J Neurosurg 119:1603–1610, 2013
©AANS, 2013

Effect of antiplatelet therapy on thromboembolism after flow diversion with the Pipeline Embolization Device

Clinical article

Robert S. Heller, M.D.,[1] Venkata Dandamudi, M.D.,[1] Michael Lanfranchi, M.D.,[2] and Adel M. Malek, M.D., Ph.D.[1]

[1]Cerebrovascular and Endovascular Division, Department of Neurosurgery, and [2]Department of Radiology, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts

Object. Flow-diverting stents offer a novel treatment approach to intracranial aneurysms. Data regarding the incidence of acute procedure-related thromboembolic complications following deployment of the Pipeline Embolization Device (PED) remain scant. The authors sought to determine the rate of embolic events in a bid to identify potential risk factors and assess the role of platelet inhibition.

Methods. Data in all patients receiving a PED for treatment of an intracranial aneurysm were prospectively maintained in a database. Diffusion-weighted 3-T MRI was performed within 24 hours of PED deployment. The incident rate of procedural embolism was established, and univariate analysis was then performed to determine any associations of embolic events with measured variables. The degree of platelet inhibition in response to aspirin and clopidogrel was evaluated by challenging the platelet samples with arachidonic acid and adenosine diphosphate, respectively, and then performing formal light transmission platelet aggregometry.

Results. Twenty-three patients with 26 aneurysms were eligible for inclusion in the study. Thirty-one PEDs were deployed in 25 procedures. All ischemic lesions detected on diffusion-weighted 3-T MRI were identified as embolic based on their location and distribution, with none appearing to be due to perforator artery occlusion. Procedural embolic events were found in the target parent vessel territory in 13 (52%) of 25 procedures, with no patients harboring lesions contralateral to the deployed PED. The number of embolic events per procedure ranged from 3 to 16, with a mean of 5.4. There was no significant difference between cases with and without procedural embolism in platelet inhibition by aspirin (mean 15% vs 12% residual activation; $p = 0.28$), platelet inhibition by clopidogrel (mean 41% vs 41% residual activation; $p = 0.98$), or intraprocedural heparin-induced anticoagulation (mean activated clotting time 235 seconds vs 237 seconds; $p = 0.81$). By multivariate analysis, the authors identified larger aneurysm size ($p = 0.03$) as the single variable significantly associated with procedural embolism. There was no significant relationship between aneurysm size and the number of embolic events ($p = 0.32$) or the total burden of the embolism lesion area ($p = 0.53$).

Conclusions. Acute embolism following use of the PED for treatment of intracranial aneurysms is more common than hypothesized. The only identifiable risk factor for embolism appears to be greater aneurysm size, perhaps indicating significant disturbed flow across the aneurysm neck with ingress and egress through the PED struts. The strength of antiplatelet therapy, as measured by residual platelet aggregation, did not appear to be associated with cases of procedural embolism. Further work is needed to determine the implications of these findings and whether anticoagulation regimens can be altered to lower the rate of complications following PED deployment.
(http://thejns.org/doi/abs/10.3171/2013.7.JNS122178)

Key Words • **Pipeline Embolization Device** • **aneurysm** • **vascular disorders** • **platelet inhibition**

Flow-diverting stents are rapidly altering the basic principles for the embolization of intracranial aneurysms.[15,16] Through diversion of hemodynamic force from the aneurysm and restoration of anatomical arterial flow through the parent artery, flow-diverting stents such as the Pipeline Embolization Device (PED; Chestnut Medical) promote targeted aneurysm occlusion and involution.

Initial reports of PED use demonstrated high rates of aneurysm occlusion, with complication rates comparable to those of other intracranial stents used for the treatment of aneurysms.[18,21] Although the authors of previous studies in the literature have evaluated the rate of clinically evident complications following PED deployment, to our knowledge there have been no study authors who have described the total incidence of acute ischemic infarcts following PED deployment in all patients. Using routine

Abbreviations used in this paper: ACT = activated clotting time; ADP = adenosine diphosphate; ICA = internal carotid artery; LTA = light transmission aggregometry; PED = Pipeline Embolization Device; PRU = P2Y12 reaction units.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

MRI including diffusion-weighted sequences, we sought to define that incidence and identify risk factors for acute embolism.

Additionally, given the higher stent strut density of the PED and flow-diverting mechanism of treatment, early concerns over thromboembolism gave rise to the clinical practice of diligent pre-, peri-, and postprocedural anticoagulation. We hypothesized that patients unresponsive to dual antiplatelet anticoagulation therapy with aspirin and clopidogrel were more likely to experience an acute thromboembolic ischemic event periprocedurally. Using light transmission aggregometry (LTA), considered the gold standard for platelet inhibition testing, we sought to evaluate the effect of antiplatelet therapy on acute procedural thromboembolism.

Methods

Demographic information for all patients undergoing treatment of an intracranial aneurysm at Tufts Medical Center is prospectively collected in a database maintained by the senior author (A.M.). All patients who underwent PED deployment were identified, and their clinical and radiographic charts were reviewed for collection of pertinent data. The study was approved by the institutional review board of Tufts Medical Center.

The PED became available at our institution in October 2011, and patients included in this study were treated through June 2012.

In response to concerns of thromboembolism and the need for diligent platelet inactivation with use of the PED, all patients received their initial dose of aspirin and clopidogrel dual antiplatelet therapy beginning at least 7 days prior to the procedure. Platelet aggregation studies were performed immediately preprocedure using LTA: Platelet samples were challenged with arachidonic acid (500 μg/ml) to assess platelet response to aspirin and with adenosine diphosphate (ADP; 20 μM) to assess platelet response to clopidogrel (brand name Plavix). Platelet function was then reported as the maximum percentage of platelets aggregating when challenged with each agent. Per the reporting standard of the laboratory at our institution, patient samples where greater than 20% of platelets aggregated after challenge with arachidonic acid were deemed to have high on-aspirin reactivity, and samples where greater than 60% of platelets aggregated after challenge with ADP were deemed to have high on-clopidogrel reactivity. These cutoff values were determined based on cardiac literature in which platelet function tests were evaluated in relation to adverse events following coronary stent implantation.[4]

As the VerifyNow platelet function analyzer (Accumentrics) has become more readily available than LTA in neuroendovascular practice, we performed an additional analysis on LTA test results by converting the residual percentage of platelet activation to VerifyNow P2Y12 reaction units (PRU) using a correlation curve. The correlation curve was constructed from an institutional standardization data set consisting of 23 random samples from patients on dual antiplatelet therapy in whom platelet function was analyzed simultaneously using both LTA and VerifyNow methods.

Aneurysm measurements were determined from pretreatment digital subtraction angiography and 3D rotational angiography studies. Aneurysm size was defined as the greatest diameter of the aneurysm in any plane, and aneurysm neck was similarly defined as the greatest diameter of the aneurysm neck at the junction with the parent artery.

During PED deployment, patients are maintained on an intravenous heparin drip with a goal partial thromboplastin time of 240 seconds. Per protocol at our institution, all patients receiving a PED are maintained on heparin overnight for 12–18 hours with a goal partial thromboplastin time of 50–70 seconds. Daily clopidogrel (75 mg) is maintained for at least 3 months postprocedure, and daily aspirin (325 or 81 mg) is maintained indefinitely.

Per the protocol of the senior author (A.M.), all patients undergoing embolization of an intracranial aneurysm undergo MRI, including diffusion-weighted sequences, on postoperative Day 1 for quality-control surveillance and follow-up purposes. An attending neuroradiologist at our institution initially reviewed all diffusion-weighted MR images for the study. Blinded to the initial radiology report, the study radiologist (M.L.) reassessed all images for the presence of acute ischemic lesions. The study authors reviewed these findings, with differences in opinion adjudicated by the senior author after discussion among all parties.

Statistical analysis was performed using JMP (version 8.0, SAS), with differences in values evaluated with 1-way ANOVA, likelihood ratios, and chi-square tests. Statistics are reported to 2 significant figures, and statistical significance was defined as $p < 0.05$. Mean values are presented ± SD.

Results

Demographics and Clinical Presentation

Twenty-four patients with 27 intracranial aneurysms received a PED for treatment of their aneurysms in this series. The population had a mean age of 55.6 years (range 17–77 years) and consisted of 5 men and 19 women. Twelve patients presented with incidentally found aneurysms, 7 with headache, 2 with cranial nerve deficits, 1 with pulsatile tinnitus, 1 with residual aneurysm filling following previous aneurysm coiling, and 1 with a traumatic pseudoaneurysm. One patient was unable to undergo MRI because of an implanted cardiac pacemaker and is herein excluded from further reporting, as the primary end point of this study is based on MRI findings.

Aneurysm Location and Morphology

The 26 treated aneurysms were located in segments of the internal carotid artery (ICA; 11 ophthalmic, 9 cavernous, 4 supraclinoid, 1 posterior communicating artery, and 1 extradural cavernous); one of these aneurysms was a posttraumatic pseudoaneurysm. The mean aneurysm size was 0.8 cm, with 7 aneurysms at least 1 cm in size. Of the 11 aneurysms in the ophthalmic segment of the ICA, 73% (n = 8) incorporated the origin of the ophthalmic artery in the dome of the aneurysm (Fig. 1). These aneurysms trended toward a smaller size than did those in the remain-

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

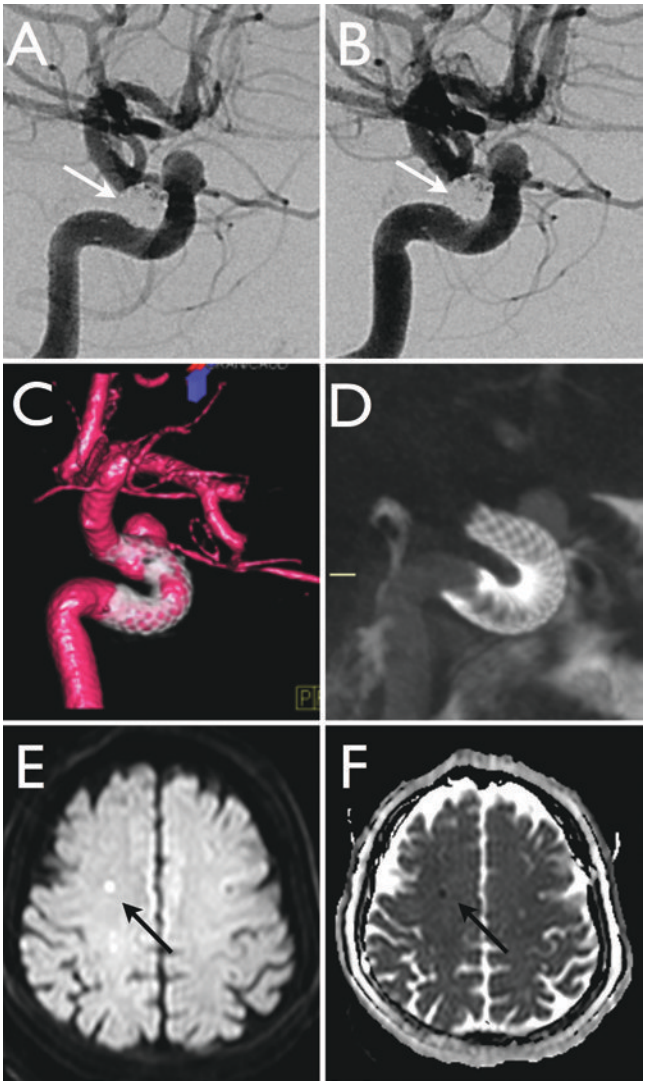


Fig. 1. A 66-year-old woman presented with an intracranial aneurysm, located in the ophthalmic segment of the right ICA. **A:** The aneurysm was visualized using lateral view digital subtraction angiography, with the origin of the ophthalmic artery emanating near the aneurysm neck. Note is made of a coil pack *(white arrow)* seen from a previous Neuroform stent–mediated coil embolization of a mirror-image aneurysm on the contralateral side. **B:** A post-PED embolization lateral angiogram demonstrates persistent anterograde filling of the ophthalmic artery. **C and D:** 3D reconstruction and multiplanar reconstructed dyna-CT image demonstrate the deployed PED covering the aneurysm neck. **E and F:** A postoperative Day 1 MR image demonstrates a hyperintense lesion *(black arrows)* in the right frontal white matter on the diffusion-weighted sequence (E), corresponding to loss of signal on the apparent diffusion coefficient map (F), which is consistent with acute embolic infarction.

der of the population (0.4 ± 0.1 cm vs 1.0 ± 0.6 cm; p = 0.02).

PED Embolization

Thirty-one PEDs were deployed in 25 procedures. In 1 patient, a single PED was used for the treatment of 2 adjacent aneurysms in the supraclinoid segment of the ICA in a single procedure. The number of PEDs deployed in each procedure ranged from 1 to 3, with a single PED being most common (n = 20), followed by 2 PEDs (n = 4) and 3 PEDs (n = 1). A single aneurysm (1/26, 3.8%) required repeat treatment following initial PED embolization. In this case, the mass effect of the partially thrombosed aneurysm induced parent vessel stenosis; this remodeling of the vessel caused the initial PED to inadequately cover the aneurysm neck, requiring deployment of a second device.

The degree of heparin-induced clotting cascade inhibition was measured intraprocedurally using serial activated clotting time (ACT) measurements. The mean baseline ACT was 144 ± 15 seconds, which was increased to a mean of 236 ± 17 seconds during embolization. The mean difference between peak ACT and trough ACT during PED deployment was 66 ± 48 seconds, with a mean trough ACT of 202 ± 26 seconds and a mean peak ACT of 269 ± 33 seconds.

Light transmission aggregometry was performed immediately before the procedure, per routine, in all patients to assess platelet response to aspirin and clopidogrel. The mean percentage of on-aspirin platelets with residual aggregation when challenged with arachidonic acid was 14% ± 7% (range 4%–30%). Per the reporting standards of our laboratory, 84% (n = 21) of platelet samples assayed were found to have adequate response to aspirin, and 16% (n = 4) had high on-aspirin reactivity. The mean percentage of on-clopidogrel platelets with residual aggregation when challenged with ADP was 41% ± 12% (range 16%–61%). Per the reporting standards of our laboratory, 96% (n = 24) of platelet samples assayed were found to have adequate response to clopidogrel, and 4% (n = 1) had high on-clopidogrel reactivity.

Postembolization Monitoring

Postembolization 3-T MRI was performed on postoperative Day 1 in all cases. Diffusion-weighted imaging was used to identify acute ischemia in the territory of the PED following 13 (52%) of 25 procedures (Fig. 2); all cases of acute ischemia were clinically silent. No acute ischemic lesions were identified in any case in territories not served by the parent vessel containing the recently deployed PED. All 13 lesions appeared embolic in nature based on their location in a distribution distal to the location of the PED, with no infarct patterns indicative of perforator occlusion. Additionally, there were no signal changes on MRI gradient echo sequences to suggest the presence of petechial hemorrhage within the lesions. The number of lesions per procedure ranged from 3 to 16, with a mean of 5.4 ± 3.9. The burden of ischemia, as measured by the total area of the embolic lesions, ranged from 14 to 64 mm^2, with a median of 18 mm^2.

Univariate analyses were performed with the goal of identifying risk factors predictive of periprocedural infarcts (Table 1). Older patient age (p = 0.02), larger aneurysm neck diameter (p = 0.04), and greater aneurysm size (p < 0.01) were associated with increased incidence of thromboembolism, with risk appearing to be the greatest for aneurysms of at least 1 cm. Using LTA to measure platelet reactivity, we did not identify any antiplatelet parameters that were significantly associated with the occurrence of a procedural embolic event (Fig. 3). Aneurysm

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

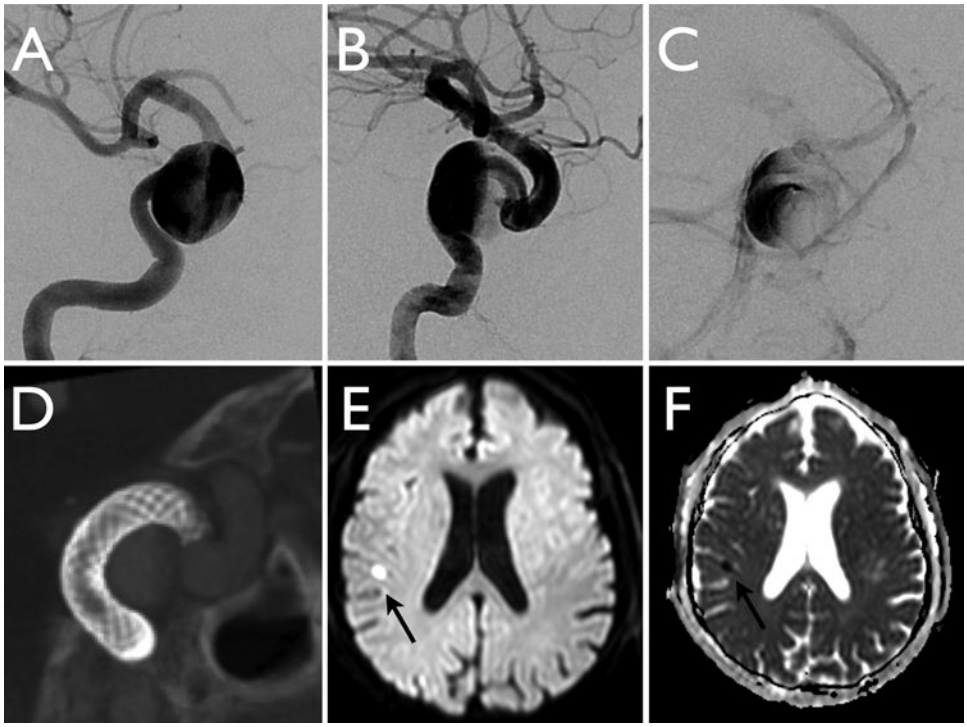


Fig. 2. A 76-year-old woman presented with an incidentally found, large intracranial aneurysm, located in the cavernous segment of the right ICA and seen on a lateral view digital subtraction angiogram **(A)**. Post-PED embolization lateral angiograms show reduction of flow into the aneurysm dome in the arterial phase **(B)**, with retention of contrast through the venous phase **(C)**. Multiplanar reconstructed dyna-CT imaging **(D)** obtained postembolization with dilute contrast injection enables visualization of the deployed PED covering the neck of the aneurysm. MRI was performed on postoperative Day 1, with the diffusion-weighted sequence **(E)** revealing a hyperintense lesion (*black arrow*) in the white matter of the right frontal lobe, corresponding to loss of signal on the apparent diffusion coefficient map **(F)**, which is consistent with acute embolic infarction.

size was not significantly associated with the number of embolic lesions ($p = 0.32$) or the total burden of ischemia ($p = 0.53$) on univariate analyses.

Multivariate analysis was performed on a limited number of variables because of the small study population, with patient age, aneurysm size, and aneurysm neck diameter included in the model to determine whether they are associated with acute thromboembolism. Results dem-

TABLE 1: Univariate analysis for prediction of procedural embolism detected by diffusion-weighted 3-T MRI*

Variable	Procedural Embolism	No Embolism	p Value
no. of PED deployment procedures	13	12	
demographics			
age (yrs)	63 ± 11	49 ± 16	0.02
male/female ratio	2:11	2:10	0.93
aneurysm neck diameter (cm)	0.56 ± 0.30	0.36 ± 0.12	0.04
aneurysm size (cm)	1.1 ± 0.7	0.5 ± 0.2	<0.01
<1	6	12	
≥1	7	0	
no. of PEDs deployed	1.3 ± 0.6	1.2 ± 0.4	0.51
anticoagulation			
platelets w/ on-aspirin reactivity (%)	15 ± 7	12 ± 6	0.28
platelets w/ on-clopidogrel reactivity (%)	41 ± 15	41 ± 8	0.98
mean procedural ACT (secs)	235 ± 20	237 ± 13	0.81
procedural ACT fluctuation (secs)	71 ± 39	62 ± 57	0.63
trough ACT (secs)	200 ± 29	205 ± 22	0.61
peak ACT (secs)	271 ± 29	267 ± 38	0.76

* Values are reported as mean ± SD unless otherwise indicated.

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

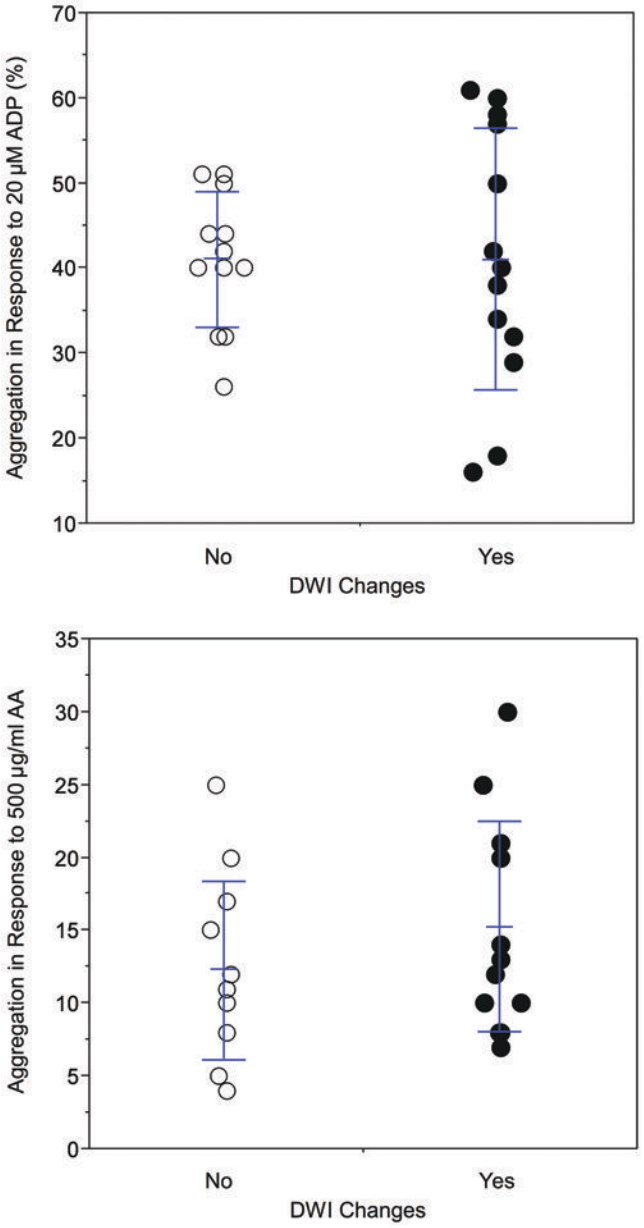


Fig. 3. Distribution of the maximum percentage of platelets with residual aggregation following challenge with adenosine diphosphate (ADP; **upper**) and arachidonic acid (AA; **lower**), as measured by LTA in patients with and without acute ischemic lesions detected by diffusion-weighted imaging (DWI).

onstrate that for the whole model ($p < 0.01$), larger aneurysm size was associated with thromboembolism ($p = 0.03$; chi-square = 4.54), while patient age and neck diameter were not significantly associated ($p = 0.15$ and 0.41; chi-square = 2.05 and 0.69, respectively).

There were no patients who developed a permanent new neurological deficit upon hospital discharge after experiencing a thromboembolic event after PED deployment.

Discussion

Since its first clinical use in humans in 2008,[9] the PED has continued to gain popularity throughout the neurovascular community. Based on the principle of flow diversion, the PED may represent a shift away from treatment of the target aneurysm itself and toward restoration of normal arterial anatomy.[6]

Published series describing initial use of the PED demonstrated universally high rates of aneurysm obliteration at 6 months (reported greater than 85%) and 1 year (reported greater than 95%).[18,21,28] In their recent analysis of 57 aneurysms treated with a PED, McAuliffe et al.[20] replicated this trend with a 93% obliteration rate after 6 months of previously untreated aneurysms, with the additional finding of a more modest 50% obliteration rate of aneurysms previously treated with another stent, indicating that the in vivo architecture and deployment of the PED may be crucial for its ability to effectively remove aneurysms from the cerebrovascular circulation.

Despite these promising results, concerns have grown surrounding the complications of PED use in clinical practice. Initially, the flow-diverting nature of the PED and the close proximity of stent struts to one another were thought to convey the risk of occluding small perforator arteries. Reports of this phenomenon have included 2 cases of basal ganglia infarcts caused by occlusion of lenticulostriate perforating arteries.[21,29] Both of these cases featured situations where multiple PEDs were required for adequate coverage of the aneurysm neck and reconstruction of the parent artery. In another article, Phillips et al.[23] reported a 14% rate of perforator infarcts following deployment of a PED in the basilar artery. Together, these 3 studies indicate that placement of multiple PEDs and deployment of a PED within the basilar artery may be risk factors for perforator artery infarcts. Puffer et al.[26] demonstrated that, although 21% of ophthalmic arteries were occluded following deployment of a PED over the ophthalmic artery origin, development of symptoms was rare, and there often existed sufficient collateral flow to prevent infarction. The current series, with all patients treated for aneurysms in the anterior circulation and 20% of procedures requiring use of multiple PEDs, features a 0% rate of perforator occlusion. This finding, which is consistent with the literature, may indicate that the PED carries a relatively low risk of perforator artery infarction in the anterior circulation.

Previous series have also indicated that the PED may carry a risk of acute thrombosis. Szikora et al.[28] reported that 1 of 18 cases was complicated by in-stent thrombus formation, while Fischer et al.[10] reported that 2 of 88 cases were complicated by thrombosis (1 acute and 1 delayed). Delgado Almandoz et al.[8] reported clinically evident thromboembolic events following 4 (8.3%) of 48 PED procedures. A recent multicenter analysis demonstrated a major complication rate (permanent disability and/or death) of 8.5% in the periprocedural time period.[17] Though several studies such as these have reported on the occurrence of acute thrombosis in the setting of PED deployment, these studies have been limited by restriction of analyses to those lesions detected through the presence of symptoms. There have been no previous reports on the total incidence of acute infarcts, both symptomatic and asymptomatic, following aneurysm treatment with the PED.

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

In the current series, dedicated postoperative MRI allowed us to detect a 52% (13/25 patients) rate of acute ischemic lesions. Based on the distal location of the infarcts and 100% rate of lesions detected in the perfusion territory of the parent artery, we hypothesize that these lesions were embolic in nature. For comparison, Bendszus et al.[1] detected a 26% (17/66 patients) rate of acute ischemic lesions in patients undergoing diagnostic angiography and an 18% (6/34 patients) rate of such lesions following interventional angiography. In a previous prospective study conducted at our institution,[13] we detected a 45% (15/33 patients) rate of acute ischemic lesions following closed-cell design Enterprise stent–mediated coiling and a 4% (1/25 patients) rate of such lesions following open-cell design Neuroform stent–mediated coiling. The higher rate of acute ischemic lesions after diagnostic versus interventional angiography may be explained by a higher rate of inexperienced operators performing diagnostic angiograms, the lack of standard dual antiplatelet therapy with aspirin and clopidogrel prior to diagnostic studies, and less aggressive heparinization during diagnostic studies.

By conducting a univariate analysis, we identified 3 risk factors for procedural ischemic lesions detected on postoperative imaging. Older age may contribute to risk because of atherosclerosis, more inherently diseased parent vessels, and less pliable parent arteries. Greater aneurysm size, especially a size of at least 1 cm, conferred greater risk for procedural thromboembolism when the aneurysm was treated with a PED. The finding that aneurysm neck diameter was significantly associated with thromboembolism in univariate analysis but not in multivariate analysis may be due to the fact that larger aneurysms naturally harbor greater neck diameters. Multivariate analysis demonstrated that aneurysm size was the only persistently significant factor among the factors associated with acute procedural thromboembolism.

In a previous study[27] in which the PED was evaluated with computational aneurysm models, researchers found an immediate reduction in flow velocity within the aneurysm, up to a mean of 82%, immediately after deployment. We hypothesize that larger aneurysms, with more inherent flow through the aneurysm, experience a more significant change in the ingress/egress flow pattern across the stent struts when flow diverters are deployed over the aneurysm neck. This potential for mechanical shear-induced platelet activation may predispose to platelet plug initiation and thrombus formation,[22] both within the aneurysm itself and perhaps within the flow diverter-containing parent artery, resulting in distal embolization. This mechanical shear-gradient platelet activation may be only lowered, but not completely eliminated, by current dual antiplatelet inhibition regimens. Another explanation for the association between larger aneurysm size and thromboembolism may be that the PED lacks significant radial force and is therefore unable to anchor itself securely to the vessel wall, inducing greater vibration and micromotion of the stent construct in the setting of larger lesions, which predispose to distal embolization. The finding that aneurysms of at least 1 cm in size are more susceptible to thromboembolic complications is compelling because it is for treatment of these larger lesions that the PED has been targeted for use.

Platelet inhibition testing and response to aspirin and clopidogrel therapy were performed using LTA, which is considered the historic gold standard in the evaluation of platelet function. Several studies have been performed to evaluate the accuracy and reliability of LTA against other platelet function analyzers, such as VerifyNow,[2,3,11,12,19,31] vasodilator-stimulated phosphoprotein phosphorylation (commonly known as VASP),[2,11,31] multiplate analyzer,[12,31] PFA-100,[12] and thromboelastography,[3,19] among others. The results of the studies are variable, and there is consensus agreement within the literature that while individual tests or platelet analyzers may correlate with one another, there is poor reliability when compared with LTA, with common underestimation of patients nonresponsive to antiplatelet therapy. Poor response to aspirin and clopidogrel therapy, as evaluated by LTA, has been associated with an increased risk of thrombotic events.[7,32]

Jakubowski et al.[14] studied the correlation between the VerifyNow assay and LTA for evaluation of platelet response to clopidogrel and observed similar patterns of inhibition between the 2 modalities. By plotting 23 random samples from our institution, we generated a correlation curve for the 2 assays (Fig. 4), with a linear fit ($r = 0.826$) representing the most accurate model: LTA % = 20.1 + 0.14 × PRU. The most widely accepted PRU cutoff for determining high on-clopidogrel platelet reactivity is 230, used in the GRAVITAS (Gauging Responsiveness with a VerifyNow Assay—Impact on Thrombosis and Safety) trial[24] and verified by receiver-operating characteristic analyses[25] for maximal detection of adverse events. According to our model, a PRU of 230 corresponds to 52.3% residual aggregation by LTA at our institution.

Notably, the anticoagulation parameters evaluated in this study, as determined by LTA and ACT measurements, failed to significantly predict the occurrence of acute embolism, even in the setting of adequately inhibited platelets and coagulation factors. It is noteworthy that while 16% of procedures were performed with high on-aspirin reactivity and 4% with high on-clopidogrel reactivity by LTA standards, there were no patients that were grossly uninhibited, and there was no trend toward an association between poor responsiveness and the presence of acute ischemic lesions. Patients who were most unresponsive to antiplatelet therapy were also evenly divided between a presence and absence of acute ischemic lesions.

In the current study, we observed that the range of platelet reactivity in patients without thromboembolism was smaller than the range in patients with thromboembolism (Fig. 3), with a higher incidence of events at abnormally elevated and depressed aggregation levels. In concurrence with this finding, Delgado Almandoz et al.[8] found that patients both under- and overresponsive to clopidogrel therapy were more likely to experience clinically evident thrombosis and hemorrhage. These findings may indicate that the relationship between platelet inhibition and thromboembolism following PED deployment is a threshold response rather than a dose response. With the understanding that the VerifyNow assay may be less sensitive to test results at the extremes of the data range,[14] these results indicate a need for further study of this relationship.

Additionally, these findings may indicate that platelets

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

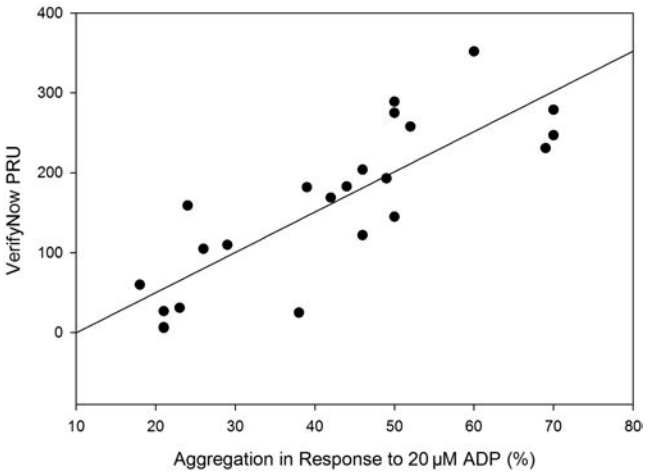


Fig. 4. Linear fit model of the correlation between LTA and VerifyNow PRU. Samples were obtained from 23 random patients undergoing cerebral angiography at our institution. For the model, $r^2 = 0.682$, and LTA % = 20.1 + 0.14 × PRU.

and coagulation factors are aggregating despite appropriate inhibition in response to the PED, either in response to a highly thrombogenic substrate on the PED or to the high shear forces and flow disruption that occur during PED deployment. Further work is necessary to distinguish the causative factors that predispose platelets and coagulation factors to aggregate. It is also possible that the thromboembolic events are related to the more bulky and complex guide catheter arrangements required for PED deployment; this is less likely given the use of similar equipment throughout all cases and the adoption of the more pliable low-profile 0.058" Reflex (Navion) intermediate guide catheter in patients who undergo PED deployment.

The major limitation of the current study is the size of the cohort studied (n = 25 procedures). Further analysis remains to be performed to evaluate the role of platelet inhibition prior to flow diversion for intracranial aneurysms, and larger patient populations will aid in this pursuit. A strength of this study is the primary use of LTA rather than other platelet function analyzers. LTA has been lauded for its accuracy.

Major concerns regarding PED use have also centered on the occurrence of intraparenchymal hemorrhage in the vascular territory served by the parent artery receiving the PED.[30] Fischer et al.[10] reported on the treatment of 88 patients with 101 aneurysms: 3.4% of cases were complicated by hemorrhage distal to the PED site. Briganti et al.[5] evaluated 131 patients receiving a PED for treatment of intracranial aneurysms and noted a 7.6% rate of hemorrhagic complications.

Given the high rate of acute embolic infarcts detected in the current study, we hypothesize that the observed intraparenchymal hemorrhages may have been caused by hemorrhagic conversion of the ischemic infarcts. The tendency to aggressively anticoagulate patients following PED deployment and follow with dual antiplatelet therapy may make patients more susceptible to delayed hemorrhages, especially in the setting of an existing acute embolic infarct.

Conclusions

The findings of the current study indicate a high rate of silent procedure-related ischemic events, as measured by diffusion-weighted MRI. Greater aneurysm size was found to be significantly associated with the occurrence of these events. Effectiveness of antiplatelet inhibition alone was not sufficient to explain the rate of events, though it is possible that a threshold effect may contribute to the observed findings. These early results support a need for close clinical observation of patients treated using flow-diverter devices given the higher rate of periprocedural ischemic lesions compared with equivalent conventional stent-mediated coiling procedures. Our results point to a clear need for furthering our understanding of the underlying fundamental mechanism of platelet and thrombus interactions with the PED device within the vessel wall.

Disclosure

Dr. Malek has received unrestricted research support from MicroVention-Terumo, Inc.; Stryker Neurovascular; Codman Neurovascular; Siemens, Inc.; Ansys, Inc.; and CD-Adapco for unrelated work. None of the other authors report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Malek. Acquisition of data: all authors. Analysis and interpretation of data: Malek, Heller. Drafting the article: Malek, Heller. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Malek. Statistical analysis: Malek, Heller. Administrative/technical/material support: Malek. Study supervision: Malek.

Acknowledgments

The authors would like to thank Daniela Pasi, R.T., for her assistance with collection of procedural charts and Monika Pilichowska, M.D., Ph.D., for her assistance with platelet function testing.

References

1. Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L: Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: a prospective study. **Lancet 354:**1594–1597, 1999
2. Bidet A, Jais C, Puymirat E, Coste P, Nurden A, Jakubowski J, et al: VerifyNow and VASP phosphorylation assays give similar results for patients receiving clopidogrel, but they do not always correlate with platelet aggregation. **Platelets 21:**94–100, 2010
3. Blais N, Pharand C, Lordkipanidzé M, Sia YK, Merhi Y, Diodati JG: Response to aspirin in healthy individuals. Cross-comparison of light transmission aggregometry, VerifyNow system, platelet count drop, thromboelastography (TEG) and urinary 11-dehydrothromboxane B(2). **Thromb Haemost 102:** 404–411, 2009
4. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, et al: Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. **JAMA 303:**754–762, 2010
5. Briganti F, Napoli M, Tortora F, Solari D, Bergui M, Boccardi E, et al: Italian multicenter experience with flow-diverter devices for intracranial unruptured aneurysm treatment with periprocedural complications—a retrospective data analysis. **Neuroradiology 54:**1145–1152, 2012

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC

6. D'Urso PI, Lanzino G, Cloft HJ, Kallmes DF: Flow diversion for intracranial aneurysms: a review. **Stroke 42:**2363–2368, 2011
7. De Miguel A, Ibanez B, Badimón JJ: Clinical implications of clopidogrel resistance. **Thromb Haemost 100:**196–203, 2008
8. Delgado Almandoz JE, Crandall BM, Scholz JM, Fease JL, Anderson RE, Kadkhodayan Y, et al: Pre-procedure P2Y12 reaction units value predicts perioperative thromboembolic and hemorrhagic complications in patients with cerebral aneurysms treated with the Pipeline Embolization Device. **J Neurointerv Surg** [epub ahead of print], 2013
9. Fiorella D, Woo HH, Albuquerque FC, Nelson PK: Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. **Neurosurgery 62:**1115–1121, 2008
10. Fischer S, Vajda Z, Aguilar Perez M, Schmid E, Hopf N, Bäzner H, et al: Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. **Neuroradiology 54:**369–382, 2012
11. Gaglia MA, Torguson R, Pakala R, Xue Z, Sardi G, Suddath WO, et al: Correlation between light transmission aggregometry, VerifyNow P2Y12, and VASP-P platelet reactivity assays following percutaneous coronary intervention. **J Interv Cardiol 24:**529–534, 2011
12. Grove EL, Hvas AM, Johnsen HL, Hedegaard SS, Pedersen SB, Mortensen J, et al: A comparison of platelet function tests and thromboxane metabolites to evaluate aspirin response in healthy individuals and patients with coronary artery disease. **Thromb Haemost 103:**1245–1253, 2010
13. Heller RS, Miele WR, Do-Dai DD, Malek AM: Crescent sign on magnetic resonance angiography revealing incomplete stent apposition: correlation with diffusion-weighted changes in stent-mediated coil embolization of aneurysms. Clinical article. **J Neurosurg 115:**624–632, 2011
14. Jakubowski JA, Li YG, Small DS, Payne CD, Tomlin ME, Luo J, et al: A comparison of the VerifyNow P2Y12 point-of-care device and light transmission aggregometry to monitor platelet function with prasugrel and clopidogrel: an integrated analysis. **J Cardiovasc Pharmacol 56:**29–37, 2010
15. Kallmes DF, Ding YH, Dai D, Kadirvel R, Lewis DA, Cloft HJ: A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. **Stroke 38:**2346–2352, 2007
16. Kallmes DF, Ding YH, Dai D, Kadirvel R, Lewis DA, Cloft HJ: A second-generation, endoluminal, flow-disrupting device for treatment of saccular aneurysms. **AJNR Am J Neuroradiol 30:**1153–1158, 2009
17. Kan P, Siddiqui AH, Veznedaroglu E, Liebman KM, Binning MJ, Dumont TM, et al: Early postmarket results after treatment of intracranial aneurysms with the pipeline embolization device: a U.S. multicenter experience. **Neurosurgery 71:** 1080–1088, 2012
18. Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al: Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. **Neurosurgery 64:**632–643, 2009
19. Madsen EH, Saw J, Kristensen SR, Schmidt EB, Pittendreigh C, Maurer-Spurej E: Long-term aspirin and clopidogrel response evaluated by light transmission aggregometry, VerifyNow, and thrombelastography in patients undergoing percutaneous coronary intervention. **Clin Chem 56:**839–847, 2010
20. McAuliffe W, Wycoco V, Rice H, Phatouros C, Singh TJ, Wenderoth J: Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. **AJNR Am J Neuroradiol 33:**164–170, 2012
21. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D: The pipeline embolization device for the intracranial treatment of aneurysms trial. **AJNR Am J Neuroradiol 32:**34–40, 2011
22. Nesbitt WS, Westein E, Tovar-Lopez FJ, Tolouei E, Mitchell A, Fu J, et al: A shear gradient-dependent platelet aggregation mechanism drives thrombus formation. **Nat Med 15:**665–673, 2009
23. Phillips TJ, Wenderoth JD, Phatouros CC, Rice H, Singh TP, Devilliers L, et al: Safety of the pipeline embolization device in treatment of posterior circulation aneurysms. **AJNR Am J Neuroradiol 33:**1225–1231, 2012
24. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. **JAMA 305:**1097–1105, 2011 (Erratum in **JAMA 305:**2174, 2011)
25. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, et al: Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. **Eur Heart J 29:**992–1000, 2008
26. Puffer RC, Kallmes DF, Cloft HJ, Lanzino G: Patency of the ophthalmic artery after flow diversion treatment of paraclinoid aneurysms. Clinical article. **J Neurosurg 116:**892–896, 2012
27. Shobayashi Y, Tateshima S, Kakizaki R, Sudo R, Tanishita K, Vinuela F: Intra-aneurysmal hemodynamic alterations by a self-expandable intracranial stent and flow diversion stent: high intra-aneurysmal pressure remains regardless of flow velocity reduction. **J Neurointerv Surg** [epub ahead of print], 2012
28. Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al: Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. **AJNR Am J Neuroradiol 31:**1139–1147, 2010
29. van Rooij WJ, Sluzewski M: Perforator infarction after placement of a pipeline flow-diverting stent for an unruptured A1 aneurysm. **AJNR Am J Neuroradiol 31:**E43–E44, 2010
30. Velat GJ, Fargen KM, Lawson MF, Hoh BL, Fiorella D, Mocco J: Delayed intraparenchymal hemorrhage following pipeline embolization device treatment for a giant recanalized ophthalmic aneurysm. **J Neurointerv Surg 4:**e24, 2012
31. Woo KS, Kim BR, Kim JE, Goh RY, Yu LH, Kim MH, et al: Determination of the prevalence of aspirin and clopidogrel resistances in patients with coronary artery disease by using various platelet-function tests. **Korean J Lab Med 30:**460–468, 2010
32. Zimmermann N, Hohlfeld T: Clinical implications of aspirin resistance. **Thromb Haemost 100:**379–390, 2008

Manuscript submitted December 11, 2012.
Accepted July 11, 2013.
Please include this information when citing this paper: published online August 23, 2013; DOI: 10.3171/2013.7.JNS122178.

Address correspondence to: Adel M. Malek, M.D., Ph.D., Department of Neurosurgery, Tufts Medical Center, 800 Washington St., Boston, MA 02111. email: amalek@tuftsmedicalcenter.org.

Brought to you by Tufts University | Unauthenticated | Downloaded 11/15/26 12:41 PM UTC