Microporous Textured Exterior Biointerface Prevents Stenosis in Arteriovenous Grafts

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Introduction: We evaluated the in vivo performance of a modified ePTFE-based arteriovenous (AV) graft design with potential to reduce thrombosis failures. More than 430,000 End Stage Renal Disease patients in the US depend on hemodialysis to survive. Prosthetic AV grafts represent the safest vascular access option for the nearly 40% of hemodialysis patients who are unable to achieve or sustain the preferred means of functional access via a fistula between natural vessels. An AV graft device that significantly reduces thrombosis failure would provide a more reliable option for these patients.

STAR® Biointerface technology (Healionics, Seattle, WA) combines tightly controlled sphere-templated microporosity and macrotexturing to promote a highly vascularized device-tissue interface that prevents the usual formation of a dense fibrotic foreign body capsule (Marshall et al., US Patent 8372423). We hypothesized that applying the technology to the exterior of a vascular graft would improve flow stability by suppressing the mechanical squeezing effect of the perigraft capsule, thereby enabling radial expansion in response to stenotic resistance. Using a constriction-suppressing biointerface represents a novel approach to reducing thrombotic failure in arteriovenous vascular grafts.

Methods: Control grafts (N = 2) were ePTFE standard wall 6mm vascular graft tubing (Vascutek, Scotland) with no radial reinforcement. STAR-treated test grafts (N = 4) were modified by dip-coating the outer surface with MED-2214 silicone to create an adhesive layer, and then adhering a monolayer of ~300-µm size granules of sphere-templated microporous MED-4830 silicone with ~35-µm spherical pores interconnected by ~15-µm interpore openings. Sheep (65-80kg) were heparinized, and vascular grafts were implanted in a bilateral arteriovenous shunt model with straight ipsilateral configuration (distal carotid artery to proximal jugular vein). Control grafts were soaked in heparinized saline prior to implant per standard clinical practice. To minimize trapped air inside the adhesive layer, the pore spaces of the test grafts were prehydrated by immersing in heparinized saline and cycling vacuum with a syringe until bubbles no longer appeared. Animals were placed on standard antiplatelet therapy (aspirin and clopidogrel) for the duration of the study. Grafts were monitored at weeks 1, 2, 4, 6, 8, 10, and 12 with noninvasive Doppler ultrasound. At week 12, grafts were evaluated with fluoroscopic angiography and intravascular ultrasound (IVUS), and the animals were sacrificed. Student's *t* test was used for statistical comparisons.

Results: The average peak velocity ratio (PVR, calculated as peak systolic velocity at venous anastomosis divided by the midgraft peak systolic velocity) was significantly reduced in STAR-treated grafts compared to untreated controls in the 3rd (final) month of the in-life period (1.4 vs. 2.2, p = 0.0001), suggesting reduced anastomotic stenosis. Angiographic imaging at week 12 showed clearly visible focal stenosis in the flowpath at the heel of the venous anastomosis in controls, but not STAR-treated grafts. Analysis of IVUS cross sections at week 12 confirmed that the lumens of control grafts were significantly more occluded with neointimal hyperplasia and/or thrombus, as shown in Fig. 1. The average flow in STAR-treated grafts increased significantly after the 2nd month: flow was 40% higher at weeks 10 and 12 compared to weeks 4, 6 and 8 (1440 vs. 1030 mL/min, p = 0.02), while flow in the control grafts remained constant at ~1100 mL/min. The increase in flow in the STAR-treated grafts was due to significant expansion of cross-sectional lumen area at midgraft; expansion was proportional to Bernoulli's equation-based pressure drop across the venous anastomosis orifice. In contrast, midgraft lumen area of the control grafts remained constant and independent of the pressure drop. Histological analysis is pending.

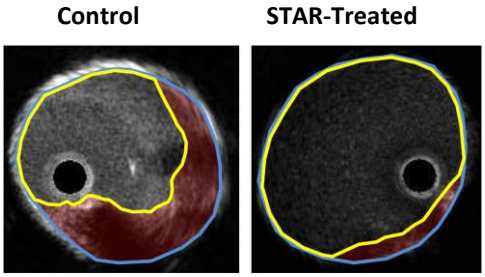

Fig. 1. Representative IVUS cross sections at heel of venous anastomosis. STAR-treated graft is less occluded than control. For clarity, lumen surface traced in yellow, graft inner wall traced in blue, and hyperplasia/thrombus pseudocolored red.

Conclusions: The results suggest that treating the adventitial surface of ePTFE AV grafts with the STAR Biointerface suppresses the neointimal hyperplasia that ordinarily causes progressive stenosis. It is possible that the tissue impermeable barrier or the prehydrated luminal surface contributed to the observed improvement in performance; but since the performance advantage did not manifest until after the 2nd month, this seems unlikely. The finding that the STAR-treated grafts, unlike controls, were capable of expanding radially in response to increased pressure suggests a significantly reduced stiffness and/or contractile force of the perigraft capsule tissue. The apparent improvement in perigraft tissue properties is consistent with our hypothesis and may have major clinical significance. Importantly, if the initial development of mild neointimal hyperplasia can cause an *increase* in flow, this would likely have a stabilizing effect on the hyperplasia. Such an effect would be the opposite of what happens usually, where stenotic resistance from progressive hyperplasia eventually causes a decrease in flow, upregulating the advancement of hyperplasia until thrombosis failure inevitably occurs.

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