X Surface Treatment: The Latest Advancement in Flow Diversion Technology

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Meeting summary

This article is based on a symposium that took place during the 14th Congress of the European Society of Minimally Invasive Neurological Therapy (ESMINT) on the 10th September 2022 in Nice, France. The symposium was sponsored by MicroVention. Jacques Dion, Vice President of Scientific Affairs at MicroVention, presented X Technology, the latest advancement to the Flow Re-Direction Endoluminal Device (FRED) system.

KEYWORDS: EFFICACY, FLOW RE-DIRECTION ENDOLUMINAL DEVICE, INTRACRANIAL ANEURYSM, SURFACE MODIFICATION, X TECHNOLOGY.

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Background

Flow diversion is an innovative and increasingly used endovascular treatment for intracranial aneurysms. The Flow Redirection Endoluminal Device (FRED) system uses a self-expanding nitinol stent comprising two integrated layers, with the inner layer composed of low porosity, 36 or 48 nitinol wire braid.[1] The device is placed across the aneurysm neck opening and extends into the parent artery on both sides. The procedure alters intra-aneurysmal blood flow patterns and redirects flow from the aneurysm, favouring intra-aneurysmal thrombosis. The efficacy and safety of the FRED system in treating intracranial aneurysms have been demonstrated in a number of prospective clinical trials in Europe, and more recently in the US.[2–6] Use of the FRED system in Europe was approved in 2013 with premarket approval by the US Food and Drug Administration in 2019.[3,6]

An overview of FRED™X™ Flow Diverter Stent Technology

The FRED™ X™ device builds on the original FRED device, with the addition of X Technology. The X Technology surface treatment, using the polymer poly(2-methoxyethyl acrylate) (PMEA), is specifically designed to reduce thrombogenicity of the device material and enhance blood vessel healing. Dr Dion described the development of this new technology and presented preliminary data from his laboratory on FRED™ X™ performance.

X Technology development

X Technology has been used and continually studied at TERUMO for over 30 years. In the early 1990s, PMEA was developed and subsequently used in blood perfusion materials. This procedure was extracorporeal, using bags, tubes and blood loops, and was non-implantable. In 2014, intracorporeal devices were developed and used as temporary

implants in oncology. In 2016, the technology was refined to be covalently bound to the metal surface, in the flow diverter.

In order to understand X Technology, it is important to appreciate the pathophysiological mechanisms affecting venous thrombosis and surface modification. Based on the triad of Virchow[7], a prominent German physician (1821-1902), there are three broad categories of factors that contribute to venous thrombosis: abnormalities of blood flow, abnormalities of blood constituents and abnormalities of the blood vessel wall. The question is, how can we modulate these factors? Blood flow may be modified using a stent or implant design, blood constituents may be modified using blood chemistry (specifically anti-platelet therapy), and abnormalities in the blood vessel wall may be addressed by material thrombogenicity, a method which is the basis of X Technology.

X Technology uses surface modification to reduce thrombogenicity of the device material and enhance blood vessel healing. Dr Dion emphasised that it is important to distinguish the term 'surface modification' from 'standard coating'. Whereas both techniques involve adhesion to the surface, surface modification is covalently bonded, with nanometer (nm) thickness, using several atomic layers of polymer chains and a solution-based chemical reaction application process to prevent it from peeling off. In contrast, a coating is physically bonded to the surface, with micrometer (μm) thickness, using a mass amount of polymer chains and a dip, spray, or brush application process.

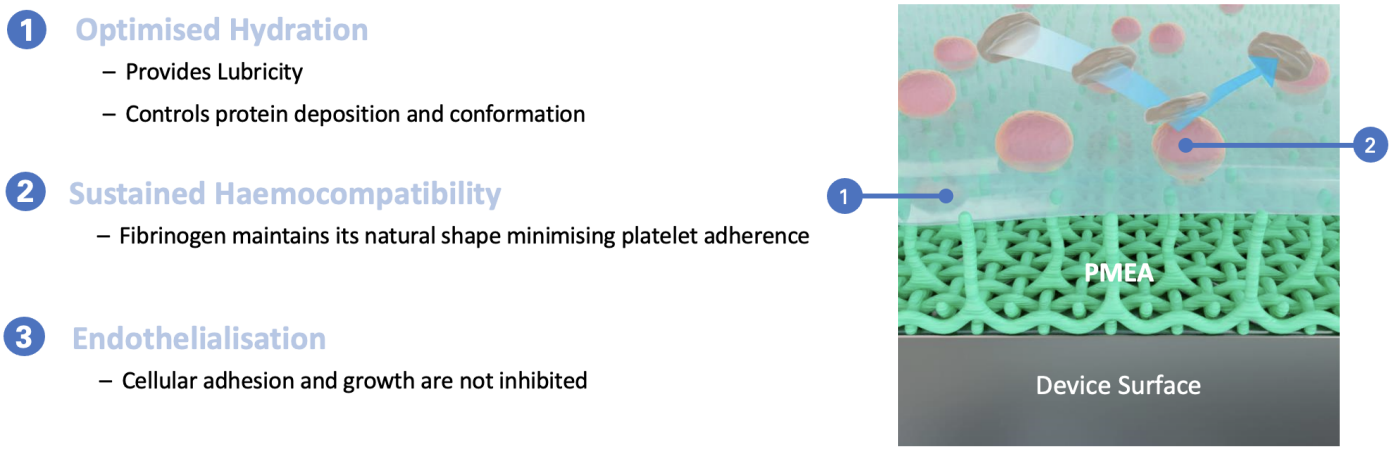
There are three main biological interactions relevant to surface modifications: protein adsorption, protein conformation and cellular adhesion. When proteins come in contact with the surface of a biomedical device, it is important that these proteins do not become deformed. For example, deformed fibrinogen attracts and activates platelets. The optimised hydration of FRED™ X™ Technology controls protein adsorption[8], retains fibrinogen protein structure[9] and controls the structure of fibronectin[10], a protein essential for cell adhesion and growth. In this way, it creates a haemocompatible surface, repealing platelet activation while supporting cell adhesion (Figure 1).

FRED™ X™ performance

The thrombogenicity of the FRED™ X™ system was assessed using an in vitro human blood loop model. Using this system, blood drawn from the antecubital vein of healthy volunteers (n=4 per test device), was fed directly into a single closed blood loop, where it was heparinised and then rotated via a pulsatile drive system for one hour at body temperature. Test devices were placed into the lumen of the blood loop

Figure 1. X Technology Summary.

Figure 2: X Technology Summary



[7]Tanaka, M. *et al.* Design of biocompatible and biodegradable polymers based on intermediate water concept. *Polymer Journal* **47**, 114–121 (2015).

and thrombogenicity was assessed by measuring thrombin generation (thrombin-antithrombin complex, TAT) and platelet activation (beta-thromboglobulin, ßTG). FRED™ X™ thrombogenicity was found to be low and comparable with that of the Pipeline™ Flex Embolization Device with Shield Technology™. For both devices, very low blood levels of TAT and ßTG were detected, compared to those observed using the bare device (publication in process). X Technology has also proven to be a good support for endothelial cell growth in vitro[11], with results comparable with those observed for bare nitinol and superior to those for PMPC (poly(2-methacryloyloxyethyl phosphorylcholine) (publication in process). Such mechanisms are, of course, likely to be much more complex in vivo. An interesting side effect of FRED™ X™ Technology is that it lowers the forces required for the delivery and retraction of the FRED device by about one-third; FRED™ X™ deployment requires 31% less push force, and FRED™ X™ retraction requires 38% less pull force, than FRED (n=15, publication in process) allowing for easier tracking through tortuous anatomies.

Summary

X Technology allows optimised hydration, which in turn provides lubricity and controls protein deposition and conformation. With sustained haemocompatibility, X Technology allows fibrinogen to maintain its natural shape thereby minimising platelet adherence, and encourages endothelialisation by not inhibiting fibronectin-mediated cellular adhesion and growth. Compared with other surface modification approaches, this combination of antithrombogenic and cell adhesive properties makes the FRED™ X™ device a strong competitor in the latest available treatments for intracranial aneurysms.

References

1. Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, et al. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg. 2021;13(1):54-62.

2. Killer-Oberpfalzer M, Kocer N, Griessenauer CJ, et al. European Multicenter Study for the Evaluation of a Dual-Layer Flow-Diverting Stent for Treatment of Wide-Neck Intracranial Aneurysms: The European Flow-Redirection Intraluminal Device Study. AJNR Am J Neuroradiol. 2018;39(5):841-847.

3. Pierot L, Spelle L, Berge J, et al. SAFE study (Safety and efficacy Analysis of FRED Embolic device in aneurysm treatment): 1-year clinical and anatomical results. J Neurointerv Surg. 2019;11(2):184-189.

4. Guimaraens L, Vivas E, Saldaña J, et al. Efficacy and safety of the dual-layer flow-diverting stent (FRED) for the treatment of intracranial aneurysms. J Neurointerv Surg. 2020;12(5):521-525.

5. Piano M, Valvassori L, Lozupone E, Pero G, Quilici L, Boccardi E. FRED Italian Registry: a multicenter experience with the flow re-direction endoluminal device for intracranial aneurysms. J Neurosurg. 2019;133(1):174-181.

6. McDougall CG, Diaz O, Boulos A, et al. Safety and efficacy results of the Flow Redirection Endoluminal Device (FRED) stent system in the treatment of intracranial aneurysms: US pivotal trial. J Neurointerv Surg. 2022;14(6):577-584.

7. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008;143(2):180-190.

8. Hoshiba T, Otaki T, Nemoto E, Maruyama H, Tanaka M. Blood-Compatible Polymer for Hepatocyte Culture with High Hepatocyte-Specific Functions toward Bioartificial Liver Development. ACS Appl Mater Interfaces. 2015;7(32):18096-18103.

9. Tanaka M, Motomura T, Kawada M, et al. Blood compatible aspects of poly(2-methoxyethylacrylate) (PMEA)—relationship between protein adsorption and platelet adhesion on PMEA surface. Biomaterials. 2000;21(14):1471-1481.

10. Hoshiba T, Nikaido M, Tanaka M. Characterization of the Attachment Mechanisms of Tissue-Derived Cell Lines to Blood-Compatible Polymers. Adv Healthc Mater. 2014;3(5):775-784.

11. Sato C, Aoki M, Tanaka M. Blood-compatible poly(2-methoxyethyl acrylate) for the adhesion and proliferation of endothelial and smooth muscle cells. Colloids Surf B: Biointerfaces. 2016;145:586-596.

