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Review Article

Update in intracranial pressure evaluation methods and translaminar pressure gradient role in glaucoma

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ABSTRACT.

Glaucoma is one of the leading causes of blindness worldwide. Historically, it has been considered an ocular disease primary caused by pathological intraocular pressure (IOP). Recently, researchers have emphasized intracranial pressure (ICP), as translaminar counter pressure against IOP may play a role in glaucoma development and progression. It remains controversial what is the best way to measure ICP in glaucoma. Currently, the 'gold standard' for ICP measurement is invasive measurement of the pressure in the cerebrospinal fluid via lumbar puncture or via implantation of the pressure sensor into the brains ventricle. However, the direct measurements of ICP are not without risk due to its invasiveness and potential risk of intracranial haemorrhage and infection. Therefore, invasive ICP measurements are prohibitive due to safety needs, especially in glaucoma patients. Several approaches have been proposed to estimate ICP non-invasively, including transcranial Doppler ultrasonography, tympanic membrane displacement, ophthalmodynamometry, measurement of optic nerve sheath diameter and two-depth transcranial Doppler technology. Special emphasis is put on the two-depth transcranial Doppler technology, which uses an ophthalmic artery as a natural ICP sensor. It is the only method which accurately and precisely measures absolute ICP values and may provide valuable information in glaucoma.

Key words: glaucoma – intracranial pressure – non-invasive two-depth transcranial Doppler device – translaminar pressure gradient

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Introduction

Glaucoma is one of the leading causes of blindness worldwide (Quigley & Broman 2006) that continues to amass evidence of its multifactorial nature. Intraocular pressure (IOP) has been regarded as one of the main risk factors in the prevalence, incidence and progression of glaucoma (Leske et al. 2003). However, in many cases, glaucoma continues to progress, despite maintaining target IOP (Heijl et al. 2002; Leske et al. 2007). Obviously, there are non-IOP factors involved in the pathogenesis of primary open-angle glaucoma (POAG) that can impact the apoptotic process (Flammer et al. 1999). These include low systolic ocular perfusion pressure, a reduction of ocular blood flow, low systolic blood pressure, cardiovascular disease, migraine, smoking and vasospastic disorders (Bonomi et al. 2000; Hayreh 2001; Leske et al. 2008; Cherecheanu et al. 2012). Recently, researchers have emphasized intracranial pressure (ICP), as translaminar counter pressure against the IOP, role in glaucoma (Jonas 2011; Ren et al. 2011).

Intraocular and ICPs are interrelated and relatively independent pressure systems, which keeps themselves in a relatively stable state through aqueous and cerebrospinal fluid (CSF) circulations. These two circulating fluids have many similarities as they both are produced by carbonic anhydrase-catalysed reactions, generally represent an ultrafiltrate of blood and have nearly identical chemical composition, with more proteins and less ascorbates in CSF. Normal ICP varies with age but is generally considered to be 5–15 mmHg in healthy supine adults,

3–7 mmHg in children and 1.5–6 mmHg in infants (Albeck et al. 1991; Smith 2008). Physiologically, IOP and ICP are dynamic parameters, both have circadian variations (24-hr) and similar response to changes in posture, intra-abdominal or intrathoracic pressures (Dickerman et al. 1999). IOP circadian cycle is quite well known (Sit & Liu 2009); however, circadian pattern of ICP is less clear, suggesting a nocturnal elevation in ICP (Morrow et al. 1990; Maurel et al. 1996). Zhang et al. found that the Valsalva manoeuver-associated short-term increase in CSF pressure was significantly higher than increase in IOP. It led to a Valsalva manoeuver-associated decrease or reversal of the translaminar cribrosa pressure difference, which was associated with decreased optic cup-related parameters and enlarged neuroretinal rim-related parameters (Zhang et al. 2013). Other studies suggested that the risk of glaucoma is higher in patients with frequent Valsalva efforts (Schuman et al. 2000; Krist et al. 2001). Wostyn et al. (2011) hypothesized that fluctuations in ICP could result in translaminar cribrosa pressure difference fluctuations and thus fluctuations in the shear stress in the retinal ganglion cell axons, ultimately leading to glaucomatous damage. The role of ICP in glaucoma still remains unconfirmed, because only invasive ICP measurements are widely available within the contemporary medicine.

Currently, direct measurement of CSF pressure via lumbar puncture or via implantation of the pressure sensor into the brains ventricle is considered to be the 'gold standard' of ICP measurement (Digre & Corbett 2001; Lenfeldt et al. 2007; Andrews et al. 2008). CSF pressure obtained via lumbar puncture is normally determined by ICP; therefore, we use the term ICP and CSF pressure interchangeably, as it is carried out in clinical practice (Lenfeldt et al. 2007). However, the direct measurements of ICP are not without risk due to its invasiveness and potential risk of intracranial haemorrhage, infection or even cerebral herniation and hence cannot be widely used as a matter of safety concerns (Zeng & Gao 2010). Moreover, invasive methods lend themselves only to a small portion of pathological disorders in which ICP measurement can be used, and consequently, many patients who might benefit from ICP measurement, including glaucoma patients, do not do so. Therefore, development of non-invasive absolute ICP measurement method could be a tool to overcome the high risk to benefit ratio of current invasive ICP measurement methods. In this article, we present a novel non-invasive absolute ICP measurement method using two-depth transcranial Doppler device, which is currently the only available method for absolute ICP value numerical and automatic measurement that does not need an individual patient-specific calibration (Ragauskas et al. 2005, 2012).

Importance of Intracranial Pressure in Glaucoma

Contemplations of ICP role in glaucoma started more than three decades ago. Optic nerve head (ONH) is located at the junction between the relatively high-pressure intraocular space and low-pressure subarachnoid space (SAS); therefore, pressure imbalance between these two regions may be the cause of damage of retinal ganglion cell axons that cross the lamina cribrosa (Volkov 1976; Morgan et al. 2002; Burgoyne et al. 2005). The difference in pressure that occurs across the lamina cribrosa (IOP–ICP) is known as the translaminar pressure gradient (TPG) (Morgan et al. 1998). Physiologically, the average IOP is slightly higher than the average ICP, resulting in a small posteriorly directed TPG difference (mean 4 mmHg) (Gilland 1969). Normal IOP combined with low ICP produce the same pressure differential across the lamina cribrosa as elevated IOP in conjunction with normal ICP (Greenfield et al. 1997). Indeed, TPG is not only affected by IOP and ICP, but also by the thickness of the lamina cribrosa. Jonas et al. reported that lamina cribrosa is thinner in myopes and that there are morphometric changes in lamina cribrosa in glaucomatous eyes, including thinning (Jonas et al. 2003, 2004). The thinner lamina cribrosa determines a higher TPG and creates a steeper path that retrograde axonal transport must traverse. Interestingly, experimental studies revealed that lamina cribrosa thickens at the earliest stage of glaucoma (Yang et al. 2007).

Changes in TPG may lead to abnormal function and optic nerve damage due to changes in axonal transportation, deformation of the lamina cribrosa, altered blood flow or a combination of it. Experimental studies showed that chronic reduction in CSF was associated with the development of an optic neuropathy in some monkeys (Yang et al. 2014). Other researchers showed that ICP could pathogenetically be associated with structural changes in the ONH similar to glaucomatous damage (Volkov 1976; Morgan et al. 2002; Burgoyne et al. 2005). Later Berdahl et al. in retrospective analysis of patients who had lumbar puncture revealed that ICP was 3 to 4 mmHg lower in POAG (Berdahl et al. 2008a), and its subset normal-tension glaucoma (NTG), compared with age-matched control subjects and patients with ocular hypertension (OH) (Berdahl et al. 2008b). Further, they reported that the amount of glaucomatous damage to the optic nerve correlated with the TPG (Berdahl et al. 2008b). Recently, Ren et al. (2010) in a prospective study found similar results to those in the retrospective studies, with the control group having the highest CSF pressure and the smallest TPG.

However, all these studies do not represent long-term pressure variations, because only instantaneous measurements of IOP and invasive ICP were taken. It is still impossible to assess how differences in ICP over time may affect the development or progression of POAG using a single-pressure measurement. Moreover, assessment of ICP fluctuation, day–night variations and their influence in glaucoma would be very useful but limited due to invasive ICP measurement procedures.

Non-Invasive ICP Measurement Approaches

Different approaches for evaluating physiological characteristics of ICP-related cerebrospinal system have been attempted by various authors (Firsching et al. 2000; Bellner et al. 2004; Bauerle & Nedelmann 2011; Li et al. 2012; Ragauskas et al. 2012; Xie et al. 2013).

Transcranial Doppler ultrasonography (TCD) is a simple non-invasive method used to measure blood flow velocity in the middle cerebral artery (MCA). The use of TCD as a predictor of ICP was first described by Klingerhofer et al. They reported that changes

of the ICP recordings influenced the flow patterns in TCD (Klingerhofer et al. 1997). Several studies found that MCA pulsatility index (PI), which is calculated as difference between systolic and diastolic flow velocities, divided by the mean flow velocity, correlates with ICP; however, correlation range was from 0.439 to 0.938 (Moreno et al. 2000; Bellner et al. 2004; Voulgaris et al. 2005). In contrast, other researchers failed to find a relationship between PI and ICP (Figaji et al. 2009; Behrens et al. 2010; Brandi et al. 2010). Behrens et al. (2010) announced that an ICP of 20 mmHg found using PI had 95% confidence intervals of −3.8 to 43.8 mmHg. It must be known that PI depends on several factors such as arterial pressure pulsatility, heart rate, cerebral perfusion pressure, arterial carbon dioxide concentration, cerebral resistance and compliance of the big vessels (Czonsnyka 2001). Furthermore, there are intra- and interobserver variations (McMahon et al. 2007), and the technique cannot be used on 10–15% of patients due to the ultrasound not being able to penetrate the skull (Tsivgoulis et al. 2009).

Ophthalmodynamometry (ODM) is a useful method for measuring the venous outflow pressure of the central retinal vein (CRV) (Firsching et al. 2000). Physiologically, the pressure in the CRV is equal to or higher than ICP. After leaving the eye through the optic disc, the CRV goes through the retrobulbar part of the optic nerve before it traverses the SAS and subdural spaces of the optic nerve and pierces the optic nerve meninges. The technique involves applying slight pressure to the orbital sclera using a calibrated force transducer to manipulate intraocular tension. Tonometry and ophthalmoscopy are additionally employed to measure resting IOP and visualize the instantaneous moment of vein collapse. The pressure value at the point of collapse is termed the venous outflow and is found to linearly predict ICP (Motschmann et al. 2001; Querfurth et al. 2010; Firsching et al. 2011). Firsching et al. (2011) found that an increased pressure of the CRV indicated an elevated ICP, with a probability of 84.2%, whereas a normal pressure of the CRV indicated a normal ICP in 92.8% of patients. Querfurth et al. (2010) showed that ODM is able (area under curve 0.89; 95% CI 0.73–1.05) to predict raised ICP. However, ODM cannot be applied in cases of ocular trauma or conditions that selectively affect the optic nerve and give erroneously high readings in the presence of a papilledema, which may persist long after ICP has returned to normal.

Tympanic membrane displacement (TMD) technique requires a patent cochlear aqueduct, normal middle ear pressure and an intact stapedial reflex. Stimulation of the stapedial reflex causes a movement of the tympanic membrane, which is shown to correlate with ICP (Reid et al. 1990; Lang et al. 2003). Shimbles et al. found a correlation between the invasively and TMD measured ICP values. However, intersubject variability was so great that the predictive limits of the regression analysis were an order of magnitude greater than normal ICP range, thus precluding the method for clinical use (Shimbles et al. 2005). Moreover, perilymphatic duct is less passable with age; thus, tympanic membrane displacement measurements have a relatively low practicability.

Recently, research has extended into ultrasography of optic nerve sheath diameter (ONSD) and its relation with elevated ICP (Geeraerts et al. 2007). Several researchers found correlations between ICP and ONSD (Soldatos et al. 2008; Le et al. 2009; Moretti & Pizzi 2009; Moretti et al. 2009), some of them even showed 90% sensitivity and 84% specificity of the ONSD method in patients with intracranial hypertension (Bauerle & Nedelmann 2011). However, in this study, the sample size was very small (only 10 patients). Others authors found poor reliability of this method (Strumwasser et al. 2011). Analysing glaucoma patients, Jaggi et al. found that NTG patients had increased ONSD, obtained by computer tomography, similar to those of patients with increased ICP (Jaggi et al. 2012). However, Pinto et al. found no statistically significant differences in ONSD, obtained by ultrasonography, between POAG, NTG and healthy controls (Pinto et al. 2012). Furthermore, Wang et al. (2012) found decreased optic nerve SAS width measured by magnetic resonance imaging with fat-suppressed fast recovery fast spin echo T2-weighted sequence in NTG patients, compared with HTG patients and healthy controls. ONSD is a promising tool for estimation of ICP elevation (Geeraerts et al. 2007; Kimberly et al. 2008; Dubourg et al. 2011), but not for measurement of normal or decreased ICP.

Controversial data exist in correlation between IOP and ICP (Li et al. 2012). Recent studies suggested a strong correlation between ICP and IOP (Lashutka et al. 2004; Sajjadi et al. 2006; Spentzas et al. 2010), while others did not find (Czarnik et al. 2007; Han et al. 2008; Kirk et al. 2011). Li et al. (2012) also revealed a significant correlation between CSF pressure and IOP in 130 neurological patients; however, using IOP as a measurement to predict ICP, the accuracy rate was found to be 65.4%. In prospective study, Ren and colleagues found that in normal subjects CSF pressure is related to the systemic arterial BP and the IOP (Ren et al. 2010). According to several population-based studies, IOP is also related to the systemic arterial BP so that the pressures in all three fluid filled compartments are related to each other (Mitchell et al. 2005; Xu et al. 2007). Salman suggests that the CSF surrounding the optic nerve sheath transmits elevations of ICP through the eyeball, raising the IOP (Salman 1997). Other potential mechanisms suggest that the rise in the ophthalmic venous pressure could be transmitted directly to the ocular fluid raising IOP (Hartmann 1998) or increased venous pressure in the cavernous sinus is transmitted to episcleral veins by the superior ophthalmic vein and causes the rise in IOP (Lashutka et al. 2004).

Xie et al. estimated mathematical ICP formula based on three parameters of diastolic BP, age and body mass index (ICP = 0.44 × body mass index (kg/m^2) + 0.16 × diastolic BP (mmHg) – 0.18 × age (years) – 1.91). In their study, measured ICP via lumbar puncture (12.6 (4.8) mmHg) did not differ significantly from the calculated ICP (13.3 (3.2) mmHg). The Bland–Altman analysis revealed that 40 of 42 measurements were within the 95% limits of agreement (Xie et al. 2013). Withal, formula was developed in a pilot study, which included a relatively small number of neurological patients. To estimate its validity, researchers applied the mathematical ICP formula to data from participants in the Beijing Eye Study and The Central India Eye and Medical Study (Jonas et al. 2013, 2014a,b). They found that ICP was significantly lower

and TPG was significantly higher in glaucoma patients, compared with healthy subjects ($p < 0.05$). Additionally, they found that calculated TPG versus IOP showed a better association with presence of open-angle glaucoma and amount of glaucomatous optic neuropathy.

Overall, all these mentioned approaches are based on correlation between some measured parameters of an anatomic structure with ICP. Unfortunately, correlation-based approaches are not able to measure absolute ICP accurately enough for clinical treatment planning. To express such a correlation-based ICP measurement in absolute ICP units (mmHg or mmH_2O), a patient-specific calibration procedure is required. Thus, there is a need for a non-invasive absolute ICP measurement device with an accuracy similar to that of the invasive 'gold standard' ICP metres (Taylor 1997). Seeking to measure absolute ICP value, researchers created non-invasive ultrasound-based measurement – a two-depth transcranial Doppler (TCD) device – which uses an ophthalmic artery as a natural pressure sensor. Accuracy and precision of this device have been previously investigated and shown to be clinically useful (Ragauskas et al. 2005, 2012).

Future Directions – Non-Invasive Absolute ICP Measurement

Non-invasive two-depth TCD device (Vittamed 205, Kaunas, Lithuania) was developed in the Health Telematics Science Centre of Kaunas University of Technology in Lithuania. This technology is based on simultaneous measurements of blood flow velocities in the intracranial and extracranial segments of the ophthalmic artery (OA). The principle is based on the idea of non-invasive arterial blood pressure (ABP) measurement, where externally applied pressure to a segment of artery is used to find a balance point when the external pressure is equal to the arterial pressure measure of interest. Blood flow parameters in both OA segments are monitored at the same time, and two-depth TCD device is used as an accurate indicator of the pressure balance point Pe=ICP, where Pe is an external pressure applied to the non-compressible tissues of the orbit surrounding an extracranial segment of the OA. Pressure balance point is reached when measured blood flow velocity pulsations in both segments of the OA are approximately equal. The absolute ICP measurement value is expressed in mmHg.

A head frame with ultrasound transducer for placement over the closed eyelid is positioned on a patients head. An external pressure Pe produced by a small inflatable ring cuff placed over the tissues surrounding the eyeball is automatically increased gradually from 0 to 20–28 mmHg by 4 or 2 mmHg pressure steps. This amount of pressure applied to the external orbital tissue is equivalent to the underwater pressure of a person diving at a depth of 38 cm. The duration of the measurement procedure is up to 10 min. The structure of non-invasive two-depth TCD device components is shown in Fig. 1.

Study with 62 neurological patients showed that non-invasive two-depth TCD device is precise (standard deviation = 2.19 mmHg) and accurate (mean systemic error = 0.12 mmHg) compared with gold standard CSF pressure measured via lumbar puncture. Mean ICP measured with non-invasive two-depth TCD device was 12.76 (3.23) mmHg (range 4.04–23.71), via lumbar puncture 13.18 (2.99) mmHg (range 4.41–24.26) (Ragauskas et al. 2012).

Diagnostic reliability of non-invasive two-depth TCD device has also been compared to findings of increased ICP on ONSD ultrasonography in neurological patients. In this study, all non-invasive ICP measurements were compared with invasive CSF pressure measurements obtained via lumbar puncture. Study showed that two-depth TCD device has better reliability and relationship with CSF pressure than ONSD method (Figs 2 and 3) (Ragauskas et al. 2014). To estimate its validity in glaucoma patients, researchers have made a pilot study and found that TPG was higher in glaucoma patients compared with healthy controls ($p < 0.001$). Additionally, reduction of neuroretinal rim area was related to higher TPG in NTG patients (Siaudvytyte et al. 2014).

An interesting point of this methodology is that the systemic error of this ICP measurement is close to zero, and obtained results are very close to the Association for the Advancement of Medical Instrumentation requirements for invasive ICP measurements (Brain Trauma Foundation et al. 2007). Therefore, method is suitable for 96% or more of patients with normal OA anatomy, which is normal if OA is a branch of internal carotid artery and it has an intracranial segment compressed by ICP. However, the method depends on the pathway from the intracranial to the orbital portion of the SAS of the optic nerve. What happens if that pathway in the optic

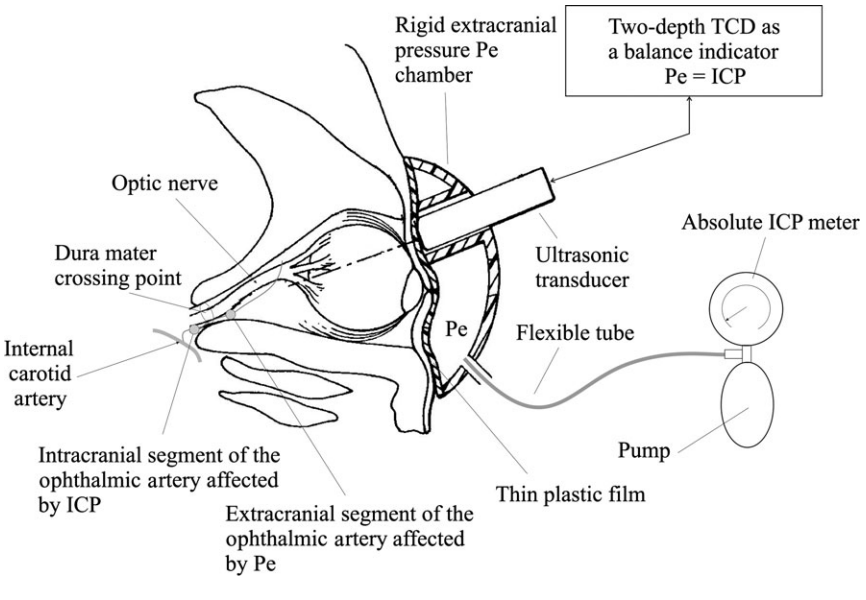

Fig. 1. Non-invasive two-depth TCD device for absolute ICP measurements. The ultrasound transducer of the Doppler subsystem is surrounded by an externally applied pressure chamber with a controlled external pressure (Pe) source and measurement. (Reprinted with permission from Ragauskas et al. 2012).

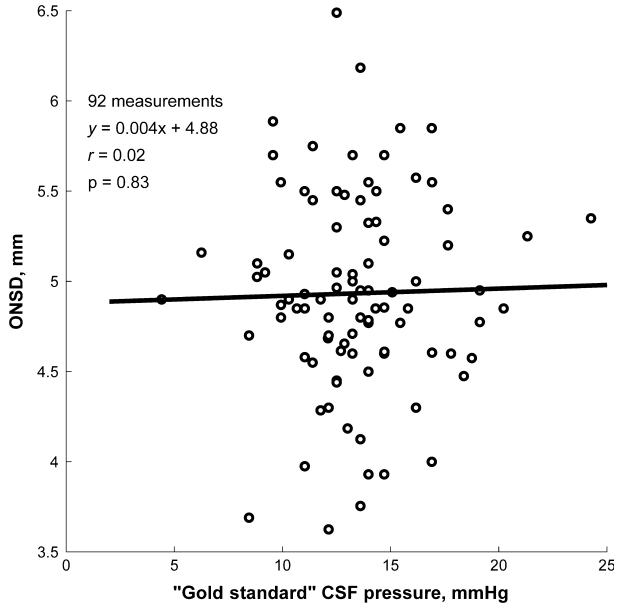

Fig. 2. Relationship between invasive CSF pressure via lumbar puncture and non-invasive ONSD measurement. Linear regression analysis did not showed relationship between ONSD and CSF pressure. (Reprinted with permission from Ragauskas et al. 2014).

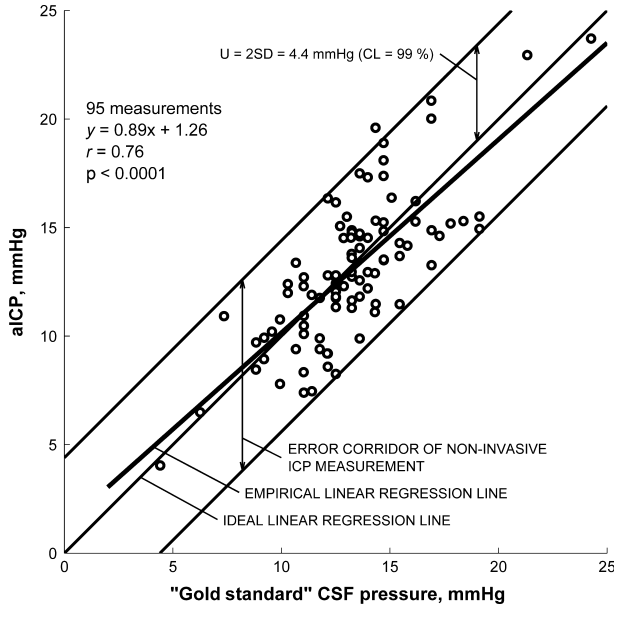

Fig. 3. Relationship between invasive CSF pressure via lumbar puncture and non-invasive absolute ICP measurement. Linear regression analysis showed linear relationship between CSF pressure and non-invasive absolute ICP measured with two-depth TCD device. (Reprinted with permission from Ragauskas et al. 2014).

nerve canal or at the inner aperture of the optic nerve canal is blocked (for example, by a suprasellar meningioma, by circular adhesions as a sequel of a tuberculous meningitis or in patients with an intracanalicular ophthalmic artery aneurysm).

Moreover, it still remains unclear whether the lumbar CSF pressure is directly related to the CSF in optic nerve SAS. There are communicates between CSF in the optic nerve SAS and CSF in the brain at the site of the chiasmatic cistern. The CSF dynamics of the retrolaminar space probably have unique properties as there are numerous septae present that could limit free flow of CSF (Jaggi et al. 2007). Moreover, the dura of optic nerve sheath contains atypical meningeal tissue with lymphoid characteristics (Killer et al. 1999, 2008). Killer et al. (2012) found reduced CSF exchange between the basal cisterns and the SAS surrounding the optic nerve in NTG patients, but not in control subjects. Lower ICP in NTG could explain the reduced density of the contrast-loaded CSF in the SAS of the optic nerves. Nevertheless, experimental studies showed that CSF pressure in optic nerve SAS is identical to CSF pressure at the same vertical level (Hedges & Zaren 1973; Rios-Montenegro et al. 1973). However, these studies were made with cats, whose vasculature of the distal segment of the optic nerve is dissimilar to that of the primates, and only few monkeys. Later Morgan et al. (1995) revealed that CSF pressure in canine optic nerve SAS and in the lateral ventricle at the level of eye is identical, demonstrating hydrostatic continuity of the CSF along the canine optic nerve sheath. In recent study, Lenfeldt et al. (2007) found that CSF pressure measured by lumbar puncture accurately represents ICP in the lateral decubitus position. Magnaes et al. showed that CSF pressure at eye level falls by an average of 14 mmHg as a subject changes its position from the left lateral decubitus posture to the sitting or standing posture (Magnaes 1976). Furthermore, studies have shown that the retrolaminar tissue pressure is about 4 mmHg when CSF pressure is 0 mmHg (Morgan et al. 1998).

Conclusion

In conclusion, CSF pressure as translaminar counter pressure against IOP seems to be of major importance in glaucoma, and future investigations are needed to elucidate the involvement of CSF pressure and its fluctuations in the development, progression and management of glaucoma. Up to the present, time research in glaucoma was limited due to invasive ICP measurement methods. The role of the two-depth transcranial Doppler based non-invasive technology for measuring absolute ICP in glaucoma patients would be innovative and may provide an important aspect currently missing information in glaucoma pathology assessment and even change our whole understanding about glaucoma. Importantly, to date, this non-invasive absolute ICP measurement method is the only available method that does not need an individual patient-specific calibration.

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