Design and Analysis of Surface Engineered and Bioresorbable Flow Diverting Stents

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Abstract

Flow diverting stents (FDS) has become a promising endovascular treatment method for intracranial aneurysms. However, late thrombosis, perforator infarction, incomplete occlusion, and clotting are still a challenge. Our research aims to resolve this challenge by i) surface engineering nitinol FDS and ii) developing bioresorbable FDS. Nitinol FDSs with 3 µm, 6 µm and 12 µm depth micro-grooved patterns were fabricated using a solid-state 1064nm fiber laser with an in-house robotic arm. Thin PCL (Poly-ε-caprolactone) fiber was extruded through a precision electromelt nozzle on a micro-controlled rotating arm and 3-axis motion stage to form FDS. Surface quality, groove depths, and profile were evaluated using a SEM and 3D Profilometer. Cell studies were conducted by infusing collagen and human umbilical vein endothelial cells (HUVECs) in FDS on a silicon mold. Collagen loaded with HUVECs contracted tightly around FDS. After 2 days of incubation time, the collagen with the endothelial cells were stained for cell studies. Cytotoxicity analysis were also conducted with flow diverters using HUVECs. Surface characterization shows smooth and elliptical micro-grooved nitinol without any cracks, and also PCL FDS shows smoother surface finish. Radial compression, bending, and longitudinal strength of PCL FDS are comparable with the commercial stents. Cell studies show that enhanced adhesion and proliferation on PCL and grooved nitinol FDS compared to the un-grooved control nitinol FDS. Furthermore, the coverage of endothelial cells on grooved FDS resembles similar morphology of the natural endothelium. There is no significant increase in toxicity level in PCL flow diverters. These studies will contribute to the development of more efficient FDS for the treatment of intracranial aneurysms.

Background

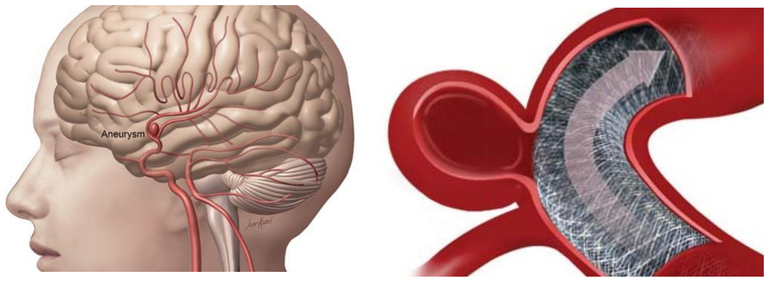

Figure 1: Left: A graphical illustration of brain aneurysm [1]. Aneurysm is a localized dilation or bulging out of blood vessel; Right: An schematic of aneurysmal blood vessel [2] with flow diverter. Flow diverters control blood flows inside the aneurysm, induce thrombosis and supports blood vessel to complete cure of aneurysm.

Aneurysm is a localized dilation of blood vessel which can cause it to swell out beyond control and eventually to rupture if not treated. Upon rupture it becomes deadly and every 18 minute there is a rupture in USA [3]. Particularly, brain aneurysm is one of the deadly diseases that claims 30,000 lives per year in USA upon rupture. Current treatment plan such clipping, clipping and wrapping, coiling and mesh techniques were reported to have serious consequences such as delayed cerebral ischemia (DCI), acute and chronic hydrocephalus, vasospasm, seizures, delayed aneurysm rupture, coil migration and restenosis etc. [4]. Recently flow diverters such as pipeline embolization device (PED), a fine mesh metallic stent approved by FDA in 2011, is claimed to be more effective in treating aneurysm [5]. However, challenges such as late thrombosis, rupture, non-IA related intracerebral hemorrhages (ICH), incomplete occlusion, still remain unresolved. Permanent metallic PED can be a source of mechanical stress, persistent inflammation and low-grade injury of the vascular wall [6]. Therefore the long term goal of this research is to develop bioresorbable fine meshed flow diverter. The immediate goal is to develop surface engineered find meshed nitinol flow diverting stents that can be firmly stayed in-place without micromovement, with reduced mechanical stress on the blood vessel and microinflammation.

Composition of Nitinol FDS Design

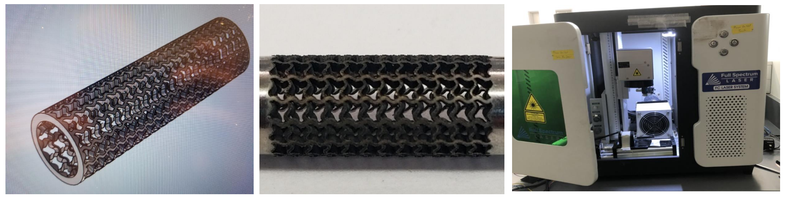

Figure 2: **Left:** Flow Diverting Stent CAD Design **Middle:** Fabricated nitinol 5mm (outer diameter) flow diverting stent **Right:** High precision laser machining system

Composition of PCL FDS Design

Figure 3: **Left:** PCL Flow Diverting Stent CAD Design. **Middle:** PCL 12mm FDS **Right:** Electromelt PCL Printer with Micromotion platform

SEM Flow Diverter Surface Quality

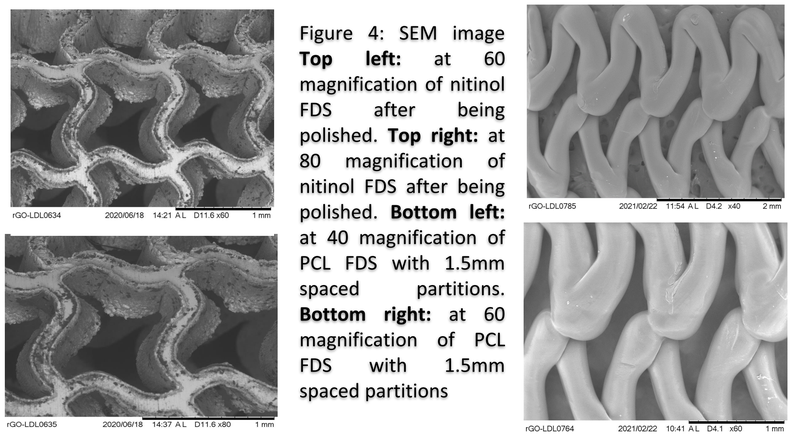

Figure 4: SEM image **Top left:** at 60 magnification of nitinol FDS after being polished. **Top right:** at 80 magnification of nitinol FDS after being polished. **Bottom left:** at 40 magnification of PCL FDS with 1.5mm spaced partitions. **Bottom right:** at 60 magnification of PCL FDS with 1.5mm spaced partitions

SEM Measurements for Fabricated FDS

Figure 5: Scan electron microscope (SEM) characterization of microgrooves on nitinol flow diverters and stud width of PCL flow diverters. A correlation between the depth and width of the grooving was also developed. The correlation shows that the deeper the grooving the wider the groove. The speed at which the PCL FDS were made was directly correlated to the width at which the PCL was applied.

Profilometer Analysis of Nitinol FDS

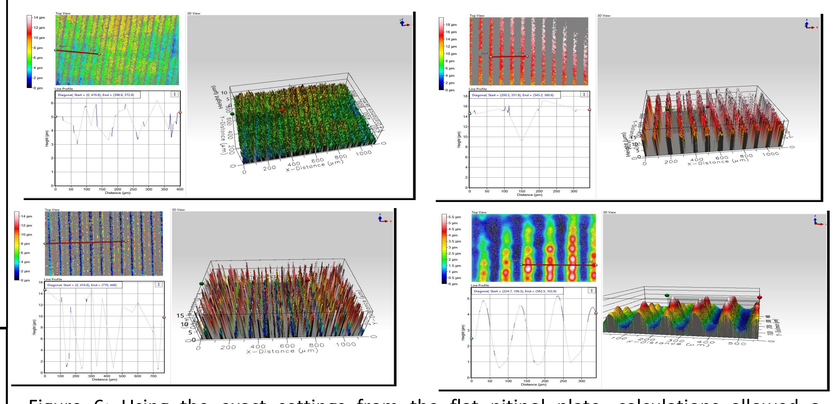

Figure 6: Using the exact settings from the flat nitinol plate, calculations allowed a determination for the depth of the grooving on the nitinol tubing. The STL design for the laser is 30mm long by 0.5mm wide at 200 micrometer grooving. With the settings predetermined for the laser machine it took the STL file 0.375 seconds to run completely through. The circumference of the tube is 15.708mm, the STL files fits into the circumference 31.416 times. plate was multiplied 32 times giving us an approximation of the depth on the tubing. Multiplying the speed of one STL file and multiplying it by the time, a value of 11.781 seconds for 360-degree rotation was derived. The Arduino code was change accordingly. Thirty-two partitions of the laser machine is equivalent to one revolution so the original partitions for the flat nitinol

Biological Analysis of PCL FDSs

Cell Proliferation on Flat PCL FD Stent Samples

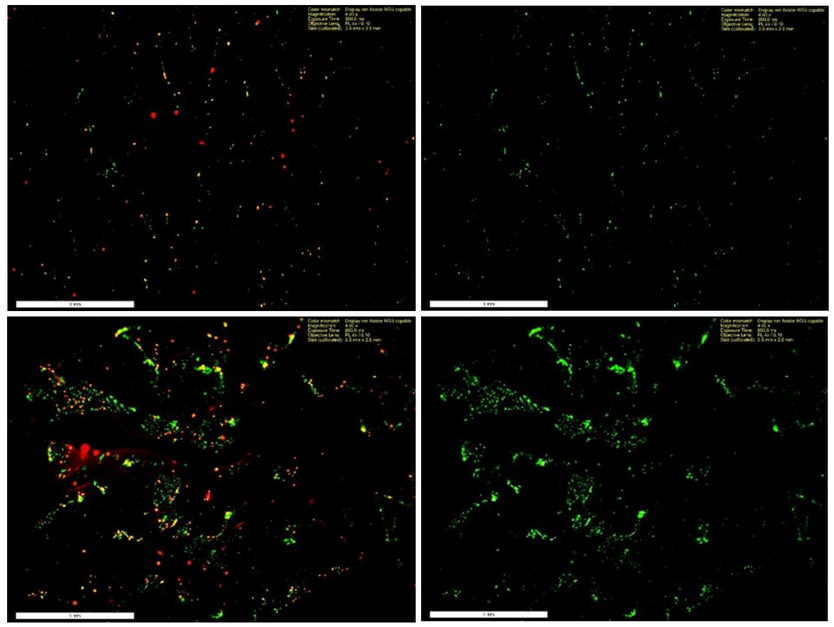

Figure 7: Incubated HUVEC Cells on PCL FD Stent **Top Left**: Combined NucSpot 470 Nuclear Stain (Green) and BaseClick EdU Proliferation Stain (Red) of 24 Hour **Top Right**: NucSpot 470 Nuclear Stain of 24 Hour **Bottom Left**: Combined NucSpot 470 Nuclear Stain (Green) and BaseClick EdU Proliferation Stain (Red) of 48 Hour **Bottom Right**: NucSpot 470 Nuclear Stain of 48 Hour

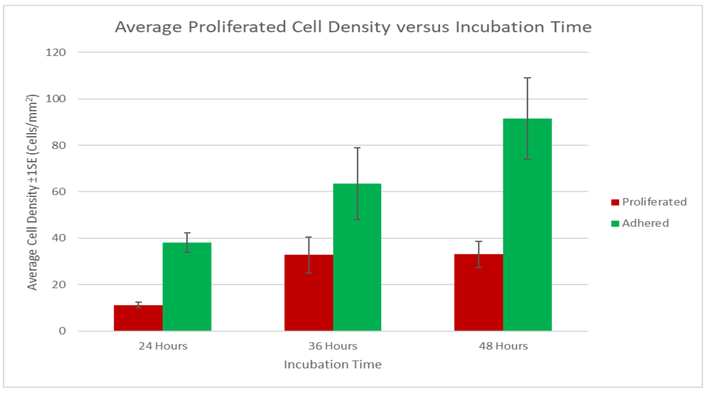

Figure 8: Average Cell Density per mm2 of Proliferated and Adhered Cells for 24-, 36-, and 48-Hour Incubation Times

Cytotoxicity of PCL FD Stent on HUVEC Cells- LDH Cytotoxicity Assay

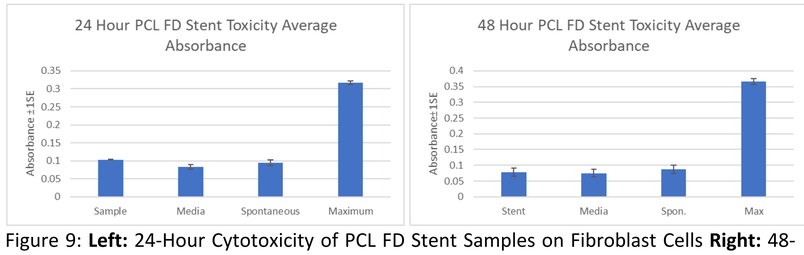

Figure 9: **Left:** 24-Hour Cytotoxicity of PCL FD Stent Samples on Fibroblast Cells **Right:** 48-Hour Cytotoxicity of PCL FD Stent Samples on Fibroblast Cells

Relevance of Study

The novelty of this research is to develop a functional bioresorbable flow diverting stent to treat a brain aneurysm. The outcome of the research is not only contributing to the development of engineering processes for the fabrication of novel bioresorbable flow diverting stent but also demonstrating precision laser engineered surfaces for more efficient metallic flow diverting stents for endovascular treatment.

References

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