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Characterization of mechanical properties of pericardium tissue using planar biaxial tension and flexural deformation

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ABSTRACT

Flexure is an important mode of deformation for native and bioprosthetic heart valves. However, mechanical characterization of bioprosthetic leaflet materials has been done primarily through planar tensile testing. In this study, an integrated experimental and computational cantilever beam bending test was performed to characterize the flexural properties of glutaraldehyde-treated bovine and porcine pericardium of different thicknesses. A strain-invariant based structural constitutive model was used to model the pericardial mechanical behavior quantified through the bending tests of this study and the planar biaxial tests previously performed. The model parameters were optimized through an inverse finite element (**FE**) procedure in order to describe both sets of experimental data. The optimized material properties were implemented in FE simulations of transcatheter aortic valve (**TAV**) deformation. It was observed that porcine pericardium TAV leaflets experienced significantly more flexure than bovine when subjected to opening pressurization, and that the flexure may be overestimated using a constitutive model derived from purely planar tensile experimental data. Thus, modeling of a combination of flexural and biaxial tensile testing data may be necessary to more accurately describe the mechanical properties of pericardium, and to computationally investigate bioprosthetic leaflet function and design.

1. Introduction

Bioprosthetic heart valves (**BHV**) have been widely used to treat valvular disease for over forty years (Brewer et al., 1977) and offer excellent hemodynamic performance and low risk of thrombogenesis. Glutaraldehyde-treated bovine pericardium (**BP**) is recognized for its attractive mechanical properties and has been considered one of the standard sources for BHV leaflets (Vesely, 2003). Some recent generations of transcatheter valve designs have elected to use glutaraldehyde-treated porcine pericardium (**PP**). PP tissue is substantially thinner than BP (Caballero et al., 2017), which lends itself to a more low-profile valve design, consequently, improving the safety of transcatheter delivery.

The long-term durability of BHVs is limited by structural deterioration and calcification of the tissue leaflets (Vyavahare et al., 1999). There have been many studies showing that the regions of BHV leaflet tearing correspond with regions of high tensile and bending stresses acting on the leaflets during opening and closing (Sacks et al., 2009). Therefore, it is important to understand the stresses acting on the leaflets to mitigate BHV failure. Several groups have used computational approaches to investigate structural and hemodynamic valve function (Sun et al., 2014, 2010, 2005; Li and Sun, 2016, 2010; Vy et al., 2016; Kim et al., 2008; Christie, 1992; Krucinski et al., 1993; Leat and Fisher, 1995, 1994; Cacciola et al., 2000; Martin and Sun, 2014). Numerical simulations allow for rapid, resource-efficient, quantitative analyses compared to experimental methodologies; however, the accuracy of computational modeling hinges on the accuracy of the prescribed material properties (Saleeb et al., 2013).

The mechanical properties of glutaraldehyde-treated BP and PP, have been investigated and characterized primarily through uniaxial and biaxial tensile tests (Caballero et al., in preparation; Aguiari et al., 2016; Hulsmann et al., 2012; Crofts and Trowbridge, 1988; Garcia Paez et al., 2007; Garcia Paez et al., 2003; Gauvin et al., 2013; Oswal et al., 2007; Garcia Paez et al., 2002), which are both planar tests. Studies on the out-of-plane, flexural behavior of pericardia are limited (Mirnajafi et al., 2005; Nicosia, 2007) despite the critical role leaflet bending plays in bioprosthetic heart valve function and durability (Sacks and Yoganathan, 2007). In-plane tensile testing data cannot be directly used to derive off-plane properties unless certain material symmetry or isotropy conditions are assumed. Pericardial tissues, along with many

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other soft tissues, are highly compliant, and offer very little resistance to bending, which complicates tissue bending experiments. Even less has been done to implement both the tensile and flexural behaviors into a single constitutive model to more accurately describe the pericardial tissue mechanical behavior. While data from isolated bending experiments of pericardia can offer insight on BHV function, these experiments cannot replicate the complex in vivo loading conditions of BHVs. Consequently, there is still a jump between understanding the BHV tissue material flexural response and the BHV structural response. Constitutive models describing both the tensile and flexural responses of BHV biomaterials are needed to interpolate and extrapolate the isolated experimental data to different loading states. Simulation-based analyses can then be used to translate tissue-level responses to accurate BHV device-level responses.

In this study, an integrated experimental and inverse finite element (**FE**) procedure was developed to characterize the biaxial tensile and flexural properties of pericardial tissue and implement these properties into a single nonlinear, anisotropic, constitutive model. Biaxial testing data of BP and PP tissues were obtained previously (Caballero et al., 2017). A beam bending experiment was performed to characterize the tissue flexural responses. Thin and thick BP and PP tissues were tested. The material response for each tissue type was described with a structural-based constitutive model. The material parameters were optimized through inverse FE analysis in order to capture both the biaxial tensile and beam bending experimental data. The optimized material parameters for each tissue type were then implemented in simulations of BHV opening to assess the impacts of tissue type and thickness on performance.

2. Materials and methods

2.1. Tissue preparation

Fresh bovine and porcine pericardia stored on ice were obtained from Animal Technologies (Tyler, TX). Details on tissue pericardium preparation have been previously described (Caballero et al., 2017). Briefly, the pericardial sacs were dissected, the fatty nodules were removed cautiously, and large sections were pinned in a trampoline fashion without overextension. Fresh BP and PP sheets were treated with 0.625% glutaraldehyde (GL) solution, and a crosslinking solution (6% Formaldehyde, 2.2% Ethanol, 1.2% Tween 80) before final transfer to a 0.25% GL storage solution at 4 °C. Rectangular samples of BP (12 × 5.75 mm) (n = 23) and PP (7.5 × 6.5 mm) (n = 27) tissue were prepared. Tissue thickness was measured in three areas along the length of the sample using a non-rotating thickness gauge (Mitutoyo, Model 7301) and the mean value was documented. The samples were divided into two distinct thickness groups for each tissue type. The thickness of thick bovine pericardium (**BPK**) (n = 12), thin bovine pericardium (**BPN**) (n = 11), thick porcine pericardium (**PPK**) (n = 15), and thin porcine pericardium (**PPN**) (n = 12) were 0.45 ± 0.03 mm, 0.32 ± 0.03 mm, 0.20 ± 0.03 mm, and 0.14 ± 0.02 mm, respectively.

2.2. Experimental bending

A cantilever beam bending experiment was setup in a 0.9% saline bath by sandwiching a tissue specimen on one end and allowing the rest of the specimen to free float in water as shown in Fig. 1**A**. A small needle with suture was fed through the free end of the tissue such that the weight of the needle deformed the tissue in a beam bending fashion (Fig. 1**A**). A calibration ruler was fixed in place near the beam for calibration during subsequent image analysis. Two needles of differing weights were applied to each BP (56 mg and 125 mg) and PP (19 mg and 45 mg) specimen. Images were taken of each sample with each applied load in order to measure the tissue deformation. The edge of the tissue specimens were darkened to enhance the contrast between the tissue and background to facilitate the image-based measurements.

Image digitization was carried out using custom Matlab (MathWorks Inc., Natick, MA) scripts. A representative example of the digitization process is shown in Fig. 1. Images were individually cropped and converted to binary using a background-level threshold as shown in Fig. 1**B**. The sample position along its length was digitized by selecting points along the specimen in the thresholded image, and converted to units of mm using the pixel-to-mm ratio determined from the calibration ruler (Fig. 1**C**). After digitization of all the experiments, points along the deflection curve were fit to a third-order polynomial. The vertical coordinates at set horizontal intervals along the length of the tissue were averaged between specimens of each group to obtain a mean ± standard deviation flexural response.

2.3. Inverse finite element analysis

An inverse FE procedure was conducted to obtain the tissue flexural material properties from the tissue cantilever beam experiments. Commercial software for FE analysis, Abaqus/Standard 6.13, and process automation, Isight 5.9 (Dassault Systemes Simulia Corp, Johnston, RI), were used. The 3D tissue geometries were created using the average dimensions of BPK, BPN, PPK and PPN specimens. Tissue finite element models were developed with 6732 solid continuum elements (Abaqus C3D8I) with 51 elements along the length, 33 elements along the width, and 4 layers of elements through the tissue thickness. Cantilever bending was simulated by fixing the nodes along one end of the tissue and applying a concentrated force to the free end mimicking the experimental protocol. In each simulation, two forces were applied: the first corresponding to the lighter weight applied experimentally and the second corresponding to the heavier weight applied experimentally. The tissue deformation due to the application of each weight was exported from the simulations as the position of the nodes along the tissue length midway through the thickness using custom python scripts as shown in Fig. 2. The position of the nodes in the region that was fixed were not extracted.

BP and PP were assumed to be anisotropic, incompressible, hyperelastic materials. Therefore, the strain energy function, W, was defined using a modified version of the fiber-reinforced, hyperelastic material model based on the work by Holzapfel et al. (2000) given by

$$W = C_{10}\{\exp[C_{01}(\bar{I}_1 - 3)] - 1\} + \frac{k_1}{2k_2}\sum_{i=1}^{2}\{\exp[k_2(\bar{I}_{4i} - 1)^2] - 1\} + \frac{1}{D}(J-1)^2, \quad (1)$$

where C_{10}, C_{01}, k_1, k_2, and D are material constants, and $\bar{I}_1$ and $\bar{I}_{4i}$ are deviatoric strain invariants. Parameters C_{10} and C_{01} characterize the material response of the ECM and collagen cross-links, while k_1 and k_2 represent the mechanical response of the collagen fibers. Material constant D controls incompressibility and J is the determinant of the deformation gradient tensor. The fiber orientation was defined by structural tensor, $\boldsymbol{M}_i = \boldsymbol{m}_{0_i} \otimes \boldsymbol{m}_{0_i}$ with $\boldsymbol{m}_{0_1} = [cos\theta, sin\theta, 0]$ and $\boldsymbol{m}_{0_2} = [cos\theta, -sin\theta, 0]$. It has been shown that Eq. (1) can capture the biaxial response of chemically-treated pericardia to a high degree of accuracy (Martin and Sun, 2015) and can describe 3D out-of-plane deformations necessary to model the tissue bending response. Eq. (1) was implemented in a user-defined material (UMAT) subroutine in Abaqus.

The material constants of Eq. (1) were obtained through an inverse FE procedure. The initial material constant values were obtained through fitting the stress-strain data from recent biaxial testing of BP and PP (Caballero et al., 2017) in the least-squares sense. Previous work by Mirnajafi et al. (2005) has shown that the BP bending response is dominated by the non-collagenous tissue components as well as inter-fiber cross-links as opposed to the stiffness of the collagen fibers themselves. Therefore, in the inverse FE procedure, parameters C_{10} and C_{01} controlling the material response of the ECM and collagen cross-