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A mechanistic model on the role of "radially-running" collagen fibers on dissection properties of human ascending thoracic aorta

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ABSTRACT

Aortic dissection (AoD) is a common condition that often leads to life-threatening cardiovascular emergency. From a biomechanics viewpoint, AoD involves failure of load-bearing microstructural components of the aortic wall, mainly elastin and collagen fibers. Delamination strength of the aortic wall depends on the load-bearing capacity and local micro-architecture of these fibers, which may vary with age, disease and aortic location. Therefore, quantifying the role of fiber micro-architecture on the delamination strength of the aortic wall may lead to improved understanding of AoD. We present an experimentally-driven modeling paradigm towards this goal. Specifically, we utilize collagen fiber micro-architecture, obtained in a parallel study from multi-photon microscopy, in a predictive mechanistic framework to characterize the delamination strength. We then validate our model against peel test experiments on human aortic strips and utilize the model to predict the delamination strength of separate aortic strips and compare with experimental findings. We observe that the number density and failure energy of the radially-running collagen fibers control the peel strength. Furthermore, our model suggests that the lower delamination strength previously found for the circumferential direction in human aorta is related to a lower number density of radially-running collagen fibers in that direction. Our model sets the stage for an expanded future study that could predict AoD propagation in patient-specific aortic geometries and better understand factors that may influence propensity for occurrence.

1. Introduction

Aortic dissection, characterized by delamination of the aortic wall layers, is one of the most common forms of aortic disease (Jondeau and Boileau, 2012; Lu et al., 2012; Matsushita et al., 2012; Takigawa et al., 2012). It usually begins with a tear of the intimal layer in the ascending thoracic aorta (ATA), which permits blood to enter the wall, split the media, and create a false lumen that can reenter the true lumen anywhere along the course of the aorta or exit through the adventitia causing frank rupture. The occurrence of aortic dissection is typically 5–30 cases per million of the population annually, while the mortality rate during first 24–48 h in patients not treated surgically is 74% (Davies et al., 2002; Knipp et al., 2007).

A possible mechanism for aortic dissection is the occurrence of mechanical wall stresses in excess of the delamination strength between the aortic wall layers. This strength most likely primarily depends on the transmural content and arrangement of elastin and collagen fibers, which are the principal load-bearing elements of the aortic wall. Several studies have been carried out to gain insight into the dissection propagation in aortic tissue. Peeling experiments have been performed on human abdominal aorta (Sommer et al., 2008) and human carotid artery (Tong et al., 2011) to quantify fracture energy required for dissection. Gasser and Holzapfel (2006) developed a nonlinear continuum framework to investigate the dissection failure in the arterial wall during a peeling experiment. However, these studies do not attempt to relate the fracture energy with the load bearing components of the artery wall. Recently, Pasta et al. (2012) quantified the delamination strength (S_d) of non-aneurysmal and aneurysmal human ATA

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by conducting peel tests on tissue samples that were artificially dissected across the medial plane. The induced peel tension reached a plateau when the dissection started propagating and the average mean value of this plateau was taken as S_d. Scanning electron microscopy images of the dissected planes revealed the presence of broken and disrupted elastin and collagen fibers. Moreover, the experimental delamination curves exhibited considerable oscillations leading to the conclusion that these fibers may have acted as "bridges" between the delaminating layers of ATA, resisting dissection and contributing towards S_d.

The aim of the current study is to present a theoretical framework that will relate S_d as obtained from the previously reported peel tests by Pasta et al. (2012) to the biomechanical properties of collagen fiber bridges. We will also make use of state-of-the-art multi-photon microscopy analysis in the longitudinal–radial (LONG–RAD) and circumferential–radial (CIRC–RAD) planes of human ATA wall tissue that exhibits the presence of "radially-running" collagen fibers that may act as fiber bridges (Tsamis et al., 2013). We have formulated a fiber bridge failure model that incorporates the biomechanical properties of collagen, and have calibrated the model parameters using peel experiments on LONG-oriented ATA specimens from two patients. Finally, we have predicted the S_d of the CIRC-oriented ATA for the same patients using these model parameters and compared our results with experimental findings. In the future, our validated fiber bridge failure model can be used to seek associations between resistance to delamination of dissected aortic tissue and failure energy of collagen fiber bridges. This analysis will be further advanced towards identification and measurement of biological markers associated with potential decrease in the failure energy of collagen fiber bridges in presence of aneurysm and subsequent propensity of the tissue to dissect.

2. Methods

We have developed a predictive mechanistic framework to characterize the delamination strength of human non-aneurysmal (control, CTRL) ATA tissues from the experimentally determined micro-architecture and biomechanical properties of radially-running collagen fibers. The specimens were collected from organ donor/recipient subjects with tricuspid aortic valve according to guidelines of our Institutional Review Board and Center for Organ Recovery and Education. We used results from a separate multi-photon microscopy analysis of the fiber micro-architecture in the LONG–RAD and CIRC–RAD planes of these tissues (Tsamis et al., 2013). As depicted in the schematic flowchart of Fig. 1, the developed model was first calibrated using peel experiments of LONG-oriented ATA specimens from two patients (Pasta et al., 2012) and the number of radially-running collagen fibers in the LONG–RAD plane (N_{LR}). Finally, we used the model and the radially-running collagen fibers in the CIRC–RAD plane (N_{CR}) to predict the delamination strength of the CIRC-oriented ATA for the same patients. Here, we describe the method to count the number of radially-running fibers and the theoretical model development as well as the finite element implementation.

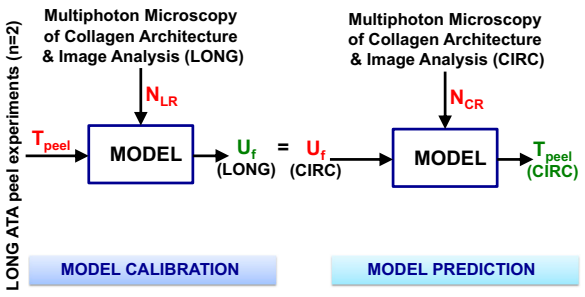

Fig. 1. A flowchart for the model calibration and model prediction procedure as discussed in the text. Quantities in red denote input to the model, while green quantities are output. T_{peel}, peel tension; U_f, energy required to fail a single fiber bridge; N, number of fiber bridges per unit length in the direction of the peel test propagation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.1. Characterization of radially-running collagen fibers using multi-photon microscopy

Tsamis et al. (2013) recently used state-of-the-art multi-photon microscopy (Cahalan et al., 2002; Jiang et al., 2011; Konig et al., 2005) to observe the elastin and collagen fiber arrangements in the LONG–RAD and CIRC–RAD planes of human CTRL ATA tissue specimens that were artificially dissected along the medial plane in the previous study by Pasta et al. (2012). Their analysis of these images provided quantitative fiber micro-architectural characteristics in the LONG–RAD and CIRC–RAD planes of aortic tissue near the plane of artificial dissection (Tsamis et al., 2013). From these images, we extracted the number density of radially-running fiber bridges (Fig. 2) for two separate specimens from two patients, see Table 1. A radially-running fiber bridge is defined as either a radially-oriented fiber component or a radially-oriented segment of a fiber owing to its undulation about LONG or CIRC axis. In short, this data was obtained by manually counting the number of fiber bridges within a distance of 100 μm (1/5 of the image height) from the delaminated plane for all specimens of ATA for both adventitial–medial and medial–intimal delaminated halves in the LONG–RAD and CIRC–RAD planes, and by converting the number of fiber bridges into a number density (number of radially-running components/mm), see Table 1.

2.2. Theoretical model for peel test of ATA tissue

Propagation of delamination or dissection in an elastic solid requires an expenditure of energy supplied by its potential energy, a combination of energy due to applied loads, and strain energy arising from deformation of the body (Fig. 3). Using this concept, we can quantify the peel tension T_{peel} as

$$T_{peel} = \frac{w}{2(\lambda - \cos\theta)}\left[G_c + h\int_1^{\lambda} d\Psi\right], \tag{1}$$

where λ is the stretch of the peeling arms, θ denotes the angle between the delamination plane and direction of applied tension, and w and h stand for the width and thickness of the peeling arm, respectively. Ψ is the strain energy function that embodies the constitutive behavior of the material and G_c is the fracture toughness of the material, or the energy required for a dissection to propagate by a unit distance. G_c depends on the structural features of the material, i.e., on different microstructural components present in the vicinity of the dissection, such as collagen and elastin, as well as their mechanical properties.

When a dissection propagates, it will cause failure in the radially-running fibers bridging the delamination plane. While a continuum description suffices to describe the matrix failure, the fiber bridges fail sequentially with the propagation of dissection. Denoting the energy required for a fiber bridge to fail as U_f, the fracture toughness can thus be written as

$$G_c = G_{matrix} + nU_f, \tag{2}$$

where G_{matrix} is the fracture toughness of the matrix material and n is the number density of the fiber bridges ($\#/m^2$). As the external loading increases, individual fibers can stretch to a maximum fiber force F_{max} where they either break or debond from the surrounding soft matrix ultimately resulting in zero fiber force. This occurrence denotes failure of the bridge and complete separation of the delaminating planes (Fig. 3(d)) (Dantluri et al., 2007). The area under the load–displacement curve is equivalent to U_f. In absence of direct experimental observations, we present a phenomenological model of fiber bridge failure embodying these events.

The initial loading response of a fiber is modeled using a nonlinear exponential force–separation law, which is typical for collagen fibers (Gutsmann et al., 2004), while the post-peak behavior is assumed to be linear. We have assumed that the visco-elastic effect in the force–displacement behavior of collagen fiber is negligible. The fiber force F depends on the separation between the ends of the fiber Δ_f through the following relationship

$$F = \begin{cases} A[\exp(B\Delta_f) - 1] & \text{if } \Delta_f \le \Delta_p \\ F_{max}\left(\frac{\Delta_{max} - \Delta_f}{\Delta_{max} - \Delta_p}\right) & \text{if } \Delta_f > \Delta_p \end{cases}, \tag{3}$$

with A and B denoting two shape parameters that control the nonlinear rising response of the fiber. The linear drop is controlled by Δ_{max}, the maximum separation at which bridging force becomes zero, and the separation at the maximum force, Δ_p. The energy required for complete fiber bridge failure is given by the area under force–separation curve, i.e.

$$U_f = \frac{F_{max}}{B}\frac{(\exp(B\Delta_p) - B\Delta_p)}{(\exp(B\Delta_p) - 1)} + \frac{1}{2}F_{max}(\Delta_{max} - \Delta_p), \tag{5}$$

where F_{max} denotes the maximum force a fiber bridge can sustain. Shape of our bridge failure model thus depends on four parameters: A, B, F_{max} (or Δ_p), and Δ_{max}.

2.3. Finite element implementation and simulation procedure

A custom nonlinear finite element code incorporating energetic contribution from a propagating dissection was developed in house. Numerical simulations of a