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Age-related posterior ciliary muscle restriction – A link between trabecular meshwork and optic nerve head pathophysiology

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Abstract

The ciliary muscle plays a major role in controlling both accommodation and outflow facility in primates. The ciliary muscle and the choroid functionally form an elastic network that extends from the trabecular meshwork all the way to the back of the eye and ultimately attaches to the elastic fiber ring that surrounds the optic nerve and to the lamina cribrosa through which the nerve passes. The ciliary muscle governs the accommodative movement of the elastic network.

With age ciliary muscle mobility is restricted by progressively inelastic posterior attachments and the posterior restriction makes the contraction progressively isometric; placing increased tension on the optic nerve region. In addition, outflow facility also declines with age and limbal corneoscleral contour bows inward. Age-related loss in muscle movement and altered limbal corneoscleral contour could both compromise the basal function of the trabecular meshwork. Further, recent studies in non-human primates show that the central vitreous moves posteriorly all the way back to the optic nerve region, suggesting a fluid current and a pressure gradient toward the optic nerve. Thus, there may be pressure and tension spikes on the optic nerve region during accommodation and these pressure and tension spikes may increase with age. This constellation of events could be relevant to glaucomatous optic neuropathy.

In summary, our hypothesis is that glaucoma and presbyopia may be literally linked to each other, via the choroid, and that damage to the optic nerve may be inflicted by accommodative intraocular pressure and choroidal tension “spikes”, which may increase with age.

Keywords

Accommodation; Presbyopia; Outflow facility; Glaucoma; Choroid; Trabecular meshwork; Optic nerve

David L. Epstein was a giant in our field, and will long be remembered for numerous seminal accomplishments. Given his intellect and stature, he was of course asked to organize many meetings and symposia, and took on not only those he was invited to do but also many that emanated from his own vision. His annual meetings on Cape Cod each summer were the

high point of the year for many of us, and became the model for what we now know as variously named glaucoma/trabecular meshwork/aqueous humor outflow study clubs in several venues around the country, organized by contemporary glaucoma thought leaders. Dave's specific mandate to each participant was to start his/her presentation with "My hypothesis is ..." then use no more than 3 slides and 5 min to make the case, and then open the floor for an in-depth guided discussion. Following that model, here is one that Dave might have liked

1. Accommodation and presbyopia

Presbyopia is the age-related loss of accommodation (the ability to focus on near objects). Age-related loss of lens deformability was long regarded as "explaining" presbyopia, and as the sole factor/target in designing accommodating intraocular lenses (AIOLs). However, it is now known that: (1) humans and rhesus monkeys have anatomically and physiologically similar accommodative apparatus and mechanisms (Duane, 1922; Bito et al., 1982; Koretz et al., 1987; Lütjen-Drecoll et al., 1988a,b; Koretz et al., 1989; Neider et al., 1990; Croft et al., 1996; Lütjen-Drecoll et al., 2010; Croft et al., 2013a,b); (2) both species develop presbyopia on the same timescale relative to lifespan (Duane, 1922; Bito et al., 1982; Croft et al., 2006a,b; Croft et al., 2013a,b); (3) ciliary muscle mobility is restricted in both by progressively inelastic posterior attachments (Lütjen-Drecoll et al., 1988a,b; Tamm et al., 1992; Lütjen-Drecoll et al., 2010); (4) ciliary muscle anatomy, muscarinic receptors, and neurotransmitter biosynthetic and biodegradative enzymes remain constant throughout most of life (Gabelt et al., 1990); (5) ciliary muscle contractility is maintained throughout most of life but the posterior restriction makes the contraction progressively isometric (Tamm et al., 1992; Poyer et al., 1993); (6) the restriction can be partly alleviated by enzymatic lysis of the posterior (intermediate) vitreous zonule with resulting increased mobility of the contracting ciliary muscle and the lens (Lütjen-Drecoll et al., 2010); (7) there is a highly complex sensori-motor regulation of focus dependent upon different regions of the ciliary muscle and the zonular apparatus (Flügel-Koch et al., 2009); (8) there are accommodation- and perhaps outflow facility-relevant changes in limbal corneoscleral contour in the aging monkey and human eye (Croft et al., 2013a,b). Some of these findings may explain the poor performance and limited accommodative amplitude provided by current AIOLs, and new AIOL designs are now beginning to take these findings into account and incorporating compensatory strategies.

2. Accommodation, aqueous humor outflow facility and glaucomatous optic neuropathy

The ciliary muscle plays a major role in controlling both accommodation and outflow facility in primates (Croft et al., 1996).

With increased age, movement of the muscle (Tamm et al. 1992, Croft et al., 2006a,b, 2008; Wasielewski et al., 2008; Croft et al., 2009; Lütjen-Drecoll et al. 2010), (Croft et al., 2013a,b) accommodation (Tamm et al. 1992, Croft et al., 2006a,b, 2008; Wasielewski et al., 2008; Croft et al., 2009; Lütjen-Drecoll et al. 2010), and outflow facility decline (Croft et al., 1996), and limbal corneoscleral contour changes in both

monkeys and humans (Croft et al., 2013a,b). Age-related loss in muscle movement and altered limbal corneoscleral contour could both compromise the basal function of the trabecular meshwork. There is an age-related inward bowing of the sclera/muscle in the region of the limbus (Croft et al., 2013a,b) which is more pronounced during accommodation and this phenomenon could dampen outflow facility. Restoring muscle movement and limbal contour by relaxing the muscle's posterior attachments and restoring limbal elasticity, perhaps via a gene therapy approach, may not only restore accommodative amplitude but could be instrumental in enhancing fluid flow through the trabecular meshwork.

The ciliary muscle and the choroid functionally form an elastic network that extends from the trabecular meshwork all the way to the back of the eye (Fig. 1) and ultimately attaches to the elastic fiber ring that surrounds the optic nerve and to the lamina cribrosa through which the nerve passes (Fig. 2) (Tektaş et al., 2010). The ciliary muscle governs the accommodative movement of the elastic network. During the accommodative response the posterior attachments of the ciliary muscle to the choroid pull the entire choroid – and the retina – forward by about 1 mm at the ora serrata (Video Clip#1) (Croft et al., 2014) and 0.1 mm at the optic nerve head (Fig. 1) (Croft et al., 2014); exerting tensional forces on the elastic fiber ring and the lamina, and thereby on the optic nerve. With age the elastic network stiffens and these accommodative movements decrease (Croft et al., 2014) but the contractile force generated by the muscle is maintained (Poyer et al., 1993), generating an isometric contraction. This means that the tensional forces at the optic nerve head may increase with age.

Supplementary video related to this article can be found at <http://dx.doi.org/10.1016/j.exer.2016.07.007>.

Further, real-time high resolution ultrasound biomicroscopic videography has shown that during centrally stimulated accommodation in non-human primates, central vitreous fibrils move posteriorly all the way to the optic nerve region (Video Clip#2) (Croft et al., 2015), suggesting a fluid current and a pressure gradient toward the optic nerve. Thus, there may be pressure and tension spikes on the optic nerve region during accommodation and these pressure and tension spikes may increase with age.

This constellation of events could be relevant to glaucomatous optic neuropathy.

Scleral rigidity may also play a role in the tension placed on the choroid and the optic nerve head, and there may be regional differences in scleral stiffness that may change with age, given the age-related inward bowing of the sclera in the region of the limbus (Croft et al., 2013a,b).

There are reports of optic nerve head stresses and strains of tissue groups but the tissue boundaries were not clear (Girard et al., 2016). Currently there are no direct measures of choroid biomechanics during accommodation. That needs to be studied and is what we propose to do in future work. The amount of pharmacologically-induced force generated by longitudinal ciliary muscle contraction is ~80 mg for a 5 by 4 mm rhesus ciliary muscle strip in organ culture (Poyer et al., 1993), but, it is unknown how much tension is directly placed on the optic nerve head during accommodation in vivo. However, we can say that optical

flow analysis based on movement of retinal landmarks in the current paper indicates that at least some of that force is transmitted to the optic nerve head region (Fig. 1).

It is unknown how the backward movement of the vitreous during accommodation would increase the pressure on the optic nerve if the vitreous cavity is a communicating lumen system. We do know that vitreous fibers and fluid move toward the optic nerve region during the accommodative response and then move anteriorly during disaccommodation. Therefore, there must be a pressure gradient toward the optic nerve during the accommodative response. Measurement of these parameters is beyond the scope of this hypothesis paper. We are collaborating with an engineering team to measure scleral rigidity and insert sensors into the vitreous to measure the tensional forces, intravitreal pressure, and how they change with accommodation and age.

Restoring muscle movement and limbal contour might inhibit the inception or progression of glaucomatous optic neuropathy independent of their effects on the outflow pathways. Perhaps our somewhat arbitrary anatomic division of ocular physiology, pathophysiology and clinical ophthalmology into anterior and posterior segment dichotomies over the past few centuries has been premature. While this may be necessary for hyperspecialized clinical training, it may be counterproductive for understanding basic disease pathophysiology for glaucoma, the world's most common cause of irreversible visual loss, and presbyopia, the world's most common ocular disease.

In summary, our hypothesis is that glaucoma and presbyopia may be literally linked to each other, via the choroid, and that damage to the optic nerve may be inflicted by age-related changes in scleral rigidity, and by accommodative intraocular pressure and choroidal tension “spikes” that may increase with age.... We only wish we could have presented these outrageous, audacious hypotheses at a meeting that Dave was chairing.

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Fig. 1.

Results of optical flow analysis in the region of the optic nerve in one young monkey (courtesy of Bosco Tjan). Arrows represent choroid movement and the direction of the movement during accommodation. The data show that the choroid is stretched during accommodation and that the center of the stretch is around the optic nerve region, suggesting accommodative tension spikes on the region of the optic nerve.

Fig. 2.
Diagram of the elastic network connections (choroid) to the elastic ring which surrounds the optic nerve.