SLIPS Surface Treatment of Medical Devices that Prevents Blood Clot Formation in the Absence of Anticoagulants

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Statement of Purpose: Despite decades of intense research into hemocompatible surfaces and coatings, systemic administration of anticoagulants is still required for patients on ECMO and hemodialysis, which often leads to internal bleeding and dangerous complications. Our goal is to eliminate the need for anticoagulants when blood is exposed to synthetic surfaces during these lifesaving procedures. Wong *et al.* recently described a new type of Slippery Liquid-Infused Porous Surface (SLIPS) treatment methodology inspired by the pitcher plant. A porous surface of Teflon was infused with a perfluorinated liquid to provide a SLIPS surface that broadly repels surface interactions with both hydrophilic and hydrophobic materials (omniphobicity). We have extended this work to generically treat surfaces of a variety of different materials to retain medical grade perfluorinated liquids as a way to prevent blood adhesion and coagulation. These liquids, such as perfluorodecalin (PFD), have been used as blood substitutes and are well tolerated at high concentrations, making them ideal for medical applications. We present a two-part surface modification for medical devices to reduce thrombus formation and enable the use of synthetic surfaces without administration of anticoagulants.

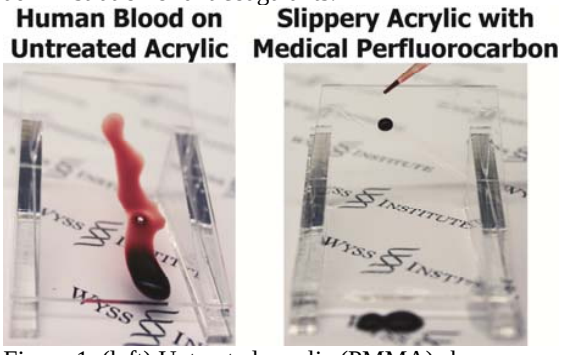

Figure 1. (left) Untreated acrylic (PMMA) shows significant adhesion of human blood while (right) slippery acrylic coated with medical grade perfluorodecalin (PFD) repels blood adhesion.

Methods: Surfaces were plasma treated and coated with 1H,1H,2H,2H-perfluorooctyltrichlorosilane in dehydrated ethanol. Perfluorinated liquids (perfluorodecalin (FluoroMed), FC-70 (Sigma)) were applied and tilted to remove the excess. Blood was obtained with informed consent from healthy, male volunteers who had not take aspirin within 2 weeks of donation and who did not smoke. Blood was drawn in accordance with the Declaration of Helsinki with approval from the Harvard Committee on Human Studies (Protocol Number M20403-101). Blood tilt experiments were conducted at an angle of 90 degrees. For blood adhesion experiments, polysulfone or poly(methyl methacrylate) (PMMA) pieces (11mm x 8mm) were incubated for 30, 60 or 90 minutes with heparinized blood (0.25U/ml) containing 15 ug/mL of fluorescent fibrinogen in wells blocked with BSA (1% (w/v)). Pig blood was flowed through PVC tubing at 30ml/min for 2 min using a syringe pump. The blood was re-activated with 100mM $CaCl_2$ and 75mM $MgCl_2$ and protamine sulphate 10ug/U. Arteriovenous shunts were established in the femoral artery and vein of Yorkshire swine using 8F catheters (Medtronic) and ¼" tubing (Sorin Group).

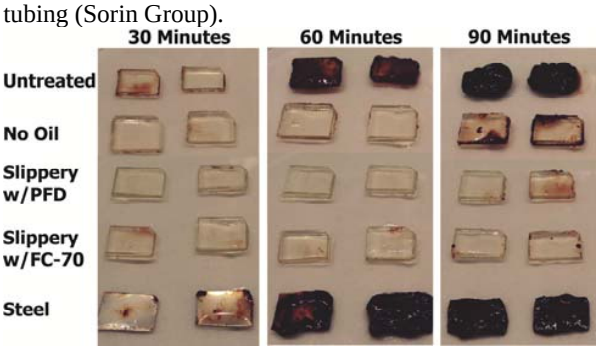

Figure 2. Slippery polysulfone pieces showed reduced thrombus formation over 90 min exposure to blood.

Results: A variety of surfaces (plastics, glass, metals) were shown to repel non-anticoagulated human blood with both a chemical surface treatment and perfluorinated liquid coating (denoted 'Slippery' hereafter). Either of these conditions alone did not provide a repellant surface. We have investigated the rate of thrombosis from whole human blood on slippery PMMA and polysulfone (Figure 2) and quantified the adhesion by spiking the blood with fluorescent fibrinogen. We observed reduced surface adhesion and fibrin formation on all slippery surfaces investigated over untreated surfaces. Chemical surface modification significantly decreased fibrin adhesion from untreated PMMA ($P<0.001$). Fibrin formation was reduced by 97% on slippery PMMA with FC-70 after 90 min, which was statistically significant ($P<0.001$). We further extended our studies to state-of-the-art, medical-grade indwelling arterial cannulae and blood perfusion tubing treated with a slippery coating. Blood adhesion on slippery medical-grade PVC tubing with PFD was reduced in *in vitro* assays with reactivated porcine blood. We further tested slippery surfaces in a porcine femoral ateriovenous shunt. The slippery shunt remained unobstructed (patent) over 8 hours of ~1 L/min of blood flow, while the untreated shunt occluded completely within 90 minutes.

Conclusions: Slippery surface modification and coating with medical grade perfluorinated liquids reduced the thrombogenicity of surfaces when in contact with non-anticoagulated blood both *in vitro* and *in vivo*.

Reference: Wong T.-S. Nature 2011;477:443-447.