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Review

Biomechanics of the optic nerve head

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ABSTRACT

Biomechanical factors acting at the level of the lamina cribrosa (LC) are postulated to play a role in retinal ganglion cell dysfunction and loss in glaucoma. In support of this postulate, we now know that a number of cell types (including lamina cribrosa cells) are mechanosensitive. Here we briefly review data indicating cellular stretching, rate of stretching and substrate stiffness may be important mechanosensitivity factors in glaucoma. We then describe how experiments and finite element modeling can be used to quantify the biomechanical environment within the LC, and how this environment depends on IOP. Generic and individual-specific models both suggest that peripapillary scleral properties have a strong influence on LC biomechanics, which can be explained by the observation that scleral deformation drives much of the IOP-dependent straining of the LC. Elegant reconstructions of the LC in monkey eyes have shown that local strains experienced by LC cells depend strongly on laminar beam microarchitecture, which can lead to large local strain elevations. Further modeling, suitably informed by experiments, is needed to better understand lamina cribrosa biomechanics and how they may be involved in glaucomatous optic neuropathy.

1. Ocular biomechanics in glaucoma

Elevated intraocular pressure (IOP) remains the primary risk factor for development of glaucomatous optic neuropathy (Heijl et al., 2002; Lesk et al., 2003; Bengtsson and Heijl, 2005), and consistent, sustained and significant reduction of IOP slows or eliminates visual field loss in glaucuma (AGISInvestigators, 2000; Anderson et al., 2001; Heijl et al., 2002; Lesk et al., 2003). IOP is, by definition, a mechanical entity – the normal force per unit area exerted by the intraocular fluids on the tissues that contain them – and it is therefore natural to consider that biomechanics may play a role in glaucomatous optic neuropathy. A key challenge is to understand how, and if, ocular biomechanics are transduced into a biological response and/or tissue damage in glaucoma.

The ONH is a natural site of interest because it is the ONH, and the lamina cribrosa (LC) in particular, that is the principal site of retinal ganglion cell (RGC) axonal insult in glaucoma (Anderson and Hendrickson, 1974; Quigley and Anderson, 1976; Quigley et al., 1981). In addition, the ONH is of biomechanical interest because it is a discontinuity ("weak spot") in the corneo-scleral shell (Bellezza et al., 2000). Such discontinuities typically give rise to stress or strain concentrations in mechanical systems.

In the biomechanical paradigm of glaucomatous optic neuropathy, IOP acts on the tissues of the eye, producing stress, deformations and strain within these tissues, eventually leading to an IOP-related cascade of cellular events that culminate in damage to the RGC axons. This mechanical response is a function of the individual eye's anatomy (geometry) and composition (mechanical properties), which therefore contribute to determine the individual's susceptibility to IOP. The mechanical and vascular mechanisms of glaucomatous injury are inseparably intertwined: IOP-related mechanics determines the biomechanical environment within the ONH, mediating blood flow and cellular responses through various pathways. Reciprocally, the biomechanics depend on tissue anatomy and composition, which are subject to change through cellular activities such as remodeling (Burgoyne et al., 2005).

2. Cellular mechanobiology

Cells are sensitive to many stimuli, including mechanical stimuli. Before describing some of the evidence supporting mechanical factors as important influences on cellular behavior, it is worth introducing some terms from biomechanics.

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Strain is the change in length of a tissue element divided by its initial length (Humphrey, 2002; Ethier and Simmons, 2007), and is thus a measure of the local tissue deformation, usually expressed as a percentage. As it deforms, a material can undergo tension, compression and shear, which are often referred to as the three modes of strain. Note that since strain is a measure of local tissue deformation it may not appear to correspond precisely with total tissue deformation. For example, it is possible for part of a structure to displace substantially while the local deformation, and consequently the strains, in the part remain low. Similarly, it is possible for a structure to displace little in one direction yet experience substantial strain in another direction. *Stress* is the force divided by the cross sectional area over which it acts, and is thus a measure of the forces transmitted through, or carried by, a material or tissue. Like strain, stresses can be compressive, tensile or shearing. Note that mechanical stress is not synonymous with notions of stress typically used in physiologic or metabolic contexts (*e.g.* ischemic or oxidative stress).

Stress and strain (*i.e.* forces and deformation) in a material are two different quantities, and hence may not be used interchangeably. However, they are related to each other through *material properties*. In the simplest case, stress and strain are linearly proportional to one another, with a proportionality constant known as Young's, or elastic, modulus. Unfortunately, this simple description does not account for many of the complexities that occur in soft tissues, such as anisotropy, nonlinearity and viscoelasticity (Fung, 1990, 1993). These complexities may be fundamental to understanding ocular mechanics, and will be discussed in the context of scleral mechanics below.

It has been known for many years that vascular endothelial cells are mechanosensitive, especially to shear stress (Dewey et al., 1981), and that this sensitivity is central to arterial remodeling and homeostasis (Langille and O'Donnell, 1986). Shear stress occurs when a force is applied parallel to a surface; in the case of vascular endothelial cells, the force is due to friction between flowing blood and the lining endothelium of the artery wall. More recently, it has emerged that mechanosensitivity is the rule rather than the exception for many cell types. The reader is referred to existing reviews on cellular mechanobiology for more details, e.g. (Ingber, 2003; Huang et al., 2004; Pedersen and Swartz, 2005; Buckwalter et al., 2006); here we simply mention some specific examples that may be relevant in glaucomatous optic neuropathy.

Kirwan and colleagues (2005) subjected glial fibrillary acid protein negative primary LC cells from human donor eyes to cyclic 15% stretch and showed that in excess of 1400 genes were up- or down-regulated by more than a factor of 1.5 in stretched cells compared to unstretched controls. These included genes encoding for proteins that constitute or modify extracellular matrix, including TGF-β2, BMP-7, elastin, collagen VI, biglycan, versican and EMMPRIN. In an earlier study the same group (Kirwan et al., 2004) showed that MMP-2 activity was increased by stretch. These results are potentially important, since there is data suggesting that the ONH of glaucomatous eyes may experience more pulsatile stretching than the ONH of non-glaucomatous eyes. For example, there is a small increase in ocular pulse amplitude in glaucoma patients (2.2 mmHg in normals (Schmidt et al., 2000) vs. 2.6 mmHg in POAG (Kerr et al., 1998)), while diurnal pressure variations are approximately 4 mmHg in normals and 10 mmHg in patients with glaucoma (Zeimer, 1996). More work on the effects of stretch on ONH cells under biomechanical conditions mimicking those of the normal and glaucomatous ONHs is needed to understand the role that stretch may have on inducing extracellular matrix remodeling in the LC.

In addition to the magnitude of the stretch, the rate at which stretch is applied is important. For example, Cullen et al. (2007) subjected 3D co-cultures of astrocytes and neurons to deformations at different rates, as a model of traumatic brain injury, observing major influences on cell death and astrogliotic behavior. It should be noted that these results were obtained at very large shear strains (50%), which are likely greater than those experienced in the ONH (Sigal et al., 2007a). Nonetheless, investigation of the effects of stretching rate on ONH cells would be of interest, as would adoption of some of the techniques used for 3D co-cultures developed in the traumatic brain injury community (Laplaca et al., 2005).

Mechanics can influence cellular behavior in other ways. For example, the stiffness of the substrate on which a cell resides has a profound effect on cell migration (Edwards et al., 2001), proliferation and apoptosis (Wang et al., 2000) (Fig. 1). This implies that cells engage in an active process of continually probing the stiffness of their surroundings, reacting accordingly, see e.g. (Collin et al., 2008). Recent data (Saha et al., 2008) even indicate that substrate behavior can influence whether adult neural stem cells differentiate into a neural or glial phenotype. These observations are potentially very important in glaucoma, where changes in the composition of the LC extracellular matrix (Morrison et al., 1990; Quigley et al., 1991; Pena et al., 1998) presumably influence LC stiffness, and hence could impact on the behavior of resident LC cells.

3. Quantifying lamina cribrosa biomechanics

Based on the above, as well as the possibility that mechanical forces may lead to direct failure (tearing) of connective tissue fibers in the ONH (Burgoyne et al., 2005), it seems important to understand the biomechanical environment within the LC. Unfortunately, it is difficult to make measurements on the LC directly because it is small, fragile and relatively inaccessible.

Some researchers have studied the movement of the vitreoretinal surface of the ONH as a surrogate for LC motion (Zeimer and Chen, 1987; Meredith et al., 2007; Wells et al., 2008). Imaging of the ONH surface has shown, for example, that the volume of the optic cup increases with IOP, and that these changes can sometimes be partially reversed by reducing IOP (Lesk et al., 1999). This information has allowed development of empirical relationships that are helpful in predicting risk for onset and development of glaucoma, but that add little to the understanding of ONH biomechanics *per se*. A large fraction of what is known about the biomechanical response of the LC to IOP is actually information about the ONH surface. This difference may be important because, as we explain below, models have suggested that IOP-induced deformations of the ONH surface may not be good surrogates for those of the underlying lamina, which is ultimately where we need to understand the biomechanics.

Other techniques have been used to measure the deformation of the lamina cribrosa, including radiographic (Levy and Crapps, 1984) and histologic (Yan et al., 1994; Jonas et al., 2004) approaches. Particularly noteworthy are the elegant 3D histologic reconstructions of the ONH tissues from monkey eyes performed by Yang and colleagues (Downs et al., 2007a; Yang et al., 2007a,b). Using an early glaucoma model of induced ocular hypertension, laminar thickening and posterior displacement of the peripapillary sclera and lamina were observed after only 3 weeks of detectable change in nerve topography. These data suggest an active remodeling of the lamina cribrosa and peripapillary sclera, reinforcing the idea that the connective tissues of the optic nerve are mechanically important structures that respond actively to IOP.

The above studies highlight the desirability of being able to directly measure the acute deformations of the tissues interior to the ONH, ideally in a non-invasive manner. Recent advances in imaging, such as second harmonic imaging (Brown et al., 2007), or

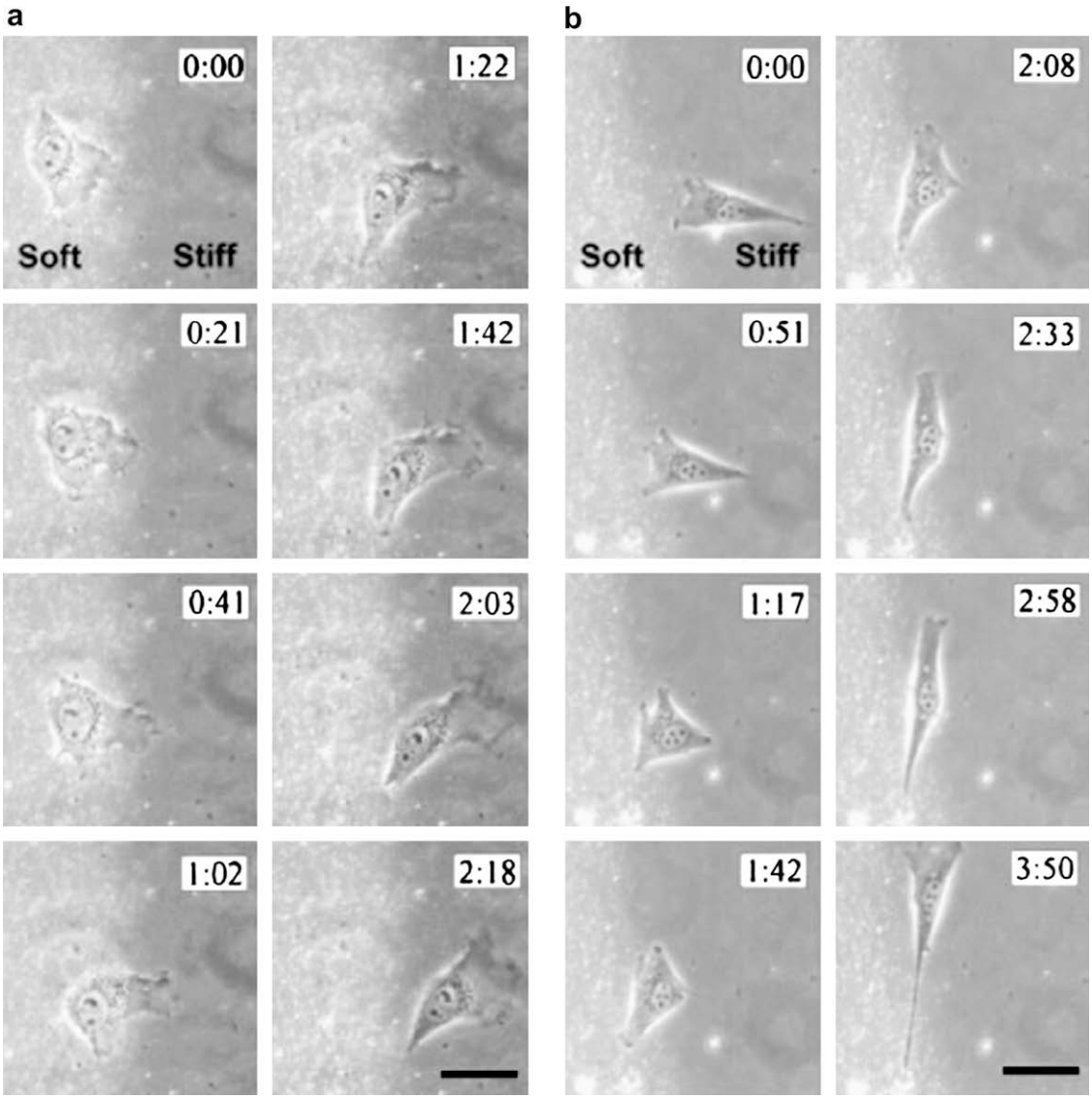

Fig. 1. Cells sense the mechanical stiffness of their substrate, which influences cell migration (among other activities). These images show time lapse photographs of NIH 3T3 fibroblasts placed on collagen-coated acrylamide gels prepared in such a way that the underlying acrylamide had a stiffness transition zone ("Soft" vs. "Stiff") of width 50–100 μ. Cells were photographed as they migrated towards this transition zone, either from the soft to the stiff side (panel a) or from the stiff to the soft side (panel b). There was consistent preferential migration of cells from the soft to the stiff side, but not vice versa ($p = 0.0001$). This phenomenon has been termed durotaxis. The time stamps on each image are in hours:minutes; the scale bar is 40 μm. From Lo et al. (2000).

deep-scanning OCT (Burgoyne et al., 2008; Srinivasan et al., 2008), may soon be able to make some of these measurements, and thus may help clarify the relationships between surface and deeper tissue movements. Although promising, these technologies are still in development, and therefore modeling has become the leading approach for studying LC, and more generally, ONH biomechanics.

Modeling approaches to study ONH biomechanics can be broadly divided into analytical and numerical. Numerical models themselves are subdivided into generic and eye-specific. All three of these approaches have been followed for the study of ONH biomechanics. Below we discuss each of them in more detail.

3.1. Analytical models

Analytical models are mathematical models that have a closed form solution, i.e. one in which the relevant stresses and strains can be written in terms of known mathematical expressions. The simplest analytical models of ocular biomechanics are those based on Laplace's Law, which relates the tension (S) on the wall of a spherical vessel to the magnitude of the pressure (P) the radius (R) and the thickness of the wall (t) by $S = PR/2t$. Another popular analytical approach was introduced by Friedenwald and involves the derivation of a coefficient of ocular rigidity (Ethier et al., 2004). There have been refinements to the methods mentioned above (Greene, 1985; Silver and Geyer, 2000) to provide estimates of whole globe mechanics. However, these approaches provide little information about the biomechanics of the ONH *per se* because the eye is composed of tissues with different mechanical properties and complex geometries; this complexity violates the assumptions underlying Laplace's Law and is considered only in a lumped manner by analyses of ocular rigidity.

Analytical models specific to the LC have also been developed (Dongqi and Zeqin, 1999; Edwards and Good, 2001; Sander et al., 2006). The authors found that the levels of strain within the LC due to an increase in IOP depended on the canal size and eccentricity, and the thickness and mechanical properties of the LC. Analytic

approaches are attractive for their elegance, but they can only consider simplified geometries, tissue mechanical properties and loading conditions. Comprehensive analytic models eventually become so complex that they also have to be solved numerically. Researchers have therefore turned to numerical modeling to understand ONH biomechanics.

3.2. Numerical models

The most commonly used numerical approach for quantifying tissue biomechanics is the finite element (FE) method, which can incorporate more realistic conditions than analytical models can and has been widely used in engineering to determine the mechanical response of complex structures (Zienkiewicz et al., 2005). It allows the deformation of all parts of an object to be computed if the mechanical loading, material properties and geometry of the object are known.

As mentioned above, numerical models of ocular biomechanics are often classified as generic or eye-specific. Generic models are developed from general, often population-based, dimensions and material properties. A particularly useful advantage of generic models is that they can be parameterized, which means that the model is constructed so that aspects of its shape, mechanical properties or loading can be easily varied by specifying a few high-level parameter values. In this way it is possible to produce models which differ only in the parameter of interest, and nothing else. For example, it is possible to produce a sequence of models which are identical, except for globe size. This allows the effects of the parameter of interest to be isolated and studied.

Despite their advantages over analytic models, generic numeric models cannot, by design, make predictions about the biomechanics of a specific eye, and sometimes it is specific eyes for which we would like to predict the effects of IOP. In addition, the simplifications involved in producing generic models could possibly have inadvertently left out one or more biomechanically important features. To address these limitations, eye-specific models have been developed, which incorporate more of the details that make an eye or ONH individual. Naturally, eye-specific models tend to be more complex than generic models, and therefore their development and analysis are often longer and more complicated. Still, all models are approximations and even eye-specific models involve simplifications that are important to consider when interpreting the predictions.

3.2.1. Generic models

An early example of generic FE modeling is the work of Bellezza et al. (2000) who studied the effects of the size and eccentricity of the scleral canal on the mechanical response of the ONH. They found that IOP-related stresses within the connective tissues of the ONH could be substantial, up to two orders of magnitude larger than IOP, even at low levels of IOP. Sigal et al. (2004) developed a more comprehensive generic model to study ONH biomechanics. Unlike the initial models by Bellezza et al., these models incorporated a simplified central retinal vessel and pre- and post-laminar neural tissues, which allowed comparison of the simulated IOP-induced displacements and deformations of the ONH surface with those of the LC. The central retinal vessel had only a minimal effect on ONH biomechanics and was not included in later models. More importantly, they found that the IOP-induced deformations of the ONH surface and LC, while related, were far from identical, and therefore that the displacements of the ONH surface might not be a good surrogate for those of the LC. This result was later also obtained with more complex models with eye-specific geometry of the ONH (described below).

In a later study, Sigal et al. (2005a) parameterized various geometric and material details of their ocular model, and varied them independently to assess their impact on a host of outcome measures, including changes in the shape of the ONH tissues (such as cup to disc ratio), and stress and strain within the LC and neural tissues. This work identified the five most important determinants of ONH biomechanics (in rank order) as: the compliance of the sclera, the size of the eye, IOP, the compliance of the LC, and the thickness of the sclera. This study was the first to quantify the important role of scleral properties on ONH biomechanics (Fig. 2). Parametric studies such as these are important because they can be used to identify the biomechanical factors that warrant more in-depth study, as well as those factors that are unlikely to have a significant influence, thus providing information useful for focusing future experimental efforts.

More recently, Sigal (2009) extended the generic model to allow simultaneous variations of the parameters. Analysis of these models yields information on the strength of the interactions between the parameters, that is, how the level of one parameter influences another (Sigal, 2009). An example is represented by the concept of structural, or effective, stiffness, where the mechanical response of the sclera depends on both its thickness and its material properties. Independently increasing either the stiffness or thickness of the sclera leads to reduced deformations being transmitted to the ONH. However, if the sclera is quite stiff, then changing its thickness has relatively little

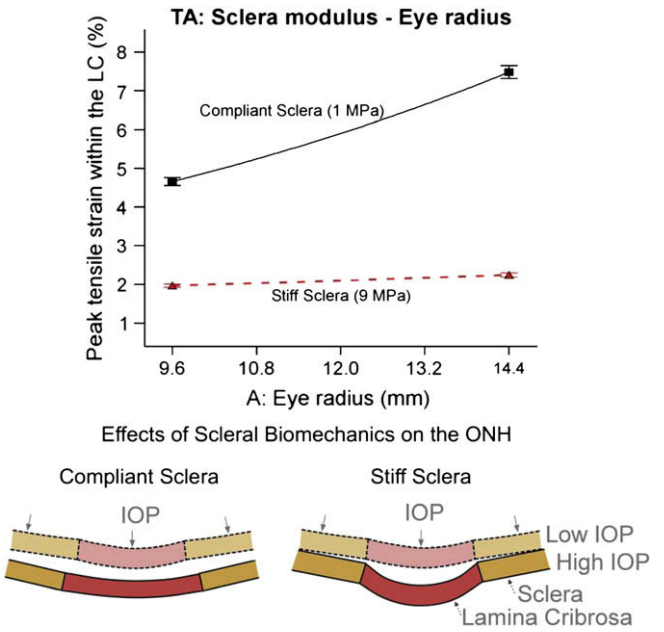

Fig. 2. Interactions between biomechanical factors can have a large influence on LC biomechanics. The top graph plots computed tensile strains in the lamina cribrosa vs. globe radius for two different scleral stiffnesses, demonstrating a strong interaction between scleral modulus and eye radius. Specifically, when the sclera was compliant (upper curve) an increase in globe size led to an increase in LC strain, whereas when the sclera was stiff (lower curve), changes in the globe size had virtually no effect on LC strain. Conversely, the effects of an increase in scleral modulus (the distance between the two lines) were less in small globes (left side) compared with large globes (right side). The bottom panels show schematically how IOP can act on the sclera to influence LC biomechanics. In the case of a compliant sclera (left), IOP induces large scleral deformations which are transmitted to the scleral canal, resulting in a large scleral canal expansion that pulls the LC taut, despite the direct posterior force of IOP on the LC. Conversely, a stiff sclera deforms little under IOP (right), with corresponding small scleral canal expansion and little stretching of the LC, thus allowing the LC to be displaced posteriorly by the direct action of IOP on its anterior surface. Top graph from Sigal (Sigal, 2009); bottom images from Sigal et al. (in press). Reproduced with permission from the Association for Research in Vision and Ophthalmology.

effect on ONH biomechanics, while if the sclera is thick then changes in its stiffness matter less. Another strong interaction (which is less obvious than the above example) is that between scleral modulus and globe radius (Fig. 2). Identifying the interactions between parameters is important because it facilitates interpretation of experiments that find, or fail to find, correlations between factors and effects.

3.2.2. Eye-specific models

Eye-specific models have been developed based on 3D reconstructions of human (Sigal et al., 2005b, 2008a,b) and monkey (Downs et al., 2007b) eyes. Sigal and coworkers (2005b) reconstructed eye-specific models of human eyes based on imaging of histological sections of donor tissue, which they then used to study the relative influences of geometry and material properties of the ONH to changes in IOP (Sigal et al., 2007a, 2008a,b). Like their generic models discussed above, the eye-specific models incorporated lamina cribrosa and sclera, as well as pre- and post-laminar neural tissues and pia mater. The challenges and limitations of the reconstruction and modeling are discussed in the above references. They found that ONH biomechanics were influenced more strongly by variations in the properties of the sclera than by differences in geometry (anatomy) between individual ONHs. They also confirmed the predictions made with generic models, namely that the IOP-induced deformations of the ONH surface are likely not a good surrogate for the deformations of the LC (Fig. 3). The FE models also showed that as IOP increases the tissues of the ONH are exposed simultaneously to various modes of strain and stress: tensile, compressive and shearing. In both the generic and eye-specific models the magnitudes of the compressive strains are higher than those of shear or tensile strains. This is of interest because the biological response of tissues and cells depends on the mode of the stimulus, as well as on its magnitudes and temporal profiles (Edwards et al., 2001; Laplaca et al., 2005).

Researchers using eye-specific models based on monkey eyes have followed a different approach than Sigal et al., above, instead focusing on characterizing and modeling the load-bearing sclera and lamina cribrosa. Their models do not incorporate neural tissues or pia mater, but their block-imaging technique has allowed them to reconstruct the beam-level details of the laminar microstructure

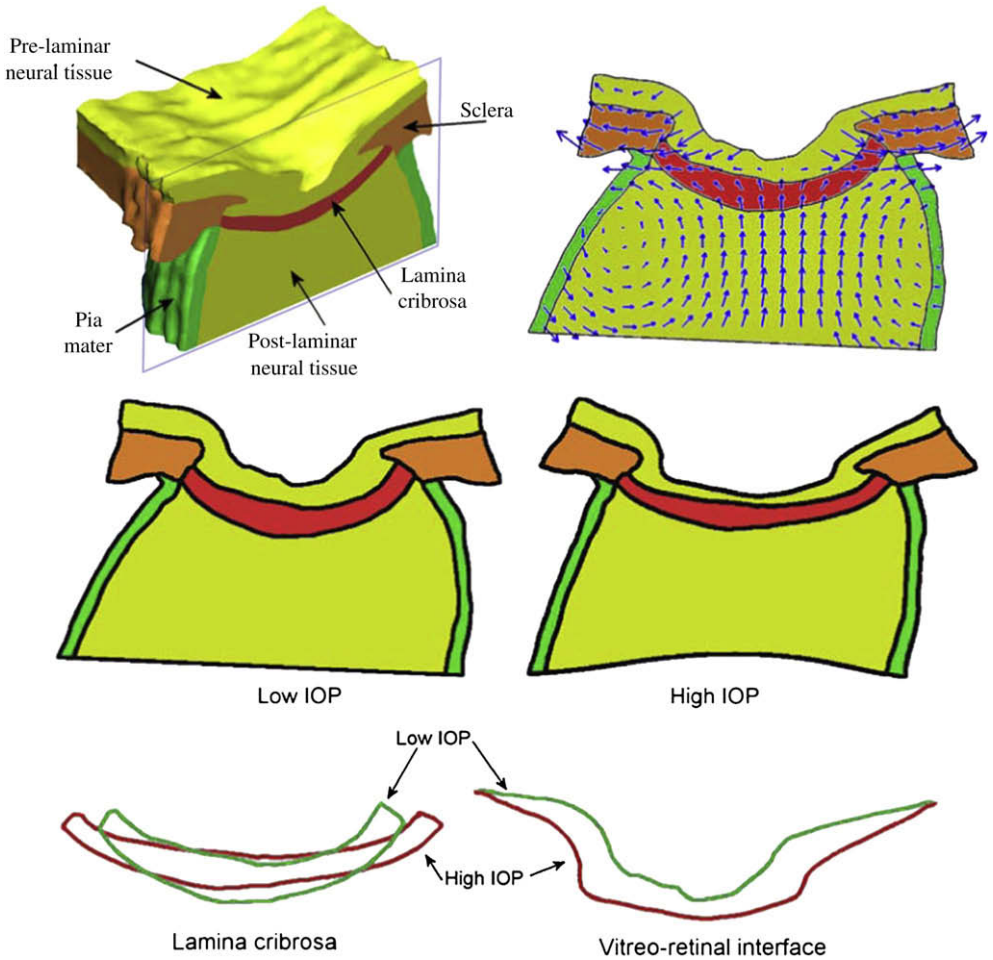

Fig. 3. Computational analysis of human LC biomechanics can be performed on eye-specific models. The top left panel is a 3D view of one such model reconstructed from an ostensibly healthy human donor eye. The model is cut sagittally to show its interior. The top right panel shows tissue displacement vectors, overlaid on a sagittal cross section, computed for an increase in IOP from 5 to 50 mmHg. The vectors were computed in 3D, with their 2D projections shown, and their lengths are proportional to the magnitude of the total displacement, with the scale exaggerated for clarity. The middle row shows sagittal cross-sections of the model at low (left) and high (right) IOP. Deformations are exaggerated fivefold for clarity. Note how elevation of IOP induces posterior rotation of the peripapillary sclera, flattening of the cup floor, thinning of the LC and pre-laminar neural tissues and anterior movement of the central regions of the optic nerve relative to the LC. The bottom row highlights the deformations of the LC and vitreoretinal interface by overlaying low-IOP (green) and high-IOP (red) outlines, showing the stretching of the LC in the plane of the sclera, and the deepening of the cup. Note that these simulations were carried out assuming incompressible tissues; therefore the thinning of the LC and the pre-laminar neural region do not represent a reduction in tissue volume, only a redistribution. From Sigal et al. (in press).

in 3D (Burgoyne et al., 2004), providing a higher level of detail within the lamina cribrosa than that the models of Sigal and colleagues. For example, Downs et al. applied this technique to contralateral normal and glaucomatous monkey eyes, which they have analyzed to provide insights into morphometric changes occurring in response to chronic IOP elevations (Downs et al., 2007a,b). They have used these reconstructions to describe LC mechanical properties in a way that includes the inhomogeneity and anisotropy of the LC connective tissue structure (Fig. 4, top row). Early results suggest that these details of the LC properties are altered in early glaucoma (Roberts et al., 2009), and are also likely influential in the mechanical response of the LC (Roberts et al., 2007).

Despite being aware of the LC microstructure, the models described above homogenize tissue regions and provide only a bulk description of the deformations, stresses and strains produced due to the increases in IOP. This is important because the biological effects on cells are likely to be more strongly dependent on the local levels of stress and strain than on bulk levels. To address this limitation and study its implications Downs, Roberts and colleagues have developed a two-scale approach, in which predictions obtained from larger-scale models of the lamina cribrosa and sclera are used as boundary conditions for smaller-scale models of the laminar beams. In their early stages these studies have suggested that beam-level stresses and strains can be substantially higher than those calculated using models that do not explicitly model the LC beams (Downs et al., 2007b) (Fig. 4, bottom row).

4. The influence of the sclera

A somewhat surprising outcome of the above models is the suggestion that the properties of the sclera have a stronger-than-expected influence on the biomechanics of the ONH. Soft tissues, such as the sclera, often exhibit complex mechanical responses to loading, which may be necessary for the proper description of the effects of IOP on the ONH (Fung, 1993). This motivates studies designed to characterize the biomechanical properties of the sclera, particularly of the peripapillary sclera. The scleral tissue has been shown to have nonlinear (Woo et al., 1972; Girard et al., 2008b, submitted for publication), anisotropic (Rada et al., 2006; Girard et al., 2008b), and viscoelastic (Siegwart and Norton, 1999; Girard et al., 2007) mechanical properties. A nonlinear material varies in stiffness as it deforms. For example, the tangent modulus (a measure of stiffness) of monkey sclera has been shown to increase by a factor of five as IOP increases from low to elevated (Girard et al., in press). An anisotropic material exhibits different stiffness in different directions. Studies in monkey and human eyes suggest some degree of scleral anisotropy (Battaglioli and Kamm, 1984; Olesen et al., 2007; Girard et al., in press), yet the extent of this

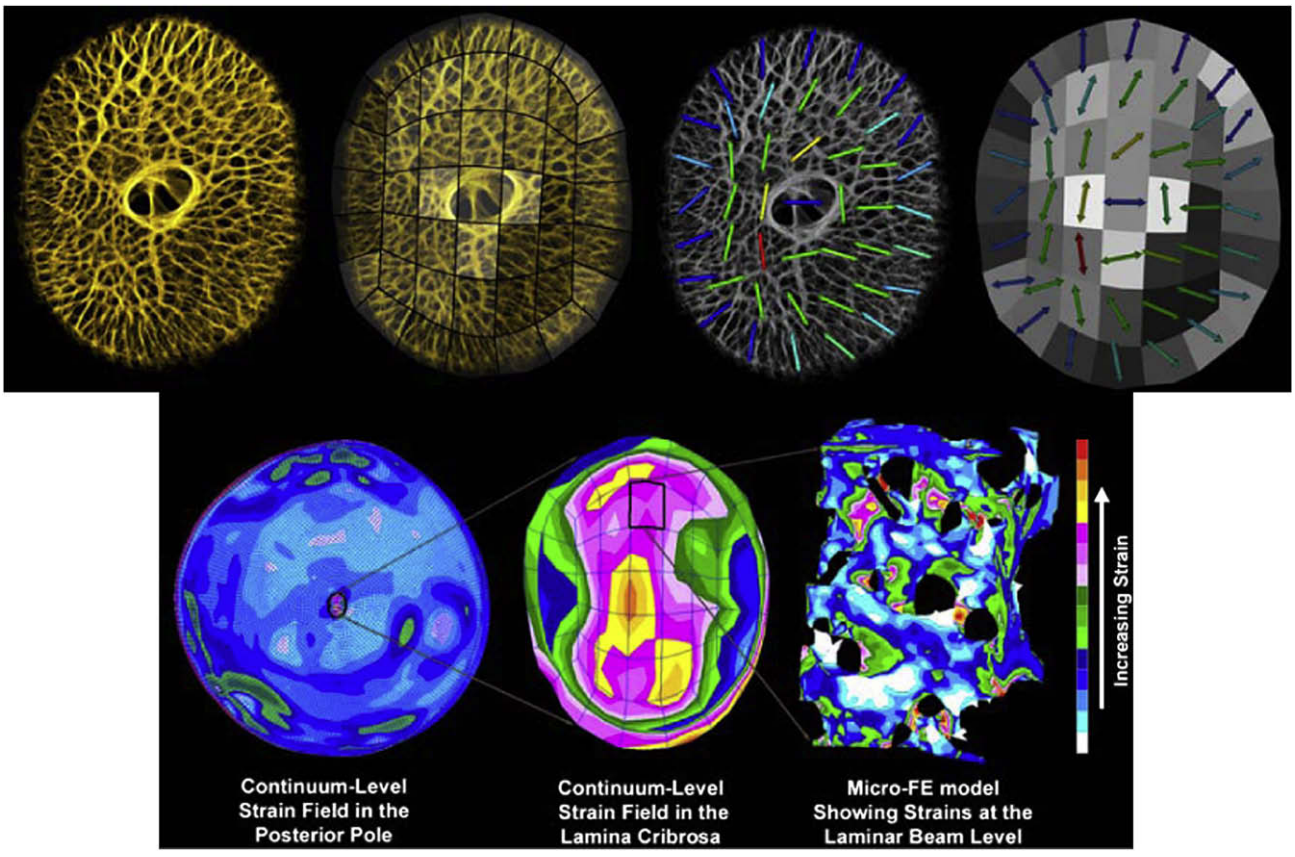

Fig. 4. Lamina cribrosa biomechanics depends on LC microarchitecture. The top row shows (from left to right) a representative 3D reconstruction of the lamina cribrosa of a normal monkey eye; the same lamina subdivided into 45 volumetric elements (black lines); and predominant laminar beam orientation within each element (arrows). The rightmost panel in the top row shows the regional variations in both connective tissue density (inhomogeneity, shown in greyscale) and predominant laminar beam orientation (anisotropy, shown by the arrows). The bottom row indicates how regional properties are used to represent bulk mechanical properties in a two-scale model of the load-bearing tissues of the posterior pole, and hence to make predictions of the mechanical response of the sclera and LC to IOP. From left to right, the panels in the bottom row show strains computed for the entire ocular shell; a zoomed-in view of strains in the lamina cribrosa computed using a continuum model of the LC; and strains in individual laminar beams. Note that local strains in laminar beams can markedly exceed average strains in the corresponding laminar volumetric element. Top row panels adapted from Roberts et al. (2009); bottom row panels from Sigal et al. (in press). Reproduced with permission from the Association for Research in Vision and Ophthalmology.

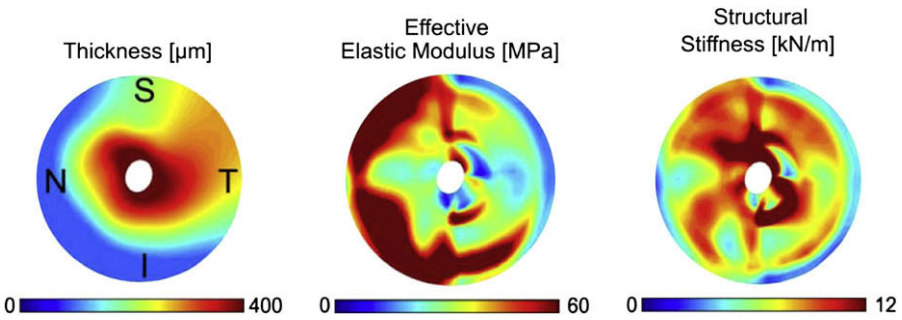

Fig. 5. Maps of posterior scleral thickness (left), effective elastic modulus (center) and structural stiffness (right) from the sclera of an elderly monkey, determined at an IOP of 30 mmHg. The elastic modulus quantifies the relationship between applied forces and the resulting deformation. A higher modulus means that a larger force is needed for the same amount of deformation, or that the same force produces a smaller deformation. Structural stiffness was computed as the product of thickness and effective elastic modulus. Note how the thinner regions (nasal and inferior poles) are also those with the highest effective elastic modulus, resulting in a relatively homogeneous map of structural stiffness. See Girard et al. (2008a,b) for a more detailed description of the terms and definitions. N: nasal, S: superior, T: temporal, I: inferior. Adapted from Girard et al. (2008a). Reproduced with permission from the Association for Research in Vision and Ophthalmology.

property, and how it varies between individuals, is still unclear. A viscoelastic material exhibits higher stiffness when loaded quickly rather than slowly. Downs and coworkers have shown that the mechanical properties of normal rabbit and monkey peripapillary sclera are highly time-dependent (Downs et al., 2003, 2005). This behavior is often described as protecting the ocular tissues from large deformations during short-term spikes in IOP, such as during blinking or eye rubbing.

The shape of the sclera is also an important factor in its response to loading (Sigal et al., 2005a, 2007b) (Fig. 5). Studies of the scleral thickness in humans (Olsen et al., 1998; Rausch et al., 2007; Norman 2008) and monkeys (Downs et al., 2002) show that there are substantial variations in thickness within and between individuals. The sclera is thinnest near the equator and thickest near the posterior pole. Several geometrical parameters of the human eye, including posterior scleral thickness, volume of scleral tissue and axial length appear to co-vary (Norman 2008). More studies of scleral properties and their variation in health and disease are needed.

5. The influence of retrolaminar tissue pressure

When considering LC biomechanics it is natural to focus on the role of IOP, since it is clinically observable and clearly important. However, from a biomechanical viewpoint, we should remind ourselves that it is the difference between IOP and retrolaminar tissue pressure (RLTp) that directly loads the LC. Put another way, if this pressure difference were zero, then the LC would experience zero net direct loading. Note however this does not mean that the lamina would be free of all biomechanical influences: axons would still experience a compressive force, and the LC would still be acted upon by the sclera, whose deformation is controlled by the difference between IOP and orbital pressure.

Recognising this fact, several investigators have studied this so-called translaminar pressure gradient. For example, Jonas and colleagues have noted that the lamina is thinner in myopes (2004) and that there are morphometric changes in the lamina of glaucomatous eyes, including thinning (Jonas et al., 2003). Interestingly, different effects are seen in early experimental glaucoma in monkeys, where the lamina thickens and deforms posteriorly (Yang et al., 2007b; Roberts et al., 2009). Whether laminar thinning in more advanced glaucoma in human eyes is cause or effect is unclear, but the observed laminar thinning will act to increase the magnitude of the translaminar pressure gradient, presumably leading to a greater biomechanical insult to the LC. RLTp is not clinically measurable, but fortunately Morgan and colleagues (1995, 1998, 2008) have shown that cerebrospinal fluid pressure (CSFp) is usually a good surrogate for RLTp. They directly measured both CSFp and RLTp in vivo, and observed that RLTp tracked CSFp when the latter was greater than −0.5 mmHg, but did not drop when CSF pressure dropped below −0.5 mmHg. They have also shown (Morgan et al. 2002) that direct manipulation of CSF leads to movement of the optic disc and variations in the pressure distribution within the ONH.

Most intriguingly, Berdahl et al. (2008) have recently shown, in a retrospective review of a large cohort of glaucoma patients and controls, that the POAG patients had CSF pressures that were nearly 4 mmHg lower than those in controls. This suggests that translaminar pressure gradient is clinically and biomechanically important, and that low CSF pressure could be an important independent risk factor for glaucomatous damage. Further research is needed in this area.

6. Conclusions

The biomechanics of the LC are complex and potentially important in glaucomatous optic neuropathy. The stiffness and thickness of the peripapillary sclera and the microarchitecture of the laminar beams both have a strong effect in the mechanical insult experienced by cells in the LC. Studies in which numerical modeling is informed by experiments offer a powerful way to better understand LC biomechanics. Such characterization of the biomechanical environment within the LC must in turn be coupled to studies of the cellular and molecular responses to mechanical insults in the glaucomatous LC.

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