

# Impact of Electrospun Conduit Composition on Vascular Graft Production and Remodeling after Aortal Implantation

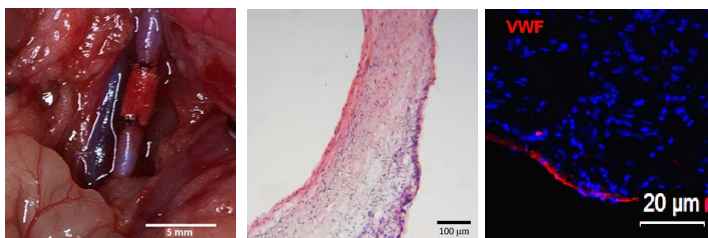
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**Introduction:** Tissue engineered vascular grafts are a promising alternative to current surgical options. However, they still have some limitations including compliance mismatch and extended inflammatory response that need to be overcome. It has been shown that collagen-based scaffolds modulate macrophage phenotype after in vivo implantation [1]. Our strategy is to develop conduits with compositions that enhance endothelialization by reducing the inflammatory response. The goal of study is to determine the amount of collagen needed to modulate the accumulation of oxidized lipid species, which is part of the inflammatory response, and maintain graft structural stability when implanted in the rat peritoneal cavity and then the abdominal aorta of the same rat.

**Materials and Methods:** We produced electrospun conduits from 100%, 90%, and 75% blends of PCL/ collagen (w/w) in 1,1,1,3,3,3-hexafluoro-2-propanol, and characterized the fiber diameters and orientations with SEM. We enclosed 10 mm long conduits in PTFE porous pouches, performed ethylene oxide sterilization, and then implanted the conduits in the rat peritoneal cavity for 4 weeks. In order to analyze mechanical properties, we used a ring test procedure at physiological condition for both non-implanted and implanted conduits. High performance liquid chromatography (HPLC) / mass spectrometry was used to quantify levels of specific lipids and their oxidation products (e.g., HETE-species from oxidation of arachidonic acid). In order to assess remodeling and endothelialization we performed grafting into abdominal aortae of the same rat for 6 weeks. The grafts were analyzed with H&E to visualize its patency and IF imaging to assess endothelialization. Statistical significance was determined using one-way ANOVA with Tukey multiple comparison for a significance criterion of  $p < 0.05$ .

**Results and Discussion:** SEM images showed average electrospun fiber diameters of  $1.07 \pm 0.2$ ,  $0.95 \pm 0.17$ , and  $1.14 \pm 0.78$   $\mu\text{m}$  for 100%, 90% and 75% PCL conditions, respectively. Mechanical testing results demonstrated that percent elongation and ultimate tensile strength (range: 1.5 to 2.1 MPa) increased with increasing collagen percentage. After peritoneal implantation, the tensile moduli increased for 100% and 75% PCL and the percent elongation decreased for all the samples, indicating construct remodeling. Further, the reduction in ultimate tensile strength for 90% PCL, but not 100% PCL, suggests that the collagen/synthetic ratio is important for remodeling. According to PCR results, the 90% blend conduits also had the highest gene expression of contractile markers, such as  $\alpha$ -SMA ( $p=0.041$  vs. 75% PCL). IF images confirm the expression of myofibroblast and smooth muscle cell markers. Incorporation of collagen reduced the overall lipid oxidation, with the most noticeable reduction for all-HETE species with 25% collagen incorporation ( $p=0.034$  vs. 100% PCL). Aortic grafting studies are ongoing. In preliminary data, we verified that 100% PCL and 75% PCL/collagen samples without initial peritoneal cavity implantation remained patent and endothelialized over 6 weeks (Fig. 1). A 100% PCL construct, with pre-implantation in the peritoneal cavity, is currently grafted and the rat is moving well after  $> 2$  weeks. We are analyzing the impact of construct composition on graft remodeling and intimal hyperplasia formation.



**Figure 1.** Aortic graft, 100% PCL, without peritoneal implantation. Shown are A) picture of the construct grafted into rat abdominal artery, B) H&E image of a cross-section, and C) immunofluorescent image of longitudinal 100% control PCL graft for von Willebrand Factor.

**Conclusions:** This study demonstrated that incorporating collagen reduces inflammation, and this effect might be collagen ratio dependent. Also it showed that 90% PCL scaffolds appeared to degrade more in the peritoneal cavity. However, all of the scaffolds exhibited mechanical properties similar to native human coronary arteries (1.8 MPa)[2]. Finally, aortic grafting showed that these grafts remain patent and endothelialize after 6 weeks.

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References: 1. van Aalst et al. J. Vasc Surg, 2004, 40:1208 2. Holzapfel et al. J Physiol Heart Circ Physiol, 2005, 5, 2048