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Biomechanics of the optic nerve head and sclera in canine glaucoma: A brief review

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Abstract

Glaucoma is a leading cause of irreversible blindness, a progressive optic neuropathy with retinal ganglion cell (RGC) death beginning in the optic nerve head (ONH). A primary risk factor for developing glaucoma is elevated intraocular pressure (IOP). Reducing IOP is the only treatment proven to be effective at delaying disease progression. Nevertheless, even when patients have their IOP reduced, the majority of them continue to lose vision. There are, in both humans and dogs, significant interindividual variabilities in susceptibilities to IOP-induced optic nerve damage. Vision loss progresses much more slowly in Beagles with open-angle glaucoma (OAG) caused by *ADAMTS10* mutation. This can be attributed to the mutation-related altered ocular biomechanical properties. The principal site of optic nerve (ON) damage in glaucoma is the ONH. It is suggested that the biomechanical properties of the ONH and the surrounding peripapillary sclera (PPS) contribute to glaucoma development and progression. As far as the beneficial biomechanical properties of the ONH and PPS for a decreased susceptibility and slow progression of glaucoma, data are inconsistent and conflicting. Recent biomechanical studies on beagles with *ADAMTS10* mutation demonstrated that the mutant dogs have mechanically weak posterior sclera. This weakness was associated with a reduced collagen density and a lower proportion of insoluble collagen. These changes, observed before glaucoma development, were considered intrinsic characteristics caused by the mutation rather than a secondary effect of IOP elevation. Further studies of ADAMTS10-OAG may elucidate the effects of altered biomechanical properties of ONH and PPS in determining the glaucoma progression.

Keywords

ADAMTS10 ; dog; neuroprotection; open-angle glaucoma; stiff; viscoelastic

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CONFLICT OF INTEREST

None.

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1 | INTRODUCTION

Glaucoma is a leading cause of irreversible blindness in dogs[1,2] and significantly affects many mammalian species including humans.[3–5] The loss of vision resulting from glaucoma occurs from optic neuropathy and the death of RGCs. Glaucoma pathogenesis is not fully understood, though it appears that multiple factors can contribute to its risk. It is generally agreed that elevated IOP contributes to the development and progression of RGC death and vision loss.[6–8] The elevated IOP damages RGC's axons within the ONH at the level of lamina cribrosa (LC) (Figures 1 and 2).[9–12] The pathogenesis of glaucoma is contributed, some evidence strongly suggests, by the biomechanical properties of the ONH and peripapillary sclera.[13–15] Other possible disease mechanisms contributing to RGC loss, that may or may not be related to IOP, include excitotoxic death[16–18] caused by excessive release of excitatory neurotransmitters (eg, glutamate, aspartate)[19,20] excessive intracellular calcium levels,[21] impaired blood flow to ONH and retina,[22–28] oxidative stress,[29,30] inflammation and autoimmunity against retinal and optic nerve antigens,[31–34] and reactive gliosis.[35–38] This article reviews the current literature on one important glaucoma risk factor—the biomechanical effects of the ONH and peripapillary sclera on IOP-related RGC damage.

2 | VARIABLE VISUAL OUTCOME IN GLAUCOMA

Intraocular pressure is strongly associated with RGC death in glaucoma, but susceptibility to IOP-induced optic nerve (ON) damage varies widely. Some human patients with IOP within the physiologic range develop normal-tension glaucoma, yet others with elevated IOP exhibit no disease.[8,39,40] This variance has also been observed in dogs. Most dogs with primary glaucoma exhibit vision loss within hours to days of acute IOP elevation, while some breeds, including Norwegian Elkhound, Samoyed, Chinese Shar-Pei, and Chow Chow, are reported to remain visual for an extended time with severely elevated IOP.[2] Our group noted that Beagles with OAG caused by a G661R missense mutation in *ADAMTS10*[41] exhibited much slower RGC loss compared to other types of canine glaucoma. These dogs, with IOPs of up to 60–80 mmHg, also retained retinal function and vision for an extended time—up to 20 months (unpublished data, Figure 3). We suggest that mutation-related altered ocular biomechanical properties contribute to a slow glaucoma progression in canine *ADAMTS10-OAG*.[42]

3 | STUDIES ON BIOMECHANICAL PROPERTIES OF THE ONH AND THE SCLERA

Even normal physiological fluctuations in IOP can cause mechanical stress and strain that cause ONH compression and deformation at the scleral canal. This is where RGC axons exit through the posterior scleral wall—thought to be the principal site of glaucomatous ON damage (Figure 1C).[15-17,43-48] The lamina cribrosa (LC) within the scleral canal represents a mesh-like structure that is formed by multilayered networks of collagen fibers, where ~1–1.5 million RGC axons in humans and ~150,000 in dogs traverse pores (Figure 1A and B).[43,49,50] The axon passage through the LC is influenced by IOP and a counter-pressure from the retrolaminar ON against the LC, known as retrolaminar tissue pressure (Figure 4).[51,52] In dogs, retrolaminar tissue pressure is largely determined by the surrounding

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cerebrospinal fluid pressure.[53] Elevated IOP causes an increased pressure gradient across the LC. Additionally, IOP-induced stress applied to the cornea and sclera is concentrated to the ONH margins generating circumferential (hoop) stress. The degree of LC deformation with elevated IOP is influenced by the two simultaneous loading conditions: 1) the direct action of IOP causing an increased pressure gradient across the LC that pushes the LC posteriorly and 2) the IOP-induced in-wall hoop (circumferential) stress applied to the cornea and sclera.[54,55] In-wall hoop stress is concentrated to the PPS that contributes to scleral canal expansion, pulls the LC taut, and displaces the LC anteriorly.[54] The extent and direction of LC displacement for a given IOP are dictated by anatomical factors (eg, LC thickness and position) and material properties (eg, stiffnesses of the PPS and LC).[54] These stresses with different directions interplay and result in permanent deformation of the posterior pole including ONH cupping, scleral canal expansion, and laminar beam thickening resulted from the tissue remodeling.[51,56–59] (Figure 4). Intraocular pressure elevation elicits initial deformation and secondary remodeling of the LC that leads to mechanical axonal damage and disruption of axonal transport (Figure 1C).[60–62] The density of connective tissue in the ONH is lower than in the surrounding collagen-rich peripapillary sclera (PPS), and the resulting stiffness gradient (from outside to inside ONH) causes further magnification of IOP-induced stresses within ONH.[14] Therefore, the development and progression of glaucoma are believed to be strongly impacted by biomechanical factors in the posterior pole of the globe, especially those elicited by IOP elevation in ONH and PPS and their extracellular matrix (ECM).[15,52,55,60]

Ischemia has been suggested as one of glaucoma pathogeneses.[63,64] Variable susceptibilities of IOP-induced ON damage have been proposed to be associated with a varying capacity for autoregulation to reduce IOP-induced ischemia.[2,49] It has also been described that tensile, compressive, or shear strains within the LC beam that are still within the beam's elastic limit may cause the occlusion of the capillaries.[15] IOP-related strain or non-IOP-related factors such as systemic nocturnal hypotension have been thought to be associated with capillary occlusion.[65] Therefore, one of the important research questions to better understand glaucoma pathogenesis would be how the mechanical loading of ONH, the vascular anatomy, and structural composition affect vascular perfusion.[60]

Various methods have been used to analyze biomechanical properties of the ONH and PPS and their effects on glaucoma development. These include computational models,[13,14,66–82] experimentally induced ocular hypertension/glaucoma in animals,[45,46,83–92] and patient cadaveric/enucleated eyes.[56,60,93–102] *Computational studies* suggested that stiffness of the sclera, radius of the eye, stiffness of the LC, IOP, and thickness of the sclera, in order, were found to be the largest influential factors on the biomechanical response of the ONH to IOP changes.[75] Computational modeling with finite element analysis also showed that scleral canal size, shape, and scleral thickness are the principal determinants of the magnitude of the IOP-related stress within the ONH.[14] A study using a porohyperelastic model considering the complex porous behavior of ocular tissues suggested changes in stiffness of the sclera may have a greater impact on LC strains compared to LC stiffness itself.[13] A microstructure motivated approach suggested that IOP elevation results in LC thickening caused by an increased collagen fibril mass and that is in agreement with findings in monkey eyes with early experimental glaucoma.[46,72] *In vivo studies* on monkeys revealed

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age-related stiffening of the sclera, which was suggested to be associated with increased susceptibility to glaucomatous vision loss with aging in humans.[86] Scleral stiffening has also been observed in monkey eyes with experimentally induced IOP elevation.[87] *Studies with human cadaveric eyes* demonstrated increased stiffness of the sclera with aging and in eyes with glaucoma[94,98]; however, it is yet to be elucidated whether and to what extent the biomechanical differences are the baseline properties of the glaucomatous eyes or the secondary effect of IOP increase.

These studies have improved our understanding of the influence of variations in material and geometric parameters on stress and strain on LC and PPS. Nevertheless, we still lack an understanding of how intrinsic biomechanical properties of the ONH and PPS in glaucomatous eyes contribute over time to the extent of axonal damage. It remains controversial which biomechanical properties of ONH and PPS are beneficial. Some studies suggest that a weak sclera increases the risk of glaucomatous optic neuropathy, such that scleral stiffening might be a beneficial treatment for glaucoma.[60,74,75,81,96,103–105] In these studies using computational models, mean strain levels within prelaminar neural tissue and LC decreased when the sclera is stiffened.[74,75,96] This was also supported by *ex vivo* studies using porcine eyes: Cross-linked PPS led to a decreased strain of the ONH.[105] Others have suggested that a stiff posterior sclera and ONH with great strains increases the magnitude of IOP spikes, a known risk factor for glaucoma progression and increased axonal damage.[89,90,99,106] In human patients, age-related sectoral scleral stiffness was found to closely match the areas of glaucomatous changes in the ONH.[98] Experimental studies also revealed that stiffened sclera by crosslinking increased susceptibility to IOP-induced retinal ganglion cell damage in mice.[89] An *ex vivo* study using porcine globes demonstrated that eyes with stiffer sclera were associated with larger IOP spikes during micro-intraocular volume changes.[106]

This is also supported by the clinical observations in puppies with congenital glaucoma. They often present with severe buphthalmia because of the abundance of elastin fibers within the immature sclera. In these puppies, if IOP is reduced fast enough, the globe size may become normal. This rapid buphthalmia is thought to be somewhat protective of the ONH against the elevated IOP.[2] Studies investigating the factors affecting the reversal of the LC with IOP lowering treatment in humans reported that younger age was associated with higher reduction in LC depth, suggesting an age-related decrease in the compliance of the LC as a possible reason.[107,108]

These conflicting results reported based on computational or experimentally induced *in vivo* or *ex vivo* glaucoma models emphasize the need for studies to determine how intrinsic ocular biomechanical properties of glaucomatous eyes contribute to extent of axonal damage, including longitudinally while IOP is elevated in clinically relevant naturally occurring disease models.

4 | BIOMECHANICAL STUDIES ON BEAGLES WITH *ADAMTS10*-OAG

As noted above, Beagles with OAG caused by *ADAMTS10*-mutation have much slower glaucoma progression compared to other forms of glaucoma (Figure 3). A recent study,

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using dynamic mechanical analysis and a tensile ramp, compared the biomechanical properties of the posterior sclera of dogs with *ADAMTS10* mutation with non-mutant controls (Figures 5 and 6).[42] In this study, the viscoelastic properties of the posterior sclera were analyzed using complex modulus, overall resistance to deformation under dynamic loading, and tan (δ)—the damping ability of the tissue. The mutant dogs exhibited weaker posterior scleras with significantly lower complex modulus and tan (δ) than did the non-mutant controls.[42] The mechanically weak sclera in the mutant dogs was associated with a significantly lower proportion of insoluble collagen.[42] These changes were observed in young mutant dogs prior to IOP increase and clinical indications of ON damage. This suggests that the altered scleral biomechanical properties and collagen solubility are inherent differences with the *ADAMTS10* mutation rather than a secondary effect of IOP elevation.[42] Regardless of *ADAMTS10*-genotype and chronic IOP elevation in the mutant dogs, age-associated scleral stiffening occurred at a similar rate in affected and non-mutant control dogs (Figure 6).[109] In all age groups examined, the posterior scleral modulus of the mutant dogs was consistently lower than the non-mutant controls, including before and after the onset of glaucoma onset.[109]

Furthermore, the microstructure of the posterior scleral collagen microstructure has been studied in dogs with *ADAMTS10* mutation prior to detectable glaucoma onset.[110] Compared to the non-mutant controls, collagen density was significantly reduced in the mid-posterior sclera in the mutant dogs while no marked differences in the general pattern of preferential collagen fibril orientation were noted (Figure 7).[110] The authors suggested that in mutant dogs a reduction in fibrous collagen density likely contributes to the mechanical weakening of the sclera.[110] These intrinsic scleral abnormalities have the potential to delay the progression of IOP-induced ONH damage in mutant dogs.[110] ADAMTS10 protein is a member of the ADAMTS family of secreted storage and activation of TGFβ, a known regulator of collagen turnover,[111–113] that suggests *ADAMTS10* mutations alter ECM composition, structure, and mechanical properties. Changes in scleral biomechanical properties, altered collagen solubility, and reduced collagen density in *ADAMTS10*-mutant dogs prior to IOP elevation or ONH damage are thought to be the effect of the mutation. While yet to be investigated, it is possible that LC collagen within ONH is also altered with *ADAMTS10* mutation. Further studies are warranted to address how the altered posterior polar biomechanics may affect the rate of glaucoma progression following IOP elevation in different types of canine glaucoma, including OAG caused by mutations in *ADAMTS10* and *ADAMTS17*, various forms of PACG, and secondary glaucoma.

5 | FUTURE DIRECTION

Currently, published biomechanical studies in dogs with *ADAMTS10*-OAG focuses on the posterior sclera.[42,109] In these studies, a sclera strip adjacent to the ONH was used to characterize the mechanical properties of the posterior sclera. While this method demonstrated viscoelastic properties of the area of the sclera tested, it does not provide complex stress and strain applied to the PPS and ONH of the globe caused by changes in IOP. A more recently reported method using ultrasound biomicroscopy speckle tracking method combined with inflation test enabled measurement IOP-associated strain and deformation of the ONH and PPS as a whole eye and was validated in porcine eyes.[114]

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This method may be applicable to study biomechanical properties of the posterior pole in canine eyes with glaucoma. Further studies of canine glaucoma including *ADAMTS10*- and *ADAMTS17*-OAG may elucidate the effects of the inherently altered biomechanical properties of PPS and ONH, and their potential interactions with elevated IOP, in determining the course of glaucoma progression. Finding a path to potential novel therapeutic targets would be facilitated by a better understanding of the beneficial biomechanical properties of ONH and PPS and how they slow IOP-induced ON damage. The biomechanics of PPS and ONH could potentially be modified by gene therapy, chemical ablation, or collagen crosslinking.

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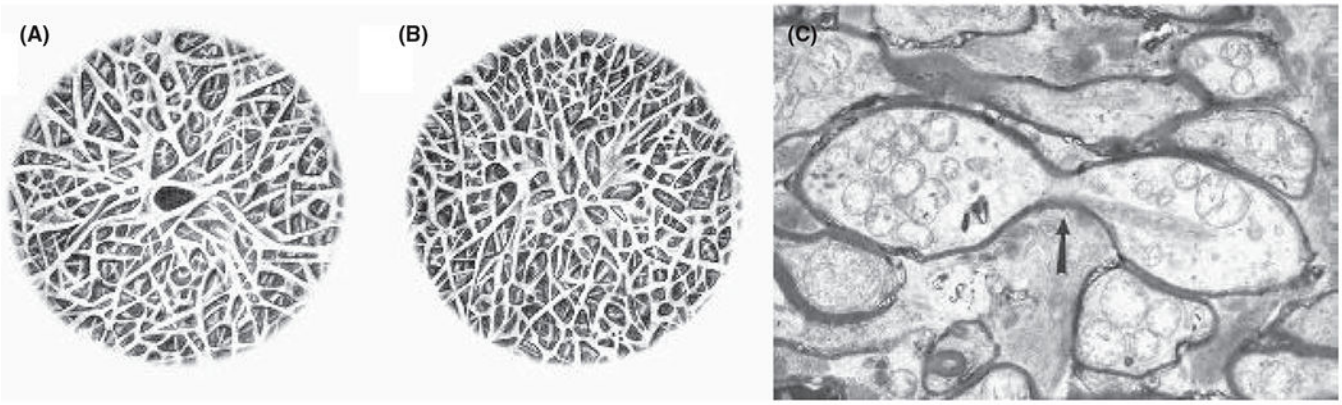


FIGURE 1.

Comparable anatomy of lamina cribrosa (LC) in humans (A) and dogs (B). (C) IOP-induced mechanical compression (arrow) causes axonal swelling and mitochondrial accumulation in a canine ocular hypertension model, suggesting LC as a principal site of glaucomatous optic nerve damage, Panel C: Martins et al., with permission[61]

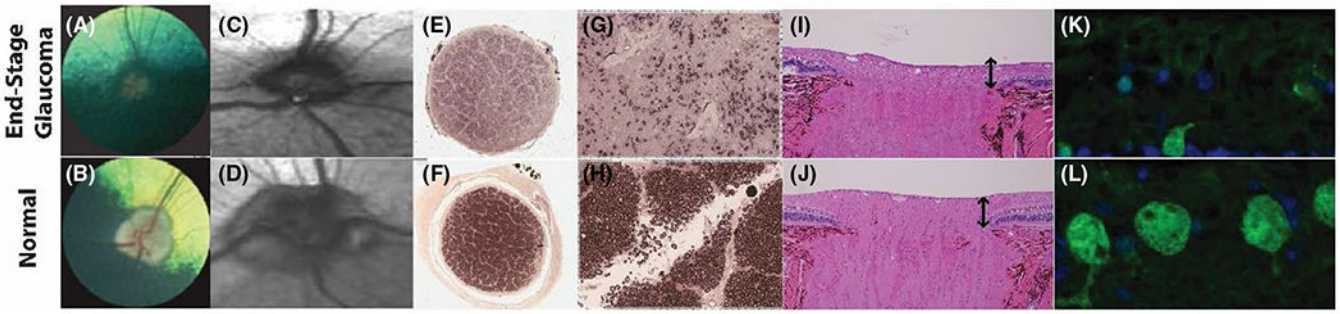


FIGURE 2.

Optic disk cupping and loss of optic nerve axons in a dog with end-stage glaucoma (top row) vs. normal control (bottom row). (A and B) Fundus images; (C and D) OCT of the optic nerve head; (E and F) cross sections of the whole nerve for axon counting; (G and H) high magnification (40x) of the optic nerve cross section; (I) histopathology of the ON showing thinning of the prelaminar optic nerve (arrows) tissue in the glaucomatous eye compared to (J) normal; (K) immunohistochemistry of the canine glaucomatous retina shows loss of RGC (NeuN) (L) compared to the normal eye

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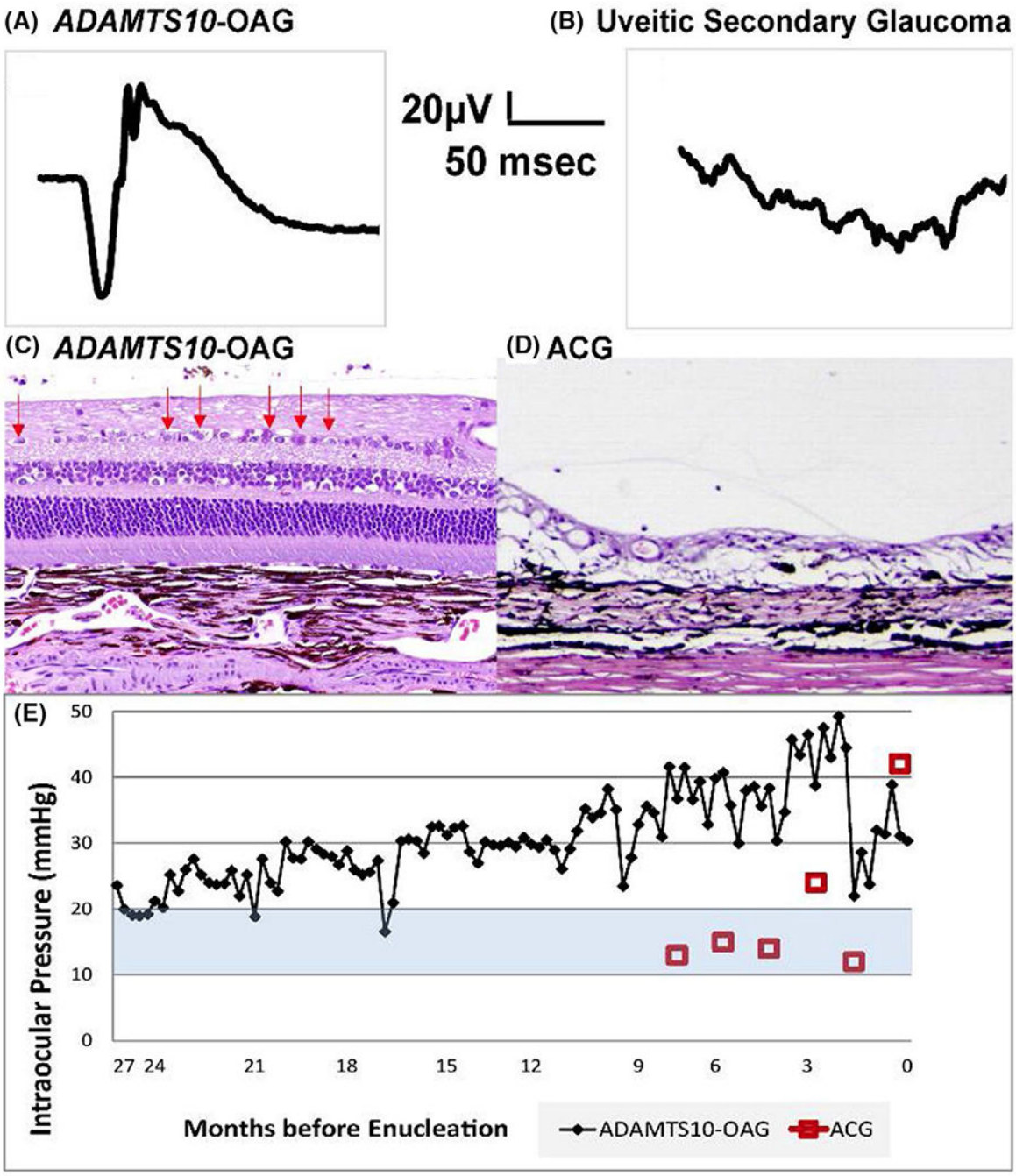


FIGURE 3.

(A) Electroretinograms (ERG) show well-preserved retinal function in a Beagle with *ADAMTS10*-OAG and documented diurnal IOP of 30–65 mmHg for >6 weeks vs (B) essentially non-recordable retinal function in a non-mutant dog with uveitic glaucoma developed post-phacoemulsification and recorded IOP of 62 mmHg for less than 1 day. The globe was enucleated 2 days later and histopathology of the globe showed typical findings of glaucoma including diffuse inner and segmental full-thickness retinal atrophy and the suggested etiology was pre-iridal fibrovascular membrane causing peripheral

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anterior synechia. No overt inflammation was noted in the posterior segment. (C) Relatively well-preserved RGCs (red arrows) and retinal layers in a dog with *ADAMTS10*-OAG after elevated IOP >30 mmHg for 14 months (including documented 40–50 mmHg during the 5-month period) vs (D) a dog with angle-closure glaucoma (ACG) showing extensive full-thickness retinal degeneration after measured IOPs of up to 42 mmHg for less than 3 days. (E) Longitudinal mean diurnal IOPs of the dog with *ADAMTS10*-OAG (black diamond, same dog as C) and individual IOP measurements taken during office visits from a dog with ACG (red square, the same dog as D)

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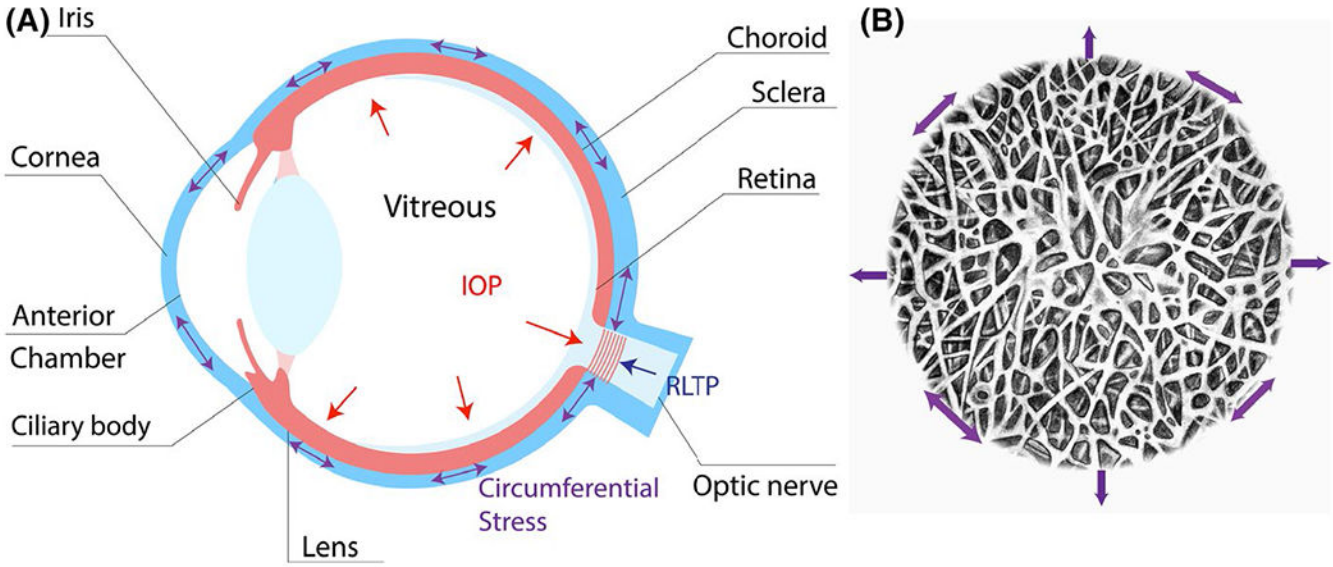


FIGURE 4.

Intraocular pressure (IOP) induced stress in the eye (A) IOP elevation results in increased translaminar pressure gradient (IOP—retrolaminar tissue pressure: RLTP) that leads to ONH cupping. A circumferential (hoop) stress is applied to the cornea and sclera that is concentrated to the peripapillary sclera (PPS) and contributes to scleral expansion. (B) Directions of circumferential stress on the peripapillary sclera surrounding the LC. Figures modified from Quigley et al., 2013[51] and Burgoyne et al., 2011[52]

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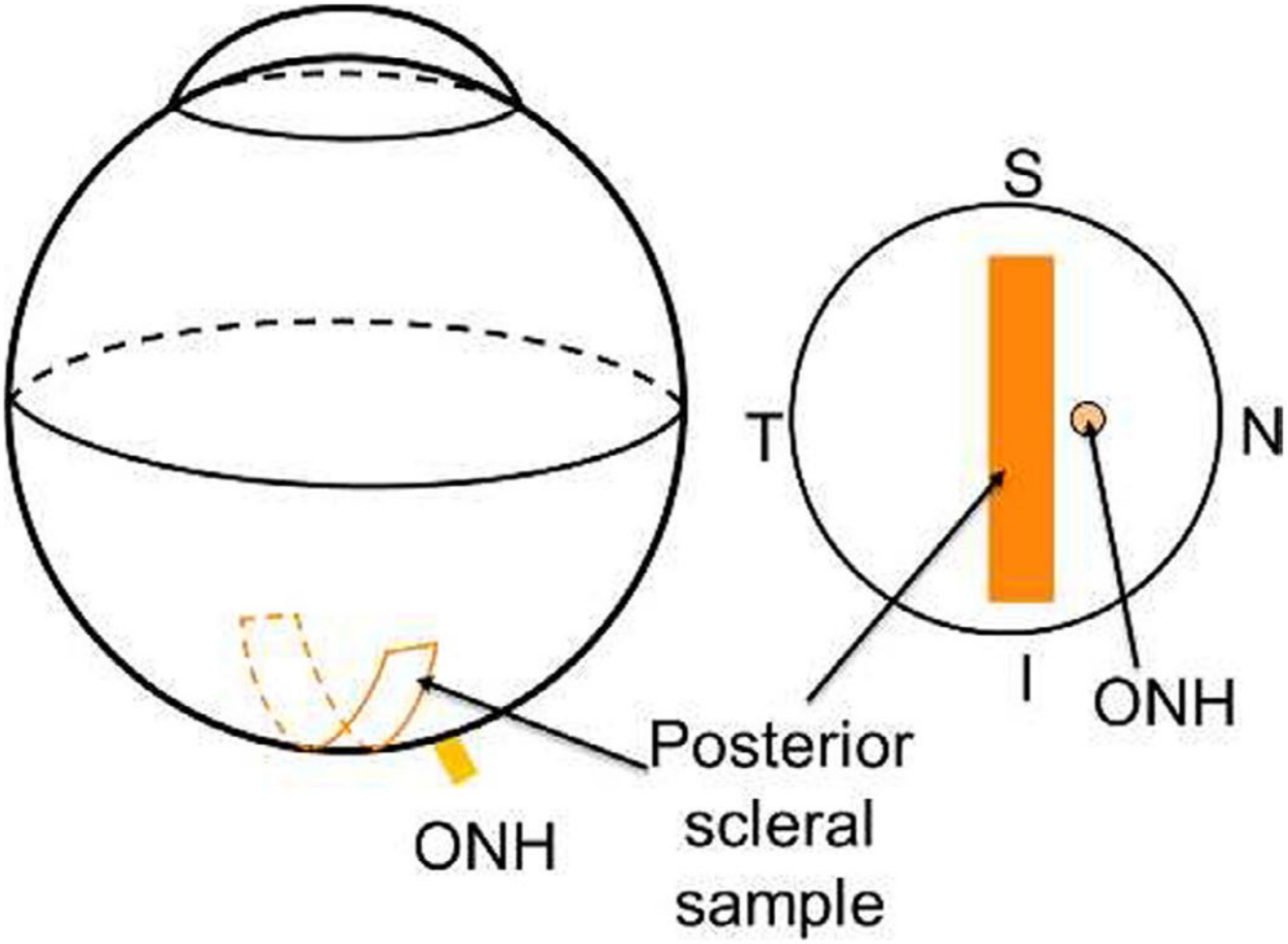


FIGURE 5.

A schematic of the excision location of the posterior scleral strip. The strip was cut adjacent to the temporal side of the ONH. S, superior; I, inferior; N, nasal; and T, temporal. From Palko et al., 2013[42]

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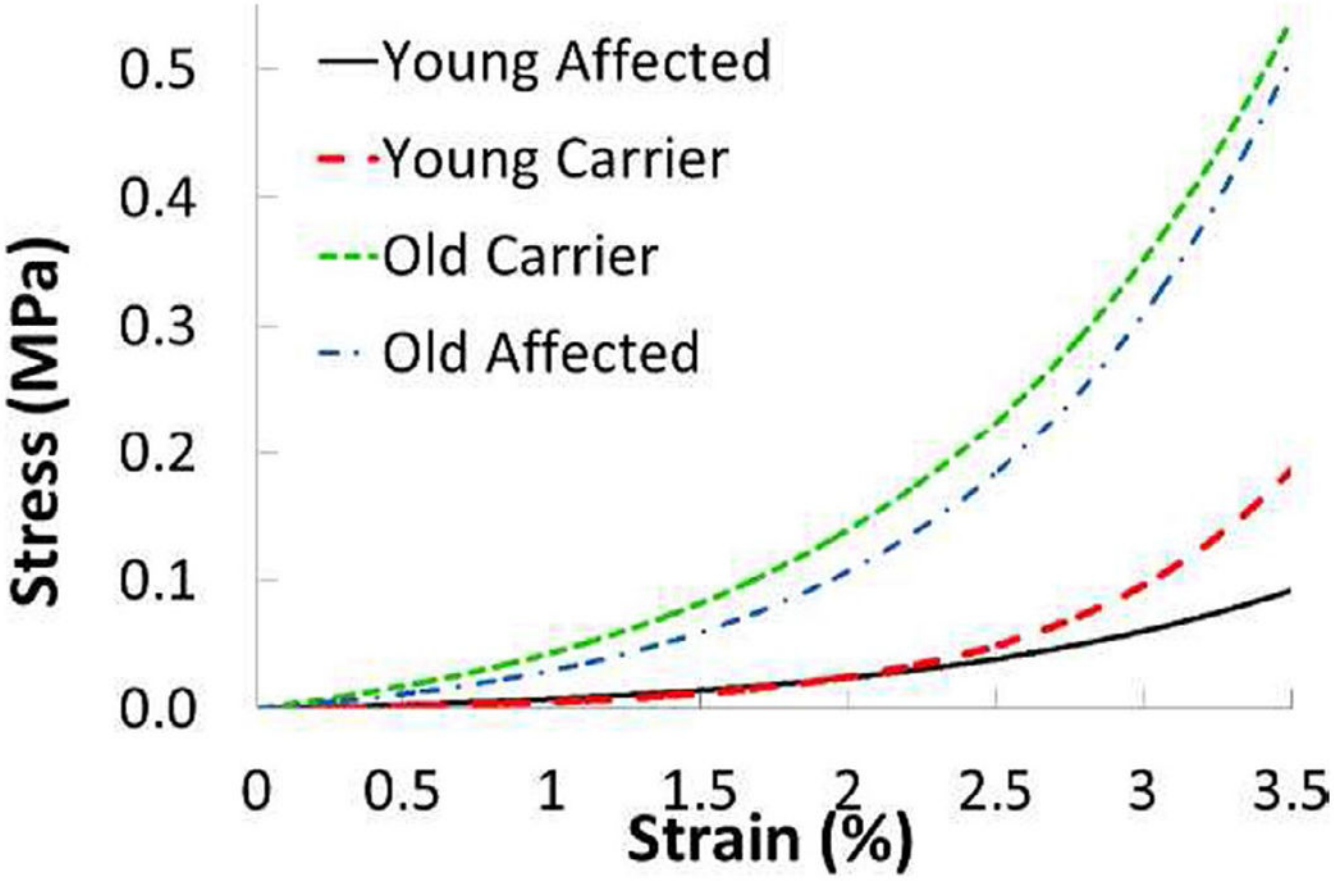


FIGURE 6.

Exponential fitting of the stress-strain curves from the tensile ramp tests. The two older samples were noticeably stiffer than those from the young dogs. From Palko et al., 2013[42]

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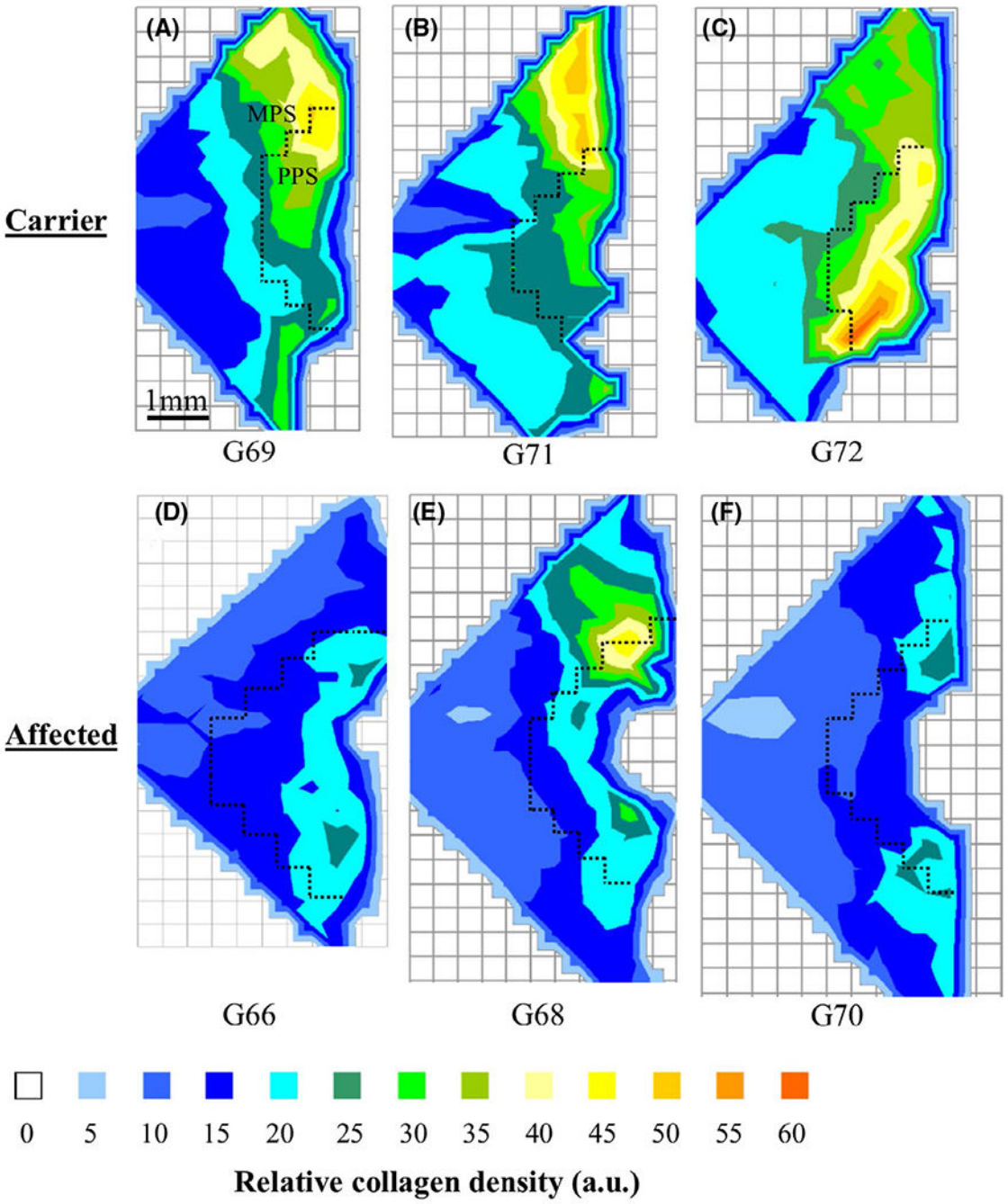


FIGURE 7.

Collagen density maps. Contour maps of relative fibrillar collagen density across the (A–C) carrier and (D–F) affected *ADAMTS10* mutant posterior canine scleras. *Broken line*: border of the mid-posterior (MPS) and PPS regions. Collagen density is visibly reduced in all areas of the affected specimens as compared to carrier controls. Data sampling interval: 0.4 mm. From Boote et al., 2016 with permission[110]