The Impact of Choroidal Swelling on Optic Nerve Head Deformation

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PURPOSE. Choroid geometry and swelling have been proposed to contribute to ocular pathologies. Thus, it is important to understand how the choroid may impact the optic nerve head (ONH) biomechanical environment. We developed a finite element model to study how acute choroidal swelling and choroid geometry affect ONH deformation.

METHODS. We developed two geometric models of the ONH: one with a “blunt” choroidal insertion and another with a “tapered” choroidal insertion. We examined how choroidal volume changes (2.1–14.2 mL, estimated to occur during the ocular pulse) impact biomechanical strain in three tissue regions: the prelaminar neural tissue, lamina cribrosa, and retrolaminar neural tissue. Then, we performed a sensitivity analysis to understand how variation in ONH pressures, tissue material properties, and choroidal swelling influenced the peak tissue strains.

RESULTS. Choroidal swelling in the blunt choroid geometry had a large impact on the strains in the prelaminar neural tissue, with magnitudes comparable to those expected to occur due to an IOP of 30 mm Hg. Choroidal swelling in the tapered choroid geometry also affected strains but to a lesser extent compared to the blunt geometry. A sensitivity analysis confirmed that choroidal swelling was more influential on prelaminar neural tissue strains in the blunt choroid geometry.

CONCLUSIONS. Choroid anatomy and swelling can interact to play an important role in prelaminar neural tissue deformation. These findings suggest that the choroid may play an important, and previously unappreciated, role in ONH biomechanics, and motivate additional research to better define the in vivo effects of choroidal volume change.

Keywords: choroid, swelling, ocular biomechanics, computational modeling, finite element modeling

The tissues of the optic nerve head (ONH) experience a complex and dynamic biomechanical environment. They are exposed to various biomechanical loads, including intraocular pressure (IOP), intracranial pressure (ICP), retrolaminar tissue pressure, and blood pressure.1,2 Deviations in these loads from the physiological range are proposed to play a role in several ocular pathologies, including glaucoma, idiopathic intracranial hypertension (IIH), and space flight-associated neuro-ocular syndrome (SANS).3,4 For example, elevated IOP is the primary risk factor for glaucoma, the second leading cause of blindness worldwide.5 Similarly, changes in ICP play a role in visual impairment in IIH. The alteration in ICP magnitude, or its daily variation, is also thought to contribute to visual impairment in SANS. These loads cause deformations of ONH tissues which, if they exceed some unknown threshold, may lead to either direct (e.g., mechanical insult) or indirect (e.g., occlusion of blood flow or astrocyte activation) injury and damage to retinal ganglion cells (RGCs). The lamina cribrosa is of special interest in this context because it undergoes remodeling and is an early and major site of RGC injury in glaucoma.

Researchers have studied ONH biomechanics using experimental and/or computational approaches. In the latter category, researchers have created increasingly complex finite element (FE) models to understand how variations in pressures, ONH tissue material properties, and geometry influence deformation of the ONH.6–8 However, to date, few FE models have considered the effects of the choroid on ONH biomechanics.9,10 and in general, the impact of changes in choroidal volume and geometry on ONH deformation is largely unknown.

It was recently proposed that relatively large variations in choroidal geometry are associated with nonarteritic anterior ischemic optic neuropathy (NAION).11 Specifically, Nagia et al.11 showed that choroidal thickness is larger in NAION patients compared to controls. We thus wondered how choroidal volume changes would affect ONH tissue biomechanics. We hypothesized that choroidal swelling would lead to appreciable deformations of the ONH, which in turn could lead to crowding of structures at the optic disc or activation of remodeling pathways leading to RGC injury. Such biomechanical changes could induce a compartment syndrome in the prelaminar neural tissue or potentially cause nonphysiological loading on ONH tissues.
The goal of this work was thus to investigate the biomechanical effects of choroidal swelling. We specifically developed two geometric models of the human ONH to study how choroid geometry at the ONH and acute swelling of the choroid impacted ONH tissue deformation.

METHODS

Geometry and Finite Element Model

We developed two representative geometric models of the eye. In one, the choroid had a "blunt" termination near the ONH, while in the second the choroid "tapered" in the vicinity of the ONH (Fig. 1). Both model geometries were extensions of established generic models of the posterior eye in humans, and incorporated the following tissue regions: posterior sclera, peripapillary sclera, annular scleral ring, lamina cribrosa, prelaminar neural tissue (PLNT), pia mater, dura mater, and optic nerve.\(^7\)\(^{12}\)\(^{13}\) We also incorporated a single central retinal vessel to reflect both the central retinal artery and vein. This idealized vessel allowed us to simulate the effects of blood pressure through specification of a mean arterial pressure (MAP). Finally, these ocular models included two novel components: the choroidal tissue and Bruch’s membrane (Fig. 1).

In the blunt choroidal geometry model, the choroid geometry was based on literature reports.\(^6\)\(^{14}\)\(^{15}\) specifically an average thickness of 136 \(\mu m\) over the first 500 \(\mu m\) adjacent to the scleral canal margin,\(^3\)\(^5\) increasing anteriorly to 250 \(\mu m\) at 2000 \(\mu m\) away from the scleral canal margin.\(^4\)\(^{14}\)\(^{16}\) After this maximum thickness was achieved, the choroid thinned anteriorly until it reached the ora. Similarly, farther than 2000 \(\mu m\) away from the scleral canal margin, the thickness of the PLNT decreased anteriorly. The rate of choroidal thinning with anterior location was based upon a constraint on the total volume of the choroid. Specifically, the total choroidal volume was calculated based on ocular parameters such as eye diameter and maximum choroidal thickness\(^6\)\(^7\) to obtain a choroidal blood volume of 192 \(\mu l\). It has been suggested that the choroidal blood volume represents up to 75\% of the total choroidal volume; thus, the unloaded choroidal volume, that is, the combination of the blood and tissues, was taken as 256 \(\mu l\).\(^7\)

Lastly, our model included an idealized Bruch’s membrane between the choroid and PLNT, spanning from the termination of the choroid at the ONH to the ora. We modeled this structure as having a uniform thickness of 3 \(\mu m\).

In the tapered choroidal geometry, the choroidal thickness at the ONH was based on studies by Nagai et al.\(^{11}\) and Rhodes et al.\(^{16}\) The choroidal thickness was taken from optical coherence tomography (OCT) measurements as 61, 102, and 136 \(\mu m\) at locations 125, 375, and 750 \(\mu m\) away from the scleral canal opening, respectively. Similar to the blunt geometry model, we ensured that the maximum choroidal thickness was 250 \(\mu m\) at a distance 2000 \(\mu m\) from the scleral canal margin. The unloaded choroidal volume was again set to be 256 \(\mu l\); that is, the baseline choroidal volume was identical between the two geometries, and a uniform Bruch’s membrane was included in the model between the choroid and PLNT.

In our study, the major geometric change between the blunt and tapered models was the choroid. These changes in the choroidal geometry also lead to secondary, minor changes in the length of the Bruch’s membrane and the surrounding PLNT.

In our study, the choroid was the major geometric parameter to change between the blunt and tapered models. These geometries and meshes were generated in the open-source program Gmsh (V.2.8.3),\(^{18}\) while our FE simulations were performed in the FE solver FEBio.\(^{19}\) The geometry of the eye for FE analysis was treated as axisymmetric—represented as a 3\(^{rd}\) wedge about an axis of symmetry passing through the central retinal vessel. This wedge geometry represents an axisymmetric model in the FEBio solver. In brief, we performed a convergence study, considering our outcome measures (peak first and third principal strains) at each loading condition within the lamina cribrosa, optic nerve, and PLNT. Our production meshes resulted in less than a 5\% relative error in the peak first and third principal strain in each tissue region compared to the most refined mesh. The production meshes contained 106,671 elements for the blunt geometry and 101,368 elements for the tapered geometry.

Tissue Mechanical Models

Based on our previous work, the posterior sclera, peripapillary sclera, annular ring, pia mater, and dura mater were modeled as neo-Hookean solid matrices with embedded collagen fibers following von Mises distributions.\(^{20}\)\(^{21}\) The fiber orientation, alignment, and material properties were based on an earlier published FE model. In brief, the preferred fiber orientation (\(h_f\)) and degree of alignment (\(k_f\)) were defined for each tissue region. In the posterior sclera, the fibers were planar isotropic (\(k_f=0\)) lying within the local tangent plane of the sclera.\(^{22}\)\(^{25}\) In the peripapillary sclera and annular ring, the fibers were oriented circumferentially around the scleral canal with fiber concentration factors (\(k_f\)) of 0.85 and 1.85, respectively.\(^{25}\) Similar to the posterior sclera, the pia mater and dura mater fiber distributions were taken as planar isotropic (\(k_f=0\)) with the fibers lying within the local tangent planes.

For the above tissues, we must define four additional coefficients to describe each tissue’s mechanical behavior (Table 1). One coefficient described the stiffness of the ground substance (\(c_4\)), representing all the constituents except the collagen fibers (e.g., proteoglycans, cells, elastin). We then defined two coefficients that described the stiffness of the collagen fibers (\(c_1\) and \(c_2\)). Lastly, we defined a bulk modulus to enforce tissue incompressibility (\(K = 100 \text{ MPa}\)).

For this study, the lamina cribrosa, optic nerve, central retinal vessel, PLNT, and Bruch’s membrane were modeled as linear-elastic, isotropic, and homogeneous, resulting in two coefficients to describe each tissue’s mechanical behavior: Young’s modulus (\(E\)) and the Poisson ratio (\(\nu\)). Young’s modulus values were adopted from previous experimental and FE studies of the posterior eye.\(^6\)\(^{22}\)\(^{24}\) Consistent with earlier FE models, we assumed that the neural tissue (e.g., the PLNT and optic nerve) were partially compressible (\(\nu = 0.45\)) while the remaining tissues were nearly incompressible (\(\nu = 0.49\))\(^{5}\)\(^{15}\)

The choroid was represented as a mixture material composed of a linear-elastic solid matrix capable of swelling based on Donnan equilibrium. The use of Donnan equilibrium swelling was a convenient vehicle that allowed us to apply a prescribed amount of volume change, that is, swelling, through a single coefficient\(^{25}\)\(^{27}\) (\(c_s\)), for further details on the Donnan equilibrium swelling and relationship between \(c_s\), mEq/L, and volume/swelling, please see the Supplementary Materials). For simplicity, we report these inputs as equivalent changes in choroidal volume (Table 1).

Loading Conditions

To simulate the loading environment at the ONH we specified three pressures: IOP, ICP, and MAP. Our models represented an individual in an upright position, for which we set IOP to 15 mm Hg, ICP to 0 mm Hg, MAP to 57 mm Hg, and specified no choroidal swelling. Here, we denote a change in choroidal...
Kaufmann et al., who reported ocular pulse amplitudes of the ocular compliance. Specifically, we used data from ocular pulse can be translated into a volume change through measurements, since measured changes in IOP due to the simulations was estimated from ocular pulse amplitude choroidal volume. The amount of choroidal swelling in our conditions: (1) IOP = 15 mm Hg and 0 \( \mu \)L of choroidal swelling, (2) IOP = 15 mm Hg with 6.5 \( \mu \)L of choroidal swelling, (3) IOP = 15 mm Hg with 6.5 \( \mu \)L of choroidal swelling, and (5) IOP = 30 mm Hg. For simplicity, we refer to these loading conditions by the primary parameter being investigated: (1) IOP = 15 mm Hg, (2) \( \Delta V = 2.1 \mu L \), (3) \( \Delta V = 6.5 \mu L \), (4) \( \Delta V = 14.2 \mu L \), and (5) IOP = 30 mm Hg.

**Outcome Measures**

Our outcome measures were the computed strains in select ONH tissues. Strain is a measure of normalized tissue deformation that excludes rigid body motion, and it can be represented as a second-order tensor with three orthogonal principal components, namely, a first, second, and third principal strain. Based on our model assumptions these strains have the largest positive and negative magnitudes, respectively. Within each tissue region there is a distribution of each of these strains, and thus to quantify these strains with a table:

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<tr>
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<td>kPa</td>
<td></td>
<td>50</td>
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<tr>
<td>c4</td>
<td></td>
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<td>( \mu L )</td>
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Baseline parameter values are suitable for an individual in the upright posture with no choroidal swelling. The sclera, peripapillary sclera, annular ring, pia mater, and dura mater were modeled as neo-Hookean solids with embedded collagen fibers. \( c_1 \) represents the stiffness of the ground substance in these tissues, and \( c_2 \) and \( c_3 \) describe the collagen fiber stiffness. The low and high values were used in the Latin hypercube sampling sensitivity analysis and were adopted from previous work.
single value, we reported “peak” values of these strains in tissue regions of interest. The rationale for focusing on peak values is that cells are mechanosensitive, and it has been proposed that the largest mechanobiological effects are induced by the greatest strain magnitudes. The peak first and third principal strains were specifically defined as the 95th and 5th percentile strain within each region of interest, respectively. This definition excludes numerical outlier values of strain, due, for example, to poorly formed FE mesh elements. We focused our analysis on three regions: the PLNT within 1 mm of the lamina cribrosa; the lamina cribrosa; and the retrolaminar neural tissue (RLNT). The RLNT was defined as the optic nerve region within 1 mm of the posterior lamina cribrosa surface.

We first assessed how strains in each tissue region changed relative to our baseline condition. This allowed us to understand how choroidal swelling influenced the peak strains in the blunt and tapered choroid geometries compared to how elevated IOP influenced these strains, since IOP is a known risk factor for developing glaucoma.

Next, we wanted to understand the effects of choroidal baseline geometry, that is, tapered versus blunt. We thus compared the distributions of the first and third principal strains within the tissue regions of interest (i.e., PLNT, lamina cribrosa, and RLNT) for our five loading conditions between the blunt and tapered choroid geometries. To compare the strain distributions between the two choroidal geometries, we used a Kruskal-Wallis 1-way analysis of variance (\( z = 0.05 \)), and a two-sample Kolmogorov-Smirnov test to perform a pairwise comparison between each condition with Bonferroni correction for multiple comparisons (\( z = 0.05 / 5 = 0.01 \)).

### Sensitivity Study

We also investigated how sensitive ONH biomechanics were to choroidal swelling, using a Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC) approach, which allowed us to compare how each input parameter influenced our outcome measures. LHS is an efficient Monte Carlo sampling approach that utilizes “stratified sampling” without replacement to ensure sampling across the entire parameter space. LHS allowed us to define the specific distribution and range of each input parameter. Here, all tissue material properties and choroidal swelling were assumed to follow uniform distributions, as described in Table 1. The IOP, ICP, and MAP followed normal distributions based on ranges reported for healthy individuals in the upright position.

Adopting an approach from our earlier work, we chose to perform four independent LHS passes across the parameter space, with 100 divisions per pass. This resulted in a total of 400 unique simulations per geometry in our sensitivity analysis. The outcome measures we considered were the peak first and third principal strains in the PLNT, lamina cribrosa, and RLNT. The input parameters were related to each outcome measure by a partial rank correlation coefficient ranging between −1 and 1. The closer to 1 a value is in either the positive or negative direction, the greater the linear relationship between that input parameter and the resulting peak first and third principal strains. A value of zero means there is no linear relationship between the input parameter and outcome measure. After the partial rank correlation coefficients were calculated, the input parameters were ranked based on their proximity to ±1, with the strongest correlation given a rank of 25 and the lowest correlation given a rank of 1. These ranked scores were calculated for each tissue region (e.g., PLNT, lamina cribrosa, and RLNT) and outcome measure (i.e., peak first and third principal strains), added together, and then normalized to the maximum possible score (150, i.e., maximum score of 25 in three tissue regions with two strain measures). An input parameter with the most influence across each tissue region would thus have a normalized score closer to 1 while the least influential parameter would have a normalized score near 0.

To further understand which input parameters most influenced strains in each individual tissue region, we performed a refined sensitivity analysis. We separately assessed the PLNT, lamina cribrosa, and RLNT, and focused only on input parameters that were significantly correlated to the peak strains in that tissue region after correcting for multiple comparisons (\( z = 0.05 / 25 = 0.002 \)). We then ranked only these input parameters and normalized them to the maximum possible score. This score was determined for each tissue region based on the number of input parameters significantly correlated with the peak strains within that each tissue region. Again, input parameters with a normalized score closer to 1 were considered to be the most influential, while those with a normalized score closer to 0 were the least influential.

### Results

Choroidal swelling significantly affects strains within ONH tissues, particularly in the PLNT, and choroidal geometry modulates this effect (Fig. 2). Specifically, in the blunt choroidal geometry, choroidal swelling of 14.2 μL led to a 68% increase in peak first principal strain in the PLNT, but less than a 30% change in the other tissue regions (Fig. 3). The tapered choroidal geometry showed qualitatively similar results, that is, increased strains with choroidal swelling in all three tissue regions, but the magnitudes of the strain changes were smaller than for the blunt geometry. These results can be put into context by comparing them to strain changes induced by elevating IOP from 15 to 30 mm Hg, which increased the peak first and third principal strains across all the tissue regions and for both choroidal geometries (Fig. 3). We conclude that choroidal swelling can have a significant impact on tissue strains, but that its effects are strongly dependent on choroidal geometry near the ONH and are more localized than the effects of IOP changes.

Next, we directly investigated the effects of choroidal geometry on strains. For the baseline case (IOP = 15 mm Hg and no swelling, i.e., \( \Delta V = 0 \) μL) we found no significant differences in the first and third principal strain distributions between the blunt and tapered choroid geometries in any tissue region (Table 2). However, we did find a significant difference in the third principal strain distributions in the PLNT for a choroidal swelling of 2.1 μL, but no significant differences in strain distributions in the lamina cribrosa or RLNT. For more choroidal swelling (\( \Delta V = 14.2 \) μL), there were significant changes in the first and third principal strain distributions in the PLNT between the blunt and tapered choroid geometries (Table 2). Finally, we noted that the strain distributions in the RLNT were not significantly different when IOP was elevated to 30 mm Hg (\( \Delta V = 0 \) μL) when comparing the blunt and tapered choroid geometries. However, elevating IOP did significantly change the third principal strain distribution within the PLNT and the lamina cribrosa (Table 2), indicating that choroid geometry interacts with elevated IOP to affect ONH tissue strains.

Lastly, we performed a sensitivity analysis, examining which factors most influenced the peak strains within all three tissue regions in the ONH (Fig. 4). For the blunt choroid, the stiffness of the optic nerve and lamina cribrosa, along with IOP and choroidal swelling, were the most important factors influencing ONH strains. For the tapered choroid geometry, we found...
that stiffnesses of the PLNT, lamina cribrosa, and optic nerve and IOP all strongly influenced peak strains in the ONH.

We also examined which factors most impacted the peak strains within the PLNT, lamina cribrosa, and RLNT individually (Fig. 5). In the blunt choroid geometry, we found that the stiffness of the PLNT and choroidal swelling had the largest impact on peak strains in the PLNT. Interestingly, in the tapered choroid geometry, the peak strains in the PLNT were largely influenced by the stiffness of the PLNT and optic nerve. The peak strains in the lamina cribrosa were most impacted by the stiffness of the optic nerve and lamina cribrosa, and IOP for both models. Lastly, optic nerve stiffness and IOP had a large

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**Figure 2.** Contour plots of the first and third principal strains in the blunt choroid geometry (top) and tapered choroid geometry (lower). Compared to the baseline simulation (IOP = 15 mm Hg), choroidal swelling (ΔV = 14.2 μL) in the blunt geometry increased the first and third principal strains predominately in the prelaminar neural tissue. In the tapered choroid geometry, choroidal swelling altered the strain distributions but to a lesser extent. However, elevating IOP to 30 mm Hg altered the strain distributions in the prelaminar neural tissue, lamina cribrosa, and retrolaminar neural tissue for both geometries. The dark red region represents the choroid and Bruch’s membrane.

**Figure 3.** Effects of choroidal swelling and IOP increase on ONH tissue strains. The plotted quantity is the change in the peak first and third principal strain magnitudes (PS1 and PS3) from the baseline case (IOP = 15 mm Hg and no choroidal swelling, i.e., ΔV = 0 μL). We examined PS1 and PS3 in the prelaminar neural tissue (PLNT), lamina cribrosa (LC), and retrolaminar neural tissue (RLNT). We observe that small choroidal swelling (2.1 and 6.5 μL) led to minor changes in PS1 and PS3 in both choroidal geometries, but more pronounced choroidal swelling (14.2 μL) had a major impact on strain in the blunt choroid geometry though not the tapered choroid geometry. Elevating IOP to 30 mm Hg increased the peak first and third principal strains in all three tissue regions for both geometric models.
It is important to consider the temporal profile of the choroidal swellings that we simulated, which examined an acute choroidal volume change due to the ocular pulse. The resulting strain on the ONH tissues would be of short duration (on the order of milliseconds) but would repeat continuously with each cardiac cycle, similar to the transient changes in IOP caused by the ocular pulse pressure, blinks, or saccades. Since the ocular pulse is physiological, it is unlikely that such fast, transient stimuli would induce pathology without additional factors. However, persistent choroidal swelling above a certain physiological range could activate ONH mechanosensitive cells and result in pathology. From glaucoma studies, we hypothesize that a sustained deformation due to elevation of IOP can stimulate mechanically sensitive cells in the ONH, thereby initiating a biological cascade that results in permanent pathological remodeling. The impact of persistent choroidal swelling on the surrounding tissues in the ONH thus merits further investigation, particularly since the choroid is a dynamic tissue that is responsive to multiple stimuli, including pharmacological and positional challenges among others.

Importantly, our findings illustrate the strong importance of choroidal anatomy on ONH biomechanics. This point was made both by direct comparison between our two models (blunt versus tapered choroid) and in the subsequent sensitivity analysis, which was also consistent with previous results on nonchoroidal factors, giving us confidence in the model. Our results are also generally consistent with previous work showing that other ocular anatomic features (e.g., scleral thickness) influence ONH strains due to elevated IOP. Interestingly, clinical evidence suggests that IOP and choroidal volume themselves may be linked. A reduction of IOP via trabeculectomy or deep sclerectomy has been shown to cause a subsequent change in choroidal thickness. Thus, studies aimed at understanding the interaction of IOP and choroid volume and their combined influence on ONH biomechanics will be critical in the future.

**Limitations**

A limitation of this work is the number of choroidal geometries we included in this initial study. In the blunt choroid geometry, we assumed a constant thickness for the choroid near the ONH, which is an oversimplification of its complex geometry. In the tapered geometry, the choroid was taken to be thinner near the ONH before reaching a more uniform thickness roughly 1000 to 1500 μm away from the scleral canal opening. These geometries used average values across several studies, yet represented only two potential geometries. Nonetheless, we believe these data provide us valuable and novel insight into how variations in choroid geometries and swelling influence ONH deformation and motivate further study of this effect. In addition, we used an axisymmetric geometric model to represent the complex anatomy of the eye, which by definition cannot include variations in choroidal thickness between the inferior, temporal, superior, and nasal regions. Thus, we used an average value to represent choroidal thickness at various locations and aimed to match an overall calculated volume of the choroid for each geometry. To capture more realistic aspects of choroidal anatomy, it will be necessary in future to develop full three-dimensional, data-driven geometric models of the posterior eye with varying choroidal thicknesses. This, while these simplifications are a limitation of the present study, they also clearly highlight the need to collect additional individual-specific experimental data about choroid anatomy and swelling throughout the entire eye.

A limitation of our geometric model concerns the tissues we chose to model. While we have expanded upon our previous...
FE models to include the choroid and Bruch's membrane, there are still more details that could be added. For example, we have not included the Elschnig and Jacoby border tissues of the ONH. These are small structures but may provide some support during choroidal swelling. Recent advancements in OCT have helped with visualization of this border tissue, but unfortunately, the material properties and detailed geometry of this tissue remain elusive and their consideration is beyond the scope of this work.

A second limitation in our geometric model involves the orientation of collagen fibers. We divided the posterior eye into three separate regions—the sclera, peripapillary sclera, and annular ring—to account for changes in the collagen orientation near the scleral canal. In our present geometries, the annular ring had a higher degree of circumferentially aligned collagen fibers and was the closest to the scleral canal. However, some evidence suggests that the location of this highly aligned region can vary, with some eyes showing high alignment near the scleral canal and others showing maximum alignment farther from the canal. Since such effects were beyond the scope of the present study and research question, we have not assessed how variations in the location, degree, and width of circumferentially aligned collagen fibers impacts deformation at the ONH. Understanding how this variation affects deformation could provide additional insight into ONH biomechanics.

Another limitation is the degree of choroidal swelling we considered. We translated experimental data on IOP changes due to the ocular pulse into estimated choroidal volume changes. These choroidal volume change estimates assumed an ocular compliance, the vitreous was incompressible, and that the short time frame of the ocular pulse should minimize viscoelastic effects. To test these assumptions, we can compare our volume changes against independent estimates of choroidal volume change under various conditions. Berisha et al. estimated an average volume change of 3.98 μL (min 1.87 μL and max 7.19 μL) over a cardiac cycle, which encompasses the two smaller volume changes we simulated in the present study (2.1 μL and 6.5 μL). A drawback of these estimates is they assumed a simplified choroidal shape and estimated blood flow into the choroid. We also estimated choroidal volume changes of 13.1 μL from reported OCT measurements, which is similar to the largest choroidal volume change we specified in our models (14.2 μL). An important limitation of using OCT measurements is the limited field of view of the choroid, so that OCT measurements must be extrapolated to the entire choroid.

\[ \text{FIGURE 4. A ranking of how variations in each input parameter influenced the peak first and third principal strains across all three tissue regions of interest.} \]

\[ \text{The plotted quantity is the cumulative influence factor (see text), which quantifies the effect on our outcome measures of variations in input parameters, with a value of 1 representing the largest possible impact over all three tissue regions. For a list of abbreviations and parameter ranges, please see the Supplementary Materials.} \]
choroid. However, these independent studies led to choroidal volume change estimates comparable to the values we derived from ocular pulse amplitudes, increasing confidence in our approach. Future studies should seek to use more directly measured changes in choroidal volume under various conditions, which we hope will arise from advances in OCT and better understanding of ocular blood flow. In addition, our simulations do not directly account for the changing IOP over the ocular pulse; that is, we applied a constant IOP within each simulation. This is a limitation of the quasi-steady modeling framework used in the present study, but allows us to directly interrogate the effects of choroidal volume change.

Similar to other FE modeling studies, we were limited in our knowledge of certain connective tissue material properties in the posterior eye. We assumed several tissues were linear, elastic, isotropic, and incompressible. Specifically, the lamina cribrosa is known to consist of nonuniformly distributed collagen fibers that have a high degree of anisotropic behavior. Most relevant for this study was the assumption regarding the Bruch’s membrane. This tissue may play a role in how choroidal swelling impacts PLNT deformation as it provides a barrier between the PLNT and choroid. Due to its size and limited accessibility, few studies have examined the biomechanical properties of this tissue, yet changes in the mechanical properties of the Bruch’s membrane and retinal basement membrane have been shown with age.2425 This indicates that the mechanical properties of the Bruch’s membrane may be important, and a better understanding of how the Bruch’s membrane and choroid interact biomechanically will improve future FE models of the eye. In addition, Bruch’s membrane is a complex tissue with five sublayers, which may impact its biomechanical behavior; thus, our assumption of a linear-elastic and homogenous material is likely an oversimplification.

Further, a limitation of our approach is that we cannot assess how the effective stiffness of the choroid changes due to swelling. When the choroid swells in vivo its structural stiffness may increase with the internal blood pressure. This may play a role in how the choroid affects ONH and is currently poorly understood. The material properties of the choroid are also complex and poorly understood. As a highly vascular tissue, it is challenging to develop detailed and accurate geometric models of the choroid. Here, we chose a simplified approach to overcome these limitations, in which we modeled the choroid as a Donnan equilibrium material, which allowed us to assess how choroidal volume changes impacted the surrounding tissues in the ONH. The Donnan equilibrium formulation enables us to generate a desired...
degree of choroidal swelling and is not related to negative tissue charge or other physiological changes that may occur in various pathologies. In addition, this approach did not allow us to study the biomechanics of the choroid itself. Understanding the stresses and strains within the choroid may provide better insight into ocular pathologies including glaucoma, NAION, or IIIH.

Summary

Even with the limitations noted above, we were able to address the central question posed in this study: Does acute swelling of the choroid influence strains in the ONH? Our results predict that the choroid plays an important and previously underappreciated role in ONH deformation. Taken together, these findings provide rationale for further study on the choroid’s role in ONH biomechanics and tissue function. It is notable that the effects that we observed occurred at the high end of the physiological range for choroidal swelling. Extrapolating further, we anticipate that future studies are likely to find a significant role for the choroid in conditions such as NAION, IIIH, and SANS where choroidal engorgement has been identified. While our data cannot address those hypotheses directly, they do support the idea that choroidal swelling is important in ONH biomechanics and warrants additional research.

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