

# Pathogenesis of Arcuate Field Defect in Glaucoma

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The arcuate field defects, produced due to selective destruction of the arcuate fibers, are a pathognomonic feature of both high-tension (HTG) and normal-tension glaucoma (NTG). The statistically normal range of intraocular pressure is 10 to 21mmHg. Although these arcuate field defects were discovered more than 100 years ago by Bjerrum and Ronnie, we still have not come to a consensus as to why they are produced. There are several theories ranging from: the undue sensitivity of the arcuate fibers to raise intraocular pressure (IOP) and to their increased vulnerability due to larger size holes in the region of arcuate fibers in the lamina cribrosa,<sup>(1)</sup> but none of these theories satisfactorily explain the selective destruction of arcuate fibers in the early stages of glaucoma, especially in NTG. This article focuses on this controversial subject as this may be the crucial key to finding the true pathogenesis of glaucoma.

Being cognizant of all possible factors, it is hypothesized that the optic disc may be sinking in the scleral canal in chronic glaucoma. As a result of sinking of the disc, the pre-laminar nerve fibers are stretched and ultimately severed against the scleral edge, starting with the most peripheral fibers and ending with the most central in a sequential and orderly fashion. Due to inherent temporal tilt of the optic disc, the entire group of temporal fibers (macular, superior and inferior arcuate) are being stretched and severed. However, the superior and inferior arcuate fibers being fewer in number compared to the macular fibers will be depleted earlier resulting in sharply defined arcuate field defects/ring scotoma. Therefore severance, not atrophy of the nerve fibers, is involved in the production of the arcuate field defects.

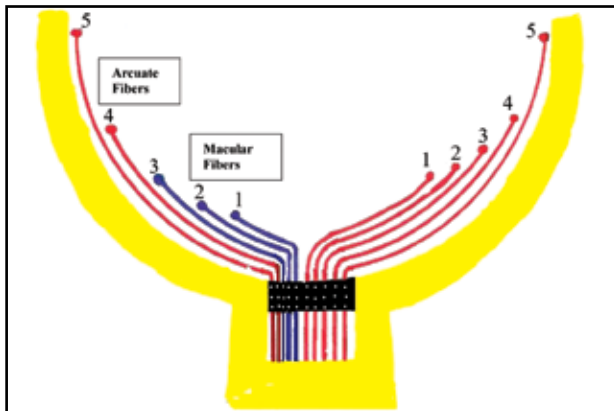
## Introduction

Before we enter on the subject, it is imperative to mention the arrangement of the nerve fibers in the retina and optic disc and the sequence in which the nerve fibers are being destroyed in chronic glaucoma. There are about one million nerve fibers originating from the retinal ganglion cells (RGC) which leave the eye ball through meshwork of the lamina cribrosa and form the optic disc.

There are four main aspects in which the nerve fibers are arranged in the retina and in the optic disc. First, the 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 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 (**Figure 1**). Third, the nerve

fibers 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 fibers originating from the nasal aspect of macular area proceed directly to the central temporal part of the disc. The fibers originating from the temporal macular and peripheral retina have to arch above and below the macular fibers to reach the superior and inferior poles of the optic disc respectively and hence are known as arcuate fibers (**Figure 2**). Fourth, the nerve fibers of the superior and inferior hemifield are separated by horizontal meridian and they do not cross over to the opposite hemifield.

Regarding the sequence in which the nerve fibers are being destroyed in glaucoma, usually the most peripheral temporal fibers, due to inherent temporal tilt of the disc, are destroyed first, resulting in the loss of most peripheral nasal field. However, the very early nasal field loss has little diagnostic value because of large normal variation in the extent of peripheral fields. Moreover, there are hardly



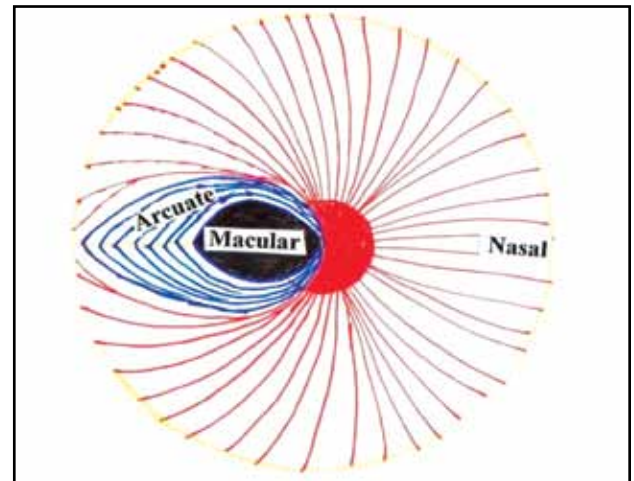
**Figure 1: Normal Disc: Arrangement of nerve fibers in retina and optic disc. The most peripheral fibers (5) originate farthest from the optic disc, lie deep, closest to the sclera and exit closest to the scleral edge. Whereas, the most central fibers (1) originate closest to the disc, lie superficial, closest to the vitreous and exit from most central part of the disc.**

any noticeable glaucomatous changes occurring in the optic disc at this early stage. However, when the nasal field loss extends inward and produces a horizontal nasal step, then this feature becomes diagnostic of glaucoma. This initial stage is followed by production of isolated scotomas in the 10 to 20 degrees of the paracentral region which coalesce to form superior and inferior arcuate field defects. Both arcuate field defects combined together are called ring scotoma.

At this stage we begin to notice changes in the optic disc like sloping/kinking of blood vessels at the disc margin and also notching at the site of entry of the arcuate fibers in the upper and lower poles of the disc. When double arcuate field defects are produced, the subjects develop tunnel vision because of retention of central vision fibers which last until the end-stage of glaucoma. Therefore, based on glaucomatous visual field defects, the nerve fibers, invariably, are being destroyed in a specific sequence and orderly fashion, yet never haphazardly in glaucoma. This important feature of orderly destruction of the nerve fibers will be the focus of my presentation in finding the pathogenesis of arcuate field defects in glaucoma.

## Discussion

Reviewing literature, the subject of pathogenesis of glaucomatous field loss appears quite controversial. There are two main theories: mechanical and vascular, which were put forward 150 years ago, the time chronic glaucoma was given a separate entity. According to mechanical theory, the raised IOP directly compresses



**Figure 2: Arrangement of nerve fibers in the retina and optic disc. The arcuate fibers, arch above and below the macular fibers, are selectively destroyed in the early stages of glaucoma.**

the nerve fibers or causes posterior bowing of the lamina cribrosa resulting in distortion of the lamellar holes.<sup>(1)</sup> This in turn causes interruption of the axoplasmic flow resulting in the death of RGCs.

The second school of thought, vascular theory, suggests that the raised IOP directly compresses the blood vessels resulting in ischemia and thus death of the nerve fibers. Some believe that both mechanical and ischemic events are occurring in glaucoma.

Duke-Elder,<sup>(2)</sup> Henkind,<sup>(3)</sup> Harrington,<sup>(4)</sup> and Hayreh,<sup>(5)</sup> were proponents of the vascular theory. Henkind suggested the occlusion of radial peripapillary capillaries as the cause of selective destruction of the arcuate fibers. It has also been suggested that glaucoma is due to varying degree of sensitivity of the nerve fibers to IOP: the ocular hypertension cases would be those in whom the nerve fibers are the most resistant whereas normal-tension glaucoma subjects will have the nerve fibers least resistant to IOP. Neurodegeneration is also being implicated in glaucoma akin to Alzheimer's or Parkinson's disease.

There was very comprehensive discussion on "Pathogenesis of Visual Field in Glaucoma" by Edward Maumenee, published in *Controversy in Ophthalmology*.<sup>(6)</sup> Maumenee had challenged the direct role of both mechanical and vascular theory for the production of the glaucomatous field defects. Maumenee argued against the vascular theory because of normal electroretinogram and fluorescein angiography in glaucoma, which he expected to be abnormal if

vascular theory was valid. Maumenee remarked that both mechanical and vascular theories were not convincing and concluded “the exact cause of loss of visual field in glaucoma is not known at present time”. This well-reasoned conclusion was stated almost 30 years ago, and it still holds true today.

By deductive reasoning, we have raised and dismissed not only the mechanical and vascular theories, but also any pathology acting directly on the nerves or their RGCs, on the ground of the orderly destruction of nerve fibers in glaucoma.

#### ***Can the Peripheral Nerve Fibers be Destroyed First, if Cupping of the Optic Disc is Occurring?***

The term ‘cupping’, given by Heinrich Muller in 1856,<sup>(2)</sup> implies that the pathology starts from the central part of the disc and extends peripherally. According to the distribution of nerve fibers in retina, the fibers for the central vision originate closer to the optic disc, lie superficial (closer to the vitreous) and exit from the central part of the disc. Therefore, if cupping was truly occurring then the central vision fibers should have been destroyed first and peripheral fibers at the last, but in actuality, the opposite is occurring in glaucoma. Moreover, if cupping was taking place, there should have been immediate blindness due to loss of central vision. Therefore, keeping in view the distribution of the nerve fibers of the retina/optic disc and the glaucomatous field defects, the cupping theory appears to be invalid and mistakenly given 150 years ago.

#### ***Can the Nerve Fibers be Destroyed in an Orderly Fashion due to Direct Role of Raised IOP?***

It has been postulated over 150 years ago that retinal nerve fibers are destroyed either due to direct effect or via ischemia induced by direct compression of the blood vessels by raised IOP. Arguments against the direct role of IOP: how is it possible that raised IOP will always destroy the peripheral and arcuate fibers first, among the million or so densely packed nerve fibers in the optic disc, and not the central fibers?

It is also hypothesized that raised IOP causes posterior bowing of the lamina cribrosa, resulting in distortion of its holes, resulting in interruption of the axoplasmic flow and thus death of the RGCs.<sup>(1)</sup> Arguments against the posterior bowing of the lamina believe that if this is occurring, then the central vision fibers, because of their central location, should be more likely affected, not the peripheral fibers.

Moreover, if the bowing of the lamina was occurring due to high IOP then how can we explain the bowing of the lamina occurring in the case of NTG where the IOP is within normal range. It appears unlikely that any pathology occurring within the holes of the lamina cribrosa can be as precise as to result in an orderly destruction of nerve fibers. In view of the above rationale, it appears unconvincing that raised IOP acting directly can cause selective destruction of arcuate fibers in glaucoma.

#### ***Can the Arcuate Fibers be Selectively Destroyed if Glaucoma is a Neurodegenerative Disease?***

Glaucoma is implicated as a neurodegenerative disease akin to Parkinson’s disease, Alzheimer’s or ALS. Arguments against glaucoma being a neurodegenerative disease will also be based on the orderly destruction of nerve fibers occurring in glaucoma.

How is it possible that the neurodegeneration, in glaucoma, will always start with those RGCs which serve the peripheral vision and not occur randomly? The random degeneration of the neurons is a characteristic feature of a neurodegenerative disease, therefore the course of a neurodegenerative disease varies in each individual. In view of above facts, if glaucoma is a neurodegenerative disease then we should neither be having orderly destruction of the nerve fibers nor the selective destruction of arcuate fibers in the initial stages of glaucoma.

Other theories for the production of the arcuate field defects include occlusion of radial peripapillary capillaries<sup>(3)</sup> because of their arcuate shaped blood vessels distribution. Arguments against this will question: how can the occlusion of the retinal blood vessels be so precise as to result in an orderly destruction of nerve fibers in glaucoma? It is also being hypothesized that glaucoma may be due to varying degree of the sensitivity of the nerve fibers to IOP. This theory appears unlikely on the ground that if someone is born with unduly sensitive nerves to IOP, then that subject should develop glaucoma in early childhood and not usually after age 50 or more. Secondly, it would be difficult to convince us that undue sensitivity of the nerve fibers to IOP, though variable, would still result in an orderly destruction of nerve fibers in glaucoma.

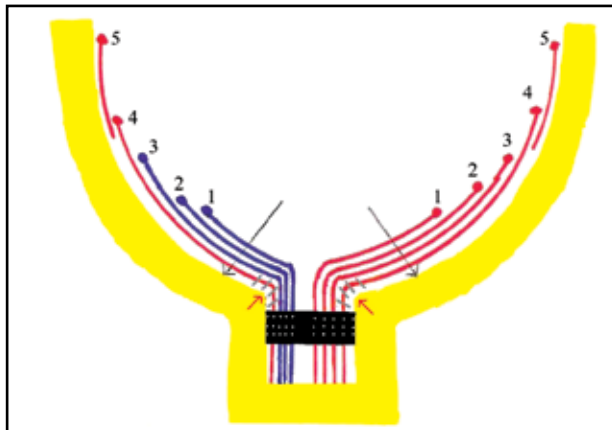
In summary, it appears unlikely that any pathology acting directly on the nerve fibers or their RGCs will result in an orderly destruction of the nerve fibers in glaucoma. If the nerve fibers are being destroyed in an orderly fashion, then we should expect the mechanism causing their destruction to be orderly as well.

***Then, Why are the Nerve Fibers Being Destroyed in an Orderly Fashion?***

In order to answer this question, we will have to change the current ‘cupping disc’ paradigm with ‘sinking disc’ paradigm. I hypothesize that the optic disc may be sinking,<sup>(7,8)</sup> not cupping in glaucoma.

**Paradigm Shift**

Due to sinking of the disc, the prelaminar nerve fibers, prior to their entry in the lamina cribrosa, are being stretched as one end is attached to the RGC and the other end anchored in the sinking optic disc and ultimately severed against the scleral edge. Since the peripheral nerve fibers lie deeper and exit closer to the scleral edge, the peripheral fibers would be the first to be affected and severed. As the peripheral fibers are being severed, the central fibers will move towards the periphery to occupy the vacant space (**Figure 3**). This movement of the central fibers to the periphery will break or enlarge the physiological cup which may be mistaken as true cup enlargement, known as cupping.

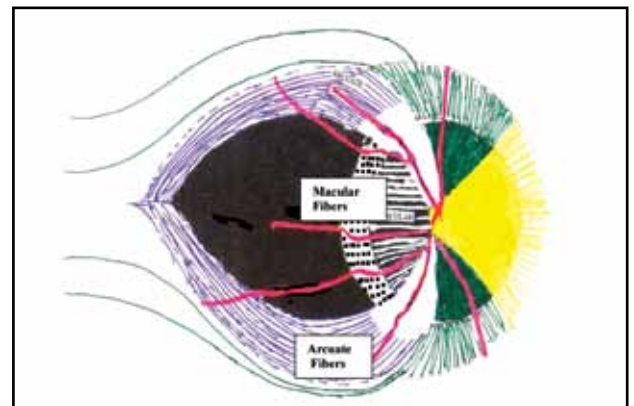


**Figure 3:** Due to sinking of the disc, the most peripheral and deepest prelaminar fibers (5) are stretched and severed against the scleral edge (red arrows) first, and ending with the most central fibers (1). Thus, the central fibers move to be periphery (black arrows) resulting in enlargement of the original cup, known as cupping.

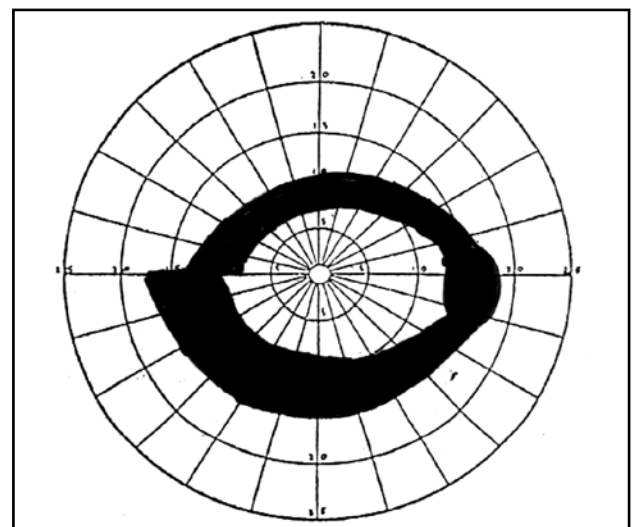
***Returning to Our Main Question: Why are the Arcuate Fibers Being Selectively Destroyed in Glaucoma?***

Due to inherent temporal tilt of the optic disc, the entire group of temporal fibers (macular, superior and inferior arcuate) are being stretched and severed (**Figure 4**). However, the superior and inferior arcuate fibers being fewer in number compared to the macular fibers will be depleted earlier, resulting in arcuate field defects/ring scotoma (**Figure 5**). During this process

of sporadic depletion, there would initially be isolated scotomas in the paracentral area, but as glaucoma progresses and all the arcuate nerve fibers are severed and depleted, these isolated scotomas will coalesce to form complete arcuate field defects. Thus the sinking of the disc and severing of the nerve fibers may explain the selective destruction of the arcuate fibers in glaucoma. Therefore, the severance, not atrophy, of the nerve fibers appears to be involved in the production of the arcuate field defects. Sinking of the disc will become self-propagated due to severance of nerve fibers, which also provide anchorage to the optic disc as roots do to a tree. Sinking of the disc will continue until all the nerve fibers are severed in an orderly sequence from the peripheral to central fibers.



**Figure 4:** Due to temporal sinking, all of the temporal fibers (macular, superior and inferior arcuate) are being stretched and severed. However, the arcuate fibers being fewer in number, compared to macular fibers will be depleted earlier, resulting in arcuate field defects as shown in figure 5.



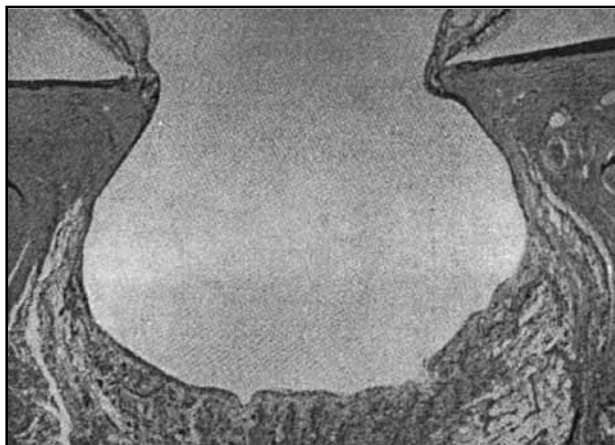
**Figure 5:** Right eye: Double arcuate/ ring scotoma produced after severance and depletion of the arcuate fibers. Due to macular fibers being abundant, the central vision is retained until the end. This may explain the selective destruction of the arcuate fibers in the early stages of glaucoma.

**Since I have Proposed that Severing be the Cause of Selective Destruction of Arcuate Fibers: Do We have any Evidence for Severing?**

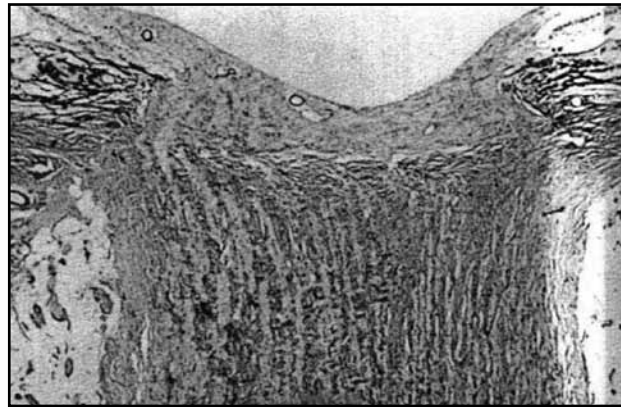
Although we may never witness the actual process of severing of the nerve fibers, we may infer this fact by deductive reasoning of the changes occurring in a glaucomatous disc. The continuous severing of the nerve fibers is supported by the phenomenon of progressive thinning of the RNFL as observed on optical coherence tomography (OCT). Moreover, the end-stage histology of glaucomatous disc resembles an empty bean-pot. Interestingly, the bean-pot appears quite huge compared to the size of original disc. Is this large bean-pot really a deeply cupped disc (lamina)? Is the lamina so inflatable that it has ballooned into a large bean-pot? If not, where did the lamina and nerve fibers go?

In order to answer the aforementioned questions, we may resort to the histology of the glaucomatous disc and non-glaucomatous atrophic disc such as due to multiple sclerosis. The histology of end-stage glaucomatous disc reveals a large crater (bean-pot), with an entrance appearing to be the scleral opening and its body formed of dura mater, not lamina cribrosa (Figure 6). In contrast, the histology of a flat atrophic disc reveals shrunken and collapsed nerve fibers, not an empty bean-pot as in glaucomatous disc (Figure 7). Moreover, the non-glaucomatous atrophic disc is pale and flat, there is neither sloping/kinking of the blood vessels at the disc margin nor excavation of the disc occurring.

Question arises: **Why doesn't excavation occur in a flat atrophic disc?** The answer may be that the flat atrophic discs are not sinking in the scleral canal,



**Figure 6. End-stage glaucomatous disc. Not a deeply cupped disc but a large crater left over after the severance and disappearance of all of nerve fibers. (Copy: Kolker AE, Hetherington Jr J. Becker-Shaffer's diagnosis and therapy of the glaucoma, Mosby, 1976, p 146).**



**Figure 7: Flat disc atrophy due to multiple sclerosis. Note the nerve fibers though shrunken are still present, in contrast to total disappearance of nerve fibers in glaucomatous disc in figure 6. There is no excavation since no sinking and thus no severance of nerve fibers is occurring in flat disc atrophy. (Copy from Yanoff, Ocular Pathology: Harper & Row 1975).**

therefore no severing of the nerve fibers and thus no excavation of disc occurring. In flat atrophic disc, though the nerve fibers are shrunken, but are still present, whereas in glaucomatous disc the nerve fibers have totally disappeared. Therefore, the flat atrophic disc and glaucomatous disc are distinctly different. End-stage glaucomatous disc cannot be a deeply cupped disc, but is a left over empty crater after the severance of all of the nerve fibers and the freed lamina may be lying at the bottom. In conclusion, the end-stage glaucomatous disc resembling an empty crater can only be explained by severance, not due to atrophy of the nerve fibers.

**If the Severance of the Nerve Fibers is due to Sinking Disc: Do We Have Any Evidence of Sinking Disc?**

I believe we do. First, the photographs of the glaucomatous optic discs vividly reveal sloping and kinking of the blood vessels at the disc margin prior to any change in the contour of the physiological cup. This suggests that the optic disc may be sinking, not cupping in glaucoma. The physiological cup may not be truly enlarging, but instead, excavating due to severance of the nerve fibers. Second, the new enhanced imaging technique of the optic disc (EDI-SD-OCT) has enabled us to visualize the deeper structures in the scleral canal well beyond the entire width of the lamina cribrosa which was previously not possible with standard SD-OCT. Therefore, EDI technique has opened a new chapter and is providing us very valuable information of the glaucomatous disc. EDI of the glaucomatous optic disc, *in vivo*, has shown the posterior migration of the lamina cribrosa as far back as pia mater or in other words total sliding outward of the lamina from the scleral opening, from the very early stages of glaucoma.<sup>(9-12)</sup> This is very

significant discovery as it suggests that lamina (optic disc) is detachable from the scleral wall and is able to slide posteriorly (sink) in the scleral canal. EDI findings support the phenomenon of sinking, not cupping of the disc. If true, then chronic glaucoma may be a mechanical problem, in fact, a herniation of the disc.

### ***Why is the Optic Disc Sinking Both in HTG and NTG?***

I hypothesize that the collagenous border tissue of Elschnig lying between the lamina cribrosa and the scleral edge may be the primary site of pathology, not the lamina cribrosa itself. Border tissue acts like a 'O' ring seal which keeps the optic disc firmly in the scleral opening. If the border tissue atrophies, the optic disc will start sinking in the scleral canal. Why will the border tissue atrophy in both HTG and NTG? It is a complex and multifactorial subject.

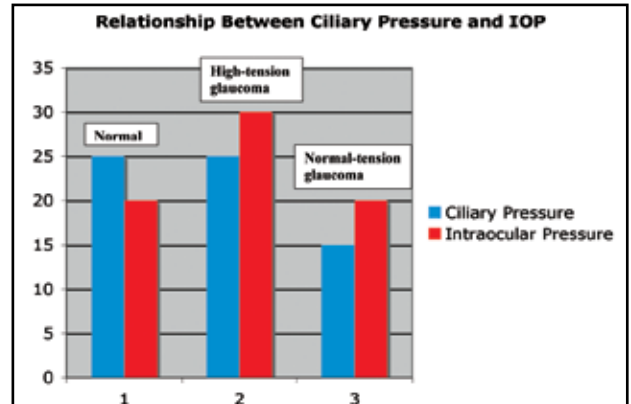
First, the interaction between the circulation of the border tissue and IOP. Second, the structural integrity of the border tissue itself, inherent or acquired. The border tissue is supplied exclusively by the short posterior ciliary arteries (ciliary circulation), a weaker circulation compared to the central retinal artery, which unfortunately, does not participate in its blood supply.<sup>(13)</sup>

Normally the ciliary pressure of the border tissue should be higher than the IOP for its good perfusion and healthy maintenance. However, if either the IOP becomes higher than the ciliary pressure due to an ocular disease or if due to some systemic circulatory problems like chronic hypotension, the ciliary pressure becomes lower than IOP, then the IOP will take the upper hand and will compress the circulation of the border tissue, resulting in chronic ischemia and its atrophy. In latter scenario, if the ciliary pressure becomes lower than any normal range IOP level then that normal range IOP level will act as a higher IOP for that subject, thus NTG will result (**Figure 8**). Therefore it is still the IOP, whether within or above the statistically normal range, which appears to be the culprit in both HTG and NTG. Moreover, it is not only the IOP important, but also the oxygen carrying capacity of the blood which may also cause chronic hypoxia and atrophy of the border tissue. This may explain the higher incidence of NTG in cases of long term smokers and those with sleep apnea. Therefore, the normal tension glaucoma may be a systemic disease.

In addition to circulation we may have to consider the structural integrity of the border tissue. Keeping all these factors in view, the pathogenesis of atrophy of the border tissue becomes multifactorial for which further research is warranted.

## Conclusion

The sinking of the disc and severing of the nerve fibers explains the selective destruction of the arcuate fibers in the early stages of glaucoma. Moreover, the sinking of the disc explains the orderly destruction of the nerve fibers, starting with the peripheral and ending with the central fibers. Glaucoma may not be an optic disc neuropathy but an optic disc axotomy.



**Figure 8:** Interaction between ciliary pressure and IOP. Normally the ciliary pressure supplying the border tissue should be higher than IOP for good perfusion as in column (1). In column (2) the IOP is increased to 30 whereas the ciliary pressure remains the same at 25, resulting in high-tension glaucoma. In column (3) the ciliary pressure is decreased to 15 but the IOP remains the same, normal at 20, resulting in normal-tension glaucoma.

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