



## Chronic Glaucoma: A Two-Stage Disease

Syed S Hasnain\*

General Ophthalmology, 560 W, Putnam Ave, USA

\*Corresponding Author: Syed S Hasnain, General Ophthalmology, 560 W, Putnam Ave, Suite #6 Porterville, CA 93257, USA, Tel: 559-781-7482; Fax: 559-781-8446; E-mail: [hasnain40@sbcglobal.net](mailto:hasnain40@sbcglobal.net)

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### Abstract

Chronic glaucoma, commonly known as glaucoma, is an unsolved mystery since given a separate entity 160 years ago [1]. Although we have an abundance of glaucoma theories, none of them has addressed the most crucial and pathognomonic feature of glaucoma - the one million or so densely packed nerve fibers (NFs) in the optic nerve head (ONH) being destroyed in an orderly tandem fashion from peripheral to central, but never randomly. The orderly loss of NFs is perhaps the only lead we have in solving the mystery of glaucoma, but surprisingly this aforementioned pathognomonic feature has never been discussed while postulating various glaucoma theories. The raised intraocular pressure (IOP) is the established risk factor of glaucoma. However, raised IOP acting directly on the densely packed NFs cannot result in their orderly destruction. In fact, there is no biological mechanism acting directly on the NFs leading to their orderly loss. There must be some mechanical scenario for the orderly loss of NFs even though that mechanism may have resulted from the biological affect of raised IOP on some important component of the ONH. Therefore, it is hypothesized that glaucoma is a two-stage disease: a biological latent stage leading to atrophy/degeneration of the border tissue of Elschnig (BT), followed by sinking of the lamina cribrosa (LC) resulting in initiation of the mechanical stage leading to the orderly loss of NFs in glaucoma.

**Keywords:** Chronic Glaucoma; (ONH) Optic Nerve Hypoplasia; IOP; Neurodegeneration

### Discussion

There is plethora of glaucoma theories: the direct role of IOP on the NFs of the ONH, lack of optic nerve perfusion, increased sensitivity of the ONH to IOP, neurodegeneration, apoptosis and low cerebrospinal fluid pressure however these prevalent theories can't explain the orderly loss of NFs in glaucoma. In fact there is no biological scenario when acting directly on the NFs could result in their orderly loss.

Since high IOP is the established cause of glaucoma, ironically the raised IOP acting directly on the NFs couldn't result in their orderly loss. Therefore it is proposed that glaucoma is a two-stage disease - a biological stage followed by the mechanical stage.

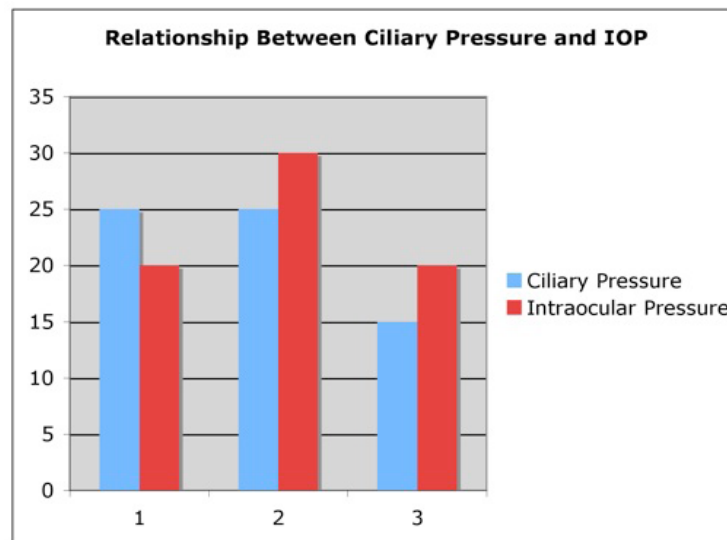
In the biological stage there is development of atrophy/degeneration of the BT due to chronic ischemia induced by IOP, whether within or above the normal range (10 to 21 mmHg). The biological stage is latent and pre-perimetric. The circular BT keeps the LC firmly in place in the scleral canal. Due to degeneration of the BT, the LC starts sinking in the scleral canal and leads to the initiation of the mechanical and perimetric stage of glaucoma. As a result of the sinking LC, the most peripheral NFs, being closest, are stretched and broken at the scleral edge first and ending with most central NFs in an orderly tandem fashion.

### Why is the border tissue being degenerated?

The border tissue of Elschnig is supplied solely by the ciliary circulation which is a low pressure circulation compared to the central retinal artery circulation (CRA). Systemic circulation supplying the BT and IOP are opposing forces. Systemic circulation supplying the BT is normally higher than the IOP for its proper perfusion and healthy maintenance. If this healthy relationship is reversed due to a rise in IOP from an ocular problem as in high tension glaucoma (HTG) or due to reduction in ciliary pressure due to a systemic problem, IOP will take the upper hand.

In the latter scenario any normal range IOP level can become higher than the reduced perfusion pressure of BT and will act as high IOP for that particular subject. Thus normal tension glaucoma (NTG) will ensue. The raised IOP will chronically compress and starve the perfusion of the BT resulting in chronic ischemia and its degeneration. Thus, it is

IOP whether above the normal range or within the normal range acting as high IOP in both HTG and NTG respectively resulting in glaucoma (Figure 1).



**Figure 1:** Note the sinking of the disc resulting in stretching and severing of the peripheral fibers. The most peripheral fiber (5) has been severed and disappeared and this process will continue until the central most fiber (1) has been severed. There will be movement of nerve fibers from the center to the periphery to occupy the space created by severance of the preceding fibers

Chronic glaucoma is indeed a chronic disease as it may take years in the degeneration of the BT in contrast to acute glaucoma in which the IOP suddenly becomes higher than the CRA pressure and causes acute ischemia and immediate death of the retinal cells.

In acute glaucoma the IOP becomes higher than CRA pressure whereas in chronic glaucoma the IOP becomes persistently higher than the perfusion pressure of the BT. The latent period in chronic glaucoma is the start of IOP becoming higher than perfusion pressure of the BT- the reversal of a normal healthy relationship. The latent period varies due to several factors; the higher IOP compared to perfusion pressure of BT, the shorter the latent period.

Moreover, if the BT is inherently weak as in high myopia, the latent period will also be short. Other factors like sleep apnea and smoking resulting in systemic chronic hypoxia will also lead to early degeneration of the BT. Therefore, chronic glaucoma is a multifactorial disease but high IOP is the main risk factor. The more risk factors, the shorter the latent period in a glaucoma subject. Ocular hypertension is not a benign condition but a pre-perimetric glaucoma (latent stage) and should always be treated.

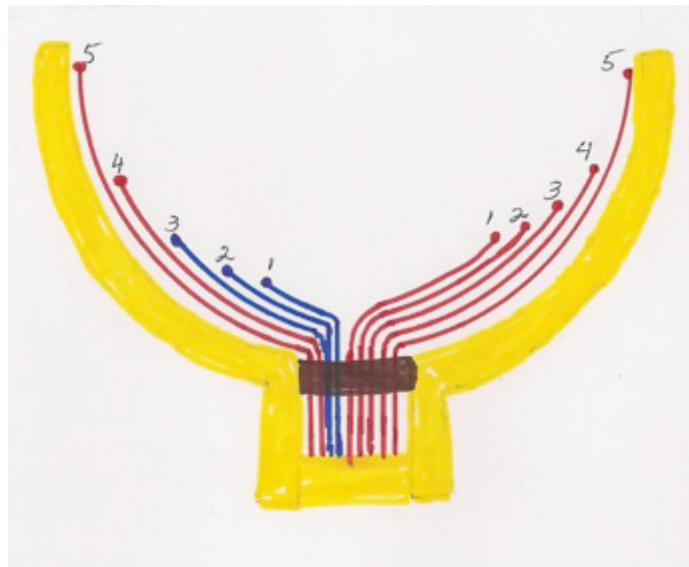
### Why is the sinking LC resulting in the orderly loss of nerve fibers?

Before we discuss the orderly loss of NFs in glaucoma, it is imperative to study the arrangement of NFs in the retina and ONH. First, the one million or so nerve fibers in the retina are arranged in layers superficial to deep. Second, the most central vision fibers originate closest to the disc, lie most superficial (closest to vitreous) and exit from the most central part of the disc. In contrast, the most peripheral nerve fibers originate from the most distant retina or farthest from the optic disc, lie deepest (closest to sclera) and exit closest to the edge of the scleral opening.

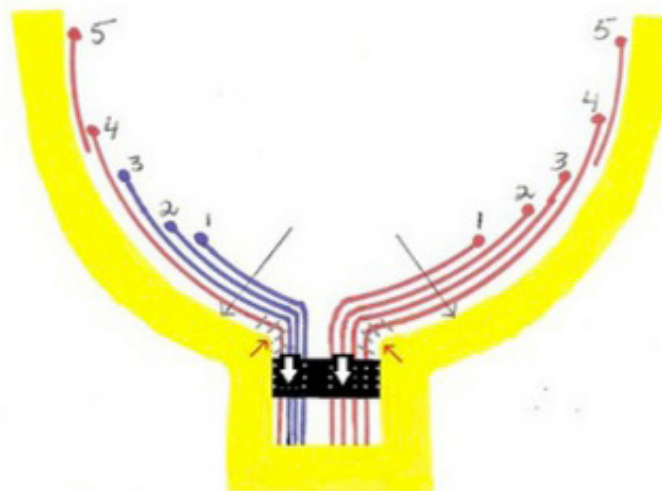
Third, the NFs originating from the nasal retina proceed directly to the nasal part of the optic disc. However, the situation is different in the temporal retina because of the presence of the macular fibers. The NFs originating from the nasal aspect of the macular area proceed directly to the temporal part of the disc. The fibers originating from the temporal macular and temporal retina arch above and below the macular fibers to reach the superior and inferior poles of the optic disc respectively. They are hence known as the arcuate fibers (Figure 2).

Returning to the question of orderly loss of NFs in glaucoma: as the LC sinks, the peripheral NFs being closest to the scleral edge are stretched and broken first (Figure 3). As a result, the next in line fiber will move towards the scleral edge and get severed.

The peripheral fibers are destroyed first but as the disease progresses to the paracentral region (10 to 20 degrees) there is occurrence of isolated scotomas in the paracentral area. The isolated scotomas become enlarged and ultimately coalesce to form superior and inferior arcuate scotomas - together known as the ring scotoma.



**Figure 2:** Arrangement of nerve fibers in the retina and optic disc. The most peripheral fiber (5) originates farthest from the disc, lies closest to the sclera and exit closest to the scleral edge. The most central fiber (1) originates closest to the disc, lies closest to vitreous and exits from the most central part of scleral opening



**Figure 3:** Relationship between ciliary pressure and IOP. Normally, ciliary circulatory pressure supplying the border tissue should be higher than IOP for healthy perfusion as in column (1). In column (2), the IOP is increased to 30 whereas the ciliary pressure remains the same at 25, this will result in HTG. In column (3), the ciliary pressure is decreased to 15mm but the IOP is same, normal at 20, resulting in NTG

The severance of NFs leads to further LC sinking due to loss of anchorage provided by the NFs as roots anchor a tree. The cascade of severance of NFs and sinking of LC would become self-propagated and continue until all the NFs have moved in an orderly tandem fashion to the scleral edge and become severed. This may explain the unstoppable nature of glaucoma despite maximum lowering of IOP. The severed segments undergo phagocytosis, thus creating excavation (empty spaces) that we are interpreting as cupping of the ONH. The sinking of the LC and severance of nerve fibers can explain the orderly loss NFs in glaucoma as revealed in glaucomatous visual field.

Why do scotomas appear early in the paracentral area? Although the 360 degrees of NFs are being severed simultaneously, the arcuate fibers lying in the paracentral area being fewer in number compared to the rest of NFs, are depleted earlier. Also, because of the characteristic arcuate shape arrangement, their loss results in easily recognizable arcuate scotomas. After the peripheral and paracentral visual field (VF) is lost, the remaining 10 degrees of central VF is retained for longer periods due to abundance of macular fibers even though they are also being destroyed from day one.

### Do we have evidence of sinking ONH/LC?

It has been well documented that LC starts migrating posteriorly from the early stages of glaucoma [2,3]. There is

no histology available supporting posterior bowing of the LC in glaucoma. Sloping and kinking of the blood vessels observed on the surface of the glaucomatous disc indicate that the blood vessels are sloping in pursuit of sinking LC.

### **Do we have evidence of severance of NFs?**

The notching at the poles of the ONH is due to severance and depletion of the arcuate fibers at the point of their entry. The progressive thinning of the RNFL and empty arcuate spaces in the retina are due to depletion of NFs after being severed. All the temporal fibers (macular, superior and inferior arcuate) are being severed simultaneously.

However, the arcuate fibers being fewer in number are depleted earlier resulting in the sharply defined arcuate scotoma. Progressive thinning of the RNFL is the salient feature of glaucoma. Atrophy of the NFs will not result in progressive thinning of the RNFL. We do not observe progressive thinning of the RNFL in cases of optic atrophy due to multiple sclerosis in which the NFs are truly being atrophied. The 'floor effect' when OCT cannot measure any further thinning of RNFL in glaucoma subjects is due to the fact that the entire RNFL has been severed and depleted so none is left for further thinning. The end-stage glaucomatous disc is not 100% cupped LC but an empty crater left over after the severance and phagocytosis of NFs [4]. The splinter hemorrhages on the margin of ONH are due to severance of vasculature, meeting the same fate as NFs.

### **Conclusion**

Based on the orderly loss of NFs in glaucoma, the prevalent glaucoma theories such as direct role of IOP on NFs, neurodegeneration and others become invalid since none of them can explain the orderly loss of NFs - despite the raised IOP being the established cause of glaucoma. Therefore, it is hypothesized that glaucoma is a two-stage disease: First, a biological stage in which there is degeneration of the BT resulting from chronic ischemia due to raised IOP. Second, the degeneration of the BT results in sinking of the LC which results in stretching and breakage of NFs starting with the most peripheral and ending with most central NFs in an orderly tandem fashion. The histology of end-stage glaucomatous disc reveals an empty crater reinforcing that severance of NFs and vasculature has occurred. Glaucoma may not be an optic neuropathy, but an axotomy [5-8].

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