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Influence of stent surface microstructuring on endothelial cell migration and substrate thrombogenicity

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Background: Coronary stent implantation is currently one of the most performed cardiac interventions, but requires a long-term therapy with anti-platelet agents to prevent stent thrombosis. Stents with microstructured surfaces should improve stent vascularisation, reduce thrombotic events and consequently shorten the length of anti-thrombotic therapy.

Methods: Differently designed, 2-5 µm high elevations or hollows were lithographically etched on silicon plates, subsequently coated with silicon carbide. As controls, smooth silicon plates, bare metal substrates, and cell culture plastic were used. The migration of human umbilical vein endothelial cell (HUVECs) was assessed in a modified barrier assay using cell culture inserts (n=10). Blood after cell seeding, inserts were removed and cell migration was monitored for 2, 20, 30, 40, 60, and 72 hours. Actin cytoskeleton was visualised with green phalloidin. Platelet concentrate or whole blood were incubated on the different surfaces in static and flow conditions to investigate surface thrombogenicity (n=10). For cell counting, P-selectin antibody conjugated with fluorescein was used. Images were taken with an incident light fluorescent microscope used for studies of non-transparent objects.

Results: Comparing different types of structured surfaces, improved endothelial cell migration over 72h was observed for 4-5 µm pillow-like structures, whereas smaller spiky structures (2 µm), hollows, and smooth surfaces (i.e. smooth silicon plates, bare metal substrates) had a negative effect on endothelial migration. Moreover, substrate specific interactions between the tested endothelial cells and the structure relief could be detected. The thrombogenicity assays under static and flow conditions performed using whole blood and platelet concentrate showed that the platelet adhesion was reduced on larger structures as compared to smaller sharp-edged structures, hollows, or the smooth surfaces.

Conclusions: Microstructured surfaces have strong influence on endothelial cell migration and platelet adhesion. These results open new possibilities to design stent surfaces which improve adherence and migration of endothelial cells, and inhibit thrombogenic processes.

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The Impact Of Triple Anti-Platelet Therapy For Endothelialization And Inflammatory Response At Overlapping Bioabsorbable Polymer Coated Drug-Eluting Stents In A Porcine Coronary Model

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Background: Differently designed, 2-5 µm pillow-like structures, whereas smaller spiky structures (2 µm), hollows, and smooth surfaces (i.e. smooth silicon plates, bare metal substrates) had a negative effect on endothelial migration. Moreover, substrate specific interactions between the tested endothelial cells and the structure relief could be detected. The thrombogenicity assays under static and flow conditions performed using whole blood and platelet concentrate showed that the platelet adhesion was reduced on larger structures as compared to smaller sharp-edged structures, hollows, or the smooth surfaces.

Conclusions: Microstructured surfaces have strong influence on endothelial cell migration and platelet adhesion. These results open new possibilities to design stent surfaces which improve adherence and migration of endothelial cells, and inhibit thrombogenic processes.

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Endovascular, Ethanol-Mediated Renal Sympathetic Denervation: Sub-Acute and Chronic Evidence of Safety and Sustained Efficacy in a Swine Model

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Background: Renal sympathetic denervation (RDN) has been shown to sustainably reduce BP. We report preclinical results using perivascular (adventitial) injection of small volumes of dehydrated alcohol (EOH) via a novel drug delivery catheter.

Methods: The three-needle delivery device, (Peregrine System™, Ablative Solutions, Inc.) was introduced via the femoral artery into renal arteries of swine using fluoroscopic guidance. Following deployment of the needles into the perivascular space, EOH was injected circumferentially. Three doses of EOH/renal artery (0.15, 0.30, and 0.60 ml) and sham (0.4 ml saline) control were evaluated at 2-weeks. The 0.3 ml dose was studied at 3-mos. (n=6). Renal tissue norepinephrine (NE) was used as a surrogator mark of the effectiveness of RDN. Renal NE was also measured in 20 (naive control) kidneys.

Results: Histopathology at 2-weeks, and 3-mos. revealed substantial circumferential sympathetic nerve injury, at 2-10 mm depth from the intima. At 3-mos, the nerves exhibited a range of injury from focal regions of nerve swelling with minimal cellular infiltrates to almost complete neurolysis (typically replaced with fibrous tissue). The injury and the NE levels reduction were dose-dependent, with highly significant NE reductions at all doses compared to the sham and naive groups. At 2 weeks, the mean renal NE reductions were 52%, 77% and 87%, respectively for 0.15, 0.30 and 0.60 ml doses (p < 0.001). At 3 mos, the 0.3 ml dose showed a mean renal NE reduction of 69% compared to the controls (p < 0.01). Angiographically, there was no evidence of vascular injury, stenosis or negative remodeling at any time point. Histopathology confirmed that the integrity of the renal artery was maintained, and at 3 months the treated area appeared healthy and with advanced healing. There were no systemic or renal toxic effects noted in any animal. Safety was further confirmed in a separate study in which 0.6 ml of EOH was injected directly into each renal artery.

Conclusions: Circumferential and deep peri-adventitial delivery of low doses of EOH catheter to be a simple, safe, predictable and viable alternative to energy-based systems to achieve substantial, sustained renal sympathetic denervation.