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Editorial

Glaucoma - A disease of multiple pressures; new glaucoma pressures discovered!

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Introduction

Glaucoma was defined as an eye disease of characteristic structural change of optic nerves and specific visual field change caused by increased intraocular pressure (IOP)1. It is well recognized as a pressure-related disease. Although many traditional theories have been brought up to explain the mechanism of glaucomatous optic nerve damage, such as mechanical theory and vascular theory, none of them succeeded in revealing the whole truth about the pathogenesis of glaucoma[1].

For example, some glaucoma patients' IOP is in the normal range (normal-tension glaucoma NTG), while some have long-term IOP higher than the normal range (ocular hypertension) with no pathological changes of the optic nerves. Also, there are some glaucoma patients who still have IOP controlled to normal range with drugs or surgeries, yet they have impaired optic nerves with gradually worsening vision. Additionally, some patients with disease of the nervous system also have glaucoma at the same time.[2] Considering these aforementioned dilemmas, can we still believe that IOP is the only pressure related to glaucoma disease? Or are there other new discovered pressures and systemic diseases related to the glaucoma condition? These new discovered pressures and systemic conditions, are they correlated or is there any relationship between their pathophysiology and pathogenesis of glaucoma?

In order to answer all the aforementioned questions, eye care scientists have started discovering other new related glaucoma pressures such as systemic blood pressure (BP), Ocular perfusion pressure (OPP), Cerebro-spinal fluid pressure (CSF-p) and Trans-Laminar Cribrosa Pressure (TLPD)[1-2]. They have started to explore the pathophysiological theories behind these new pressures concept that defines glaucoma as ''a disease of central visual pathway with multi-related pressures'' by considering both ocular pathological changes and body fluid circulation, which will open new discoveries in the pathogenesis and pathophysiology of glaucoma disease as it relates to its diagnosis and management[2]. In this editorial, we briefly reviewed some of the milestone studies of these new related pressures and their roles in the road map for the pathogenesis of glaucomatous optic neuropathy.

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Systemic Blood Pressure (BP) and Glaucoma

The role and the relationship of systemic blood pressures i.e., systolic blood pressure (SBP) and diastolic blood pressure (DBP) to ocular perfusion pressures (IOP and OPP) in glaucoma and hypertensive patients cannot be over emphasize. Although, as reported by Zheng et al[3]., IOP remains an important risk factor for glaucoma as it is clear that other factors can also influence disease development and progression. More recently, the role that blood pressure (BP) has in the genesis of glaucoma has attracted attention, as it represents a clinically modifiable risk factor and thus provides the potential for new treatment strategies beyond IOP reduction. The interplay between blood pressure and IOP determines the ocular perfusion pressure (OPP), which regulates blood flow to the optic nerve. If OPP is a more important determinant of ganglion cell injury than IOP, then hypotension should exacerbate the detrimental effects of IOP elevation, whereas hypertension should provide protection against IOP elevation[3].

Zheng and his associates, hypothesised that both elevated IOP and blood pressure might be driven by a common extrinsic factor such as an age-related increase in sympathetic tone. Alternatively, an increase in blood pressure tends to elevate ciliary artery pressure, thus increasing the ultrafiltration component of aqueous production, resulting in IOP elevation. This is because increased arterial pressure can produce a small increase in venous pressure, aqueous clearance will be reduced, which can also contribute to a higher IOP and thus may lead to decrease in OPP[3].

Also, ocular blood flow is an autoregulated process to ensure the adequate irrigation of ocular tissues, but vascular dysfunction processes may disturb it. In patients with systemic hypertension, there have been findings that suggest an alteration in the production of endothelin-1 levels, which is related to the dysfunction processes in the endothelial regulation, reducing the ocular blood flow in patients with glaucoma[4-5]. Moreover, other studies reported that functional vascular dysregulation could play a role in the pathogenesis of glaucomatous optic neuropathy. Fluctuations in OPP from high or low BP can lead to unstable ocular blood flow and oxygen supply and to oxidative stress which may be relevant in the pathogenesis of glaucoma[6].

Some of the epidemiological studies have shown conflicting results on the role of systemic hypertension in the development and progression of glaucoma as it relates to its risk factors such as high or low SBP, DBP, IOP and OPP[7-12]. The most recent study showed that patients at both extremes of the blood pressure spectrum show an increased

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prevalence of glaucoma[13].

The Los Angeles Latino Eye Study showed that both low diastolic and high systolic blood pressure are associated with an increased prevalence of open-angle glaucoma. They found out that the relationship between ocular pressures and blood pressure parameters were U-shaped, indicating that patients at both extremes of the systemic blood pressure parameters are at greater risk of glaucoma development or progression. According to them, this apparent paradox at the extremes can be explained by two factors; one is that patients with hypotension suffer from low OPP at the optic nerve head (ONH) and secondly, those with chronic hypertension develop atherosclerosis over time leading to increased vascular resistance and compromised vascular autoregulation, as well as impaired nutrient exchange in the capillary beds at the ONH[13].

In the Beijing Eye Study, a population-based study, systolic and diastolic blood pressure in ocular hypertensive group were significantly higher (both $P < 0.001$) than normotensive group. However, the percentage difference of suffering from arterial hypertension between the ocular hypertensive group ($76.2 \pm 5.7\%$) and the normotensive group $50.4 \pm 1.0\%$ was still statistically significant ($P = 0.002$)[14].

IOP: A Dilemma in Glaucoma Diagnosis and Management

High IOP has long been considered responsible for the development and progression of glaucoma disease[2]. However, a relatively large number of glaucoma patients have an IOP in the normal range (<21 mmHg)[3]. In population-based Handan Eye Study, it was found that about 80% of Chinese POAG patients had maximum IOPs less than 21 mmHg over a 24-h period[15]. More interestingly, it was found by the Ocular Hypertension Treatment Study Group (OHTS) that only 9.5% of ocular hypertension patients would develop into glaucomatous optic neuropathy during 5-year follow-up[16]. Why would NTG patients still develop into glaucoma without high IOP? Are there factors other than IOP contributing to the pathogenesis of NTG, as the role of IOP in the pathogenesis of POAG becomes vague and controversial?

Therefore, it is imperative to clarify the pathogenesis of POAG to seek for effective targets and interventions. At present, the proposed mechanisms of POAG-induced optic neuropathy mainly include "**mechanical hypothesis**," "**Vascular hypothesis**," and "**mixed mechanical- vascular hypothesis**."1 Elevated intraocular pressure (IOP) is a known risk factor for optic neuropathy[17]. According to the mechanical hypothesis, IOP elevation induces posterior deformation of the optic disk and the lamina cribrosa, resulting in distortion of the optic nerve passing through these structures, blockage of axoplasmic flow, destruction of axonal functions, apoptosis of RGCs, and thus the occurrence of pressure-related optic neuropathy. It is postulated in

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ischemic injury hypothesis that in an environment with elevated IOP, the self-regulatory function of blood circulation in the optic disk area may become decompensated, leading to a cascade of optic neuropathies. Although these hypotheses explain the possible pathogenesis of optic neuropathy in a subset of glaucomatous patients, some clinical phenomena still remain inexplicable. For example, why do up to 83% of patients with normal tension glaucoma (NTG) still suffer from glaucomatous optic neuropathy[18]? Why does glaucomatous optic neuropathy only occur in a subset of patients with ocular hypertension (OHT)[17]? Why does optic neuropathy continue to progress in some glaucomatous patients despite well- controlled IOP? All of these cannot be explained by the current hypotheses, indicating that some other unknown mechanisms may underlie the pathogenesis of glaucoma.

Various studies documented that the elevated IOP was a significant factor in the pathogenesis of glaucoma. However, as the optic nerve is surrounded by cerebrospinal fluid in the subarachnoid space, it is exposed to not only IOP but also ocular perfusion pressure (OPP), Cerebro-spinal fluid pressure (CSF-p), Trans-Laminar Cribrosa Pressure (TLPD) and intracranial pressure (ICP)[19]. Therefore, diagnosis and management of glaucoma may not be solely dependent on the IOP variations. Other co-risk factors of ocular pressures for development and progression of glaucoma disease may be considered in the commencement of glaucoma drug therapy, especially among the subsets of NTG and OHT glaucomatous patients, even when the IOP is in normal range[20].

Ocular Perfusion Pressure (OPP) and Glaucoma

Ocular perfusion pressure (OPP) is expressed as the difference between the arterial blood pressure (BP) and the intraocular pressure (IOP), which is considered a substitute for the venous pressure. Because BP can be measured in several ways, it is necessary to distinguish among systolic, diastolic and mean perfusion pressures. Therefore, Ocular perfusion pressure (OPP) is the calculated difference between mean arterial blood pressure and IOP. It is an important parameter which determines the perfusion of the optic nerve head. OPP has been linked with glaucoma in many epidemiologic studies[21-23].

In particular, low OPP has been found to be a risk factor for the development of glaucoma. Both high IOP and low systemic blood pressure can lead to low OPP which in turn may lead to reduced ocular blood flow and ischemia of the optic nerve head[24,22].

The normal functioning of tissues depends on the maintenance of an adequate perfusion, with sufficient blood flow. Alterations of ocular perfusion could cause ischemia and poor irrigation of tissues in the optic nerve, thus having deleterious effects.

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These effects could be especially relevant for the causation of open angle glaucoma (OAG), an optic neuropathy of unknown origin, which presents with a distinctive pattern of nerve changes and visual field loss. One possible etiologic explanation for OAG pathogenesis concerns the 'vascular hypothesis', based on the premise that abnormal perfusion of the optic disc would be a major cause of glaucomatous damage[23].

The maintenance of ocular perfusion pressure depends on a complex regulation process that balances BP and IOP to ensure adequate irrigation of ocular tissues. Abnormal perfusion occurs when this process is altered due to vascular dysregulation, which has been proposed as an underlying cause for glaucoma damage[7,25]. Ocular perfusion pressure must remain above a certain minimum level (eg, ≥ 50mmHg), since too little pressure could cause ocular tissues to become ischemic. Although the venous pressure should be marginally higher than the IOP to allow for the adequate circulation of blood, IOP can effectively be substituted for venous pressure in the calculation of ocular perfusion pressure as shown below: MAP = DBP + 1/3 X (SBP – DBP) and MOPP = 2/3 X MAP – IOP. (Where MAP = mean arterial pressure and MOPP = mean ocular perfusion pressure).

Finally, many studies have shown that OPP was found to be more of a progressive risk factor in glaucomatous patients and developmental risk factor among the systemic hypertensive patients as compared with the normotensive patients[20]. Therefore, both high and low BP and OPP should be monitored with caution especially in patients with progressive glaucoma and systemic hypertension, despite their controlled IOP[20].

Cerebrospinal Fluid Pressure (CSF-p): A New Dangerous Factor

Other factors, like vascular dysregulation or impaired blood flow to the optic nerve, were also hypothesized as the risk factor for NTG[2,3], but a purely vasogenic pathogenesis of optic nerve damage contradicted with the optic disk appearance in NTG[2]. Volkov in the 1970s hypothesized that CSF-P could be a counter pressure of IOP and may be associated with glaucoma. Yablonsky et al[2]., also postulated that an abnormally low CSF-P may be the reason for barotraumatically induced glaucomatous nerve damage in NTG. Until recently, both retrospective studies by Berdahl et al[2,26] and prospective studies by iCOP study group found that the CSF-P is lower in NTG[2,26]. Moreover, the CSF-P data in POAG with normal IOP from another study by Jaggi et al[1]. also revealed a lower CSF-P. Therefore, seemingly the lower CSF-P better resolves the dilemma of IOP, and a classification of POAG with high IOP and POAG with low CSF-P can be adopted.

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As reported by Wang1, that in 1976, Volkov was the first to discuss the effect of low cerebrospinal fluid pressure (CSF-p) on glaucoma1. Yablonski et al[2]., found that chronic lowering of intracranial pressure (ICP) led to glaucomatous damage in the optic nerve and put forward the hypothesis that low CSFP might be involved in glaucoma. They lowered the CSFP to 4 mmHg in the cat model. One eye of the cat was cannulated to achieve 0 mmHg of pressure, while the other eye was the control. Three weeks later, the non-cannulated eye developed glaucomatous neuropathy, while the fundus of the eye that was maintained at a lower pressure as similar to the CSFP remained normal. That was the first animal model that suggested the role of the intraocular and intracranial pressure gradient in glaucoma. About three decades later, a retrospective study by Berdahl et al[26]., in 2008 and a prospective study by Beijing iCOP Study Group in 2010[14] found that 70–80% patients with normal tension glaucoma (NTG) had a relatively low ICP, which was the first time that the elevated trans-lamina cribrosa pressure difference (TLPD) caused by low ICP in NTG was identified through a clinical observational study[14,26]. After this breakthrough, a series of studies based on primate and rat models were carried out worldwide, providing growing evidence that the intraocular and intracranial pressure gradient or TLPD plays an essential role in the mechanism of optic nerve damage in OAG[1]. However, at the same time, a number of studies have also proved that the pressure gradient theory or TLPD theory alone cannot explain the development of all types of glaucoma, and it only serves as a potential pathogenesis for a certain proportion of NTG patients[2].

Trans-laminar Cribrosa Pressure Difference (TLPD): Is TLPD a Pathogenesis of Glaucoma?

The two optic nerves are the only cranial nerves which pass through the three sealing containers with pressure. Firstly, the RGCs and its axons belong to the ocular container. Then, the axons are surrounded by cerebrospinal fluid along its pathway until into the third container, the intracranial container. The connection between the first two containers is called the lamina cribrosa, which is the part of the sclera tissue that is pierced by the axons. The intracranial container is a bony structure without space to expand. Therefore, the intracranial pressure change could severely impair the neuro structures[26].

Meanwhile, the ocular container is constructed with compact fiber tissues, also with no space to expand. Normally, the IOP is a little bit higher than the intracranial pressure, which is 5–11 mmHg. When the pressure changes either in the intracranial or intraocular container, the pressure gradient might impose a sheared force on the site where the two pressures meet. The backward indentation of the lamina cribrosa of sclera is related to the increased IOP. The low intracranial pressure may also show the similar effects. In addition, the changes of pressure and composition of cerebrospinal fluid might also be associated with the glaucomatous

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optic neuropathy[26].

A prospective iCOP study by the Wang et al[1]., revealed that CSF-p can act as a counter pressure of IOP, in that TLPD is the pressure difference between IOP and CSF-p and may play an important role in glaucoma disease. They found that the TLPD is correlated with neuroretinal rim area and mean visual field defect (VFD)[1]. Also, the correlation coefficient of rim area / visual field defect and TLPD were also found to be higher than the association between the rim area / visual field defect and IOP or lumber CSF-p alone. Moreover, Berdahl et al[26]., discovered that TLPD was significantly corrected with cup-to-disc (C/D) ratio [26]. These evidences and more, suggest that TLPD may play a stronger role in the pathogenesis and pathophysiology of glaucoma disease, than IOP or CSF-p alone.

However, there is no method for assessment of the translaminar cribrosa pressure difference in the clinic. A single lumber CSF-p measurement can be used for calculating of TLPD, but it is not the real measurement of CSF-p found in the retrobulbar space of the orbit[2]. Therefore, it is important and urgent to develop a noninvasive way to get an estimate of the orbital CSF-p, since the direct measurement is not applicable in the clinic at the moment.

Conclusion

Many studies as aforementioned, include our study on "OPP among glaucomatous, systemic hypertensive and normotensive patients on drug therapy" showed a statistically significant relationship between blood pressure and ocular pressures among glaucomatous, systemic hypertensive and normotensive patients and they may be correlated to a V-shaped relationship, as it relates to the developmental and progression of glaucoma. The imbalance of ocular pressures differences may also play an important role in the pathogenesis of glaucomatous optic nerve damage. However, the major limitation of these newly discovered ocular pressures, is that there are no noninvasive or ophthalmic instrument used in measuring them directly or independently without deriving/calculating from other variables, as more research are encouraged.

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