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Translaminar Pressure Gradient in Glaucoma and Non-invasive Methods for Intracranial Pressure Evaluation: A Review

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Abstract

Studies have shown that intracranial pressure is correlated with some ocular diseases including glaucoma, where low intracranial pressure has been found to be correlated with disease progression and high intracranial pressure may play a protective role. Multiple hypothesis have been proposed for the role of intracranial pressure in ocular disease, including that it can act as a stabilizing force to protect the optic nerve from intraocular pressure by balancing forces across the lamina cribrosa. While currently there is no non-invasive measure of intracranial pressure that has consistently performed well across multiple large studies, there are several methods under development which have shown promising results. This paper reviews current understanding of the role of intracranial pressure in ocular diseases, non-invasive methods for measuring intracranial pressure, as well as related topics where current research will likely inform findings on the effect of intracranial pressure on the eye.

Keywords: Intracranial pressure; Glaucoma; Translaminar pressure gradient; Non-invasive methods

Introduction

Intraocular Pressure (IOP, measured in mmHg) has long been regarded as the main risk factor [1], for progression of glaucoma. However, glaucoma can continue to progress despite maintaining IOP within the target range [2]. Progression of primary open angle glaucoma (POAG) and blood flow changes in the eye have been found to be correlated with intracranial pressure (ICP, measured in mmHg) in multiple studies [3-5]. While pathologically elevated ICP has long been known to lead to papilledema, more recently studies have shown that physiologically low ICP is correlated with progression of glaucoma. This paper reviews the most current studies and insights to the role of ICP in glaucoma and ocular disease.

Role of Intracranial Pressure in Glaucoma

Berdahl et al. retrospectively studied patients undergoing lumbar punctures (LP) and found that ICP was lower in patients with normal-tension glaucoma (NTG) compared to both age-matched controls and glaucoma patients with ocular hypertension. Conversely, in patients with ocular hypertension but no glaucomatous damage, ICP was elevated compared to normal controls. These findings suggest that increased ICP may play a protective role in glaucoma and provide a countering force to IOP [5]. Later, Ren et al. found similar results in a prospective study of 43 glaucoma and 71 control patients, with ICP again lower in the NTG group vs. high tension glaucoma and normal controls. As well, Ren et al. also looked at the difference between IOP and ICP, finding that the difference was higher in both groups of glaucoma patients vs. controls [4]. Both of these studies evaluated ICP using lumbar puncture (LP). Subsequently, Siaudvytyte et al. found similar trends in a prospective study of 40 patients, though the difference in ICP between groups did not achieve significance, which may have been due to a low number of participants, and the difference between IOP and ICP was not significantly greater in the group with NTG *vs.* normal controls. Instead of using LP to measure ICP, Siaudvytyte et al. used a non-invasive, two-depth transcranial Doppler, which is not as precise as invasive measures but has the advantages of reduced risk of infections and is easier to repeat [3]. Similar to this cross-sectional human study results, an intervention study in monkeys also found that chronic reduction in ICP through draining cerebrospinal fluid resulted in decreased neuroretinal rim area vs. controls [6]. Gallina et al. analyzed patients following shunt placement for normal pressure hydrocephalus and showed that the product of shunt duration and ICP change was correlated with development of NTG [7].

While studies are ongoing on the role ICP in glaucoma and yet other studies are exploring alternative hypotheses, the leading hypothesis is that ICP acts as an opposing force for IOP at the optic nerve head (ONH) and lamina cribrosa, with the protective role of ICP being to limit the translaminar pressure gradient (TLPG) which is the difference between IOP and ICP divided by the distance between them (the thickness of lamina cribrosa), making the TLPG dependent on IOP, ICP, and the thickness of the lamina cribrosa. High TLPG is thought to create a shearing force on the optic nerve head, contributing to glaucoma progression. The TLPG has been estimated to be 20-33 mm Hg/mm on average in humans [8,9]. While ICP can be used to calculate the TLPG in most cases, the TLPG is truly dependent on the retrolaminar tissue pressure, and when ICP is below 1.33 the retrolaminar tissue pressure is less dependent on it, so the simplified equation only holds true when ICP is above 1.33 [9].

A second hypothesis explaining why low ICP maybe correlated with glaucoma progression is the effect on cerebrospinal fluid (CSF) flow to the optic nerve. Matheiu et al. showed that CSF flow to the optic nerve was reduced in mice with glaucoma vs. normal controls and hypothesized that elevated IOP may compromise CSF outflow into the orbit, thus reducing flow to the optic nerve. If this is the case, elevated or high/normal ICP would be protective by helping to maintain CSF

flow in the optic nerve sheath [10]. Separately, CSF flow in the nerve has been shown to be vital, with stoppage of flow using ligation resulting in optic nerve axonal loss in sheep [11]. These results point to reduced CSF flow as a possible mechanism of glaucoma, in which case increased ICP would be protective but for a different reason than assumed in the TLPG hypothesis.

While low ICP appears to be a risk factor for progression of glaucoma, elevation of ICP may also pose some risks. In mice, Nusbaum et al. elevated ICP to 30 for 1 week which resulted in axonal loss in the optic nerve and retinal ganglion cell (RGC) death [12]. These findings are consistent with disease processes in humans including papilledema. However, Shen et al. showed physiologic increases are damaging as well. They found that increasing ICP from a mean of ~9 to ~15 for two weeks resulted in similar levels of RGC and axonal loss in mice [13]. Future studies evaluating similar shifts in primates should be conducted to validate the findings of physiologic elevation being damaging, which would be an important consideration as it has already been shown that physiologically low ICP is associated with progression of glaucoma in humans.

Measurement of Intracranial Pressure

Invasive measurement of ICP is costly and is associated with attendant risks including infection. This has brought about the interest in non-invasive measurement or estimation of ICP for the purposes of both clinical practice and research studies. There are several methods to non-invasively measure the ICP which are safe and are without the associated risks for infection.

Currently, a method based on MRI measurement of cerebral compliance, MR-ICP, appears to be the most precise. Muehlmann et al. used it to estimate ICP in 15 patients with ICP in the normal range, and the values with this technique was estimated to be within ± 2 of the invasively measured ICP in 14 of 15 patients (93%) [14]. In yet another study, Burman et al. looked at 10 healthy and 6 traumatic brain injury patients, achieving a 95% CI for error between estimated ICP based on the linear regression and invasively measured ICP of ± 5 [15]. However, MRIs are expensive, both of these studies are small and MR-ICP has yet to be tested in large studies.

Yet another method to non-invasively measure ICP is using a device which has currently achieved approval for marketing in the European Union (EU). This machine estimates ICP based on the pressure needed to balance blood-flow waveforms in the ophthalmic artery, a method called two-depth Transcranial Doppler (TD-TCD). TD-TCD showed promising results in a study performed with 95% CI for error of ± 4 [16]. However, subsequent studies by outside groups have not achieved results that are precise enough for clinical application, Bershad et al. only achieved a 95% CI for error of ± 10 [17]. Koskinen et al. studied patients with communicating hydrocephalus and achieved a 95% CI of -1 to 9 for the difference between invasive and TD-TCD measurement of ICP [18]. Both Koskinen et al. and Bershad et al. were unable to perform measurement in a significant percentage of patients (28% and 40% respectively), and the studies indicate additional development is likely required before TD-TCD is ready for clinical applications on a large scale.

The third measurement technique is ophthalmodynamometry, and is performed by increasing IOP until the central retinal vein collapses [19]. The pressure within the vein must be at least as high as the ICP because it travels with the optic nerve and becomes surrounded by CSF in the optic nerve sheath, so the pressure required to collapse the vein can be used to estimate ICP. Quefurth et al. achieved a 95% CI for actual ICP of ± 4-5 when combining this technique with measurement of the pulsatility index ([peak systolic velocity - end diastolic velocity]/mean flow velocity) of the ophthalmic artery to estimate ICP [20]. There are commercialization efforts for a device using this principle, but so far marketing approval in the EU has not been achieved for this device.

In contrast to measurement of ICP, an alternative approach is estimation of ICP using an equation which includes the variables of age, BMI, and diastolic blood pressure. Using lumbar puncture as a reference, Jonas et al. derived the equation:

Cerebrospinal fluid pressure=0.446 × BMI+0.166 (mm Hg) × Diastolic Blood Pressure (mm Hg)-0.18 × Age (Years)-1.91 from a set of 72 Chinese patients to estimate ICP.

When testing against LP measurements in a test group of 42 Chinese patients, they found an insignificant difference between the estimated and actual ICP (p=0.29) [21,22], however they did not report limits of agreement or provide a figure illustrating the results. Kashara et al. tested the same equation in 39 Brazilian patients, finding 95% limits of agreement of -5 to +8 between LP measured and equation estimated ICP. Overall, while results were not as good as the most successful studies utilizing MR-ICP, TD-TCD, and ophthalmodynamometry, the strength of the results by Kashara et al. indicates that adjustments to measured values based on patient age, BMI, and blood pressure may improve the precision of estimates, and is something that can be considered in future development of non-invasive ICP measurement techniques [23].

Effect of Anatomical Variations in Lamina Cribrosa

Complicating any understanding of the effect of ICP on glaucoma and other diseases of the optic nerve is that the lamina cribrosa appears to play a role in disease processes and does not respond consistently to changes in ICP and IOP. The lamina cribrosa is a collagenous meshwork of trabeculae which sustains pressure forces from both IOP and ICP. RGC axons as well as capillaries pass through the lamina cribrosa. As the lamina cribrosa is thinner than the sclera at the scleral canal, it is a relatively weak spot for sustaining pressure changes. A thinner lamina cribrosa has been associated with a faster rate of retinal nerve fibre layer thinning in POAG [24], this is likely because a thinner lamina cribrosa is less able to withstand exerted pressures by IOP and ICP, and also that TLPG is higher when the lamina cribrosa is thinner. Highly myopic patients have been found to have thinner lamina cribrosa on average, which may explain why glaucoma progression is more prevalent in myopic eyes [25]. *In-vivo* testing of strain-relief on the lamina cribrosa by Girard et al. in 9 patients undergoing trabeculectomy showed that the amount of tissue strain relief, which was calculated based on changes in lamina cribrosa displacement, was significantly associated with reduction in retinal sensitivity [26]. Additionally, strain relief was not associated with IOP change following trabeculectomy, pointing to the importance of anatomical variations between patients [26]. Wang et al. tested manipulating both ICP and IOP in primates, finding that, similar to Girard et al. the responses of lamina cribrosa architecture to pressure changes varied by subject. Additionally, changes in lamina cribrosa architecture were greater with acute fluctuations in ICP vs. IOP, with particularly minimal changes in architecture when ICP ~10-30 [27]. Changes in lamina cribrosa architecture were different between acute and chronic elevations in IOP, likely reflecting collagen fibre

recruitment to counter high TLPG in chronic cases [28]. Understanding the lamina cribrosa will be an important adjunct to understanding and predicting the effects of ICP on ocular pathologies.

IOP Variation: An Evolving Piece of the Puzzle

IOP is extremely variable, exhibits nycthermeral variation, and is affected by blinking, squeezing the lids, and saccade [29,30]. While these short-term intra-day variations have not been extensively studied, fluctuation in IOP between office visits was found to be a stronger predictor of visual field loss progression vs. mean IOP in the Advanced Glaucoma Intervention Study which included 401 patients and 509 eyes [31]. Additionally, the study also found that the association between fluctuation and visual field loss was stronger in patients with low mean IOPs [32]. Other studies have had mixed results, finding both that increased IOP fluctuation was associated with glaucoma progression [33,34], and that it was not [35,36]. However, it has been pointed out that increased fluctuation in IOP was correlated with increased mean IOP in several studies that found no relationship between the amount of IOP fluctuation and visual field change. It has also been noted that fluctuations are more consequential in patients with lower mean IOPs, and so a relationship could have been masked in these studies leading to the negative results [37].

As low ICP is currently thought to be most important in patients with NTG, it will be interesting for future studies to differentiate how much effect low ICP has vs. IOP variation, or whether both factors have a complimentary impact. To date, studies on IOP fluctuation have not included comparison to ICP for calculation of fluctuation in TLPG, which is another potential avenue for further study. This in fact may turn out to be a better predictor than IOP fluctuation. As the ability to estimate ICP non-invasively improves the potential for these types of studies increases.

Conclusion

ICP has been shown to be an important factor in ocular disease and specifically in progression of glaucoma. However, there is still much to study in understanding its interplay with the anatomy of lamina cribrosa and IOP and eventually predicting effects in specific patients. There is a wide range of study findings and proposed pathogenesis for glaucoma, likely reflecting the existence of multiple pathological mechanisms. Given the complexity of this disease, longitudinal and multifactorial studies will likely be necessary to fully understand the pathogenesis of glaucoma. Non-invasive measurement techniques of ICP still require further development to achieve clinical usefulness, but progress is being made and studies looking at progression of glaucoma have already successfully used non-invasive measurement to estimate ICP.

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