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Cerebrospinal fluid pressure and glaucoma: regulation of trans-lamina cribrosa pressure

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ABSTRACT

Increased trans-lamina cribrosa pressure difference (TLCPD), the difference of intraocular pressure (IOP) and orbital cerebrospinal fluid pressure (CSF-P), has been investigated as a possible risk factor in glaucoma pathogenesis. In fact, lower CSF-P in the setting of normal IOP has been implicated as a potential risk factor for normal tension glaucoma. Increased TLCPD has been associated with decreased neuroretinal rim area and increased visual field defects. Furthermore, dysregulation of systemic blood pressure has been associated with changes in IOP. Recent studies have also suggested that increased body mass index (BMI) is associated with decreased prevalence of glaucoma, which may be due to an increased CSF-P with increased BMI found in many studies. Given the interaction of various pressures, their role in glaucoma pathophysiology has come under investigation and warrants further study in order to better understand the aetiology and progression of glaucoma.

INTRODUCTION

Glaucoma is a multifactorial disease resulting in progressive loss of retinal nerve ganglion cells, as evidenced by worsening visual fields and increased cup-to-disc ratios.¹ It is the second leading cause of blindness worldwide.² In fact, one study estimated that over 79.6 million people would have glaucoma worldwide by 2020, of whom 74% would develop open angle glaucoma (OAG).³ Additionally, the global disability adjusted life years, a measure of overall disease burden, of glaucoma has risen from 443 000 years in 1990 to 943 000 years in 2010.^{4,5} Despite its prevalence, the aetiology of glaucoma remains unclear. Various studies have documented the existence of elevated IOP in patients with and without glaucomatous damage, leading to division of patients into OAG and ocular hypertensive (OHT) groups, respectively. The existence of OHT has increased investigation of various pressures that may be implicated in glaucoma. This review will discuss the interactions of various pressures that may contribute to glaucoma: intraocular pressure (IOP), blood pressure (BP) and cerebrospinal fluid pressure (CSF-P). Special focus will be placed on the relationship between CSF-P and IOP and how these two forces contribute to glaucoma pathophysiology by creating a trans-lamina cribrosa pressure difference (TLCPD). A literature search of online databases PubMed and Medline was conducted using key term glaucoma along with cerebrospinal fluid pressure, intracranial pressure and trans-lamina cribrosa

pressure. References from articles were also considered to ensure completeness.

IOP, CSF-P AND TLCPD

The forces of IOP and CSF-P meet at the lamina cribrosa, a modified extension of the peripapillary scleral flange, composed of collagen and non-collagen components.⁶ The lamina cribrosa forms a barrier between the intraocular space and the retrobulbar space.⁷ It functions as a barrier between the posterior force of the IOP and the anterior force of the CSF-P within the orbit, also known as the TLCPD (TLCPD=IOP–CSF-P). Studies have shown that the retrolaminar tissue pressure is 4 mm Hg when CSF-P is 0 mm Hg.⁸ The ability of the lamina cribrosa to withstand the pressure gradient without deforming is dependent on its thickness, the rigidity of the extracellular matrix and the peripheral scleral tension. The lamina cribrosa's ability to maintain shape is important in protecting the structures that pass through it: the retinal ganglion cell axons, the central retinal artery (CRA) and the central retinal vein. Increased TLCPD could cause bowing of the lamina cribrosa. Such deformity may damage optic nerve ganglion cells via mechanical compression or ischaemia as the vessels pass through the lamina cribrosa.⁹

While the effect of position on pressures will be discussed in detail later, it is important to note that one study found average IOP in a healthy patient population to be 14.3 ± 2.6 mm Hg, while average CSF-P in the lateral decubitus position was found to be 12.9 ± 1.9 mm Hg.¹⁰ In a lateral decubitus position, assuming no obstruction to CSF flow, there will be a posterior force on the lamina cribrosa. TLCPD could increase further if an individual had increased IOP and/or decreased CSF-P. To this end, studies have addressed the relationship between CSF-P and glaucoma.

Yablonski and colleagues evaluated the TLCPD in cats by lowering the intracranial pressure (ICP) and by lowering IOP in only one eye.¹¹ After 3 weeks, histological examination of the optic nerve heads of eyes with unaltered IOP revealed prelaminar axonal swelling, optic disc cup enlargement and posterior displacement of the lamina cribrosa. When IOP was lowered with ICP, thus minimising alterations in TLCPD, no ocular changes were found.¹¹

LAMINA CRIBROSA STRUCTURE

Lamina cribrosa structure provides additional insight into mechanisms of glaucomatous damage.



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The lamina cribrosa allows retinal ganglion cell axons to exit the eye through 500–600 pores.⁶ These pores are of differing diameter and depth depending on location within the disc-like structure. The pores in the superior and inferior portions of the lamina cribrosa are larger and contain a greater number of nerve fibres.⁶ The optic nerve is nourished by capillaries within the lamina cribrosa, which is supplied by the short posterior ciliary arteries.¹² The superior and inferior portions are also where damage from glaucoma first occurs. Since less connective tissue exists between these pores to provide structural and nutritional support, the fibres may be more susceptible to mechanical or vascular changes from an increased pressure gradient.⁶

Recently, mathematical models have been developed to model the effect of lamina cribrosa deformation on CRA blood flow.⁹ It is hypothesised that posterior displacement of the lamina cribrosa deforms the CRA and consequently decreases blood flow. The CRA blood flow velocities were calculated with the mathematical models as a function of IOP. The latter affected lamina cribrosa displacement according to the elastic properties provided by the model. This model mirrors data previously obtained utilizing colour Doppler imaging (CDI) measurements of CRA peak systolic velocity as IOP was experimentally increased with suction ophthalmodynamometry.⁹ With further development of these models, a patient's risk for glaucoma progression based on various ocular measurements and vascular parameters can potentially be better evaluated.

Noteworthy in this discussion of TLCPD, however, is that CSF occupies a fluid-filled compartment that changes position within space and is subject to gravity. Therefore, the pressure exerted by CSF varies with position of the area in question relative to the vertical position of the whole compartment.¹³ In a sitting position, it was found that the CSF-containing lumbar subarachnoid space had a pressure of 0 mmHg at the level of the occiput of the skull, a height similar to the globe. Thus, the pressure around the optic nerve is likely less than that measured with lumbar puncture performed in a lateral decubitus position. An associated issue is that IOP has also been found to vary with posture.^{14–15} The IOP increases when moving from an upright to horizontal position. Furthermore, such an IOP increase is greater in those with glaucoma over normal controls.^{15–16} One study demonstrated a 2.9 mm Hg increase from a seated to supine position change in healthy controls and a 3.9 mm Hg change in those with glaucoma.⁵ The current explanation for IOP variation is that postural changes result in elevated episcleral venous pressure and choroidal congestion.^{17–18} In fact, an increase of episcleral venous pressure of 0.83 ± 0.21 mm Hg correlated with an increase of 1 mm Hg in IOP. Several studies found that vascular congestion increased in inverted positions, placing pressure on ocular tissues and elevating IOP. Moreover, diurnal IOP fluctuations may affect the TLCPD gradient.¹⁹ However, research suggests that aqueous production is not affected by posture.²⁰

Furthermore, recent investigations into CSF within the subarachnoid space surrounding the optic nerve suggest that there are variations in CSF flow surrounding the globe.^{21–24} The subarachnoid space encircling the optic nerve can be divided into three sections by the architecture of the trabeculae, septa and pillars that exist within the space.²¹ This divisive architecture could account for changes in CSF flow and even cause a 'compartment syndrome' in the subarachnoid space.²³ This could result in variation in CSF-P at the lamina cribrosa and thus possibly alter TLCPD gradient. Compartmentalisation or decrease in CSF flow away from the optic nerve could also lead to accumulation of toxic metabolites or decreased nutrients.

Compartmentalisation of CSF around the optic nerve is evidenced by high concentration of lipocalin-like prostaglandin D-synthase (L-PGDS) found near the optic nerve head. L-PGDS is neuroprotective of astrocytes, modulates inflammation and is apoptotic and may alter the optic nerve and disease progression. Its presence simply confirms that the subarachnoid space of the optic nerve might not have free communication intracranial subarachnoid space and thus TLCPD might be accordingly affected.²³

Early animal studies: IOP and CSF-P

Early studies by Morgan *et al* in dogs provided some of the initial data on the relationship between IOP and CSF-P as well as retinal perfusion. In dogs, Morgan *et al* looked at the effect of CSF-P on retrolaminar tissue pressure and TLCPD at low CSF-P, thought to mimic that of the erect position. This study found that TLCPD is dependent on CSF-P when that pressure is above 0.5 mm Hg.⁸ In a later study, Morgan *et al* looked at the role of CSF-P on glaucoma. This study found that CSF-P and IOP have equivalent effects on TLCPD and optic disc surface movement. It was also found that CSF-P affects axonal transport of the optic nerve, which might have an effect on glaucoma aetiology and retinal venous outflow.²⁵

Recently, there has been enhanced understanding of the retinal vein pulsation by Morgan *et al*²⁶, who determined that the central retinal vein collapse in the eye occurs in conjunction with intraocular diastole, not systole. It also occurs in time with IOP and ICP diastole. Furthermore, the central retinal vein collapse occurred in an insignificant 0.6% of a cardiac cycle before the ICP minima but a significant 3.2% after the IOP minima, suggesting that ICP pulse pressure drives ocular venous pulsation.²⁶ In general, the ICP phase occurs before the IOP phase, with ICP rising and falling slightly before IOP. The ICP pulse driving venous pulsation leads to increased outflow during the time of ICP minima. As the ICP rises first, leading to increased resistance to venous outflow, intraocular blood accumulates during systole. As the ICP falls slightly before the IOP in diastole, intraocular blood drains. Others have postulated that the phase difference would create a period of relatively higher CSF-P compared with IOP and promote retrograde axoplasmic flow of nutrients and metabolites towards the retina.²⁷ Given the association of venous pulsation with ICP, it is hypothesised that there exists a low-resistance connection between the intracranial CSF and the CSF surrounding the optic nerve.²⁶ This low-resistance connection does not have to be a continuous fluid compartment but can rather represent compartments produced by deformable septa that allow for pressure transfer.

CSF-P, TLCPD and glaucoma

In a study looking at individuals with high-tension glaucoma, normal tension glaucoma (NTG) and OHT, increased TLCPD gradient was negatively associated with neuroretinal rim area ($p=0.006$, $r=-0.38$) and positively associated with mean visual field defect ($p=0.008$, $r=0.38$).²⁸ Berdahl and colleagues observed that cup-to-disc ratio was positively correlated with TLCPD gradient.²⁹ They also found that CSF-P was 33% lower in study participants with primary open angle glaucoma (POAG) compared with non-glaucomatous controls (9.2 mm Hg vs 13.0 mm Hg).

If indeed TLCPD is associated with glaucoma, one might expect NTG patients to have reduced CSF-P causing increased gradient despite normal IOP. In a prospective study by Ren *et al*¹⁰, CSF-P was significantly lower in the NTG group (9.5 mm Hg) than both the high IOP glaucoma group

(11.7 mm Hg) and the control group (12.9 mm Hg). The TLCPD gradient was significantly higher in those with glaucoma (NTG 6.6 mm Hg, high IOP glaucoma 12.5 mm Hg) compared with controls (1.4 mm Hg). Using multivariate analysis, the TLCPD gradient was significantly associated with perimetric visual field loss. However, when IOP and CSF-P were used as individual parameters in the multivariate analysis, there was no significant correlation between these individual parameters and glaucomatous visual field loss.¹⁰

Perhaps increased CSF-P in OHT patients lowers TLCPD gradient and explains the lack of glaucomatous damage despite elevated IOP. When comparing OHT patients with non-glaucoma controls, Ren *et al*³⁰ found OHT patients to have significantly higher CSF-P than controls (16.0 ± 2.5 mm Hg and 12.9 ± 1.9 mm Hg, respectively). Berdahl *et al*²⁹ also found significantly higher CSF-P in OHT patients over controls. However, despite the association of higher CSF-P in OHT patients with higher IOP, TLCPD gradient was significantly higher in the OHT group.³⁰ Ren and colleagues hypothesised this could be explained by a pre-glaucomatous state in which detectable perimetric or morphological changes had not yet developed. They noted that patients in this group, if in fact they would eventually develop glaucomatous damage, could have benefitted from antiglaucoma treatment.³⁰ Perhaps there is a threshold pressure gradient to pass to develop damage, and such a gradient is surpassed in OAG but not OHT. In fact, a previous study showed that OHT patients have a lower TLCPD gradient than POAG patients.⁹

BP, IOP, CSF-P AND OAG RISK

Large population-based studies have determined that IOP is significantly associated with both systolic BP (SBP) and diastolic BP (DBP).^{31–36} Dielemans *et al*³⁴ demonstrated that a 10 mm Hg increase in SBP resulted in a 0.23 mm Hg increase in IOP, and a 10 mm Hg increase in DBP caused a 0.24 mm Hg IOP increase. Similarly, data from the Egna-Neumarkt Study found that 10 mm Hg increments in SBP and DBP caused IOP increases of 0.24 and 0.40, respectively.³⁶

However, more notable is the extensive literature that points towards the effect of decreased BP on OAG risk. A DBP less than 90 mm Hg due to antihypertensive therapy in non-glaucoma eyes is associated with decreased rim area and increased optic disc cupping.³⁷ Furthermore, various studies have demonstrated a relationship between glaucoma progression and hypotension.^{38–39} Patients with OAG with progression despite well-controlled IOP, as well as NTG patients, exhibited lower SBP throughout the day and night compared with healthy controls.²⁸ Patients with uncontrolled IOP did not have a BP that varied from the controls. Subsequently, Graham *et al*³⁹ found that a higher risk for glaucoma progression was associated with large decreases in nocturnal BP.⁴⁰ With this in mind, some argue that underlying impaired autoregulation of ocular blood flow causes ischaemic periods followed by reperfusion injury. In accordance, increased mean ocular perfusion pressure fluctuation has been implicated as a risk factor for glaucoma severity in NTG patients.⁴⁰ Thus, appropriate SBP control is imperative in glaucoma treatment. However, reduction of arterial hypertension will also reduce CSF-P and affect the TLCPD gradient.

The correlation between decreased BP and OAG risk could be explained by the relationship between CSF-P and BP. It has been suggested that reduction of arterial BP has been associated with greater decrease in CSF-P than IOP in NTG patients.⁴¹ Disparate pressure decrease would increase the TLCPD gradient

and could explain glaucomatous optic nerve changes in patients with normal IOP. Conversely, increased SBP may be associated with increased CSF-P and may thus protect against glaucomatous damage in OHT.⁴¹ Interestingly, arterial hypertension and elevated CSF-P have also been implicated as risk factors for retinal vein occlusion.⁴¹ Data on this topic are limited, and more research is needed.

CARBONIC ANHYDRASE INHIBITORS

Currently, the only therapeutic strategies available to treat OAG are targeted at lowering IOP. The four classes of topical medications include prostaglandin analogues, β -adrenergic receptor antagonists, α_2 -adrenergic receptor agonists and carbonic anhydrase inhibitors. It is important to discuss the use of carbonic anhydrase inhibitors specifically as they are also known to decrease CSF production.⁴² Carbonic anhydrase inhibitors remain an effective glaucoma treatment modality by lowering IOP through reduction of aqueous humour formation.⁴³ They have been used in topical forms for POAG and in systemic forms for acutely elevated IOP.¹ Additionally, carbonic anhydrase inhibitors are used to decrease CSF production and thus lower CSF-P in patients with idiopathic intracranial hypertension.⁴² With increasing evidence that TLCPD is associated with glaucoma progression, carbonic anhydrase inhibitor effects on IOP and CSF-P should be further evaluated. It is expected that systemic carbonic anhydrase inhibitor administration for acute angle closure glaucoma will reduce both IOP and CSF-P. As previously discussed, only TLCPD gradient, and neither IOP nor CSF-P alone, was significantly associated with perimetric loss.¹⁰ Data are currently lacking as to how this class of medications affects the interplay between IOP and CSF-P in glaucoma, and no conclusions can be made at this time.

Relationship between BMI, IOP and CSF-P

BMI has been shown to be positively correlated with IOP with multivariate regression analysis,^{44–47} even in children.⁴⁸ Some postulate that increased adipose tissue fills the orbit and increases episcleral venous pressure, raising IOP.⁴⁹ Others state lipid deposits could reduce aqueous fluid outflow.⁵⁰ Recently, a study found that BMI only had a statistically significant association with IOP when insulin resistance data were removed as a covariate.⁵¹ It was suggested that perhaps the BMI and IOP relationship may be a manifestation of an association between insulin resistance and IOP.

However, some studies did not reach statistical significance. For instance, several studies only found a positive correlation between IOP and BMI in men, not women.^{51–52} While the Beijing Study found a relationship using univariate analysis, no significant association was found through multivariate regression analysis.³⁵

Recently, BMI and its relation to glaucoma has been investigated. Pasquale *et al*⁵³ demonstrated that in women increased BMI was associated with reduced risk of POAG with an IOP of 21 or less at diagnosis. No association was found in women with an IOP greater than 21 at diagnosis. No relationship was found in men. The Barbados Eye Study also concluded that OAG prevalence decreased with increasing BMI.⁵⁴ Furthermore, men with a BMI ≥ 28.5 had less than one-third the odds of having OAG of men with a BMI ≤ 21.71 . Women with a BMI ≥ 32.50 had less than one-half the odds of OAG of women with a BMI ≤ 23.44 .⁵⁴ Perhaps racial differences can explain why Pasquale *et al* did not also find a correlation with men. While the Barbados Eye Study studied individuals of African descent, Pasquale *et al* investigated patients of European descent.⁵²

Another explanation could be varying study methodology, as the Barbados Eye Study did not correct for central corneal thickness. However, Leske *et al* found that central corneal thickness was not correlated with BMI.⁵⁵ In addition, the Singapore Malay Eye Study demonstrated reduced neuroretinal rim area and increased cup-to-disc ratio were associated with reduced BMI.⁵⁶ In another population-based study, neuroretinal rim area was associated with increasing BMI.⁵⁷ However, other studies suggest there is no correlation between BMI and glaucoma.⁵⁸ Furthermore, a longitudinal cohort study of patients concluded that OAG is more common in obesity with a HR of 1.06.⁵⁹

If BMI is taken to reduce glaucoma risk, then the association of increasing CSF-P with increasing BMI, and subsequent effect on TLCPD gradient, might explain why this occurs. CSF-P has been shown to be linearly correlated with BMI.⁶⁰ Another study found a trend between increased BMI and increased CSF-P but failed to reach statistical significance ($p=0.062$).⁶¹ The pathophysiology behind the increase in CSF-P with increasing BMI is not fully understood, although theories have been postulated. One such theory states that CSF-P increase is caused by hypoventilation or obstructive sleep apnoea leading to respiratory acidosis.⁵⁰ Increased intra-abdominal pressure or venous outflow obstruction may also increase central venous pressure, resulting in increased CSF-P.⁶²

Individuals with elevated BMI also are more likely to have diabetes mellitus and hypertension.⁵³ Obesity, with its associated elevated CSF-P, appears protective for glaucoma; however, diabetes, which is also associated with obesity, is also considered a controversial risk factor for OAG. Several large-scale clinical trials have reported an increased risk of OAG in diabetics^{63–66} while other large trials have shown no such association.^{67–70} Despite this, it appears the protective effect of BMI against glaucoma overcomes the supposed increased risk of glaucoma due to diabetes mellitus and dysregulation of BP.⁵⁹ Perhaps obesity's association with hypertension can also partially explain the positive correlation between BMI and CSF-P. However, much remains to be explored in this relationship as other studies have failed to reach significance between CSF-P and obesity.⁶¹

EFFECT OF AGE ON IOP AND CSF-P

Age is a well-known risk factor for OAG. Population-based studies have found OAG prevalence to increase beginning in approximately the fifth decade of life.^{71–72} However, studies are inconsistent on the relationship between age and IOP, with some studies showing no correlation and other studies showing that IOP increases with age.^{73–75} A recent study by Fleischman *et al* found a significant correlation between age and CSF-P. This study found that CSF-P pressure began to decline steadily after age 50 with a 2.5% decrease in those aged 50–54 and a decrease of 26.9% in those aged 90–94 compared with those in the age group 29–40.⁷⁶ These data suggest that TLCPD caused by a decreasing CSF-P with age might explain the increasing incidence of OAG with age.

CONCLUSION

In conclusion, regulation of pressures in the arterial system, the eye and the brain has profound influence on the development of glaucomatous change. Systemic arterial BP, IOP and CSF-P are inextricably tied to one another, and altering one often alters another. An increased TLCPD difference has been associated with visual field loss and increased neuroretinal rim area. This increased gradient, whether due to decreased CSF-P or due to increased IOP, may explain the existence of NTG and POAG, respectively. Conversely, a normal gradient, despite increased

CSF-P and IOP, may explain the lack of visible glaucomatous damage in OHT. Further research of TLCPD is warranted as some studies suggest OHT patients eventually develop optic nerve damage. Analysis of TLCPD gradients may help determine whether certain patients are more likely to develop glaucomatous damage or whether others are likely to progress more quickly with the disease. Better understanding of the IOP and CSF-P relationship could influence treatment regimens. Yet, as noted previously, the CSF-P and glaucoma relationship is complicated as CSF-P is affected by displacement of lamina cribrosa, body position, time of day and local changes in flow near the globe. Furthermore, with diabetes and hypertension on the rise, the BMI–CSF-P relationship warrants a front seat in the discussion of glaucoma. As tighter BP control in patients remains a high priority, the effects of changes in arterial BP on CSF-P should be considered. A better understanding of the relationships between such pressures and measurements has great potential in the treatment of glaucoma. Not unlike carbonic anhydrase inhibitors, glaucoma medications may influence more than one of these factors. Investigation of these factors may provide insight into disease progression in patients while on antiglaucoma medication.

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