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Original research

Poly(2-methoxyethyl acrylate) (PMEA) improves the thromboresistance of FRED flow diverters: a thrombogenic evaluation of flow diverters with human blood under flow conditions

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ABSTRACT

Background Surface modification of flow-diverting stents has been explored to reduce thrombus-related complications that may arise under clinical use. This study investigated the thromboresistant properties of the flow redirection endoluminal device (FRED) X, a flow diverter treated with a copolymer of poly(2-methoxyethyl acrylate) (PMEA; X Technology).

Methods The performance of FRED, FRED X, and Pipeline Flex with Shield Technology (sPED) was evaluated in an in vitro blood loop model. Blood activation level was assessed by the concentration of thrombin-antithrombin complex (TAT), β-thromboglobulin (β-TG), and platelet count, and qualitatively by scanning electron microscopy (SEM). Cellular adhesion characteristics were measured using human aortic endothelial cells that were seeded on flat sheets mimicking the surface of FRED, FRED X, and sPED, and evaluated with fluorescence microscopy. Statistical comparisons were conducted using one-way analysis of variance (ANOVA) with Tukey post hoc tests.

Results FRED X, sPED, and control blood loops showed significantly reduced blood activation levels (TAT and β-TG) compared with FRED ($p<0.01$). Consequently, FRED showed a significant decrease in platelet count compared with FRED X, sPED, and control loops ($p<0.01$). SEM imaging showed the lowest accumulation of blood cell-like deposits on FRED X compared with sPED and FRED, while FRED had the highest accumulation. Endothelial cells adhered and were widely spread on X Technology-treated sheets, while minimal cell adhesion was observed on phosphorylcholine-treated sheets.

Conclusion The X Technology surface modification of FRED X demonstrated superior thromboresistant properties over untreated FRED while maintaining comparable cellular adhesion. Taken together, these properties may help mitigate material-related thromboembolic complications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preclinical and clinical research has shown that surface modification of flow diverters can reduce the thrombogenicity profile of the device, potentially reducing thrombus-related complications; however, the antithrombic and cellular adhesion properties of X Technology—a novel poly(2-methoxyethylacrylate) copolymer that is covalently bonded to the surface of the flow redirection endoluminal device (FRED) flow diverter—have not yet been evaluated in preclinical experimentation.

WHAT THIS STUDY ADDS

⇒ The X Technology surface modification of FRED X demonstrated superior thromboresistant properties over untreated FRED while maintaining comparable cellular adhesion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that using FRED X in endovascular procedures could potentially decrease the risk for thromboembolic complications, and may also reduce the need for perioperative and postoperative dual antiplatelet therapy; however, further research is needed to fully elucidate the effectiveness and clinical impact of this surface modification.

INTRODUCTION

Cerebral aneurysm treatment strategies changed dramatically with the introduction of detachable intrasaccular coils. The use of coil embolization was a fundamental shift from open to endovascular methods and led to better safety and efficacy outcomes compared with prior interventions.[1] Intrasaccular coils were eventually found to be limited in their ability to completely occlude certain aneurysms—particularly large and fusiform types—which spurred research into alternative and innovative endovascular methods to manage these challenging cases.[2]

These efforts led researchers to develop flow-diverting stents, or flow diverters, which were predicated on a new approach to aneurysm management in which the aneurysm is excluded from the blood circulation. Flow diverters redirect blood flow along the parent artery by passing the vessel wall defect, allowing the aneurysm to be occluded while the parent artery is simultaneously reconstructed through endoluminal neointimal growth. The ability to repair the parent artery is the essence of flow

diverter treatment and characterizes the potential of these devices to treat many more types of vessel wall abnormalities than intrasaccular coils.[3]

Unfortunately, flow diverters carry inherent disadvantages due to the high surface area coverage (approximately 30–35%) required to achieve sufficient flow diversion.[4] Consequently, perioperative ischemic complications from intrastent thrombus formation can occur more frequently than with other therapies.[5] Aneurysm occlusion also depends highly on the device surface area and porosity, and thus, it is not possible to reduce device surface area without adversely affecting flow diversion properties.[6] To suppress the propensity of intrastent thrombus formation, patients must undergo dual antiplatelet treatment before and after flow diverter procedures to reduce the risk for thromboembolic events, which can in turn create a separate risk for hemorrhagic complications.[5]

To address this problem, surface treatments and coating technologies have been developed to improve device thromboresistance with the aim of limiting intrastent thrombus formation and potentially reducing dependence on antiplatelet drugs. A biopassive polymer called poly(2-methoxyethyl acrylate) (PMEA) has been studied for several decades and has previously been used as a surface treatment for artificial lung machines.[7] Research has shown that PMEA is biocompatible and consistently imparts thromboresistance to various surfaces.[7–9] An analog of this technology has been developed by MicroVention Inc (Aliso Viejo, CA), in which a copolymer mostly containing PMEA is covalently bonded to the surface of the flow redirection endoluminal device (FRED) flow diverter to impart permanent thromboresistance. The FRED device consists of a self-expanding dual-layered braided stent with an inner low-porosity mesh and an outer high-porosity mesh. The PMEA copolymer is referred to as X Technology and the surface-modified FRED device is therefore called FRED X. Surface modification with a PMEA homopolymer is referred to as X Coating and is physically adsorbed onto the flow diverter surface (non-covalent).

Several other flow diverters with surface modifications are also available. The Pipeline Flex embolization device with Shield Technology (sPED; Medtronic Neurovascular, Irvine, CA) has a phosphorylcholine polymer covalently bonded to its stent, while the p48 and p64 MW hydrophilic polymer coating (HPC) flow modulation devices (phenox GMbH, Bochum, Germany) are treated with a glycan-based HPC covalently bonded to its stent.[10] Although research has shown that phosphorylcholine can effectively impart antithrombogenic properties to the metal surface of sPED, it may also have a deleterious impact on cellular adhesion and growth in vitro.[11] Meanwhile, the antithrombotic properties of X Technology have not yet been evaluated in an in vitro experiment with human blood.

Therefore, in this study, we quantitatively and qualitatively assessed the performance of FRED X by analyzing in vitro blood circulation and cellular adhesion models.

MATERIALS AND METHODS

Stent devices

Three endoluminal flow diverting devices were used: (1) FRED (5.0 mm × 29 mm; MicroVention, Inc); (2) FRED X (5.0 mm × 29 mm; MicroVention, Inc); and (3) sPED (4.75 mm × 35 mm). All devices tested were commercially available and sterile. Stent sizes were selected to treat equivalent parent vessel and aneurysm size per company instructions. Four devices of each stent type were tested.

General design

The thrombogenicity of each flow diverter was evaluated with a Chandler loop circulation system, which consisted of polyvinyl chloride tubes formed into loops and implanted with a flow diverter. Stent performance was evaluated by measuring platelet count, β-thromboglobulin (β-TG) as an index for platelet activation, and thrombin-antithrombin complex (TAT) as an index for blood coagulation system activation. The surface of each flow diverter was observed after blood circulation with a scanning electron microscope (SEM). Blood was obtained from four healthy volunteers. Each donor's blood was simultaneously tested on a negative control loop and loops containing a single FRED, FRED X, and sPED. Blood draws were conducted according to a protocol approved by the institutional review board after informed consent was given.

Perfusion study with Chandler loop system

The polyvinyl chloride tubes had an inside diameter of 4.76 mm. The tubes and terminal connectors were pre-coated with the PMEA polymer (X Coating, Terumo Co., Ltd., Tokyo, Japan) to reduce the likelihood of background response intrinsic to the equipment setup. All stents were deployed directly into the blood loop tubing in a similar fashion.

The circumference of each loop, including the end connector, was 48 cm. Freshly drawn human blood was heparinized to a concentration of 1.0 IU/mL and the loop was filled with 6.5 mL of blood at a filling rate of 78%. This process continued at 37°C and a flow rate of 20 revolutions per min (rpm) for 1 hour. Before filling the blood loops, TAT, β-TG, platelet count, and activated clotting time (ACT) were measured to confirm the coagulation and platelet activity of heparinized blood. The following instruments were used for these measurements: STACIA (LSI Medience Corp, Tokyo, Japan) for TAT, Asserachrom (Fujirebio, Inc, Tokyo, Japan) for β-TG, Hemochron Response (Heiwa Bussan Co, Ltd, Chiyoda, Japan) for ACT, and Automated Hematology Analyzer KX-21V (Sysmex Corp, Kobe, Japan) for platelet count. Macroscopic observations were performed after blood circulation by first rinsing the loops three times with 5 mL of saline, then removing the sample. Samples were then placed in phosphate buffered saline (PBS) containing 2.5% glutaraldehyde for a minimum of 12 hours for thrombus fixation. The stents were then rinsed with water and dried under vacuum for a minimum of 2 hours, sputtered with platinum, sectioned longitudinally, and imaged with SEM. Images representative of the overall appearance of the stent were taken from the middle portion of each stent half.

Statistical analysis

Analysis of variance (ANOVA) was used to evaluate measurements for platelet count, TAT, and β-TG. Post-hoc Tukey tests were used to identify device groups with significant differences ($p>0.05$).

Endothelial cell adhesion test

Cell culture

Human aortic endothelial cells were cultured with the EGM-2 BulletKit (Lonza Group Ltd, Basel, Switzerland) according to the manufacturer's instructions. The cells were cultured in T-25 or T-75 flasks with 5% carbon dioxide (CO_2) atmosphere at 37°C. The medium was changed every 2–3 days.

Focal adhesion formation test

Scaffold preparation

Five types of scaffolds were prepared for the focal adhesion formation test, with two samples prepared for each type.

Electropolished nickel-titanium (NiTi) sheets (Lumenous Device Technologies, Santa Clara, CA) were tested to mimic the surface of FRED. Two NiTi sheets were untreated (henceforth referred to as NiTi) and two were surface treated with X Technology (NiTi X). Two polyethylene terephthalate (PET) sheets (Lumirror, Toray Industries, Inc, Tokyo, Japan) were untreated (PET), two were surface treated with X Coating (PET X), and two were treated with a 2-methacryloyloxyethyl phosphorylcholine (MPC)-containing copolymer (NOF Corp, Tokyo, Japan) (PET MPC) to mimic the surface treatment of sPED.

Preparation of stock solution

PBS was prepared according to the manufacturer's instructions and sterilized by autoclave at 121°C for 15 min. Triton X-100 was diluted by PBS to prepare a 1 v/v% solution. Alexa Fluor 488 Phalloidin (Thermo Fisher Scientific Inc, Waltham, MA) was diluted 400-fold by dimethyl sulfoxide (DMSO). A 5 mg/mL 4',6-Diamidino-2-phenylindole, dihydrochloride (DAPI; 14.3 mM) aqueous solution was also prepared using Otsuka distilled water (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan).

Observation of adhesive spots by immunostaining

Samples of 2 mm × 10 mm × 120 µm were prepared and then placed on white petrolatum applied to the bottom of a 24-well plate. The assembled plates were sterilized by ultraviolet (UV) irradiation for 1 hour. Next, 500 µL of growth medium (warmed to 37°C) was added to each well and incubated for 30 min at 37°C under 5% CO_2 atmosphere. Each well was washed three times with medium and 6.67×10^4 cells were seeded to each (3.5×10^4 cells/cm^2) and cultured for 24 hours at 37°C under 5% CO_2 atmosphere. Cells with passages 2 and 4 were used in these tests. The medium was removed from the wells and 500 µL of a 4% paraformaldehyde/PBS solution (prewarmed to 37°C) was added and incubated at room temperature for 20 min. The wells were washed three times with 500 µL of PBS and permeabilized with 500 µL of 1% Triton X-100/PBS solution at room temperature for 30 min. Finally, the wells were rinsed three times with 500 µL of PBS and incubated with 500 µL of Blocking One buffer (Nacalai Tesque Inc, Kyoto, Japan) at room temperature for 1 hour.

Next, 250 µL of Anti-Vinculin Antibody, clone VIIF9 (7F9), was diluted 200-fold with Can Get Signal immunostain immunoreaction enhancer solution (Toyobo, Osaka, Japan). After dilution, 250 µL of this solution was added to each well and incubated at 4°C overnight. The 24-well plate was then brought to room temperature and the wells were washed three times with 500 µL of PBS. A secondary antibody (goat anti-mouse IgG [H+L] cross-adsorbed secondary antibody, Alexa Fluor 568) was diluted 500-fold with Can Get Signal immunostain immunoreaction enhancer solution. Alexa Fluor 488 Phalloidin/DMSO solution was diluted 400-fold with Can Get Signal immunostain immunoreaction enhancer solution: 250 µL of each solution was added to each well, incubated at room temperature for 1 hour and then washed three times with 500 µL of PBS; 500 µL of 300 nM DAPI solution prepared by PBS dilution of 143 µM DAPI aqueous solution was added and incubated at room temperature for 15 min for staining. The wells were then washed three times with 500 µL of PBS, and the samples were then transferred onto glass slides. ProLong Diamond Antifade Mountant (Thermo Fisher Scientific, Waltham, MA) was applied to the samples before covering with glass coverslips. Samples were observed by a confocal laser scanning microscope using 60× and 10× objective lenses (UPLSAPO60XS, UPLSAPO10CS, Olympus, Tokyo, Japan). The cells adhered to the sample were counted by nucleus using imaging software (cellSens, Olympus, Tokyo, Japan).

RESULTS

Total stent length

The mean±SD total stent length of FRED and FRED X combined was 44.7±0.7 mm, and 39.6±1.2 mm for the flow diverting section (working length). For sPED, it was 35.6±1.3 mm, indicating that these stents were the closest equivalence for treating similarly-sized aneurysms.

Perfusion study with Chandler loop system

The mean±SD pretest value for ACT was 246.5±38.6 s. For TAT, the mean±SD pretest measurement was 1.6±0.6 ng/mL, while values after 1 hour of circulation were 5865.0±2379.9 ng/mL for FRED, 36.7±29.2 ng/mL for FRED X, 33.8±24.6 ng/mL for sPED, and 39.7±18.5 ng/mL for the negative control (figure 1A). The mean±SD pretest measurement for β-TG was 146.3±138.3 ng/mL, and post-test values were 7877.5±3468.4 ng/mL for FRED, 873.5±719.2 ng/mL for FRED X, 1062.8±725.9 ng/mL for sPED, and 1056.0±656.5 ng/mL for the negative control (figure 1B). For platelet count, the mean±SD pretest measurement was 22.7±6.0 × 10^4/mL. Comparatively, final mean±SD platelet count values were 3.8±2.6 × 10^4/mL for FRED, 19.5±5.1 × 10^4/mL for FRED X,

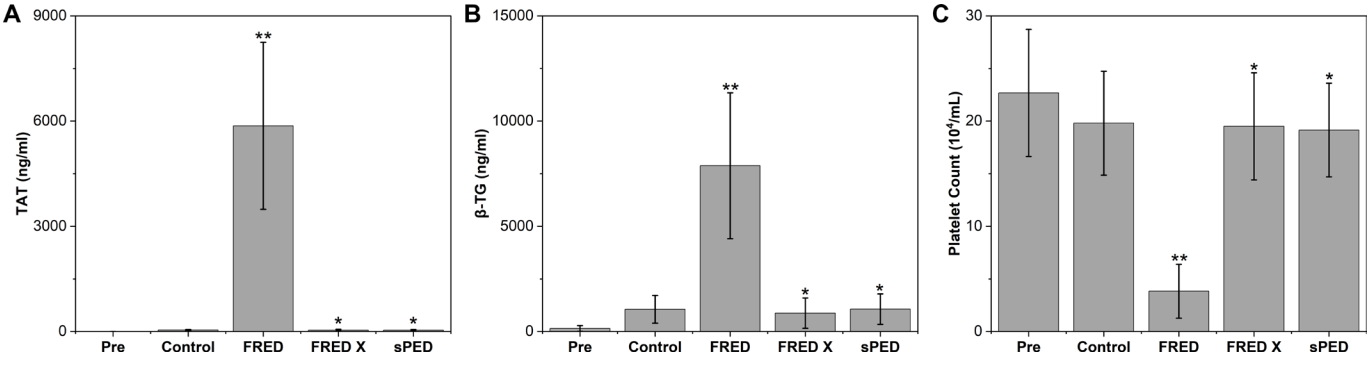

Figure 1 Blood activation after circulation. (A) Thrombin-antithrombin complex (TAT). (B) β-thromboglobulin (β-TG). (C) Platelet count. *Indicates no significant difference compared with the negative control levels based on the post-hoc Tukey analysis (adjusted p>0.8). **Indicates a significant difference between the negative control and other loops based on the post-hoc Tukey analysis (adjusted p<0.01). FRED, flow redirection endoluminal device; FRED X, FRED with X Technology; sPED, Pipeline Flex with Shield Technology.

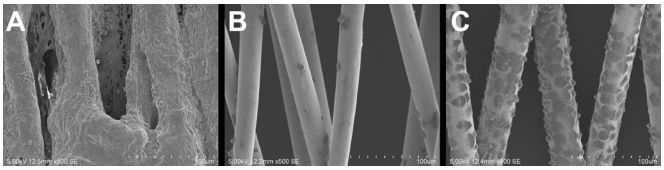

Figure 2 Representative scanning electron microscopy observations after blood circulation for one donor. (A) Flow redirection endoluminal device (FRED). (B) FRED X. (C) Pipeline Flex with Shield Technology (sPED). Scale bars: 100 µm.

$19.2 \pm 4.5 \times 10^4$/mL for sPED, and $19.8 \pm 4.9 \times 10^4$/mL for the negative control (figure 1C).

One-way ANOVAs were conducted to compare the effect of loop configuration and pretest measurements for TAT, β-TG, and platelet counts. Significant and corroborative results were determined for all measurement outcomes ($p<0.01$). Specifically, large F values F(3,12) were determined for TAT (23.98), β-TG (14.03), and platelet counts (12.80). Post-hoc comparisons using Tukey analysis indicated the mean TAT and β-TG responses were significantly higher for FRED compared with the negative control, as well as FRED X and sPED ($p<0.01$). Additionally, post-hoc Tukey comparison of platelet counts indicated the mean value was significantly lower for FRED compared with the negative control, as well as FRED X and sPED ($p<0.01$). Pairwise comparisons of all combinations of the negative control, FRED X, and sPED loops did not indicate statistical differences for TAT, β-TG, and platelet counts ($p>0.8$). Pretest levels of β-TG and TAT measurements showed a marginally lower, yet not statistically different mean values compared with the negative control, FRED X, and sPED. Similarly, pretest levels of platelets showed a marginally higher, yet not statistically different mean compared with the negative control, FRED X, and sPED.

After blood circulation, red thrombotic deposits were observed macroscopically on FRED for all four donors. No thrombotic deposits were observed on FRED X or sPED for any donor (online supplemental figure 1). According to the SEM observations, thrombi were found for all four donors on the surface of FRED in which fibrin and erythrocytes were entangled. Many blood cell-like deposits were also found on the sPED surface, while the fewest deposits were found on the FRED X surface. Representative SEM images for one donor are shown in figure 2. All SEM images appear in online supplemental figure 2.

Endothelial cell adhesion test

Focal adhesions, indicated by accumulated actin and vinculin, were observed clearly on all samples with fluorescence microscopy except for the PET MPC sheets (figure 3). The substrates with favorable cellular adhesion showed typical, widely spread cellular morphologies. Conversely, cells formed round morphologies without focal adhesions on the PET MPC sheets (figure 3C). No significant differences in cell morphologies were observed between both the NiTi and NiTi X sheets and the PET and PET X sheets.

Cell count measurement

The mean±SD number of adherent cells was 31 951±6319 cells on the NiTi sheets and 28 430±1998 cells on the NiTi X sheets. The number of adherent cells on the PET sheets (24 797±6218 cells) and PET X sheets (25 092±4228 cells) were nearly identical; however, comparatively, only about 1/25 of cells adhered to the PET MPC sheets (1003±1116 cells) (figure 4).

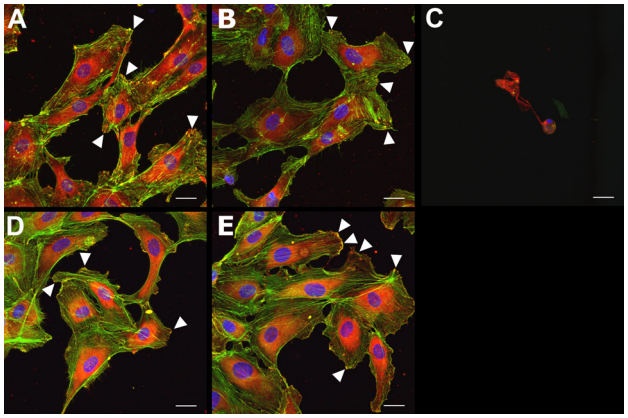

Figure 3 Fluorescence microscopy visualization of adhesion spot formation on samples. (A) Electropolished nickel titanium sheet (NiTi). (B) Electropolished NiTi sheet treated with X Technology (NiTi X). (C) Unadulterated polyethylene terephthalate sheet treated with 2-methacryloyloxyethyl phosphorylcholine (PET MPC). (D) Unadulterated PET sheet (PET). (E) Unadulterated PET sheet treated with X Coating (PET X). Red, vinculin; green, actin; blue, nucleus; white triangles, desmosomes associated with vinculin accumulation. Scale bars 20 µm.

DISCUSSION

It is highly desirable for flow diverters to possess thromboresistant properties to reduce the risk for thrombogenic events. To this end, MicroVention, Inc has treated the surface of the FRED device with a highly hemocompatible PMEA copolymer, X Technology, to produce FRED X. This is the first time the antithrombotic properties of X Technology have been evaluated in an in vitro experiment using the circulation of fresh human blood.

In our study, the blood compatibility of FRED, FRED X, and sPED were compared in a Chandler loop circulation system. The thrombogenicity of each device was assessed qualitatively by visual assessment and quantitatively by blood parameters before and after circulation. After blood circulation, red thrombotic deposits were visually observed on FRED but not on FRED X or sPED. SEM observations also revealed thrombi in which fibrin and erythrocytes were entangled on the surface of FRED, as well

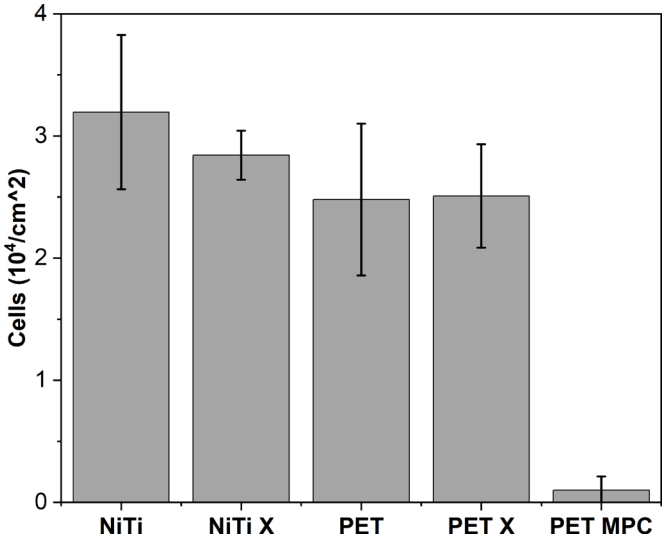

Figure 4 Number of endothelial cells adhered to each sample. MPC, 2-methacryloyloxyethyl phosphorylcholine; NiTi, nickel titanium; PET, polyethylene terephthalate.

as many blood cell-like deposits on the surface of sPED. The fewest deposits were found on the surface of FRED X.

These visual observations were corroborated with the quantitative analysis of the blood after circulation: platelet count, β-TG, and TAT concentrations for FRED X and sPED were equivalent to the negative control loop. Furthermore, the platelet count, β-TG, and TAT concentrations for FRED were significantly different from the negative control, FRED X, and sPED samples. It has been shown previously that these three parameters are indicators of device thrombogenicity,[12 13] and the minimization of the impact on these parameters demonstrates increased material hemocompatibility. As such, the positive results from the Chandler loop test highlight the superiority of the surface treatments used on FRED X and sPED devices over non-treated devices.

Interestingly, the metal surface area of intralumenal devices has been discussed as a motivator for thrombogenesis. FRED is a dual-layer device with an inner and outer scaffold, which in turn increases its metal surface area compared with other flow-diverting devices. Contrary to the high metal coverage and longer stent lengths, FRED X was found to have a similar or greater level of thromboresistance as sPED in this evaluation, indicating that X Technology successfully diminished the thrombogenic impact from the increased metal surface area and stent length. In prior research that observed large quantities of thrombus on FRED, researchers suggested that increased thrombogenicity may have been related to its dual layer construction, since thrombi were identified between layers on cross-sectional SEM views[12]; however, in our experiment, cross-sectional images were not recorded and no thrombi were identified on FRED X.

In addition to reducing the material thrombogenicity with surface treatments, it is also desirable for flow diverters to maintain or promote the rate of incorporation into the endothelium through endothelialization. Therefore, it is important to determine if the surface treatment attenuates cellular adhesion and growth.[14] Phosphorylcholine has been shown to have a deleterious impact on cellular adhesion and growth in vitro, while X Coating is known to be beneficial in these parameters.[11 15–17] Therefore, our study was designed to evaluate these surface treatments by comparing NiTi X to NiTi, PET, PET X, and PET MPC.

Aligning with prior literature for X Coating,[15–17] the X Technology surface treatment demonstrated cellular adhesion analogous to PET X and PET. As expected, the resulting cellular adhesion of PET MPC was relatively low. It is conceivable that cellular adhesion to surface treatments should preserve the endothelialization of stent constructs in vivo and is thus highly desirable in the design of surface treatments that improve material thrombogenicity. Interestingly, in vivo studies have indicated that phosphorylcholine surface treatments may not impede endothelialization over longer implant time points.[13] This phenomenon remains counter to current perspectives on biomimetics approaches, by which non-fouling polymers such as phosphorylcholine should be combined with cellular binding domains to allow endothelialization.[18 19] On the contrary, the efficacy of PMEA is imparted by the controlled adsorption of proteins, which simultaneously suppresses thrombogenesis while allowing for cellular adhesion.[20]

We selected sPED as a comparator device because its antithrombogenic properties have already been established, as preclinical studies have shown that Shield Technology reduces thrombogenicity in vitro, ex vivo, and in vivo.[13] More recently, preclinical testing has also demonstrated that the p48 and p64 MW HPC are antithrombogenic and biocompatible across different species and do not inhibit the neo-endothelialization process or induce arterial inflammation.[21] Numerous case reports and retrospective studies have also been conducted with these devices under single antiplatelet treatment (SAPT) with varied clinical success. Case reports and series of sPED and p48 MW HPC with aspirin SAPT reported significant rates of ischemic complications, which led authors to urge caution or avoidance of aspirin as the SAPT.[22–24] Conversely, several retrospective trials have demonstrated that sPED and p48 MW HPC or p64 MW HPC may be safely implanted with SAPT alone,[25–27] particularly when prasugrel is used as the SAPT.[21 28] Although these results are not definitive, they demonstrate the potential clinical benefits of surface-modified devices and the requirement for continued rigorous study.

With the potential future of surface modified devices, our study has several limitations to consider. The Chandler blood loop is frequently used to evaluate the hemocompatibility of flow diverters, but it provides only an initial estimate of thromboresistance in simplified flow conditions. Its continuous blood–air contact may lead to particulate detachment, while the chamber of air on top of its circuit may limit flow circulation speeds.[29] Some other flow models with advanced features could give a more accurate representation of antithrombogenic potential in standard conditions.

In addition, our endothelial cell adhesion test study was conducted on flat-surfaced sheets, which may not be as indicative of cell adhesion and/or endothelialization as animal models with actual stents and underlying organic tissue.[13] However, all preclinical studies, by their nature, suffer from inherent limitations. As noted, in vitro flow models and flat sheet investigations lack an endothelial layer, while in vivo animal models may not always produce results that translate to clinical populations.[29 30] Finally, the number of stent devices and blood donors (n=4) in our study was low, which limits the generalizability of these findings. Therefore, further in vivo research is warranted to explore the impact of X Technology on thromboresistance endothelialization.

CONCLUSION

The X Technology surface treatment applied to FRED X was found to improve the thromboresistance of the device without impeding cell adhesion. These characteristics suggest that the use of FRED X in endovascular procedures could potentially mitigate or reduce thromboembolic complications related to material thrombogenicity, and may also reduce the need for dual antiplatelet therapy with these procedures.

Contributors All authors have provided a substantial contribution to the conception and design of the study, the acquisition and/or analysis of the data, and/or the interpretation of the data, drafted the work or revised it for significant intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the work, including its accuracy and integrity. AB is acting as the guarantor of this study. He accepts full responsibility for the finished work and/or the conduct of the study, has access to the data, and controlled the decision to publish.

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Competing interests KY, HK, AK, MT, and TA are employees of Terumo Co., Ltd. AB and JB are employees of MicroVention Inc.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by the Terumo Research Ethics Committee. Approval ID numbers: EC-20-003 (In vitro human blood circulation study) EC-22-001 (Reanalyzing statistics). Blood draws were conducted in accordance with an institutional review board-approved protocol after informed consent was given. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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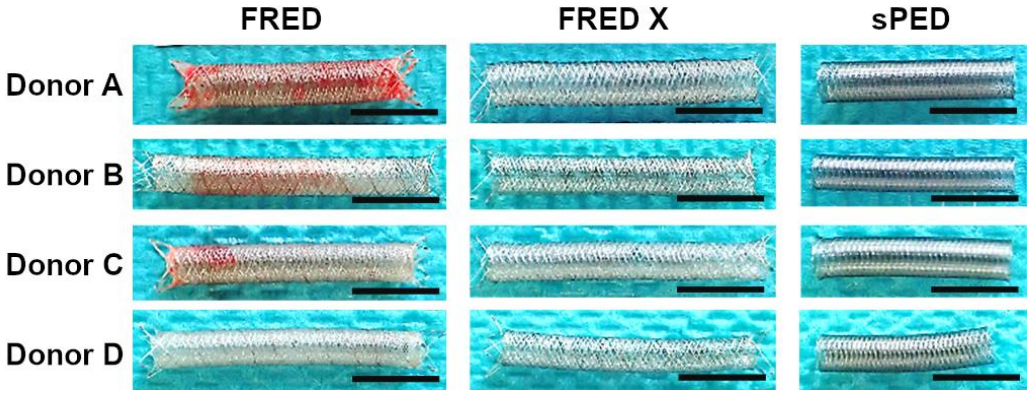
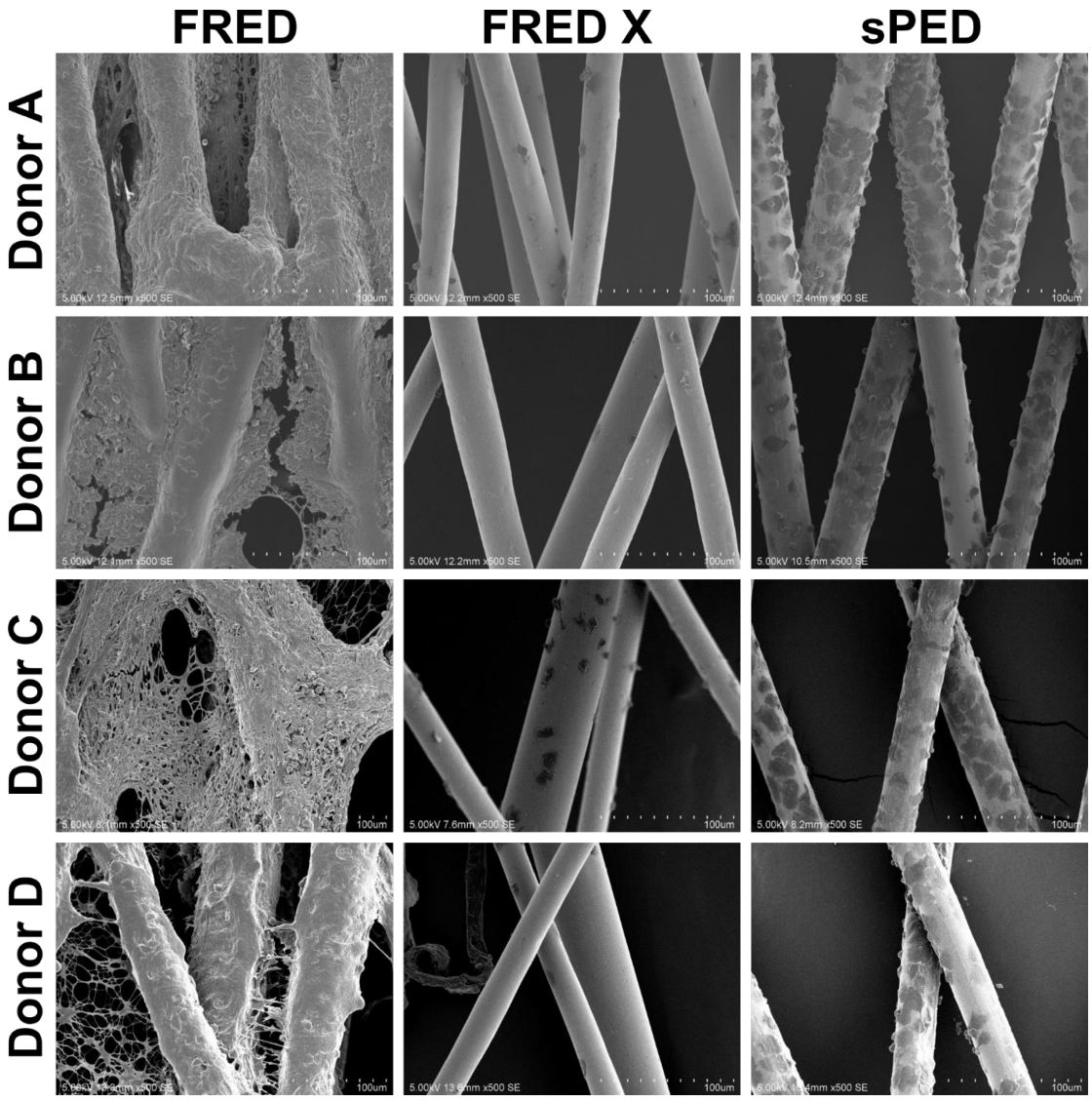
Poly(2-methoxyethyl acrylate) (PMEA) improves the thromboresistance of FRED flow diverters: A thrombogenic evaluation of flow diverters with human blood under flow conditions

SUPPLEMENTAL MATERIALS



Supplemental Figure 1. Visual observation of blood coagulation on each flow diverter. Scale bars: 1 cm. FRED, Flow Redirection Endoluminal Device; FRED X, FRED with X Technology; sPED, Pipeline Flex with Shield Technology.

Yoshizawa K, *et al. J NeuroIntervent Surg* 2022;0:1–6. doi: 10.1136/jnis-2022-019248



Supplemental Figure 2. Scanning electron microscope observation of blood coagulation after circulation. Scale bars: 100 μm. FRED, Flow Redirection Endoluminal Device; FRED X, FRED with X Technology; sPED, Pipeline Flex with Shield Technology.

ICMJE DISCLOSURE FORM

Date: 5/18/2022

Your Name: Aaron Baldwin

Manuscript Title: POLY(2-METHOXYETHYL ACRYLATE) (PMEA) IMPROVES THROMBORESISTANCE OF FRED FLOW DIVERTERS: A THROMBOGENIC EVALUATION OF THE FLOW DIVERTERS WITH HUMAN BLOOD UNDER FLOW CONDITIONS

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Your Name: John Belletto

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Your Name: Keiko Yoshizawa

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Your Name: Mika Takenouchi

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Your Name: Takao Anzai

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