3D Printed Biodegradable Polymer Vascular Grafts

Anthony J Melchiorri,[1] Narutoshi Hibino,[2] Chelsea A Kraynak,[1] John P Fisher[1]

[1]Fischell Department of Bioengineering, University of Maryland, College Park, MD. [2]Department of Cardiothoracic Surgery, Nationwide Children's Hospital, Columbus, OH

Statement of Purpose: Congenital heart diseases (CHD) are the most common birth defect, occurring in ~1% of all live births.[1] CHD may present in various forms, often life-threatening and necessitating surgical intervention. Anatomical differences in each child necessitate customizing vascular grafts during surgery. In addition, current vascular prosthetics are permanent and do not grow with a child. A child may undergo several open-heart surgeries throughout their lifetime to replace the devices and devices are expected to fail at 70-100% failure rate by 10-15 years.[2] Thus, we propose a 3D printable, biodegradable vascular graft. Such a graft can be custom-designed to fit a child before surgery by utilizing medical imaging. The graft, while supporting native tissue growth, will degrade over time to reduce long-term complications and repeated surgeries. We are utilizing poly(propylene fumarate) which is a biocompatible, biodegradable material that is photocrosslinkable, allowing it be utilized in digital light processing stereolithography. Using a 3D printing resin made with PPF, we hypothesize that we can fabricate devices that (1) have mechanical properties similar to native human vessel and (2) support cell and tissue growth *in vitro* and *in vivo*.

Methods: Poly(propylene fumarate), synthesized in the laboratory, was diluted with diethyl fumarate for the 3D printing resin. Bis(2,4,6-trimethylbenzoyl) phenylphosphine oxide was added as a photoinitiator and α-tocopherol and hydroxyl-methoxybenzophenone were added as photoinhibitors to control diffusive crosslinking. 3D models were constructed via Solidworks (Dassault Systèmes SolidWorks Corp, Waltham, MA) and printed via an EnvisionTec Perfactory 4 (Dearborn, MI). To tune mechanical properties, vascular grafts underwent a variety of post-processing techniques by varying (1) post-printing UV exposure via EnvisionTec's Otoflash photo-flash lamp (0, 1000x, 2000x) and (2) washes in various solvents (Isopropyl alcohol, acetone, 50% acetone). Tensile testing assessed ultimate tensile strength (UTS), Young's modulus, and suture retention strength. Human umbilical vein endothelial cells (HUVECs) and human umbilical smooth muscle cells (HUSMCs) were seeded on 3D printed PPF grafts to assess cell attachment and proliferation at various timepoints via a Live/Dead assay. Grafts were implanted as inferior vena cava interposition grafts in a mouse model. H&E histology staining will be performed on the grafts after excision 1, 3, and 6 months post-implantation. Immunohistochemistry will also be performed to identify cell ingrowth.

Results: A range of mechanical properties were achieved by varying post-processing washes and post-printing UV exposure as seen in Table 1. Attachment rates for HUVECS were 19.5 +2.1% and 19.8 +3.7% for HUSMCS. Cell growth on printed samples can be seen in Figure 2. 1 mm inner diameter grafts were successfully implanted in twelve mice, with no surgical complications.

Table 1. Mechanical properties of 3D printed grafts compared to native vessels used as autologous implants[3]

	Modulus (MPA)	UTS (Mpa)	Suture Retention Strength (N)
Human Saphenous Vein	6.7 ± 1.3	2.2 ± 0.2	1.9 ± 0.1
Human Femoral Artery	9.0 to 12.0	1.0 to 2.0	2.0 ± 1.2
3D Printed Graft	**11 to 350**	**1 to 32**	**0.3 to 2.4**

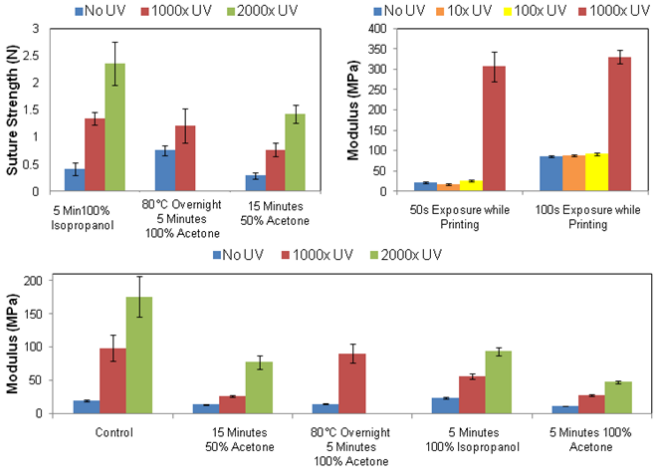

Figure 1: Preparations of PPF with a wide range of mechanical properties. **(Top Left)** Suture strength results with 3 different post processing techniques to remove uncrosslinked components, and three different UV flash curing conditions. **(Top Right)** Young's Modulus as a function of exposure time during printing and UV flash curing. **(Bottom)** Young's Modulus with various post processing rinses.

Conclusions: Through post-processing and initial resin formulation, we were able to achieve 3D printing of vascular grafts made from PPF that with a range of mechanical properties. A 5 min 50% acetone wash post-printing resulted in vascular grafts with properties most similar to native vessels. In addition, the grafts supported initial vascular cell attachment and proliferation. Implantation of the grafts into mice demonstrated suturability and feasibility of surgical procedures with the 1 mm inner diameter printed PPF grafts. We hypothesize that ongoing *in vivo* experiments will show tissue growth and graft patency even after 6 months of implantation.

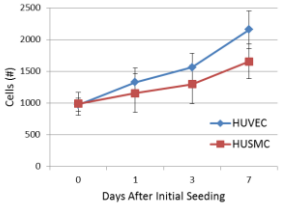

Figure 2: HUVEC and SMC growth on 3D printed PPF grafts *in vitro*

References: 1) Roger V. *Circ*. 2012. **2)** Hoffmann JIE. *J Amer Coll Cardio.* 2002:285:1890-1900. **3)** Melchiorri AJ. *J Biomed Mater Res-A*. 2013.