

Microstructural manipulation of electrospun scaffolds for specific bending stiffness for heart valve tissue engineering [☆]

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ABSTRACT

Biodegradable thermoplastic elastomers are attractive for application in cardiovascular tissue construct development due to their amenability to a wide range of physical property tuning. For heart valve leaflets, while low flexural stiffness is a key design feature, control of this parameter has been largely neglected in the scaffold literature where electrospinning is being utilized. This study evaluated the effect of processing variables and secondary fiber populations on the microstructure, tensile and bending mechanics of electrospun biodegradable polyurethane scaffolds for heart valve tissue engineering. Scaffolds were fabricated from poly(ester urethane) urea (PEUU) and the deposition mandrel was translated at varying rates in order to modify fiber intersection density. Scaffolds were also fabricated in conjunction with secondary fiber populations designed either for mechanical reinforcement or to be selectively removed following fabrication. It was determined that increasing fiber intersection densities within PEUU scaffolds was associated with lower bending moduli. Further, constructs fabricated with stiff secondary fiber populations had higher bending moduli whereas constructs with secondary fiber populations which were selectively removed had noticeably lower bending moduli. Insights gained from this work will be directly applicable to the fabrication of soft tissue constructs, specifically in the development of cardiac valve tissue constructs.

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1. Introduction

Flexural rigidity is a functional measure that quantifies a key aspect of a surgeon's perception regarding the appropriateness of a biomaterial for soft tissue repair. Beyond meeting perceived mechanical requirements prior to material implantation, the selection of a material with appropriate flexural rigidity is functionally important in avoiding a mechanical mismatch in situ, which could lead to patient discomfort, tissue damage and a disruption of the desired healing process [1]. In the specific case of heart valve tissue

engineering, flexural properties are of paramount importance to achieving appropriate valve function [2–4]. Specifically, however, scaffold flexural behavior is discussed least in the literature of the common mechanical responses.

The most common materials under development for the tissue engineering of heart valves include decellularized extracellular matrix (ECM)-based scaffolds [5,6] and synthetic fibrous scaffolds [7–9]. Decellularized ECM scaffolds are typically sourced from human or xenograft valvular tissue [10–12] or small intestinal submucosa [13,14]. However, decellularized, ECM-based scaffolds, depending upon the processing method employed, can be hindered by inconsistent performance in terms of their mechanics and local cytotoxicity due to residual processing agents [15].

Synthetic scaffolds have the advantage of consistent processing methodologies which can produce reliable and tunable mechanical properties and functional results. Varieties of non-woven fibrous scaffolds are commercially available and are typically based on polymers utilized in other devices that have obtained regulatory approval. Synthetic scaffolds can be seeded with cells [7–9] and

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have been shown to support host cell infiltration [16]. However, many of the current materials used to produce such scaffolds have been limited by their high stiffness and lack of mechanical anisotropy, and thus fail to approximate native valvular tissue [17].

One method of producing non-woven fibrous scaffolds is electrospinning, which is notable for the ability to generate structural features on the nano- to microscale [18]. Electrospun constructs are amenable to modification during, as well as following, fabrication to introduce functionality or modify microstructure and mechanical response. With respect to the latter, functional groups and peptides can be introduced onto electrospun fibers through common surface treatments [19] or by grafting them onto the polymer chain prior to solvent processing. Scaffold porosity and packing density can be altered by the introduction of a porogen such as salt crystals to create macropores [20], laser ablation of scaffolds following fabrication [21], or concurrently electrospaying an aqueous medium to loosen interactions between polymer layers [16]. It is further possible to alter electrospun scaffold microstructure in order to create anisotropy within the constructs. Fibers can be patterned [22] or aligned [17] to encourage contact guidance of seeded cells [19] and produce tunable tensile mechanical anisotropy [17]. While such structural manipulations have been employed to alter the mechanical behavior of electrospun scaffolds under tension, a reliable method of controlling the inherent bending modulus would be desirable to provide a more complete approach to meeting design objectives for soft tissue constructs.

The objective of this study was to examine specific microstructural features important to determining the flexural behavior of electrospun scaffolds suitable for heart valve tissue engineering. Methods are highlighted for tuning the flexural response by modifying fabrication parameters, or by introducing secondary fiber populations that may have a higher modulus or be selectively dissolved from the scaffold following fabrication. The effect of such construct modifications on in-plane tensile properties is also

demonstrated, and effort was made to mimic the mechanical properties of a native pulmonary valve in both flexural and equi-biaxial tensile response.

2. Materials and methods

2.1. Scaffold fabrication

Poly(ester urethane) urea (PEUU) was synthesized as described previously [23] from polycaprolactone diol ($M_n = 2000$, Sigma), 1,4-diisocyanatobutane (Sigma) and putrescine (Sigma). Scaffolds were fabricated in a manner similar to that previously reported [24]. Briefly, PEUU was dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at a concentration of 12% (w/v) and electrospun onto a rotating and translating stainless steel mandrel (6 mm diameter) by feeding through a charged capillary (1.19 mm ID) at 1.5 ml h^{-1} . The mandrel was located 17 cm from the tip of the capillary and grounded with a voltage of -5 kV . The polymer feeding tube was charged to 12 kV. The mandrel was rotated with a tangential speed of 8 cm s^{-1} and translated along its axis at 0.3, 1.5, 3.0 or 30.0 cm s^{-1} (Fig. 1a).

Scaffolds were electrospun from PEUU in HFIP alone, or concurrently with a secondary polymer stream being fed from a capillary mounted in a separate location. Polycaprolactone (PCL, Sigma, $M_n = 80,000 \text{ kDa}$) dissolved in HFIP (8% w/v) was electrospun from a capillary in a 180° opposing orientation from PEUU, at volume flow ratios of 100:0, 75:25, 50:50, 25:75 and 0:100 PEUU:PCL. In separate experiments, poly(ethylene) oxide (PEO) ($M_v = 200 \text{ kDa}$) in cell culture medium (Dulbecco's modified Eagle medium, 10% fetal bovine serum, 5% penicillin/streptomycin) was electrospun from a perpendicular orientation to PEUU in volume flow ratios of 100:0, 85:15, 75:25 and 50:50 PEUU:PEO. Following fabrication, PEO-incorporated scaffolds were placed in distilled water for at least 4 h, changing the water once, in order to dissolve the PEO fibers and to leach PEO out of the scaffold

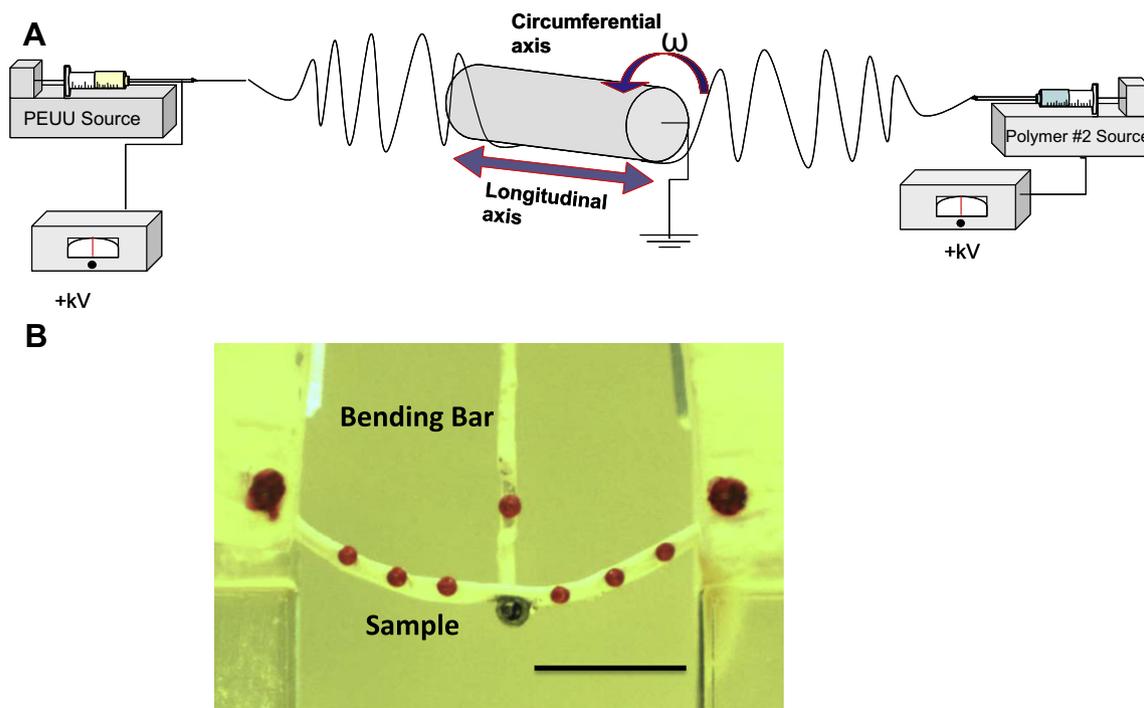


Fig. 1. (A) Schematic of electrospinning apparatus for two-component scaffolds. PEUU was fed from the same location for every group. The mandrel was rotated and translated along its longitudinal axis at varying speeds. Secondary polymer fibers were introduced through separate nozzles. (B) Image of a polymeric specimen loaded in the bending device (scale bar = 1 cm).

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