Eyes with normal-pressure glaucoma and those with high-pressure glaucoma can show a similar optic nerve head appearance, while eyes with vascular optic neuropathies show a markedly different optic disc appearance. Factors in addition to intraocular pressure (IOP) may thus play a role in the pathogenesis of glaucomatous optic neuropathy. Clinical and experimental studies showed that (1) physiologic associations between cerebrospinal fluid (CSF) pressure, systemic arterial blood pressure, IOP and body mass index exist; (2) a low CSF pressure was associated with the development of glaucomatous optic nerve damage in cats; (3) patients with normal (intraocular) pressure glaucoma had significantly lower CSF pressure and a higher trans lamina cribrosa pressure difference when compared to normal subjects; and (4) patients with normal-pressure glaucoma as compared with patients with high-pressure glaucoma have a significantly narrower orbital CSF space. A shallow orbital CSF space has been shown to be associated with a low CSF pressure. Due to anatomic reasons, the orbital CSF pressure and the optic nerve tissue pressure (and not the atmospheric pressure) form the retro-laminar counter-pressure against the IOP and are thus part of the trans-lamina cribrosa pressure difference and gradient. Assuming that an elevated trans-lamina cribrosa pressure difference and a steeper trans-lamina cribrosa pressure gradient are important for glaucomatous optic nerve damage, a low orbital CSF pressure would therefore play a role in the pathogenesis of normal-(intraocular) pressure glaucoma. Due to the association between CSF pressure and blood pressure, a low blood pressure could be indirectly involved.

Keywords: Cerebrospinal Fluid Pressure; Intraocular Pressure; Trans Lamina Cribrosa Pressure Gradient; Transcorneal Pressure Gradient; Glaucoma; Glaucomatous Optic Neuropathy; Normal-Pressure Glaucoma

In view of the observation that patients with glaucoma can markedly differ in the level of intraocular pressure (IOP), the pathogenesis of glaucomatous optic neuropathy has not yet been completely established. One may therefore consider factors in addition to IOP which may play a role in the pathogenesis of glaucomatous optic nerve damage.

Despite pronounced variability in optic disc size between individuals, studies have revealed that in non-highly myopic eyes, neither susceptibility to glaucomatous optic neuropathy nor the risk of glaucoma progression is associated with optic disc size. In highly myopic eyes, glaucoma susceptibility is increased as evidenced by a higher prevalence
of glaucomatous optic neuropathy in highly myopic subjects as compared to non-highly myopic counterparts. The reason for this greater susceptibility in highly myopic macrodiscs may be stretching and secondary thinning of the lamina cribrosa (LC) and marked thinning of the peripapillary sclera in these eyes. Thinning of the LC decreases the distance between the intracoical compartment with the so-called IOP on one side, and the retrobulbar, or better said retro-LC, compartment including the optic nerve and the cerebrospinal fluid (CSF) space. If the distance between these two compartments is decreased, trans-LC pressure gradient gets steeper at any given IOP and CSF pressure. In addition, changes in biomechanical properties of the LC tissue may occur due to myopia induced stretching of the LC based on recent research on the biomechanics of the optic nerve head. Thinning of the peripapillary sclera may be an additional biomechanical factor which may lead to increased glaucoma susceptibility by increasing tension on the LC beams.

In contrast to glaucoma, none of the vascular optic neuropathies (except for arteritic anterior ischemic optic neuropathy) show a loss of neuroretinal rim, which maintains its physiological shape despite loss of retinal ganglion cell axons. Similar findings were reported in monkeys after experimental central retinal artery occlusion. The discrepancy in the loss of neuroretinal rim in all types of glaucoma including normal-pressure glaucoma in contrast to rim preservation with vascular optic neuropathies, the normal color of the remaining rim in glaucoma in contrast to the pale color of the existing rim in eyes with a vascular optic nerve damage, the finding that loss of neuroretinal rim in normal-pressure glaucoma is related to the height of the IOP, the finding that the location of the deepest part of the optic cup in normal-pressure glaucoma spatially correlates with the location of the most marked perimetric loss, and the finding that IOP reduction is therapeutically helpful in normal-pressure glaucoma, may point against a primarily vascular pathogenesis in normal-pressure glaucoma.

Beta zone parapapillary atrophy can be found in all types of chronic open-angle glaucomas including normal-pressure glaucoma. In contrast, none of the vascular optic neuropathies, including arteritic anterior ischemic optic neuropathy show beta zone enlargement or an increased frequency of the beta zone.

Hospital-based studies have shown that eyes with normal-pressure glaucoma have significantly more disc hemorrhages than eyes with high-pressure glaucoma. They have also revealed that the size of the hemorrhage is larger in eyes with normal-pressure glaucoma than those with high-pressure glaucoma. It has been discussed that such a difference in the frequency of detected disc hemorrhages between high-pressure and normal-pressure glaucoma is due to the difference in IOP between them. Assuming that the size of the leaking part in the vessel wall is similar in both glaucoma groups, the amount of blood leaking into adjacent tissues depends on the transmural pressure difference. The latter is the difference between blood pressure inside the vessel and pressure in the surrounding space, i.e. IOP. Taking into account the lower IOP in normal-pressure glaucoma, the difference in IOP between these two types of glaucoma groups may be enough reason for the larger rate of disc hemorrhages which take a longer time to become absorbed and thus have a higher chance to be detected by ophthalmoscopy.

Thinning of the retinal arteries (arterioles) in a both diffuse and localized manner has been described in eyes with glaucoma; the amount and location of this reduction correlate with the amount and location of glaucomatous optic nerve damage. Retinal arteriolar caliber reduction has been found in normal-pressure as well as high-pressure glaucoma. However, since localized or generalized thinning of the retinal arterioles can be observed with any type of optic nerve damage, such a reduction is not pathognomonic for glaucoma in general nor for normal-pressure glaucoma in particular. Arterial caliber reduction may be a secondary phenomenon due to loss of retinal tissue and consequently reduced demand for blood supply.

Morphological analysis of the optic nerve for
differences between subgroups of chronic open-angle glaucoma may lead to various phenotypes including the highly myopic type of (primary) open-glaucoma, and the age-related atrophic type of open-angle glaucoma. Juvenile high-pressure glaucoma is characterized by the relatively young age of the patients (usually less than 40 years at the time of initial diagnosis), with steep and deep cupping, relatively small parapapillary atrophy (beta zone) and apparently diffuse loss of retinal nerve fiber layers. With a closer look, however, there are multiple small localized retinal nerve fiber layer defects which can mimic diffuse loss. The so called focal type of normal-pressure glaucoma may be typically found more commonly in female subjects at an age of about 45 to 65 years; these patients tend to have low arterial blood pressure and report vasospastic symptoms. The optic disc can show relatively deep and steep cupping, rim notches, disc hemorrhages, marked localized retinal nerve fiber layer defects and parapapillary atrophy. The location of the deepest part of the optic cup in normal-pressure glaucoma spatially correlated with the location of the most marked perimetric loss. In selected examples, there was a strikingly similar appearance in the optic nerve head between eyes with open-angle glaucoma and high IOP, and those with normal IOP. Correspondingly, monkey experiments performed by Hayreh have shown that monkeys with experimental high-pressure glaucoma develop localized retinal nerve fiber layer defects, what formerly was believed to be typical for normal-pressure glaucoma.

The question arose: why despite marked differences in IOP between eyes with high-pressure versus normal-pressure glaucoma, both subtypes sometimes have strikingly similar optic nerve head appearance, and how can one explain marked differences in the optic nerve head appearance between eyes with normal-pressure glaucoma and those with any (other) vascular optic neuropathy, if normal-pressure glaucoma was supposed to have a (partially) vascular pathogenesis. It was suggested that one may consider looking beyond the LC. The bottom of the optic cup on the inner surface of the optic nerve head is formed by the LC. On its outer surface, the LC faces the anterior region of the optic nerve. Main functions of the LC are to allow retinal ganglion cell axons and the central retinal vein to leave the eye; to let the central retinal artery enter the intraocular space; and to stabilize IOP by forming a barrier between the intraocular and extraocular spaces. Due to its barrier function, the LC prevents major leakage of aqueous humor from the intravitreal space into the retrobulbar CSF space surrounding the retrobulbar part of the optic nerve. Since the LC forms the border between the intraocular space with a higher pressure and the retrobulbar space with a lower pressure, a pressure gradient exists across the LC which is IOP minus CSF pressure in the retrobulbar space. This trans-LC pressure gradient is of great importance for ocular diseases in which pressure on one or both sides of the LC is abnormally high or low. An abnormal pressure gradient influences the physiology of optic nerve fibers and their orthograde and retrograde axoplasmic flow. Also for glaucomatous optic nerve damage, one may discuss that not transcorneal pressure difference, which has usually been called “IOP”, but the trans-LC pressure difference and the trans LC pressure gradient may be important.

Trans-LC pressure gradient depends on two factors: first is the actual pressure difference on either side of the LC and second is the distance between fluid-filled intraocular and retrobulbar compartments. This inter-compartment distance markedly depends on LC thickness. Consequently, LC thinning in highly myopic eyes may be one of the reasons for their increased glaucoma susceptibility. More than 30 years ago, Volkov pointed out that low CSF pressure could pathogenetically be associated with glaucomatous optic neuropathy. The same idea had earlier been expressed by Szymansky and Wladyczko. In a similar manner, Yablonsky, Ritch and Pokorny observed marked
glaucomatous changes in normotensive eyes of cats in which intracranial pressure was reduced to 5 cm H2O below atmospheric pressure, while artificially hypotensive eyes did not show such changes. Consequently, Berdahl and colleagues found in a retrospective chart review that mean CSF pressure was significantly higher in nonglaucomatous patients than those with open-angle glaucoma, and that ocular hypertensive subjects had significantly higher CSF pressure. In a similar manner in a recent prospective study, lumbar CSF pressure was significantly lower in normal-IOP glaucoma group (9.5 ± 2.2 mm Hg) than a high-IOP glaucoma group (11.7 ± 2.7 mm Hg) and a control group (12.9 ± 1.9 mm Hg). Trans-LC pressure difference was significantly (P<0.001) higher both in the normal-IOP glaucoma group (6.6 ± 3.6 mmHg) and the high-IOP glaucoma group (12.5 ± 4.1 mmHg) as compared to the control group (1.4 ± 1.7 mmHg). In multivariate analysis, the amount of glaucomatous visual field loss was mainly associated with trans-LC pressure difference (P=0.005) while IOP and CSF pressure as single parameters were not significantly (P>0.50) associated with perimetric loss. In the control group, CSF pressure was significantly correlated with both systolic blood pressure (P=0.04) and IOP (P<0.001). Since IOP is physiologically associated with blood pressure, trans-LC pressure difference was not significantly (P=0.97) related with blood pressure. In a parallel study, CSF pressure was significantly higher in patients with normal (16.0 ± 2.5 mmHg) than in the control group (12.9 ± 1.9 mmHg). The correlation between all three pressure parameters, i.e., CSF pressure, blood pressure and IOP may suggest a systemic mechanism simultaneously influencing all three of them. It may explain why arterial hypertension, although associated with elevated IOP, was not associated with glaucoma in population-based studies. One may assume that the elevation in IOP is compensated by an increase in CSF pressure, such that trans-LC pressure difference remains unchanged. This assumption was supported by the study by Ren and colleagues, in which trans-LC pressure difference was not significantly (P=0.97) correlated with blood pressure. The correlation between CSF pressure and arterial blood pressure supports clinical observations that patients with normal-pressure glaucoma tend to have low blood pressure. This observation was the reason to postulate a vasogenic pathogenesis of normal-pressure glaucoma. However, if low blood pressure is associated with a low CSF pressure, a barotraumatic pathomechanism in normal-pressure glaucoma with elevated trans-LC pressure gradient may become quite likely. In a parallel manner, trans-LC pressure difference was not significantly associated with arterial blood pressure. If one considers trans-LC pressure difference being the driving force for optic nerve damage in glaucoma, the lack of association between trans-LC pressure difference and systemic arterial blood pressure may contradict the idea that vascular insufficiency at the optic nerve head plays a major primary role in the pathogenesis of glaucomatous optic nerve fiber loss.

In conclusion, a primary vasogenic pathogenesis for glaucomatous optic neuropathy may be contradicted by the morphology of the optic nerve head, since normal-pressure glaucoma eyes and those with high IOP glaucoma can show similar optic nerve head appearance. These features are not found in any (other) vascular optic neuropathy except for arteritic anterior ischemic optic neuropathy. Other factors, which may be taken into account are: (1) trans-LC pressure difference (instead of the transcorneal pressure difference, i.e. the so called “IOP”) is of importance for the physiology of the optic nerve head; (2) a physiologic association exists between arterial blood pressure, CSF pressure and IOP; and (3) patients with normal (intraocular) pressure glaucoma have significantly lower CSF pressure but higher trans-LC pressure difference when compared to normal subjects. One may, therefore, discuss that low CSF pressure may be associated with normal (intraocular) pressure glaucoma. Low systemic blood pressure, particularly at night, could physiologically be associated with low CSF pressure, leading to an abnormally high trans-LC pressure difference and as such to a similar situation as if CSF pressure is normal.
but IOP is elevated. This model could explain why patients with normal (intraocular) pressure glaucoma tend to have low systemic blood pressure, and why eyes with normal (intraocular) pressure glaucoma and eyes with high-pressure glaucoma, in contrast to eyes with a primarily vascular optic neuropathy, show profound similarities in optic nerve head appearance.

Conflicts of Interest
None.

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