Evaluation of a Hydrogel-coated Electrospun Mesh as a Synthetic Heart Valve

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Statement of Purpose: Current bioprosthetic valves have a 50% failure rate within 15 years.[1] Although improvements have been made since their inception, the biological nature of these valves limits the ability to truly engineer the material for improved durability and function. The failure of the replacement valves can be placed into four categories: mechanical fatigue, calcification, infection, and thrombosis.[2] To address these limitations of current replacement heart valves, we propose the use of a synthetic composite material composed of an electrospun mesh for bulk mechanical properties that is coated with a polyethylene glycol (PEG) based hydrogel. This approach decouples the mechanical and biological requirements allowing each to be tuned independently. Previously, we showed that hydrogel coating provided thromboresistance necessary for blood contacting devices and hypothesize that the coating will also confer resistance to bacterial attachment.[3] The electrospun mesh closely mimics the structure of the native ECM and allows for precise control over the fiber microarchitecture and mechanical properties that can be used to improve durability. The ability of these two phases to be tuned independently of one another provides a platform to engineer a synthetic valve with improved durability and biocompatibility over current bioprosthetic valves. Herein, we describe the development of a synthetic electrospun composite heart valve with assessments of hemodynamic performance and resistance to bacterial attachment and calcification.

Methods: *Composite Fabrication:* Electrospinning was performed using a 24% Bionate® segmented polyurethane (DSM Biomedical) in dimethylacetamide solution. Briefly, electrospun fibers were collected on a rotating mandrel at 50 RPM and a working distance of 50 cm via a flow rate of 0.5 ml/hr. A voltage of +15 kV was applied to a 20G needle and -5kV to the collector. Meshes were hydrated in a graded ethanol ramp and hydrogel coated (10% 20 kDa Polyether urethane diacrylamide (PEUDAm), 5% N-acrylyol glycinamide (NAGA)). *Calcification:* Bovine pericardium was fixed in 0.5% glutaraldehyde for 72 hours followed by 0.2% glutaraldehyde for one week. A 2x simulated body fluid (SBF) was utilized for calcification with solution changes performed every other day for two weeks. Samples were hydrolyzed in 5 M HCl following the treatment. Calcium content was determined via the o-cresolphthalein complexone to determine calcium deposition normalized to sample dry weight. *Bacterial Attachment:* Hydrogels were made from PEG 3.4 kDa to demonstrate preliminary bacterial attachment resistance of PEG-based hydrogel coatings. ATPP 25923 non-specific staphylococcus aureus was seeded at a density of $5x10^5$ CFU/mL on the samples and incubated at 37 °C for 2 hours. Samples were washed to removed non-adherent bacteria and subsequently sonicated/vortexed to remove adherent bacteria. The collected adherent bacteria were plated and cultured overnight to quantify colony forming units. *Functional Testing:* Electrospun fibers were collected as described and hydrogel coated 10% 20 kDa PEUDAm, 5% NAGA, bisacrylamide 0.1mol% to NAGA) for valve assembly on a custom cobalt chromium stent. Hemodynamic assessments were performed in a mock flow loop under physiological conditions.

Results: The electrospun mesh had fiber diameters of 1.82 ± 0.25 µm and a mesh thickness of 0.23 ± 0.01 mm with hydrogel coating resulting in a total composite thickness of 0.56-0.80 mm. After soaking in SBF, the composite had a marked reduction in calcium deposition compared to the pericardium (0.05 ± 0.04 ug calcium/mg sample and 0.47 ± 0.03 ug calcium/mg sample, respectively). The antifouling hydrogel provided resistance to bacteria attachment ($4.5x10^4$ ± $4.1x10^4$ CFU/ml) compared to the pericardium ($6.0x10^6$ ± $1.4x10^6$ CFU/ml).

Functional assessment of the assembled valve in a mock flow loop demonstrated similar effective orifice area for the composite valve (1.78 cm^2) as the clinically used Evolute valve (1.80 cm^2) and SAPIEN 3 valve (2.10 cm^2). Although, the regurgitation fraction was notably higher for the composite valve at 23.05% (Evolute valve 15.74% and SAPIEN 3 10.92%), this was attributed to the deployment of the valve in the mock flow loop and assembly of the valve rather than the material mechanical properties and can be improved during future iterations.

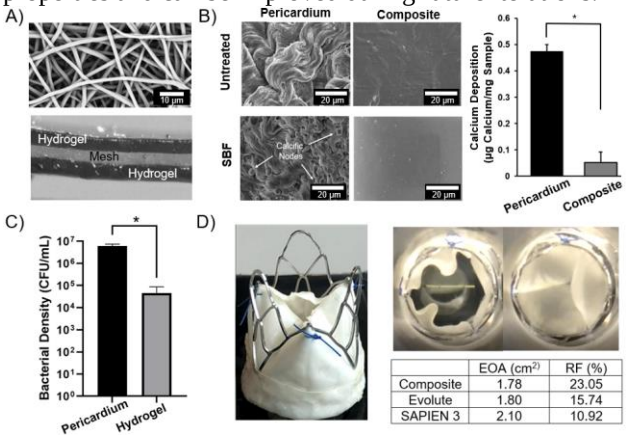

Figure 1: A) Micrograph of electrospun fibers and composite cross section B) Calcification propensity C) Bacterial attachment D) Valve assembly and flow loop functional assessment

Conclusion: Overall, these findings demonstrate the potential of an electrospun composite material as a synthetic heart valve material toward overcoming failures due to infection, calcification, and mechanical fatigue. Current studies are focused on understanding the impacts of fiber microarchitecture on mechanical properties towards improving leaflet durability.

References: (**1**) Kheradvar et al. Ann Biomed Eng. 2015; 43 (4), 844-857. (**2**) VanderLann et al. Surg Pathol. 2012; 5 (2), 353-369. (**3**) Post et al. Acta Biomater. 2018; 69, 313-322.