A BIOINSPIRED SURFACE COATING THAT PREVENTS THROMBOSIS AND BIOFOULING

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ABSTRACT

We describe a bioinspired coating that repels blood from virtually any material by covalently tethering a layer of perfluorocarbon, which holds a thin liquid film of medical-grade perfluorocarbon on the substrate surface, mimicking the liquid layer certain plants use to prevent adhesion. This coating prevents fibrin attachment, reduces platelet adhesion, and suppresses biofilm formation. Surface-coated medical-grade tubing and catheters, assembled into arteriovenous shunts and implanted in living pigs, remain patent for at least 8 hours without anticoagulation. This coating offers the potential to significantly reduce anticoagulation in patients while preventing thrombotic occlusion and biofouling of medical devices.

KEYWORDS: Surface Coating, Non-thrombogenic, Bio-inspired, Biomaterials

INTRODUCTION

Countless lives have been saved by implantable medical devices and extracorporeal devices that flow whole human blood outside the body through indwelling catheters and external circuits, during cardiopulmonary bypass (CPB), hemodialysis, and extracorporeal membrane oxygenation (ECMO). However, thrombosis and biofouling of extracorporeal circuits and indwelling medical devices cause significant morbidity and mortality worldwide. Furthermore, the need to co-administer soluble anticoagulant drugs, such as heparin, with these procedures, significantly reduces their safety. Without systemic anticoagulation, these extracorporeal and indwelling devices can rapidly occlude due to thrombosis because clots form when fibrin and platelets in the flowing blood adhere to the surfaces of these materials. Unfortunately, heparin causes significant morbidity and mortality, and its use is contraindicated in several patient populations. In fact, the leading cause of drug-related deaths from adverse clinical events in the United States is due to systemic anticoagulation.

This need to prevent blood clotting while minimizing administration of anticoagulant drugs has led to the search for biomaterial surface coatings that can suppress blood clot formation. To solve this challenge, we turned to the SLIPS technology [1], which creates omniphobic, non-adhesive surfaces by infiltrating porous or roughened substrates with liquid perfluorocarbons (LPs). However, existing medical grade materials have highly smooth surfaces. Thus, to create non-adhesive, anti-thrombogenic surfaces that might be useful for clinical medicine in the near-term, we set out to develop a way to modify the SLIPS technology so that it can be applied to these smooth surfaces. This was accomplished by covalently binding a molecular perfluorocarbon layer, or tethered perfluorocarbon (TP), on the material surface and then coating it with a freely mobile layer of LP, such as perfluorodecalin, which has been used extensively in medicine for applications such as liquid ventilation, ophthalmic surgery and as an FDA-approved blood substitute. Importantly, the TP continues to retain the free LP as a thin mobile liquid layer even when the surface is challenged with a flowing immiscible fluid, such as blood. We refer to this unique anti-thrombogenic bilayer composed of the TP and LP coating as a Tethered-Liquid Perfluorocarbon (TLP) surface (Fig. 1) [2].

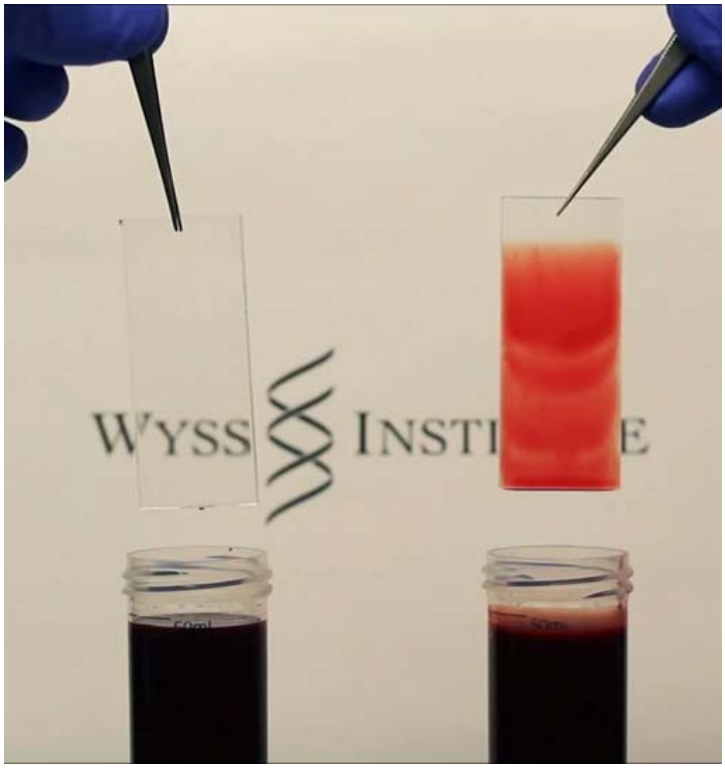

Figure 1: TLP-coated surfaces repel whole human blood. Tethered liquid perfluorocarbon (TLP) surfaces (left) showing the tethered perfluorocarbon (TP) bound to a substrate through plasma activation and silane treatment, which allows a stable film of liquid perfluorocarbon (LP) to adhere to the surface. When both the tethered and liquid perfluorocarbons are applied to the surface, TLP, the acrylic surface resists the adhesion of whole human blood even after complete immersion (left side). Surfaces without the tethered or liquid perfluorocarbon (-TP/-LP) show substantial adhesion of a blood after immersion in blood over 5 seconds (Control, right).

RESULTS AND DISCUSSION

The TLP coating reduces platelet adhesion and activation and prevents fibrin attachment (Fig. 2). To evaluate effects on platelet adhesion, polysulfone surfaces were analyzed by scanning electron microscopy (SEM) after they were exposed to whole human blood for 30 minutes. These studies revealed that TLP coating reduced platelet adhesion by 4-fold, compared to control surfaces. To evaluate the attachment of fibrin, acrylic surfaces were exposed to whole human blood spiked with fluorescently labeled fibrinogen for 90 min. These studies revealed that TLP coating reduced fibrin area by 6-fold, compared to control surfaces. We extended our studies to medical-grade polyurethane arterial cannulae, polycarbonate connectors and PVC blood perfusion tubing treated with a TLP coating and tested in a porcine femoral ateriovenous shunt model. The TLP shunts without anticoagulation remained unobstructed (patent) over 8 hours of 15 L/hr of blood flow, while 4 of 5 untreated control shunt occluded completely within 8 hours. When bacteria were grown in TLP- coated loops of PVC tubing for 6.5 weeks, there was a 8-fold reduction in biofilm formation compared to control tubing.

CONCLUSION

This TLP coating represents the first surface coating to reduce thrombosis under physiological arterial flow *in vivo* without the use of soluble anticoagulants. This coating technology offers the potential to sig-

nificantly reduce anticoagulation in patients while preventing thrombotic occlusion and biofouling of medical devices.

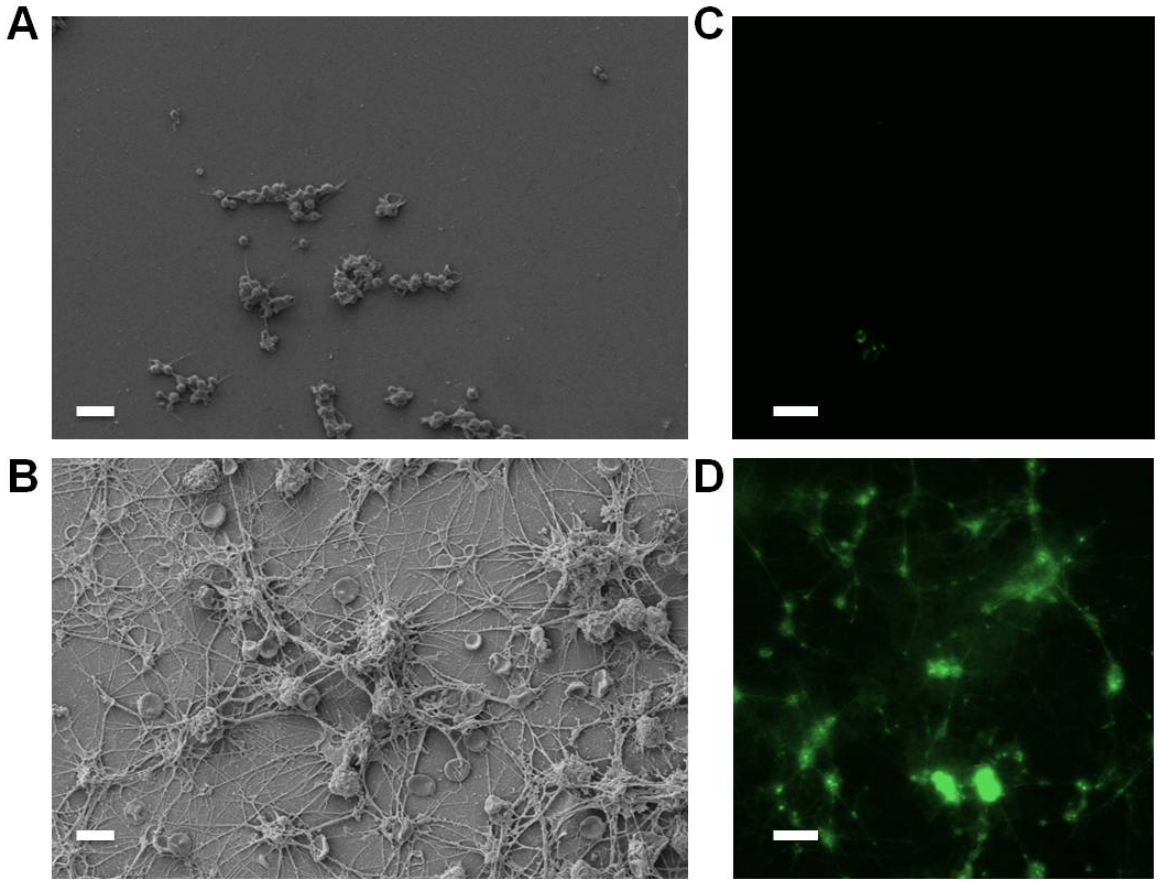

Figure 2. Whole blood interactions with TLP surfaces. Scanning electron micrographs of polysulfone surfaces after 30-minute incubation in whole blood shows reduced platelet adhesion on (A) TLP compared to (B) control surfaces. Scale bar 10μm. Fluorescent micrographs of fluorescently labeled fibrinogen in whole blood after 90-minute incubation shows substantially reduced fibrin attachment and clot formation on (C) TLP acrylic compared to (D) control. Scale bar 50μm.

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