Evaluating poly(glycerol dodecanedioate) For Cardiovascular Repair In Porcine Pulmonary Artery

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Statement of Purpose: Minimally invasive cardiovascular regenerative therapies require material vehicles suited for cardiac tissue mechanics, endothelialize well, exhibit controlled degradation rates, and provide ease of use for percutaneous delivery[1]. Shape memory biomaterials are ideal for transcatheter delivery of a programmed low profile material geometry that is thermally triggered for expansion at a transition temperature(T_{trans}) of 37ºC. Additionally, biodegradable shape memory elastomers are an emerging class of polymers used in a variety of soft tissue repair applications[2]. This study evaluates the design, percutaneous delivery, degradation and biocompatibility of poly(glycerol dodecanedioate) PGD in porcine pulmonary arteries (PAs).

Methods: *Device design:* PGD and Porcine PAs(6-10 mm inner diameter) were modeled as an Ogden materialor solid mixture Mooney Rivlin material in FEBio(2.7)[3]. Patch designs were evaluated for wall stress resulting from design unfurling(Fig.1A,B). *Manufacturing:* PGD pre-polymer, a 1:1 molar ratio of glycerol and dodecanedioate, was synthesized at 120ºC under N_2 for 24 hours followed by 90mTorr vacuum for 24hrs. Pre-polymer was poured as flat sheets and cured in a vacuum oven for an additional 24hrs at 120ºC and 90mtorr. Samples were lasercut to size and patterned (400µm x 400µm x 50µm posts) and pieces were molded into curved tubes and cured for an additional 24 hrs. *Design verification:* Samples loaded in catheter sheaths(9-14 Fr) were tested in 3D printed(Form2 and Stratasys J750) *in vitro* PA models for shape fixity(R_f) during delivery, complete recovery (R_r), and resistance to dislodgement. Selected designs sterilized using a validated low-temp ethylene oxide cycle (37.7ºC) were analyzed using differential scanning calorimetry (DSC) on a TA Instruments DSC 250 assessing T_m and ΔH_{fusion}, and rheometry using an Anton Paar MCR 302 to evaluate tanδ and G*[3]. *In vivo:* A total of 8 PGD specimens were implanted into the PAs of 4 female Yorkshire pigs using a 12Fr sheath by percutaneous access via the left internal jugular vein under ultrasound guidance. Specimens were explanted after 3 months. Material characterization(DSC), mass loss, crosslink% were assessed using half the explants(N=4) and histology and staining(Rhodamine-phalloidin, DAPI) was conducted using the remaining explants(N=4). Tissue surrounding the implant was evaluated for inflammation by a pathologist (N=8). Approved by Case Western University IACUC.

Results: Computational models revealed a peak stress of 20kPa in the PGD implant and no significant impact on vascular wall stress after deplyment. Sterilization did not affect shape memory properties R_f(99%±0.1), R_r(100%), and tan δ at (34±2.3ºC) compared to controls. There was an increase in rubbery shear modulus after the sterilization compared to controls (1.03±0.29 MPa $p<0.05$). Patterned patches tested in 3D printed benchtop PA models having increased surface roughness increased resistance to dislodgement in PA models compared to unpatterned patches, but consequently increased resistance to delivery within catheter sheaths once transitioned. Out of 8 implants, 7 were fully endothelialized (Fig.1D) and displayed similar inflammation to native pulmonary arteries. All implants exhibited surface degradation *in vivo* (Fig.1C vs. 1E). Patterned explants revealed greater mass loss compared to unpatterned explants ($p<0.001$). IHC of the implants also revealed good implant integration with the initimal layers of the vessel and signs of pitting and degradation(arrow) and cell ingrowth (* Fig. **1F**). There was a decrease in crosslink% (Fig. 1H) and a concomitant increase in T_m (Fig. 1G) indicating a stiffer and more brittle polymer structure as previously observed[4].

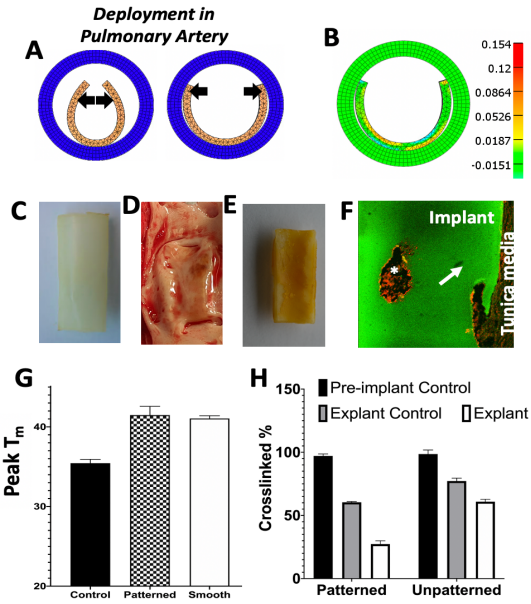

Figure 1. PGD design analysis from porcine pulmonary artery.A,B) computational modeling C) PGD implant D) endotheliaized implant E) explant F) IHC of tissue implant G) DSC T_m H) Crosslink% from swelling

Conclusion: These findings suggest that PGD patches delivered percutaneously exhibit good attachment, vascular wall apposition, endothelialization, and degradation properties suited for endovascular delivery and structural repair of cardiovascular pathologies. Finally, patterning the substrates can provide an additional approach to controlling the degradation rate of these materials. These materials can also be used for delivering drugs, growth factors and cells all areas of ongoing investigation.

References: **[1]** N. F. Huang, et al. *Commun. Biol. 2018 11* **2018**, *1*, 1. **[2]** H. Ramaraju, et al. *Adv. Funct. Mater.* **2020**, *30*, 2002014.**[3]**H. Ramaraju, et al. *J. Mech. Behav. Biomed. Mater.* **2020**, *110*, 103965. **[4]** H. Ramaraju et al. *PLoS One* **2020**, *15*, e0229112. **Acknowledgements**: Funding sources NIH R21HL126004