Acta Biomaterialia 58 (2017) 278–290

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Effects of collagen microstructure and material properties on the deformation of the neural tissues of the lamina cribrosa

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ARTICLE INFO

Article history:
Received 4 March 2017
Received in revised form 3 May 2017
Accepted 17 May 2017
Available online 18 May 2017

Keywords:
Lamina cribrosa
Optic nerve head
Biomechanics
Glaucoma
Microstructure
Finite element modeling
Intraocular pressure

ABSTRACT

It is widely considered that intraocular pressure (IOP)-induced deformation within the neural tissue pores of the lamina cribrosa (LC) contributes to neurodegeneration and glaucoma. Our goal was to study how the LC microstructure and mechanical properties determine the mechanical insult to the neural tissues within the pores of the LC. Polarized light microscopy was used to measure the collagen density and orientation in histology sections of three sheep optic nerve heads (ONH) at both mesoscale (4.4 μm) and microscale (0.73 μm) resolutions. Mesoscale fiber-aware FE models were first used to calculate ONH deformations at an IOP of 30 mmHg. The results were then used as boundary conditions for microscale models of LC regions. Models predicted large insult to the LC neural tissues, with 95th percentile 1st principal strains ranging from 7 to 12%. Pores near the scleral boundary suffered significantly higher stretch compared to pores in more central regions (10.0 ± 1.4% vs. 7.2 ± 0.4%; p = 0.014; mean ± SD). Variations in material properties altered the minimum, median, and maximum levels of neural tissue insult but largely did not alter the patterns of pore-to-pore variation, suggesting these patterns are determined by the underlying structure and geometry of the LC beams and pores. To the best of our knowledge, this is the first computational model that reproduces the highly heterogeneous neural tissue strain fields observed experimentally.

Statement of Significance

The loss of visual function associated with glaucoma has been attributed to sustained mechanical insult to the neural tissues of the lamina cribrosa due to elevated intraocular pressure. Our study is the first computational model built from specimen-specific tissue microstructure to consider the mechanics of the neural tissues of the lamina separately from the connective tissue. We found that the deformation of the neural tissue was much larger than that predicted by any recent microstructure-aware models of the lamina. These results are consistent with recent experimental data and the highest deformations were found in the region of the lamina where glaucomatous damage first occurs. This study provides new insight into the complex biomechanical environment within the lamina.

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1. Introduction

Glaucoma is a progressive neurodegenerative disease resulting in the death of retinal ganglion cells (RGC) and irreversible vision loss. While the exact causes of glaucomatous damage are not entirely clear [1–4], there is a strong association between glaucoma progression and elevated intraocular pressure (IOP) [5]. In fact the only accepted treatments for glaucoma focus on lowering IOP [6]. Experimental evidence has shown that glaucomatous damage initiates in the lamina cribrosa (LC) [7], a complex structure in the posterior pole consisting of collagenous beams and neural tissue pores containing both RGC axons and glial cells (Fig. 1). Thus, most theories regarding the initiation and progression of glaucoma center around excessive IOP-induced mechanical deformation or stress within the lamina cribrosa (LC) [3,4].

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http://dx.doi.org/10.1016/j.actbio.2017.05.042
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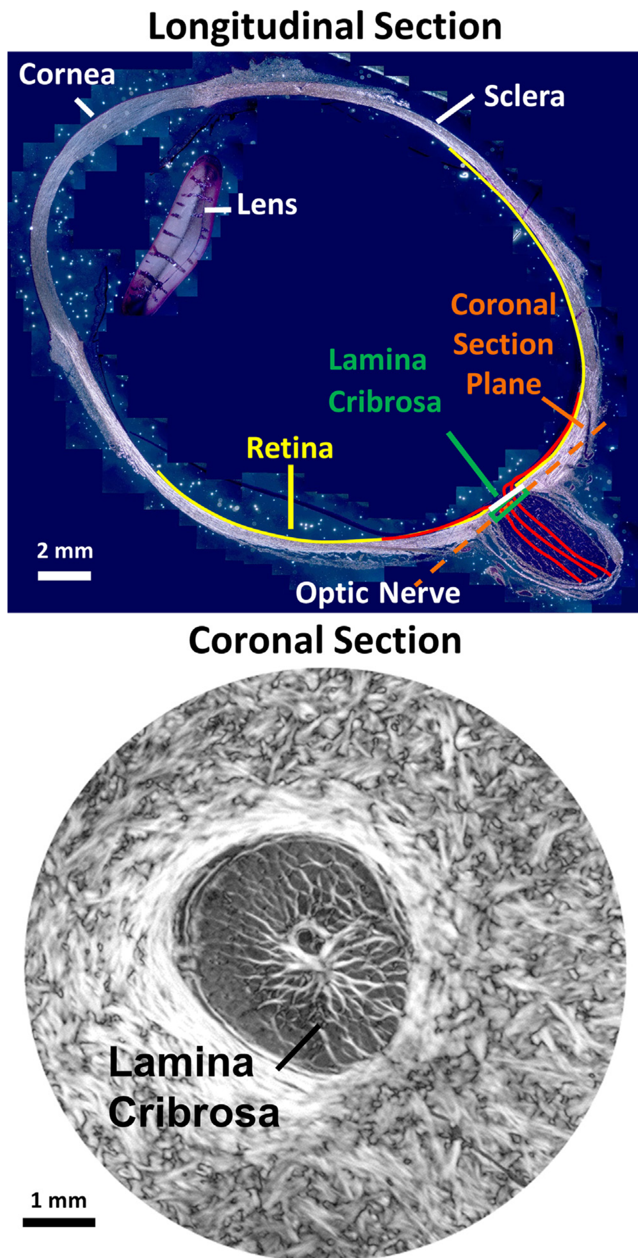

Fig. 1. The anatomy of the eye and optic nerve head. (Top) A longitudinal section of the eye is shown. Retinal ganglion cell axons (shown in red) exit the eye through a collagenous structure called the lamina cribrosa (highlighted in green) as they form the optic nerve. (Bottom) A coronal section of the optic nerve head showing the collagenous microstructure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Much work has gone into modeling the complex structures of the optic nerve head (ONH), the region of the eye including the LC where the RGC axons converge to form the optic nerve, in an attempt to understand how the LC and other tissues of the ONH deform under elevated IOP [8–14]. Over the last ten years, efforts have primarily focused on developing models that include the effects of collagen fiber alignment and material non-linearity [13–15], both improvements upon earlier isotropic linear models [9,10,16]. Despite these advances, there have been no eye-specific LC models that explicitly consider the neural tissues independent of the connective tissue. This is a major limitation because it is the mechanical insult to the neural tissues that is hypothesized to lead to neurodegeneration, and the models cannot predict that insult. Moreover, previous models have lumped the neural tissues and connective tissue microstructure together. Not surprisingly, the models have been unable to reproduce the strain fields observed experimentally. Recent models predict tensile strains within the LC to be less than 5% under elevated levels of IOP [10,13,14,16,17], whereas experimental studies by us [18,19] and others [20] have measured IOP-induced strains exceeding 10 and even 20% in some regions. Further, these experiments revealed highly heterogeneous deformation fields, with levels of stretch varying greatly from one LC pore to another.

Our goal was to study how the LC neural tissues deform under elevated IOP and how the material properties of the LC and peripapillary sclera influence the level of mechanical insult. Since these are the tissues actually injured in glaucoma, determining how they deform and the role of the collagenous LC microstructure in mitigating or antagonizing this deformation is essential for understanding glaucoma susceptibility and progression. To accomplish this goal, we made highly detailed, multiscale, specimen-specific models of the LC that included both collagenous laminar beams and neural tissue.

2. Methods

We used a two-level modeling approach. First we modeled the ONH at a mesoscale level (mean element edge length of 112 μm), using serial histological sections of the ONH and peripapilary sclera, similar to previous approaches [13,14]. These models were then used as boundary conditions for high resolution, microscale models of LC regions (mean element edge length of 7–10 μm) which included distinct material properties for LC neural tissues and beams. We conducted a sensitivity analysis in which we varied the material properties of both the neural tissues and connective tissues both to test the robustness of our conclusions to our choice of material properties and to understand the influence of the material properties on the neural tissue strains.

2.1. Histology

Three eyes from two sheep were obtained from a local abattoir. All histological methodology has been described elsewhere [21,22]. Briefly, eyes were pressure fixed via cannulation through the anterior chamber at 5 mmHg with a gravity column and bath of 10% formalin overnight. Posterior poles centered on the ONH were removed with a 11.5 mm trephine and cryosectioned coronally into 30 μm thick sections. Sections were collected serially through the depth of the tissue. It should be noted that the tissue was neither stained nor dehydrated. We have demonstrated our tissue processing protocol including formalin fixation and sectioning generally preserves both the shape and size of ocular tissues [21].

2.2. Imaging

An overview of our multiscale imaging approach can be found in Fig. 2. All imaging methods have been previously described [21,22]. Briefly, polarized filters were used in conjunction with a bright-field microscope. Images were collected with the filters in several orientations, and from these images we calculated the orientation of the collagen fibers at each pixel and the energy (an optical measure related to collagen density) [21].

Mesoscale histology images were taken with an Olympus SZX16 microscope (Olympus, Tokyo, Japan) and an Olympus DP80 camera with a 0.8x objective and 1x magnification setting (4.4 μm per pixel). Microscale images were taken with an Olympus BX60 microscope with a SPOT camera (SPOT imaging Solutions, Sterling Heights, MI) with a 10x objective (0.73 μm per pixel). Images were

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