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Thrombogenicity assessment of Pipeline Flex, Pipeline Shield, and FRED flow diverters in an in vitro human blood physiological flow loop model

Gaurav Girdhar,[1] Arielle Andersen,[2] Elizabeth Pangerl,[2] Reza Jahanbekam,[2] Samantha Ubl,[2] Kevin Nguyen,[1] John Wainwright,[1] Michael F. Wolf[2]

[1]Medtronic Neurovascular, Irvine, California
[2]Medtronic Core Technologies, Minneapolis, Minnesota

Received 22 May 2018; revised 21 June 2018; accepted 5 July 2018
Published online 22 September 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jbm.a.36514

Abstract: Endovascular treatment of intracranial aneurysms with endoluminal flow diverters (single or multiple) has proven to be clinically safe and effective, but is associated with a risk of thromboembolic complications. Recently, a novel biomimetic surface modification with covalently bound phosphorylcholine (Shield Technology™) has shown to reduce the material thrombogenicity of the Pipeline flow diverter. Thrombogenicity of Pipeline Flex, Pipeline Shield, and Flow Redirection Endoluminal Device (FRED) in the presence of human blood under physiological flow conditions—in addition to relative increase in thrombogenicity with multiple devices—remains unknown and was investigated here. Thrombin generation (mean ± SD; μg/mL; thrombin–antithrombin complex or TAT) was measured as FRED (30.3 ± 2.9), Pipeline (13.9 ± 4.4), Pipeline Shield (0.4 ± 0.3), and negative control (no device; 0.1 ± 0.0). Platelet activation (mean ± SD; IU/μL; beta-thromboglobulin or βTG) was measured as FRED (148 ± 45), Pipeline (92.8 ± 41), Pipeline Shield (16.2 ± 3.5), and negative control (2.70 ± 0.16). FRED was significantly more thrombogenic than Pipeline and Pipeline Shield ($p < 0.05$) for TAT. Additionally, Pipeline Shield had significantly lower TAT and βTG than the other devices tested ($p < 0.05$) and these were comparable to the negative control ($p > 0.05$). TAT and βTG scaled proportionately with multiple Pipeline devices ($N = 6$) but was unaffected by multiple Pipeline Shield ($N = 6$) devices—the latter being statistically similar to negative control ($p > 0.05$). © 2018 The Authors. *journal Of Biomedical Materials Research Part A* Published By Wiley Periodicals, Inc. J Biomed Mater Res Part A: 106A: 3195–3202, 2018.

Key Words: flow diversion, intracranial aneurysm, thrombosis, surface modification, phosphorylcholine

How to cite this article: Girdhar G, Andersen A, Pangerl E, Jahanbekam R, Ubl S, Nguyen K, Wainwright J, Wolf MF. 2018. Thrombogenicity assessment of Pipeline Flex, Pipeline Shield, and FRED flow diverters in an in vitro human blood physiological flow loop model. J Biomed Mater Res Part A 2018:106A:3195–3202.

INTRODUCTION

Endovascular treatment of intracranial aneurysms with flow diverters has proven to be a disruptive technology, with favorable clinical outcomes over traditional coiling and stent assisted coiling.[1,2] Flow diverters typically consist of tubular porous meshes that are deployed across the aneurysm neck that divert blood flow back into the parent vessel and away from the aneurysm. Thus, gradual coagulation of blood in the aneurysm followed by scaffolding at the neck leads to long-term healing of the aneurysm.[3] Dual antiplatelet therapy is mandatory with the use of intraluminal devices including flow diverters to mitigate thromboembolic complications. However, significant instances of thromboembolic events are still noted with flow diverters.[4] Multiple devices are sometimes implanted in one patient in overlapping or telescoping manner due to complex anatomy[5] or to achieve adequate flow diversion.[6] In some cases, implantation of up to 15 Pipeline devices in a single patient has been reported.[6] Moreover, the use of dual antiplatelet therapy limits the use of flow diverters for ruptured aneurysm treatments[2] in which overlapping devices are sometimes required.[7] Thus, there is significant interest in surface modification of flow diverters to improve hemocompatibility.

Building on the clinical success of the Pipeline Flex Embolization Device, a new development has been a novel surface treatment applied to the Pipeline implant surface (Pipeline Flex Embolization Device with Shield Technology™). The Pipeline Shield consists of a braid of 36 cobalt–chromium alloy wires together with 12 platinum wires for radiopacity. The device has a 3 nm phosphorylcholine-based surface modification (Shield Technology™) that is covalently bound to the braid surface. The surface treatment imparts a non-thrombogenic and biomimetic surface that has also been shown to reduce inflammation and increase early neointimal growth in preclinical studies,[8] in addition to reducing material thrombogenicity

Additional Supporting Information may be found in the online version of this article.
Correspondence to: M. F. Wolf; e-mail: michael.wolf@medtronic.com

and thrombus formation in several studies—in vitro,[9] ex vivo,[10] and in vivo.[11] This is supplemented by recent clinical data supporting the safety of Pipeline Shield with no major stroke or neurological death at 30 days follow-up.[12] Another device that has recently undergone clinical trial in the US is the FRED (Flow Redirection Endoluminal Device, Microvention).[13] This is a dual layer Nitinol device with a 16-wire stent-like outer structure loosely connected with two radiopaque helical strands to an inner 48-wire braided cylinder. The results of the SAFE trial show thromboembolic complications in 5% of patients with 6 months morbidity and mortality reported in 3% of the patients, at 6 months follow-up.[13] In another clinical study with FRED, thromboembolic complications were reported in 15% of the patients with 6% morbidity and mortality at 12 months follow-up.[14]

The combined effect of material and flow induced thrombogenicity for flow diverters with freshly collected human blood remains unknown, particularly with a dual-layer device. In vitro closed loop models have been used with some variations previously to investigate blood–device interactions for a range of vascular devices including coronary and vascular stents.[15–19] These models consist of short lengths of plastic tubular segments connected end-to-end in a torus configuration, some with a check value for unidirectional flow of blood. Advantages of our model include the following: (1) blood is directly filled into loops from the antecubital vein of the donor and this avoids potential for artifacts in coagulation due to blood contact with other intermediary blood storage/transfer materials; (2) no time delay in blood introduction to the test system; and (3) no exposure of blood to air. Additionally, flow is driven by a pulsatile drive unit external to the loops to impart a certain physiological blood flow and/or shear rates. Platelet activation and thrombin generation can be measured as end points with clinically relevant assays.[16]

In this study, we compare the thrombogenicity of single devices—FRED, Pipeline Flex, and Pipeline Shield—with an in vitro human blood physiological flow-loop model. Additionally, we compare the thrombogenicity of multiple Pipeline and Pipeline Shield devices in a single flow-loop relative to the negative control under two different levels of anticoagulation.

MATERIALS AND METHODS

Devices

For the study of single device thrombogenicity, the following three flow diversion devices were tested: (a) Pipeline Flex Embolization Device with Shield Technology™ (Pipeline Shield, N = 2, 5 mm × 35 mm, Medtronic); (b) Pipeline Flex Embolization Device (Pipeline, N = 2, 5 mm × 35 mm, Medtronic); and (c) Flow Redirection Device (FRED, N = 2, 5 mm × 36 mm, Microvention). Devices were deployed in medical grade PVC tubing (4.76 mm internal diameter, Medtronic). All devices tested were final sterilized products. A summary of devices evaluated is shown in Table I.

For thrombogenicity evaluation of multiple devices in one loop, the braids representative of the following two flow diversion devices were tested: (a) Pipeline Flex Embolization Device with Shield Technology™ (Pipeline Shield, N = 48, 5 mm × 35 mm, Medtronic); and (b) Pipeline Flex Embolization Device (Pipeline, N = 48, 5 mm × 35 mm, Medtronic).

TABLE I. Name and Brief Description of Flow Diversion Devices Tested in This Study

Device Name (Abbreviation)	Description of the Implant Section Of Each Device
Pipeline Flex Embolization Device (Pipeline)	A self-expanding mesh cylinder braided from cobalt–chromium alloy wires
Pipeline Flex Embolization Device with Shield technology™ (Pipeline Shield)	A self-expanding mesh cylinder braided from cobalt–chromium alloy wires, with a novel surface treatment of the implant
Flow Redirection Endoluminal Device (FRED)	A dual-layered self-expanding mesh with outer and inner cylinders braided from nitinol wires

The abbreviated form of the device name is used throughout the article.

Flow-loop model

A single closed loop consisted of a hollow circular, torus-shaped assembly of plastic tubing containing two blood injection/withdraw ports and a single one-way check valve (Fig. 1, left). Test devices are placed into the lumen as shown in Figure 1 (middle). The total volume of each loop is ~6.4 mL. Each loop is prefilled with heparin diluted in PlasmaLyte A (Baxter) buffer solution such that the final desired heparin concentration in blood is 0.6 or 1.0 U/mL (80% whole blood and 20% heparin and PlasmaLyte A; by volume). Blood is collected from healthy adult human volunteers in accordance with Institutional Review Board approved protocols. Blood is drawn from the antecubital vein of the human donor directly into each loop by saline displacement into a 10-mL syringe until each loop has 5.0 mL of blood. As they are filled, loops are mounted on a 10-cm-diameter drum which is connected to a programmable computer driven hollow rotary actuator (pulsatile drive system) that applies a defined and repeating motion profile to the drum (Fig. 1, right). The precise motion profile involves a 0.5–1.0–0.5 acceleration-constant speed–deceleration (rev/s^2–rev/s–rev/s^2) pulse followed by an 800 ms pause (see Supporting Information, video file). This motion corresponds to pulsatile flow (pulse rate of 60 per minute) profile of the blood inside the loop with an average flow rate of 100 mL/min. This flow rate is representative of the average of the lower end of reported ICA (Internal Carotid Artery) blood flow rates estimated by magnetic resonance phase contrast imaging.[20] The order of filling of loops and thereby placement on the drum was randomized. This eliminated bias in potential anomalies during the fill process, such as a slow increase or decrease in blood activation.

At some point before 60 ± 1 min from filling the first loop with blood, the clockwise motion imparted by pulsatile

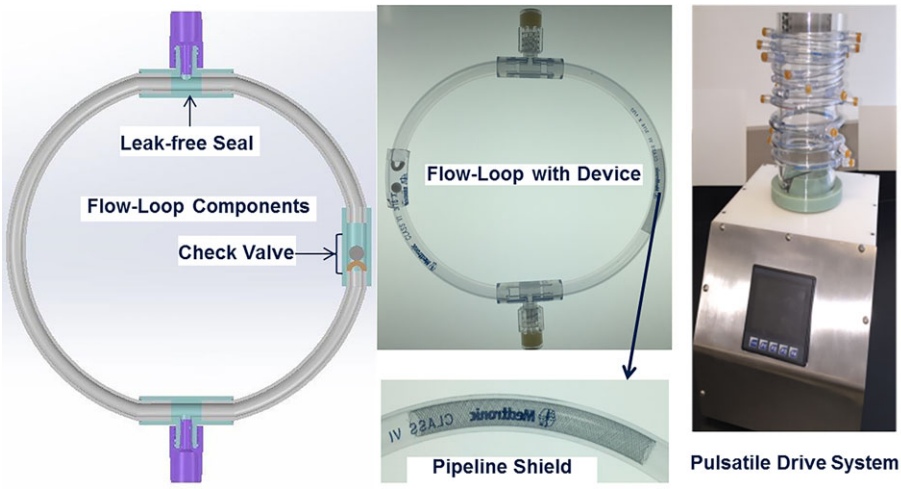

FIGURE 1. (Left) Flow-loop construction with leak-free seals. (Middle) Flow-loop with Pipeline Shield device. (Right) Pulsatile drive system with flow-loops mounted.

drive system is temporarily stopped, the drum is removed and inverted, then the drum is quickly reattached and the system restarted in counterclockwise motion. This process results in the putting the first-to-last loops filled in the top-to-bottom positions on the drum for easy removal while maintaining pulsatile flow. Loop orientation and rotational direction is critical as pulsatile flow in such loops requires the rotational motion to result in valve closure during each cycle, and, improper orientation/motion direction results in elimination of flow. Loops were therefore removed from the top of the drum in the order of blood filling. This ensured that the blood exposure time for each loop remained at ~60 ± 2–3 min.

Single device thrombogenicity study

A total of 8 loops with a single device each were used for evaluations (N = 6 test devices; N = 2 negative control/empty loops) with blood collected from one donor. After each experiment, blood was withdrawn from each loop into syringes prefilled with CTAD (citrate, theophylline, adenosine, and dipyridamole) solution (1/10th by volume) and put on ice to immediately arrest any further coagulation and platelet activation, post experiment. This blood was then centrifuged (2500g for 20 min) and the supernatant plasma frozen at −80°C until analysis with commercial ELISA kits for TAT complex generation (Ezygnost TAT Micro, Siemens) or platelet activation (βTG, Diagnostica Stago). Each loop was gently rinsed with PlasmaLyte A to remove nonadherent blood, photographed for gross thrombus, and then filled with Karnovsky's fixative for scanning electron microscopy (SEM) analysis.

Multiple device thrombogenicity study

A total of 24 loops were used for evaluations (N = 8 Pipeline; N = 8 Pipeline Shield; N = 8 negative control—empty loops). Two blood donors were utilized in addition to two heparin levels (0.6 and 1.0 U/mL). All experiments were run in duplicate for each blood donor. The post-processing steps are identical to those mentioned in the single device thrombogenicity study.

SEM analysis of thrombus

Following gentle rinsing in PlasmaLyte A to remove nonadherent blood elements and fixation in Karnovsky's reagent, a ~1.0 cm length of each flow diverter was cut out of loops leaving the tubing sheath present. These samples were secondarily fixed in osmium tetroxide for 1 h and dehydrated in graded ethanol from 40% to 100%. They were then subjected to critical point drying using a Tousimous Autosamdri-815 critical point dryer. The stents were then carefully removed from the PVC sheaths, longitudinally hemisected, mounted, and sputter coated with Au/Pd coated for 30–80 s using a Denton Vacuum Desk II sputter coater. A JEOL 6700F field emission scanning electron microscope was then used to take representative 30–2000× micrographs of the flow diverter luminal surfaces.

STATISTICAL ANALYSIS

TAT (thrombin generation) and βTG (platelet activation) values reported are mean ± SD (standard deviation). Values are reported up to three significant digits which is within the accuracy limits of the assays.

For the single device thrombogenicity study, ANOVA was performed for thrombin generation and platelet activation measurements for the three test devices and 1 negative control. A post-hoc Fisher's t test was used to identify individual differences between devices with a significance value of 0.05.

For multiple device thrombogenicity study, ANOVA was performed to evaluate the effect of blood donor, heparin level, and device type, on thrombin generation and platelet activation measurements. Post-hoc Fisher's t test was used to identify individual differences between devices with a significance value of 0.05.

RESULTS

Single device thrombogenicity study

For single device thrombogenicity study, ANOVA showed that there were significant differences between the devices for thrombin generation and platelet activation measurements ($p < 0.05$).

Gross thrombus analysis. Significant accumulation of thrombus was observed on FRED and Pipeline devices. The loops with Pipeline Shield and empty loops (negative control) did not have significant attachment of thrombus [Fig. 2(A)].

Thrombin generation. Thrombin generation was measured as follows (mean ± SD; μg/mL; TAT): FRED (30.3 ± 2.9), Pipeline (13.9 ± 4.4), Pipeline Shield (0.4 ± 0.3), and negative control (no device; 0.1 ± 0.0). The results are shown in Figure 2(B). FRED had significantly higher thrombin generation than other devices tested. Thrombin generation was significantly lower for the Pipeline Shield compared to Pipeline and FRED. Additionally, thrombin generation was comparable between the negative control (empty loop) and Pipeline Shield. A summary of p values for post-hoc Fisher's *t* test is shown in Table II.

Platelet activation. Platelet activation was measured as follows (mean ± SD; IU/μL; βTG): FRED (148 ± 45), Pipeline (92.8 ± 41), Pipeline Shield (16.2 ± 3.5), and negative control (2.70 ± 0.16). The results are shown in Figure 2(C). Platelet activation was significantly lower for the Pipeline Shield compared to Pipeline and FRED. Additionally, platelet activation was comparable between the negative control (empty loop) and Pipeline Shield. A summary of p values for post-hoc Fisher's *t* test is shown in Table II.

SEM analysis of thrombus. High-resolution scanning electron microscopy (SEM) images were obtained for each device at three magnifications (30×, 300×, and 2000×). Adherent activated platelets with significant acellular proteinaceous deposits were observed on Pipeline and FRED devices [Fig. 2 (D)]. In some instances, the struts of the devices (FRED, see 30× magnification image) were completely covered with thrombus. The thrombus appears to be an intercalated network of cross-linked fibrin with entrapped activated platelets and red blood cells. On the other hand, significantly reduced accumulation was observed on Pipeline Shield for both cellular and acellular blood components with the absence of intercalated fibrin network. Additionally, the wires of the Pipeline Shield device were clearly visible without significant accumulation even at higher magnifications (2000×). These images show strong correspondence with the measurements for thrombin generation and platelet activation reported in this study.

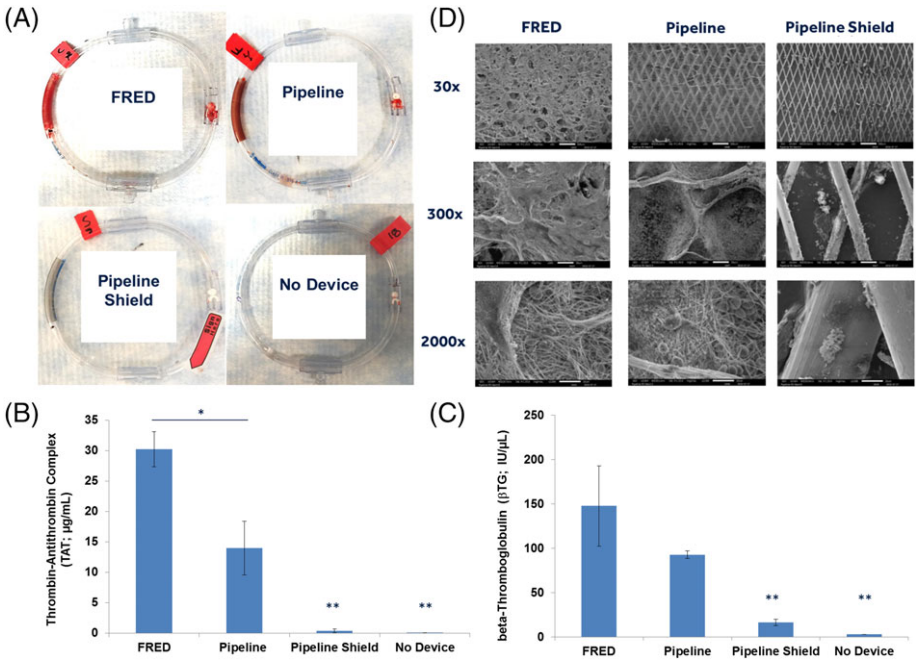

FIGURE 2. A: Images of the flow-loops for single device thrombogenicity study post-experiment. Gross observation of thrombus on the FRED, Pipeline, Pipeline Shield devices, and negative control (no device). B: Thrombin–antithrombin (TAT) complex formation measured post-experiment for single devices with 0.6 U/mL heparin concentration in blood: FRED, Pipeline, Pipeline Shield, and no device (negative control). TAT (mean ± SD) values for Pipeline Shield and no device are statistically equivalent and significantly less than FRED and Pipeline (**). TAT for FRED is significantly higher than Pipeline (*). C: beta-Thromboglobulin (βTG) release measured post-experiment for single devices with 0.6 U/mL heparin concentration in blood: FRED, Pipeline, Pipeline Shield, and no device (negative control). βTG (mean ± SD) values for Pipeline Shield and no device are statistically equivalent and significantly less than FRED and Pipeline (**). D: High-resolution scanning electron microscopy (SEM) images of thrombus accumulation on FRED, Pipeline, and Pipeline Shield devices (30×, 300×, and 2000× magnification).

TABLE II. Post-Hoc Fisher's *t* Test was Conducted to Distinguish Between Test Devices

Device Pair	p value (TAT)	p value (βTG)
Pipeline Shield and FRED	0.000	0.004
Pipeline Shield and Pipeline	0.007	0.028
Pipeline Shield and no device	0.913	0.585
FRED and Pipeline	0.004	0.073
FRED and no device	0.000	0.003
Pipeline and no device	0.006	0.017

The p values show that thrombin generation (TAT) and platelet activation (βTG) for Pipeline Shield is comparable to negative control.

Multiple device thrombogenicity study

For multiple device thrombogenicity study, ANOVA showed that there was no significant effect of blood donor and heparin concentration on platelet activation and thrombin generation measurements ($p > 0.05$). The differences were significant for platelet activation and thrombin generation measurements ($p < 0.05$) due to the test article. The individual data for thrombin generation (TAT) and platelet activation (βTG) are shown in Figure 3(B,C), respectively. As heparin concentration and blood donor did not have a significant effect on the measured parameters, the combined data are reported below.

Gross thrombus analysis. Significant accumulation of thrombus was observed on Pipeline devices. The loops with Pipeline Shield and empty loops (negative control) did not have significant attachment of thrombus [Fig. 3(A)].

Thrombin generation. Thrombin generation across all conditions was measured as (mean ± SD; μg/mL; TAT): Pipeline (39.1 ± 12), Pipeline Shield (0.63 ± 0.6), and negative control (0.31 ± 0.4). The results are shown in Figure 3(B). Thrombin generation was significantly lower for the Pipeline Shield compared to Pipeline ($p < 0.05$). Additionally, thrombin generation was comparable between the negative control (empty loop) and Pipeline Shield ($p > 0.05$).

Platelet activation. Platelet activation across all conditions was measured as (mean ± SD; IU/μL; βTG): Pipeline (146 ± 24), Pipeline Shield (23.6 ± 17), and negative control (9.05 ± 8.5). The results are shown in Figure 3(C). Platelet activation was significantly lower for the Pipeline Shield compared to Pipeline ($p < 0.05$). Additionally, platelet activation was comparable between the negative control (empty loop) and Pipeline Shield ($p > 0.05$).

DISCUSSION

In this study, we report thrombin generation and platelet activation for FRED, Pipeline Flex, and Pipeline Shield flow diverters when exposed to freshly drawn human blood under physiological flow conditions. We show that increase in thrombin and platelet activation corresponds to higher deposition of cellular and acellular blood components on these devices. We demonstrate that Pipeline Shield has the lowest thrombogenicity of all devices tested and is statistically comparable to negative control for TAT and βTG measurements. This additionally confirms our prior findings regarding the non-thrombogenic profile of Pipeline Shield with reference to platelet and fibrin adhesion to the device surface ex vivo[10] and in vivo[11] as well as reduced thrombin generation in vitro.[9] The combined effects of material and flow induced thrombogenicity becomes more apparent for dual-layer devices such as FRED, where separation between the two layers could potentially create a nidus for entrapment and growth of thrombus. This is reflected in the high-resolution SEM images for FRED and higher thrombin generation and platelet activation relative to the Pipeline device.

We also compared the relative thrombogenicity (TAT and βTG) of multiple flow diverters in a single loop. We note

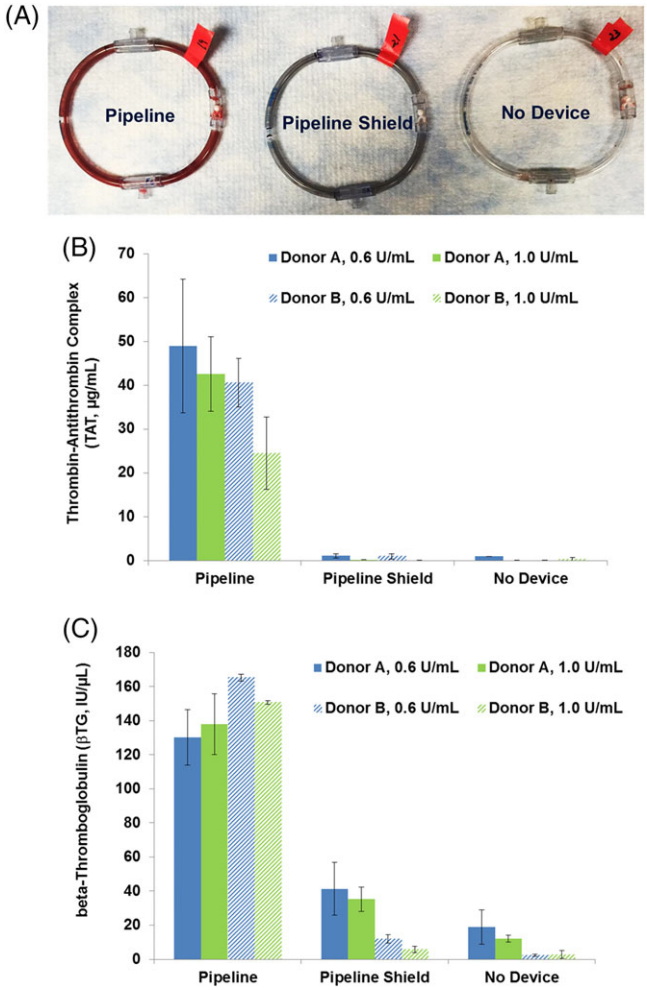

FIGURE 3. A: Images of the flow-loops for multiple ($N = 6$ devices per loop) device thrombogenicity study post-experiment. Gross observation of thrombus on the Pipeline, Pipeline Shield devices, and negative control (no device). B: Thrombin–antithrombin (TAT) complex formation measured post-experiment for Pipeline ($N = 6$ devices per loop), Pipeline Shield ($N = 6$ devices per loop), and no device (negative control). TAT values (mean ± SD) are shown for two blood donors and two heparin concentrations in blood. C: beta-Thromboglobulin (βTG) measured post-experiment for Pipeline ($N = 6$ devices per loop), Pipeline Shield ($N = 6$ devices per loop), and no device (negative control). βTG values (mean ± SD) are shown for two blood donors and two heparin concentrations in blood.

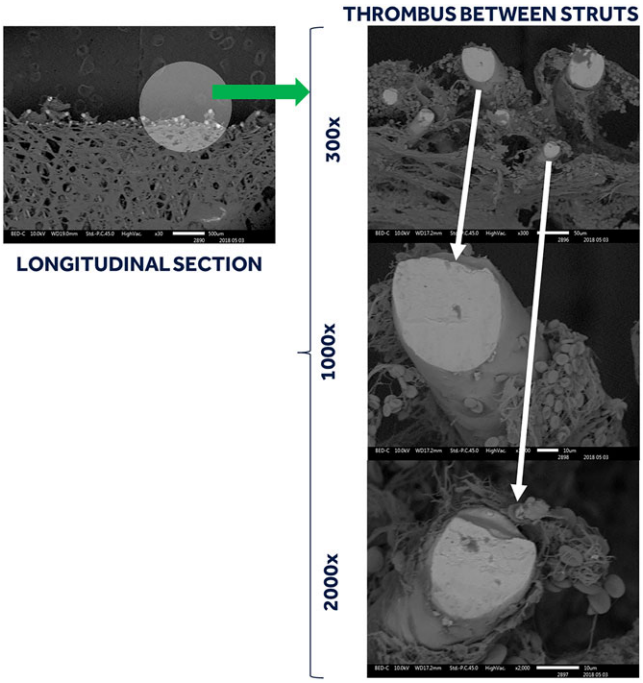

FIGURE 4. (Left) Longitudinal sectional view of the FRED device showing spacing between the inner and outer braids and thrombus accumulation. (Right) High-resolution SEM image of thrombus formation between the two layers (300×) and on the outer braid strut (1000×) and inner braid strut (2000×)

that the thrombogenicity of braids equivalent to six Pipeline Shield devices (5 mm × 35 mm) in one loop was remarkably similar to Negative Control [empty loop; TAT and βTG; Fig. 3 (B,C)] and a single Pipeline Shield device [TAT and βTG; Fig. 2(B,C)] with minimal accumulation of thrombus on the devices [Figs. 2(A) and 3(A)]. These measures were independent of blood donor and heparin concentrations. We also note that the thrombogenicity of six Pipeline devices [TAT and βTG; Fig. 3(B,C)] was higher than a single Pipeline device [TAT and βTG; Fig. 2(B,C)] as expected due to increase in the overall bare metal surface area exposed to the same volume of blood. Interestingly, the magnitudes of TAT and βTG with six Pipeline devices [Fig. 3(B,C)] are similar in magnitude to a single FRED device [Fig. 2(B,C)]. The higher thrombogenicity of FRED could also be attributed to the dual layer structure of the device (Fig. 4, left). The spacing between the two layers (∼100 μm on average, Fig. 5) could disrupt flow, increase stasis, trap activated platelets, and serve as a nidus for further thrombus accumulation. This is evident from the sectional SEM view of the FRED device post-experiment with significant accumulation of thrombus between the two layers of the device (Fig. 4, right).

We utilized two fundamental markers of thrombosis as end points in this study. The increase of TAT above baseline indicates progressive thrombin formation and the consumption of anti-thrombin, and is therefore widely accepted as a clinical biomarker for intravascular generation of thrombin.[21,22] Similarly, βTG is a measure of platelet degranulation (alpha-granule release) which is a direct consequence of platelet activation.[23] Both these markers were similar to negative control (empty loop) for the Pipeline Shield device post-experiment.

A well-established closed-loop system[16] was used to expose the devices to human blood. Although this closed-loop system has several advantages over traditional flow-loop methods,[15] some notable drawbacks are as follows: (a) the loops require a small check valve to support pulsatile flow generation—this being a first generation ball-and-cage valve does induce some flow induced thrombogenicity to the baseline negative control; (b) assuring proper anticoagulation requires leaving some of the anticoagulated buffer behind after buffer displacement—causing some blood dilution; (c) the system itself requires an expensive computer-controlled micro-stepper motor to impart a controlled rotational pattern.

All flow diverters were evaluated without an aneurysm present in the flow loop. This was done to clearly distinguish the intraluminal material and flow induced thrombogenicity—separate from the flow diversion properties of each device. Adding an aneurysm to the loop would confound results as the blood in the aneurysm would pool more effectively for a better flow diverter and—due to the closed loop nature of the setup—could thereby result in higher thrombin generation even with a non-thrombogenic surface treatment of the flow diverter (such as Shield Technology™). We also note that the sample size for the devices investigated in the single device comparison study here is low, and does not account for variability between blood donors.[24] However, the thrombogenicity differences observed here between Pipeline Shield and other flow diverters are very significant, and are therefore unlikely to be affected by blood donor variabilities or sample sizes in this context. The difference in results is qualitatively similar to that observed previously for Pipeline Shield and FRED, both in vitro[9] and ex vivo.[10]

Species wide coagulation profile differences are apparent from previous reports.[25] The result in showing reduced thrombogenicity with Shield Technology in this study with freshly drawn human blood and previous studies in nonhuman primate and rabbits[9,11] confirm the hypothesis that although species wide differences in coagulation may exist, the overall thrombogenicity differences between Pipeline Shield and other flow diverter devices are clearly evident.

With this study, we have therefore demonstrated that under clinically worse case situations (low level of heparin in a closed recirculating flow-loop), Pipeline Shield may still have favorable outcomes for such patients in the form of lower overall material thrombogenicity. This is supported by recent clinical evidence citing the safety of Pipeline Shield in such situations.[26,27] In contrast, FRED has clinical reports of high thromboembolic complications (15%) despite a full regimen of dual anti-platelet therapy until follow-up.[14] This highlights some of the deficiencies of a dual-layer device which may allow an intercalated network of thrombus to form and grow with time. In contrast, multiple Pipeline Shield devices when exposed to the same conditions in this study did not exhibit an increase in thrombogenicity as compared to a

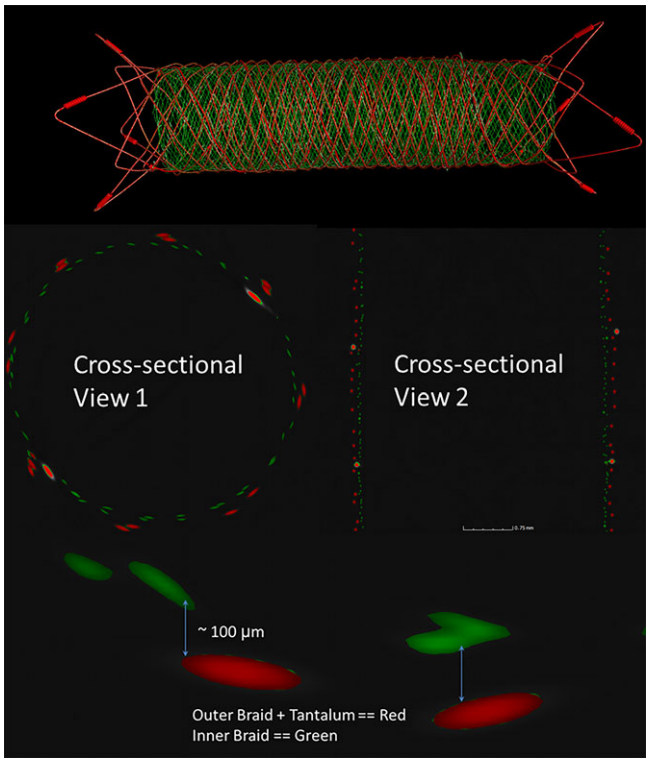

FIGURE 5. Micro-CT scanned image of the FRED device with post-processing showing the inner and outer braids, cross-sectional views showing the separation between the two layers, and an expanded view showing the approximately 100 µm separation between the two layers of the device

single Pipeline Shield device and the negative control. Given the likelihood of multiple devices being used in the same patient in a clinical setting, the reduction in thrombogenicity with Pipeline Shield could potentially reduce the rate of device material related thromboembolic events.

CONCLUSIONS

This in vitro study demonstrates significantly lower thrombogenicity of Pipeline Flex Embolization device with Shield Technology™ in a human blood flow loop model relative to Pipeline Flex Embolization Device and Flow Redirection Endoluminal Device (FRED). Additionally, FRED was significantly more thrombogenic than the Pipeline device for thrombin generation measured in this study. Multiple Pipeline Shield devices (six-fold higher material surface exposed to blood) had thrombogenicity statistically similar to the negative control in this study. These results were independent of blood donor and heparin concentrations.

REFERENCES

1. Zuckerman SL, Eli IM, Morone PJ, Dewan MC, Mocco J. Novel technologies in the treatment of intracranial aneurysms. Neurol Res 2014;36(4):368–382.
2. Alderazi YJ, Shastri D, Kass-Hout T, Prestigiacomo CJ, Gandhi CD. Flow diverters for intracranial aneurysms. Stroke Res Treat 2014; 2014:415653.
3. Starke RM, Turk A, Ding D, Crowley RW, Liu KC, Chalouhi N, Hasan DM, Dumont AS, Jabbour P, Durst CR, Turner RD. Technology developments in endovascular treatment of intracranial aneurysms. J Neurointerv Surg 2016;8:135–144.
4. 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 2011;32(1):34–40.
5. Keskin F, Erdi F, Kaya B, Poyraz N, Keskin S, Kalkan E, Ozbek O, Koc O. Endovascular treatment of complex intracranial aneurysms by Pipeline flow-diverter embolization device: A single-center experience. Neurol Res 2015;37(4):359–365.
6. Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, Moran CJ, Woo HH, Lopes DK, Berez AL, Cher DJ, Siddiqui AH, Levy EI, Albuquerque FC, Fiorella DJ, Berentei Z, Marosfoi M, Cekirge SH, Nelson PK. Pipeline for uncoilable or failed aneurysms: Results from a multicenter clinical trial. Radiology 2013;267(3): 858–868.
7. Martin AR, Cruz JP, Matouk CC, Spears J, Marotta TR. The Pipeline flow-diverting stent for exclusion of ruptured intracranial aneurysms with difficult morphologies. Neurosurgery 2012;70(1 Suppl Operative):21–28. discussion 28.
8. Matsuda Y, Chung J, Lopes DK. Analysis of neointima development in flow diverters using optical coherence tomography imaging. J Neurointerv Surg 2018;10(2):162–167.
9. Girdhar G, Li J, Kostousov L, Wainwright J, Chandler WL. In-vitro thrombogenicity assessment of flow diversion and aneurysm bridging devices. J Thromb Thrombolysis 2015;40(4):437–443.
10. Hagen MW, Girdhar G, Wainwright J, Hinds MT. Thrombogenicity of flow diverters in an ex vivo shunt model: Effect of phosphorylcholine surface modification. J Neurointerv Surg 2017;9(10):1006–1011.
11. Marosfoi M, Clarencon F, Langan ET, King RM, Brooks OW, Tamura T, Wainwright JM, Gounis MJ, Vedantham S, Puri AS. Acute thrombus formation on phosphorilcholine surface modified flow diverters. J Neurointerv Surg 2018;10(4):406–411.
12. Martinez-Galdamez M, Lamin SM, Lagios KG, Liebig T, Ciceri EF, Chapot R, Stockx L, Chavda S, Kabbasch C, Farago G, Nordmeyer H, Boulanger T, Piano M, Boccardi EP. Periprocedural outcomes and early safety with the use of the Pipeline Flex embolization device with Shield technology for unruptured intracranial aneurysms: Preliminary results from a prospective clinical study. J Neurointerv Surg 2017;9(8):772–776.

13. Pierot L, Spelle L, Berge J, Januel AC, Herbreteau D, Aggour M, Piotin M, Biondi A, Barreau X Mounayer C, Papagiannaki C, Lejeune JP, Gauvrit JY, Costalat V. Feasibility, complications, morbidity, and mortality results at 6 months for aneurysm treatment with the Flow Re-Direction Endoluminal Device: Report of SAFE study. J Neurointerv Surg 2018, 10(8):765-770.
14. Mounayer C, Papagiannaki C, Lejeune JP, Gauvrit JY, Costalat V, Drescher F. Treatment of intra- and extracranial aneurysms using the flow-redirection endoluminal device: Multicenter experience and follow-up results. J Neurointerv Surg 2017;38(1): 105–112.
15. van Oeveren W, Tielliu IF, de Hart J. Comparison of modified chandler, roller pump, and ball valve circulation models for in vitro testing in high blood flow conditions: Application in thrombogenicity testing of different materials for vascular applications. Int J Biomater 2012;2012:673163.
16. Munch K, Wolf MF, Gruffaz P, Ottenwaelter C, Bergan M, Schroeder P, Fogt EJ. Use of simple and complex in vitro models for multiparameter characterization of human blood-material/device interactions. J Neurointerv Surg 2000;11(11):1147–1163.
17. Gardner RA. An examination of the fluid mechanics and thrombus formation time parameters in a Chandler rotating loop system. J Lab Clin Med 1974;84(4):494–508.
18. Sinn S, Scheuermann T, Deichelbohrer S, Ziemer G, Wendel HP. A novel in vitro model for preclinical testing of the hemocompatibility of intravascular stents according to ISO 10993-4. J Mater Sci Mater Med 2011;22(6):1521–1528.
19. Tepe G, Wendel HP, Khorchidi S, Schmehl J, Wiskirchen J, Pusich B, Claussen CD, Duda SH. Thrombogenicity of various endovascular stent types: An in vitro evaluation. J Vasc Interv Radiol 2002;13(10):1029–1035.
20. Oktar SO, Yucel C, Karaosmanoglu D, Akkan K, Ozdemir H, Tokgoz N, Tali T. Blood-flow volume quantification in internal carotid and vertebral arteries: Comparison of 3 different ultrasound techniques with phase-contrast MR imaging. AJNR Am J Neuroradiol 2006;27(2):363–369.
21. Fernandez-Cadenas I, Mendioroz M, Munuera J, Alvarez-Sabin J, Rovira A, Quiroga A, Corbeto N, Rubiera M, Delgado P, Rosell A. And others. Lower concentrations of thrombin-antithrombin complex (TAT) correlate to higher recanalisation rates among ischaemic stroke patients treated with t-PA. Thromb Haemost 2009;102(4):759–764.
22. Sekiya A, Hayashi T, Kadohira Y, Shibayama M, Tsuda T, Jin X, Nomoto H, Asakura H, Wada T, Ohtake S, Morishita E. Thrombosis prediction based on reference ranges of coagulation-related markers in different stages of pregnancy. Clin Appl Thromb Hemost 2017;23(7):844–850.
23. Walkowiak B, Cierniewski CS. Kinetics of the beta-thromboglobulin release from alpha-granules of blood platelets activated by ADP. Thromb Res 1987;46(5):727–736.
24. Brummel-Ziedins K, Vossen CY, Rosendaal FR, Umezaki K, Mann KG. The plasma hemostatic proteome: Thrombin generation in healthy individuals. J Thromb Haemost 2005;3(7): 1472–1481.
25. Siller-Matula JM, Plasenzotti R, Spiel A, Quehenberger P, Jilma B. Interspecies differences in coagulation profile. Thromb Haemost 2008;100(3):397–404.
26. Hanel RA, Aguilar-Salinas P, Brasiliense LB, Sauvageau E. First US experience with Pipeline Flex with Shield Technology using aspirin as antiplatelet monotherapy. BMJ Case Rep 2017; https://doi.org/10.1136/bcr-2017-219406.
27. Chiu AH, Ramesh R, Wenderoth J, Davies M, Cheung A. Use of aspirin as sole oral antiplatelet therapy in acute flow diversion for ruptured dissecting aneurysms. J Neurointerv Surg 2017; 9(5):e18.