SB^{3}C2017
Summer Biomechanics, Bioengineering and Biotransport Conference
June 21 – 24, Tucson, AZ, USA

ARTERIAL DAMAGE MODEL BASED ON EMPIRICAL STRETCH THRESHOLDS OF COLLAGEN UNFOLDING AND TISSUE YIELDING

Matthew I. Converse (1), Michele Marino (2), Kenneth L. Monson (1, 3)

(1) Department of Mechanical Engineering
University of Utah
Salt Lake City, UT, USA

(2) Institut für Kontinuumsmechanik
Leibniz Universität Hannover
Hannover, Germany

(3) Department of Bioengineering
University of Utah
Salt Lake City, UT, USA

INTRODUCTION

Arteries play a critical role in carrying essential nutrients and oxygen throughout the body. However, trauma to the head and neck as well as surgical interventions such as angioplasty can distend arteries beyond their physiological range. Even in the absence of hemorrhaging, such 'subfailure' deformations can damage cells [1-2], cause permanent deformation of the tissue [2], alter vascular mechanics [3-4], and, ultimately, compromise vessel function [1].

A key constituent in all of these processes is collagen. Not only do collagen fibers dominate the passive mechanical behavior at high strains [5], but they also transfer mechanical loads to and from cells. Due to their important role, several structurally-based constitutive models of arterial mechanics have been proposed to incorporate collagen fibers [5]. However, existing models of arterial damage remain purely phenomenological in nature [4, 6]. This may be due to the lack of objectives assays of collagen disruption.

We recently presented the effectiveness of a collagen hybridizing peptide (CHP) in detecting the unfolding of collagen triple helices following arterial overstretch. Not only is this technique the first to directly identify molecular damage to collagen, but the peptide's fluorescent label facilitates straight-forward identification and objective quantification of damage. This progress opens the door to better characterizing and modeling structure-property relationships in arterial damage mechanics.

The objectives of the present work were to:

1. Use the CHP marker to characterize the progression of collagen damage in both axial and circumferential overstretch of cerebral arteries.
2. Demonstrate the relationship between such molecular damage and alterations of the tissue-level mechanical behavior.
3. Develop a constitutive model based on the empirically measured parameters that accurately captures the damaged mechanical response at the tissue level.

METHODS

Mechanical Overstretch: Building off of experiments and methods reported previously [7-8], sheep middle cerebral artery segments were preconditioned and subjected to a single quasi-static overstretch (0.1 mm/s). A total of 21 segments (3-5 mm long) were stretched axially (6 controls) while 28 rings (1 mm long) were distended circumferentially (7 controls). A range of stretch levels up to failure were explored.

Quantification of Collagen Damage: Immediately after overstretch, samples were stained with CHP and imaged with a confocal microscope. Images were taken and quantified within the adventitia for axially loaded samples and within the media for circumferentially loaded samples. Collagen damage was quantified by calculating the percentage of pixels greater than a control-specific intensity threshold. Damage-stretch relationships were graphed and fit with a piece-wise linear regression model to determine the stretch at which the onset of damage occurred.

Quantification of Tissue-Level Yielding: In order to correlate collagen damage with changes in tissue-level mechanical properties, the yield point was calculated for each sample. Yielding was defined at the earliest point in the loading curve where a 30% reduction in the tangent modulus was observed.

Constitutive Damage Model: A constitutive model was developed within the framework of Generalized Standard Materials. Strain energy density was introduced as a function of two damage variables, d_1 and d_2, which evolve from 0 to 1 with increasing damage.

Damage variable d_1 was associated with collagen unfolding (i.e., the loss of molecular structural integrity from the breaking of weak bonds between polypeptide strands). Its evolution was defined by the experimentally derived damage-stretch relationships using CHP. This variable was introduced in the definition of a generalized fourth invariant of deformation which represents the amount of fiber straightening associated with an elastic response. Therefore, evolution of d_1 resulted in a yielding behavior as the reference length of collagen fibers increased and was associated with the onset of residual strain.

Damage variable d_2 was associated with molecular covalent rupture (i.e., the rupture of covalent bonds within polypeptide strands) of collagen molecules. Its evolution was defined by the average failure stretch of the tissue as found in the experiments. This variable scaled the elastic potential energy, leading to a stress drop in the stress-strain response. Therefore, it was associated with final failure of the tissue.

The evolution laws for both variables were defined ensuring the thermodynamic consistency of the developed theoretical framework.

RESULTS

Thresholds and Accumulation of Collagen Damage: The CHP signal was found to increase with overstretch severity for both loading directions (Figure 1). CHP signal was comparable to that of controls for relatively mild stretches, then increased nearly linearly beyond a critical stretch threshold, λ_1. Piece-wise linear regression showed the onset of collagen damage to be λ_1 = 1.17 and 1.35 and the rate of damage accumulation to be m = 0.53 and 0.67 for circumferential and axial loading, respectively.

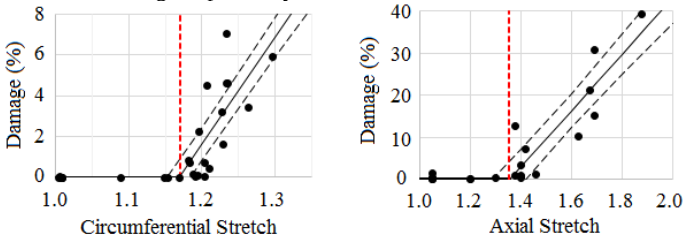

Figure 1: Percentage of pixels above control-specific threshold vs. overstretch (with reference to the in vivo length) for circumferential (left) and axial (right) directions of loading. The intersection of the horizontal and sloped regression lines defines the threshold for collagen damage (red dashed line).

Tissue Yielding: Analysis of tissue-level yielding revealed that stretch thresholds for collagen damage (λ_1) coincided with arterial yield stretches. Yield stretches were found to be 1.19 ± 0.02 (mean ± SD, n=14) for circumferential loading and 1.33 ± 0.06 (n=10) for axial loading. In both cases, the threshold of collagen damage as found by CHP staining fell within one standard deviation of the average yield point (Figure 2).

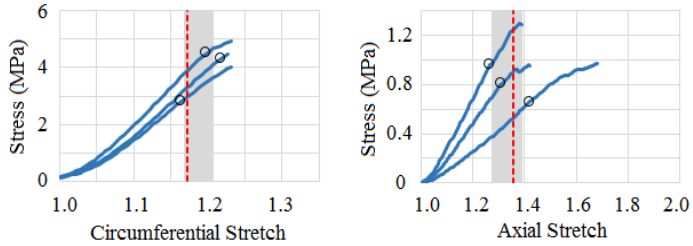

Figure 2: The stretch threshold for collagen damage (red dashed line from Fig. 1) coincided with the yield stretch for both circumferential (left) and axial (right) loading. Representative stress-stretch curves are shown with their yield points circled. The yield stretch for all samples (mean +/- SD) is overlaid in gray.

Constitutive Damage Model: Three experimental parameters were fed into the damage model: the onset of collagen damage (λ_1), the rate of damage accumulation (m), and the mean ultimate failure stretch (λ_2). The model stress response appropriately demonstrated yielding beginning at λ_1 and matched the general behavior of the experimental curve (Figure 3). Only results for the circumferential direction have been included. Furthermore, the damage model captured post-overstretch residual strains comparable to those reported previously (data not shown) [3].

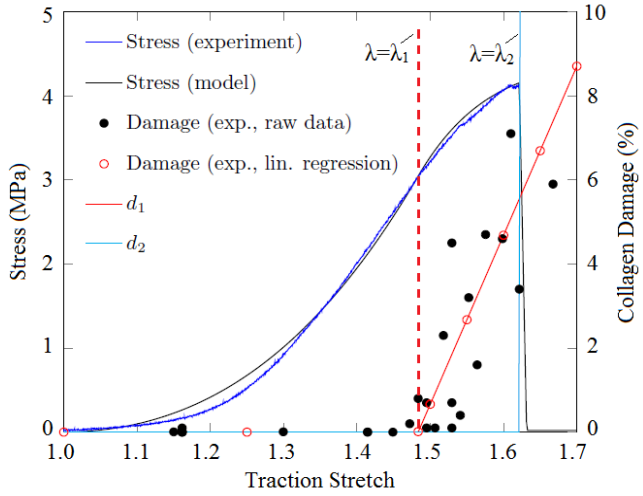

Figure 3: Uniaxial traction (along the fiber direction) of a tissue with one collagen fiber family. Relationship between stress and damage evolution vs. circumferential stretch (with reference to the unloaded length). Comparison between experimental data and model predictions. Red dashed line taken from Fig. 1, left.

DISCUSSION

In addition to the novelty of using CHP to detect molecular level collagen damage in arteries, our most significant experimental finding is the coincidence of the tissue-level yielding with the onset of this damage (inter-strand delamination). To the best of our knowledge, no studies have experimentally demonstrated this correlation before in vascular tissues.

Furthermore, these findings facilitated the development of the first-ever experimentally validated arterial damage model. In classical approaches, internal damage variables are treated as hidden quantities – having no correlation to quantitative measurements [6]. Indeed, the value of damage parameters are classically determined only from fitting the stress-strain constitutive relationship which is ultimately governed by numerous parameters. In contrast, the present work identifies the value of damage parameters from independent measurements on collagen damage and not by means of a phenomenological fit. This approach is a first step in developing experimentally validated multi-scale models of arterial damage.

ACKNOWLEDGEMENTS

3Helix, LLC for supply of the collagen hybridizing peptide (CHP).

REFERENCES

[1] Jamal, A et al., *Arterioscler Thromb Vasc Biol*, 12:307-317, 1992. [2] Castaneda-Zuniga, W et al., *Radiology*, 135:565-571, 1980. [3] Bell, E et al., *Front Bioeng Biotechnol*, 3, 2015. [4] Weisbecker, H et al., *J Mech Behav Biomed Mater*, 12:93-106, 2012. [5] Gasser, T et al., *J R Soc Interface* 3, 15–35, 2006. [6] Balzani, D et al., *Comput Methods Appl Mech Engrg*, 213:139–151, 2012. [7] Walther, R et al., *SB3C2015*-1020. [8] Converse, M et al., *SB3C2016*-734.