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Review

Optic nerve head biomechanics in aging and disease

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ABSTRACT

This nontechnical review is focused upon educating the reader on optic nerve head biomechanics in both aging and disease along two main themes: what is known about how mechanical forces and the resulting deformations are distributed in the posterior pole and ONH (biomechanics) and what is known about how the living system responds to those deformations (mechanobiology). We focus on how ONH responds to IOP elevations as a structural system, insofar as the acute mechanical response of the lamina cribrosa is confounded with the responses of the peripapillary sclera, prelaminar neural tissues, and retrolaminar optic nerve. We discuss the biomechanical basis for IOP-driven changes in connective tissues, blood flow, and cellular responses. We use glaucoma as the primary framework to present the important aspects of ONH biomechanics in aging and disease, as ONH biomechanics, aging, and the posterior pole extracellular matrix (ECM) are thought to be centrally involved in glaucoma susceptibility, onset and progression.

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1. The optic nerve head (ONH) as a biomechanical structure

Glaucoma is primarily a disease of aging (Gordon et al., 2002; Leske et al., 2003) and is one of the leading causes of blindness in the developed world (Quigley and Broman, 2006). ONH biomechanics and the posterior pole extracellular matrix (ECM) are also thought to be centrally involved in glaucoma susceptibility, as well as disease onset and progression (Zeimer and Ogura, 1989). Hence, we will use glaucoma as the primary framework to present the important aspects of ONH biomechanics in aging and disease in this review.

The ONH is of particular interest from a biomechanical perspective because it is a weak spot within an otherwise strong corneo-scleral envelope. Overwhelming evidence suggests that the lamina cribrosa is the principal site of RGC axonal insult in glaucoma (Howell et al., 2007; Nickells et al., 2012). In this sense, glaucomatous optic neuropathy can be viewed as an axonopathy, where damage to the visual pathway is driven by insult to RGC axons as they exit the eye at the ONH (Howell et al., 2007; Nickells et al., 2012). Hence, neither neuroprotection of the RGC soma or neuroregeneration of the RGC axons is likely to be effective in preventing, slowing or reversing vision loss in glaucoma unless the pathologic environment in the ONH is also simultaneously addressed. As such, glaucoma prevention and treatment is a three-legged stool in which the health of the RGC soma, its axon, *and* the axonal pathway to the brain must be simultaneously supported and maintained to prevent vision loss. The mechanisms of RGC axonal insult at the ONH insult are poorly understood, but we present a framework of IOP-driven ONH biomechanics as a central mechanism in the pathophysiology of glaucoma in this review.

The lamina cribrosa provides structural and functional support to the RGC axons as they pass from the relatively high-pressure environment in the eye to a low-pressure region in the retrobulbar cerebrospinal space (Zeimer and Ogura, 1989; Downs et al., 2008). To protect the RGCs in this unique anatomic region, the lamina cribrosa in higher primates has developed into a complex structure composed of a three-dimensional (3D) network of flexible beams of connective tissue (Fig. 1). The ONH is nourished by the short posterior ciliary arteries, which penetrate the immediate peripapillary sclera to feed capillaries contained within the laminar beams (Cioffi and Van Buskirk, 1996). This intra-scleral and intralaminar vasculature is unique in that it is encased in load-bearing connective tissue, either within the scleral wall adjacent to the lamina cribrosa, or within the laminar beams themselves. Glaucoma is a multifactorial disease, and we hypothesize that biomechanics not only determines the mechanical environment in the ONH, but also mediates IOP-related reductions in blood flow and cellular responses through various pathways (Fig. 2). Consideration of the anatomy of the lamina cribrosa and peripapillary sclera alone suggests that the classic “mechanical” and “vascular” mechanisms of glaucomatous injury are inseparably intertwined (Fig. 2) (Sigal et al., 2010).

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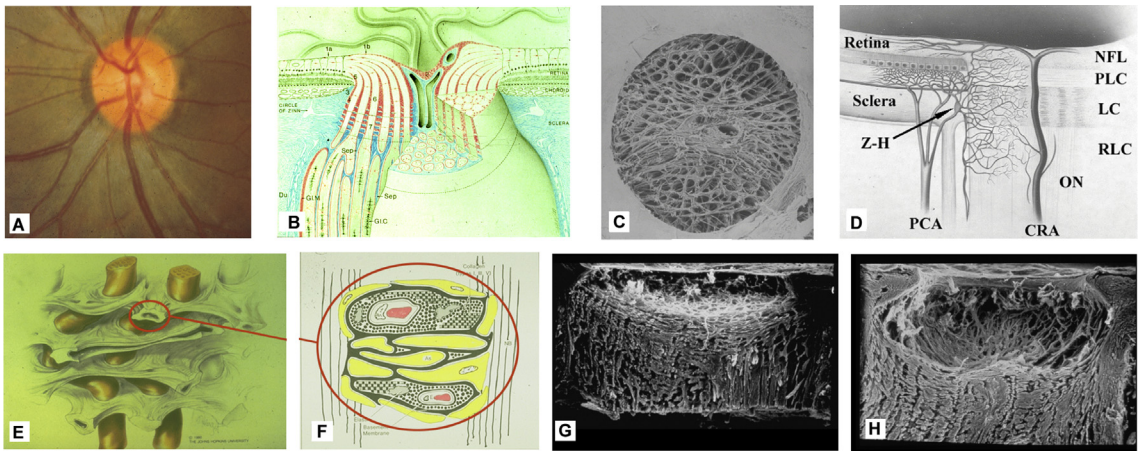

Fig. 1. The optic nerve head (ONH) is a three-dimensional (3D) structure comprised of multiple interactive tissue systems that exist on different scales. This complexity has been a formidable deterrent to characterizing its mechanical environment. (A) While clinicians are familiar with the clinically visible surface of the optic nerve head (referred to as the optic disc), in fact the ONH (B) is a dynamic, 3D structure (seen here in an illustrated sectional view) in which the retinal ganglion cell (RGC) axons in bundles (white) surrounded by glial columns (red), pass through the connective tissue beams of the lamina cribrosa (light blue), isolated following trypsin digestion in a scanning electron micrograph (SEM) of the scleral canal in (C). The blood supply for the connective tissues of the lamina cribrosa (D) derives from the posterior ciliary arteries and the circle of Zinn-Haller (Z-H). (E–F) The relationship of the laminar beams to the axon bundles is shown in schematic form in (E). (F) Individual beams of the lamina cribrosa are lined by astrocytes and LC cells. Together they provide structural and metabolic support for the adjacent axon bundles. Within the lamina, the RGC axons have no direct blood supply. Axonal nutrition requires diffusion of nutrients from the laminar capillaries (solid red), across the endothelial basement membranes, through the extracellular matrix (ECM) of the laminar beam (stippled), across the basement membranes of the astrocytes (thick black), into the astrocytes (yellow), and across their processes (not shown) to the adjacent axons (vertical lines). Chronic age-related changes in the endothelial cell and astrocyte basement membranes, as well as intraocular pressure (IOP)-induced changes in the laminar ECM and astrocyte basement membranes may diminish nutrient diffusion to the axons in the presence of a stable level of laminar capillary volume flow. In advanced glaucoma, the connective tissues of the normal lamina cribrosa (G, sagittal view of the center of the ONH; vitreous above, orbital optic nerve below) change shape and remodel into a cupped and excavated configuration (H). Adapted from Sigal et al. (2010).

To incorporate these concepts into an overarching conceptual framework, we and others have proposed that the ONH is a biomechanical structure in which IOP-related stress (force/cross sectional area) and strain (local relative deformation of the tissues) are central determinants of both the physiology and pathophysiology of the ONH tissues and their blood supply at all levels of IOP (Burgoyne et al., 2005; Downs et al., 2008; Sigal et al., 2010; Campbell et al., 2014) (Fig. 2). IOP perturbations induce not only alterations to the load-bearing ECM of the lamina cribrosa and the peripapillary sclera, but also activate the resident cells of these tissues and damage the RGC axons in the ONH (Burgoyne, 2011). Age-related changes to the cells and ECM also significantly affect the ONH biomechanical environment, so aging is an important pillar of the biomechanical framework (Burgoyne and Downs, 2008). The prevalence of glaucoma is much higher in persons of African heritage compared to persons of European descent (Quigley and Broman, 2006; Rudnicka et al., 2006). Recent studies have shown significant racial differences in scleral stiffening with age, which indicates that racial disparities in ocular biomechanics may play a role in glaucoma susceptibility.

Although clinical IOP-lowering remains the only proven method of preventing the onset and progression of glaucoma, the role of IOP in the development and progression of the disease is not well understood. This largely arises from the clinical observation that significant numbers of patients with normal IOPs develop glaucoma (*e.g.*, normal or low-tension glaucoma), while other individuals with elevated IOP show no signs of the disease. This could mean that IOP (or some factor driven by IOP) is a primary causative factor in glaucoma, and IOP vulnerability varies between individuals. Another possibility is that clinical characterization of *mean* IOP using infrequent snapshot measurements fails to capture exposure to injurious IOP *fluctuations* that are partly driving the disease in these normotensive glaucoma patients, which makes the IOP-glaucoma relationship murky.

Recent data indicate that IOP fluctuates as much as 5 mmHg day-to-day and hour-to-hour, and 15–40 mmHg second-to-second when measured continuously via telemetry in unrestrained, awake nonhuman primates (Downs et al., 2011a) (Fig. 3). Very little is known about IOP fluctuations in humans and how the eye responds to those fluctuations, but IOP levels at all timescales have the potential to injure the RGC axons in the ONH (Cullen and LaPlaca, 2006; Resta et al., 2007). Interestingly, recent work has shown that the sclera (Coudrillier et al., 2012; Geraghty et al., 2012; Fazio et al., 2014a,b), lamina cribrosa (Albon et al., 2000), and cornea (Knox et al., 2011) stiffen significantly with age. One might assume this to be protective against axon damage, as stiffer connective tissues resist mechanical deformation better than more compliant tissues. However, stiffening of the corneoscleral shell also induces larger IOP spikes related to blinks, saccades, and vascular filling, in that the eye is less able to elastically expand to absorb IOP impulse (a measure of the mechanical insult delivered by IOP spikes). Hence, it may be that in the process of age-related connective tissue stiffening, the eye has remodeled to a state wherein the ONH is subjected to much larger IOP spikes.

Whether it is mean IOP and/or IOP fluctuations that drive glaucomatous pathogenesis, there is a wide spectrum of individual susceptibility to IOP-related glaucomatous vision loss, and the biomechanical effects of IOP on the tissues of the ONH likely play a central role in the development and progression of the disease at all IOPs. The individual susceptibility of a particular patient's ONH to IOP insult is likely a function of the biomechanical response of the constituent tissues and the resulting mechanical, ischemic and cellular events driven by that response. Hence eyes with a particular combination of tissue geometry and material properties may be susceptible to damage at normal IOP, while others may have a combination of ONH tissue geometry and material properties that can withstand even high levels of IOP. Age-related changes in the ONH and peripapillary sclera alone may change the biomechanical

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