane. The pore density is 40/mm$^2$.

Fig. 2 Microscopical observation of the captured material on the filter membrane

A: Atheroma fragment dominant part
B: Fibrin precipitation dominant part

Fig. 3 Relation of captured debris and flow impairment.

A: Percentage of filter occupied area. The area is significantly more in AG group especially in cases with flow impairment.
B: Amount of the captured debris and fibrin precipitation. The total amount and the fibrin precipitation are more in AG group.
C: The relation of flow impairment and amount of the captured debris in AG. The flow impairment is significantly associated with amount of debris.
D: The relation of flow impairment and amount of the captured debris in FW. The flow impairment is not associated with amount of debris.

*Significantly different.

Fig. 4 Case 1
A: Rt. Carotid angiogram shows high grade stenosis (arrow).
B: Following stenting, angiogram reveals flow arrest (arrow indicates AG).
C: Following filter retrieval, the blood flow is recovered.
D: Postoperative MRI shows no abnormal lesion.
E: Filter observation study shows 78.4% of the area is occupied with debris.

Fig. 5 Case 2
A: Rt. Carotid angiogram shows high grade stenosis (arrow).
B: Following filter placement, angiogram reveals flow arrest (arrow indicates FW).
C: Following filter retrieval, the blood flow is recovered and spastic lesion is revealed at the filter placed portion (arrow).
D: Postoperative MRI shows multiple high intensity lesions in the right cerebral hemisphere.
E: Filter observation study shows 17.8% of the area is occupied with debris.

Fig. 6 Schematic illustration of the flow impairment of during carotid artery stenting (A & B; Angioguard XP, C & D: Filterwire EZ)
A: Attachment part to the internal carotid artery (ICA) is wider in AG and the stress to the vessel wall is less.

B: Filter tends to occlude due to its poor function and flow containing debris may be through between filter and ICA wall.

C: FW is only one size and the linear attachment for the ICA.

D: Stress to the ICA is more in FW and results in vasospasm. However, the filter tends to be patent and attach for the ICA wall, the debris is captured by the filter.
Fig. 2
Fig. 3

(A) Total debris, Fibrin, and Flow impairment (%)

(B) Total debris, Atheroma, Fibrin (X10^-2 cm^2)

(C) AG, Total debris, Atheroma, Fibrin (X10^-2 cm^2)

(D) FW, Total debris, Atheroma, Fibrin (X10^-2 cm^2)
Fig. 6

A

B

C

D