Compliance Testing and Subcutaneous Evaluation of Electrospun Polydioxanone and Elastin Vascular Grafts

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Introduction: The native human artery is a complex tissue comprised of three distinct layers: the intima, media, and adventitia. Each layer has a unique composition of collagens, elastin, endothelial cells, smooth muscle cells (SMC), fibroblasts, and proteoglycans that contributes to the mechanical behavior of the tissue as a whole. Collagen serves as the mechanical backbone of the tissue by providing tensile support and preventing vessel rupture, while arterial elasticity and the ability to recover from pulsatile deformations is provided by elastin fibers (Boland ED. Front Biosci. 2004;9:1422-1432.). It is this elastic nature of elastin that dominates the low-strain mechanical response of the vessel to blood flow and prevents pulsatile energy from being dissipated as heat (Huang L. Macromolecules. 2000;33:2989-2997.). The hypothesis of this study was that the fabrication of an electrospun tissue engineering scaffold composed of polydioxanone (Boland ED. Acta Biomater. 2005;1:115-123.) (PDO, Ethicon Inc.) and elastin would have dynamic compliance matching that of native arterial tissue, while remaining conducive to tissue regeneration. As electrospun elastin lacks the mechanical durability required for a vascular graft, PDO was chosen to provide mechanical integrity to the prosthetic, with elastin providing elasticity and bioactivity (promote regeneration *in vitro / in situ*).

Methods: Concentrations of 100 mg/ml of PDO and 200 mg/ml of elastin from bovine neck ligament (Elastin Products Co. Inc.) were dissolved in 1,1,1,3,3,3 hexafluoro-2-propanol (Sigma Aldrich) and blended in ratios of 100:0, 90:10, 80:20, 70:30, 60:40, and 50:50 (PDO:Elastin). These solutions were then electrospun (thickness ~500 µm) onto a rotating 1" square mandrel to produce thin sheets, as well as on a rotating 6 mm diameter stainless steel mandrel to produce vascular grafts with an internal diameter of the same size (L = 7 cm).

Dynamic compliance measurement was performed under simulated physiological conditions in an Intelligent Tissue Engineering via Mechanical Stimulation (ITEMS™) Bioreactor developed by Tissue Growth Technologies (Minnetonka, MN). The bioreactor provided a sinusoidal pressure change (1 Hz, representing 60 beats per minute) to the inside of the graft at one of three different pressure levels (90/50, 120/80, and 150/110 mmHg) to create a range of mean arterial pressures. External graft diameters were measured with a laser micrometer at each mean arterial pressure and compliance values were calculated.

Thin sheets (8 mm diameter) of the 70:30 blend were also implanted subcutaneously in rats and histology was performed after 10 days, 21 days, and 6 and 12 weeks.

Statistical analysis was based on a Kruskal-Wallis one way analysis of variance on ranks and a Tukey pair-wise multiple comparison procedure (α=0.05).

Results/Discussion: Compliance measurement results showed that grafts containing elastin were significantly more compliant than grafts composed of pure PDO, with the 50:50 blend (containing the most elastin) being the most compliant. Compliance values ranged from 0.25 to 5.5 %/100 mmHg. Interestingly, as the mean arterial pressures were increased the compliance of the elastin containing grafts decreased, while compliance of the pure PDO graft increased. This trend corresponds to the behavior of native artery, which stiffens under increased mean arterial pressure.

Preliminary subcutaneous implantation revealed at 10 and 21 days there to be some cell infiltration with no acute inflammatory cells and a thick capsule, mainly formed by activated fibroblasts, macrophages and some capillaries. Longer-term data showed the material to still be present with more invasion of strain cells and a thinner, more organized capsule.

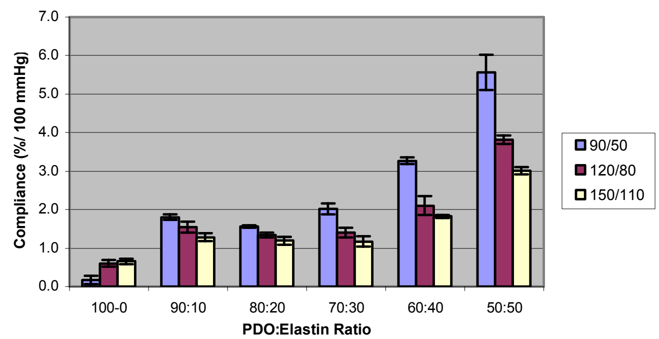

Figure 1. Dynamic compliance of PDO:Elastin grafts

Conclusions: The compliance testing performed in this study, coupled with previously performed uniaxial tensile testing results, show that from a mechanical perspective electrospun blends of PDO and elastin are at least comparable to other currently available vascular graft materials. While preliminary subcutaneous results were not as positive as expected the material still showed promise as a bioresorbable vascular graft.

Future work will include a more in depth *in vivo* study where the graft will be interposed in the infrarenal abdominal aorta of rats. In addition, a novel winding device will be employed to incorporate into the electrospun grafts a bi-directional mesh of PDO suture at varying pitch angles. This composite structure will be expected to increase the overall strength of the graft and enhance its resistance to aneurysm.

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