Experimental Eye Research 88 (2009) 799–807

Contents lists available at ScienceDirect

Experimental Eye Research

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

Review

Biomechanics of the optic nerve head

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ARTICLE INFO

Article history:
Received 2 November 2008
Accepted in revised form 3 February 2009
Available online 14 February 2009

Keywords:
glaucoma
lamina cribrosa
optic nerve head
biomechanics
strain

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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0014-4835/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.exer.2009.02.003

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