

REVIEW ARTICLE

“Dual-pressure theory” in pathogenesis of glaucomatous optic neuropathy from the Beijing intracranial and intraocular pressure study

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Abstract

The mechanical theory of glaucoma indicates that high intraocular pressure (IOP) leads to glaucomatous optic nerve damage. However, nearly half of primary open-angle glaucoma patients with normal intraocular pressure also exhibit progression of what appears to be glaucomatous optic nerve damage. Our earlier prospective study identified for the first time that the relatively low intracranial pressure (ICP) is also an important risk factor for progressive glaucomatous injury of normal-tension glaucoma. When considering the results of studies in nonhuman primates, clinical research, large-scale natural-population studies, and basic laboratory investigations, a new understanding of the pathophysiology of glaucoma, the “Dual-Pressure Theory”, has been proposed. This theory states that “either high IOP or low ICP contributes to increasing the translaminar cribriform pressure difference; it is the pressure difference rather than the IOP alone that results in the glaucomatous optic neuropathy”. Here, we provide a systematic introduction to Dual-Pressure Theory relating to glaucoma, the form of a research map, an outline of basic laboratory investigations, the main methodology, and research updates.

KEYWORDS

dual-pressure theory, intracranial pressure, intraocular pressure, primary open-angle glaucoma, translaminar cribriform pressure difference

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INTRODUCTION

Glaucoma has traditionally been characterized by optic nerve damage and loss of visual field caused by increased intraocular pressure (IOP). However, the optic neuropathy of some glaucoma patients continues to worsen despite reducing the IOP to a normal range [1]. Moreover, some patients whose IOPs are in the normal range all the time also exhibit typical glaucomatous optic neuropathy [2]. These clinical phenomena suggest the potential presence of other risk factors involved in glaucoma. Currently, although many traditional theories have been applied to explain the underlying mechanism of glaucomatous optic neuropathy, such as vascular theory [3] and immune theory [4], none of these can fully elucidate the pathophysiology of glaucoma.

As is well-known, optic disc cupping is the typical structural feature of glaucoma. This reflects the progressive loss of retinal ganglion cell (RGC) axons and remodeling of the laminar connective tissues that both contribute to the characteristic increased cup-to-disk ratio [5]. One key structure that is involved with glaucomatous injury of the optic nerve is the lamina cribrosa. Located at the junction of the eyeball and the brain, it is subject to mechanical forces mainly from both the vitreous cavity and the subarachnoid cavity. Our previous prospective study found that patients with normal tension glaucoma (NTG) are inclined to have low cerebrospinal fluid pressure (CSFP), compared to cases with high-IOP primary open-angle glaucoma (POAG) patients and healthy individuals [6]. Thereafter, we performed numerous relevant studies assessing risk factors, causal factors, molecular mechanisms of pathogenesis, as well as population-based studies; these investigations were collectively called the Beijing Intracranial and Intraocular Pressure (iCOP) Study [7]. We verified that either abnormally high IOP or low intracranial pressure (ICP) could contribute to the intraocular–intracranial pressure gradient increase; this critical finding emphasized that it is the pressure difference rather than IOP alone that leads to glaucomatous optic neuropathy. This finding is known as “Glaucoma Translaminar Cribrosa Pressure Difference (TLCPD) Theory”, also briefly termed as “Dual-Pressure Theory” [8, 9]. Here, we review the scientific investigations that provide the basis for the Dual Pressure Theory of glaucoma.

THE ESTABLISHMENT OF THE “DUAL-PRESSURE THEORY”

At present, NTG is considered to be a type of POAG, often classified as those glaucoma patients with an untreated maximum IOP below 21 mmHg. NTG is commonly seen in the Asian population, and comprises the majority of POAG cases [10, 11]. The overall pooled proportion of NTG among POAG patients in the Chinese population was 70.0%, with a prevalence of 1.0% [12].

A decade ago, two clinical studies were carried out at the same time, a prospective study from our team [6] and a retrospective study from Allingham et al. [13], found that CSFP was lower in NTG

patients, while other POAG patients with high IOP had a higher CSFP. In 2012, another prospective observational study confirmed the existence of low CSFP in patients with NTG by assessing the optic nerve subarachnoid space width (ONSASW), a magnetic resonance imaging (MRI) indicator for orbital CSFP [7]. To identify the possible causal association between decreased ICP and NTG, we established four rhesus monkey models with implantation of a lumbar–peritoneal cerebrospinal fluid (CSF) shunt to reduce ICP. Spectral-domain optical coherence tomography (OCT), verified as a suitable tool for retinal structure follow-up [14], has been utilized to measure the retinal nerve fiber layer (RNFL) and optic nerve head (ONH). After a 1-year follow-up, two of four monkeys showed bilaterally a progressive reduction in neuroretinal rim area and volume, a reduction of the retinal nerve fiber layer thickness between 12% and 30%, and an increase in cup-to-disc area ratios. The third monkey developed a bilateral splinter-like disc hemorrhage, and the fourth monkey exhibited no abnormal morphologic alteration throughout the follow-up [15]. This study revealed for the first time that lowering CSFP could induce glaucoma-like optic neuropathy in monkeys, indicating that lower ICP could serve as an important risk factor for the occurrence of NTG. Based on the previous studies, we hypothesized that the translaminar cribrosa pressure difference (TLCPD, $TLCPD = IOP - ICP$), rather than IOP or ICP alone, is more significantly correlated with glaucomatous optic neuropathy [16].

During this period, three natural population-based studies were carried out to evaluate the relationship between TLCPD and glaucomatous optic neuropathy, including the Beijing Eye Study 2011 (3468 subjects) [17], the Central India Eye and Medical Study (4711 subjects) [18], and the Korean National Health and Nutrition Examination Survey (12,743 subjects) [19]. In the Beijing Eye Study 2011, led by Beijing Tongren Hospital, eye examination and intracranial pressure measurement (formula: $ICP [mmHg] = 0.44 \times \text{Body Mass Index [kg/m}^2] + 0.16 \times \text{Diastolic Blood Pressure [mmHg]} - 0.18 \times \text{Age [Years]} - 1.91$) were performed on 3468 enrolled volunteers; the results revealed a higher prevalence of glaucoma in patients with a lower CSFP or higher TLCPD. Intriguingly, it was also noticed that taller individuals had a lower prevalence of open-angle glaucoma (OAG) [17]. Moreover, in OAG, but not in angle-closure glaucoma (ACG), calculated TLCPD could serve as a better biomarker for the presence of glaucoma and the severity of glaucomatous optic neuropathy [20]. In collaboration with the Ruprecht-Karls-University of Heidelberg, we subsequently performed the Central Indian Eye Disease Study, and verified that the TLCPD in OAG patients, rather than ACG, showed a better association with glaucoma presence and the degree of glaucomatous optic neuropathy [18]. In addition, Kim and colleagues at Yonsei University carried out the Korean National Health and Nutrition Examination Survey on 12069 subjects and identified that TLCPD was significantly related to the prevalence of NTG [19].

The Consensus and Suggestions on POAG Ocular-Cranial Pressure Gradient in China (2017) comments that the optic nerve

is located in both the intraocular cavity and the intracranial cavity. It also recognized that there is a difference between IOP and ICP at the lamina cribrosa that forms a pressure gradient along the optic nerve; this pressure difference is called TLCPD. Either high IOP or low ICP could contribute to the elevated TLCPD, thus leading to glaucomatous optic nerve damage, an observation termed the “Dual-Pressure Theory” (Figure 1). This innovative finding is cited and described in the Book “Glaucoma-Medical Diagnosis and Therapy”: “These studies have altered our understanding of the relevant pressure forces that may be at play in NTG and have opened new avenues of research” [21]. However, the questions of how the glaucomatous damage is initiated under the status of elevated TLCPD and what are the essential cell and molecular events involved in this process still need further exploration.

BASIC RESEARCH OF “DUAL-PRESSURE THEORY”

The optic nerve head is the site of primary injury that appears during the development of glaucoma, particularly at the lamina cribrosa where the axons of the RGC enter the eye. RGC axons in this region generally lack myelination and are directly surrounded by astrocyte endfeet. Astrocytes participate in maintaining the integrity of the blood–retina barrier together with vascular endothelial cells and pericytes, and the remaining space is filled with the extracellular matrix. Vascular endothelial cells, pericytes, RGC axons, and glial cells (such as microglia and astrocytes) together constitute the principal functional unit in the ONH region known as the neurovascular unit (NVU) [22]. When NVU physiological function is normal, the unit senses regional mechanical stress, neurotransmitters released by neurons, or other types of biological signals, and transmits electrochemical signals to nearby blood vessels or glial cells that trigger the downstream biological responses. The interaction between neurons, glial cells, and blood vessels within the NVU is crucial; any abnormality in these components can disrupt the microenvironment's homeostasis [23]. In this section, we discuss the cellular and molecular mechanisms of the NVU and their pathophysiological implications in glaucoma and how the function is altered with glaucomatous optic neuropathy.

Dysfunction of axonal transport affected by elevated TLCPD

RGCs have one of the highest rates of oxygen consumption of any cell type in the human body, making it heavily reliant on the mitochondria for energy production. RGC axons in the ONH region are unmyelinated; axonal transport in these mitochondria-enriched axons refers to the process whereby axonal vesicles are transported along microtubules by motor proteins such as dynein and kinesin [24]. The RGC axonal transport has two opposite directions. In the orthograde direction, proteins are transported from the cell body to the synapse, namely the eye-to-brain direction. In contrast, there is retrograde axonal transport in which neurotrophic factors move from the synapse to the cell body, namely the brain-to-eye direction [25].

The dysfunction of the axonal transport has been considered as a key pathogenic characteristic in glaucomatous optic neuropathy [25]. High IOP is known to affect axonal transport [26]. However, the influence of low ICP on axonal transport is not as widely studied. To investigate the influence of CSFP reduction on axonal transport and its variation with IOP elevation, we first established the CSFP-reduction rat model by draining cerebrospinal fluid from the cisterna magna, and analyzed the orthograde and retrograde axonal transport by using rhodamine- β isothiocyanate and fluorogold, respectively. The results suggested that a short-term (6 h) reduction of CSFP could reduce by almost 50% both orthograde and retrograde axonal transport [27]. A further study with 1-, 3-, and 6-h CSFP drainage in rats also demonstrated that the dysfunction of axonal transport occurred in a time-dependent manner. The dysfunction can be observed by 3 h of CSFP reduction, and by 6 h there is the longest-lasting and most severe decrease of axonal transport [28]. Moreover, we noticed an obvious accumulation of dynein motor protein at the optic nerve head and the retina, and a reduction of kinesin motor protein in the optic nerve with elevated TLCPD, suggesting the dysfunction of mitochondria-driven axonal transport [20]. Correspondingly, our recent bioinformatic analysis study showed that the differentially expressed proteins at day 1 and day 7 after ocular hypertension modeling in the retina, ONH, and optic nerve, which were associated with glutathione metabolism, mitochondrial dysfunction/oxidative phosphorylation, oxidative

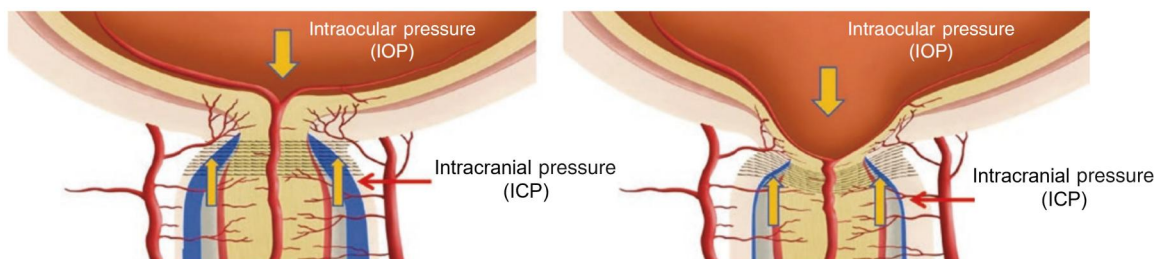


FIGURE 1 Diagram of the “Dual-Pressure Theory”. Left: the physiological condition of TLCPD formed by IOP and ICP (yellow arrows). Right: Lower ICP could lead to TLCPD elevation, which is the essential risk factor for the progression of glaucoma. Dual pressure = IOP versus ICP. IOP, intraocular pressure; ICP, intracranial pressure; TLCPD, translamina cribrosa pressure difference. Reprinted with permission from [77].

stress, microtubule, and crystallin [29]. These results implied an essential role of the mitochondria in the progression of glaucoma at the molecular level.

Impairment of retinal microcirculation affected by elevated TLCPD

The impact of high IOP on retinal microcirculation is well studied, and the presence of a significant decrease in retinal blood flow and velocity under high IOP, via both clinical and basic laboratory investigations, has been reported [30, 31]. Our previous study also found microvascular impairment (bilateral splinter-like disc hemorrhage) in the rhesus monkey model with ICP reduction after a 1-year follow-up [15].

To further investigate the potential relationship between TLCPD and retinal microcirculation, we recruited 50 healthy subjects and assessed the indexes of retinal and nailfold microcirculation; the results suggested that low nailfold capillary density and abnormalities are associated with a reduced RNFL thickness and retinal vessel density, thus providing a basis for studies on ocular diseases with microvascular abnormalities [32]. Intriguingly, the manifestations of microcirculation dysfunction share typical features of Flammer syndrome, for instance, low nailfold capillary perfusion [33]. Flammer syndrome refers to primary vascular dysregulation, accompanied by a cluster of symptoms and signs that may occur in healthy people as well as people with a variety of microvascular diseases. Patients with Flammer syndrome may react to a variety of stimuli, including cold or emotional stress. Nearly all organs' microcirculation, particularly the eye, can be involved [34]. It has been shown that patients with Flammer syndrome exhibit vasospasm symptoms with a short-time blood perfusion reduction in the optic nerve, and that they have a potential susceptibility to NTG [35]. Patients with both Flammer syndrome and NTG often display optic disc bleeding, increased retinal venous pressure, astrocyte activation, and increased retrobulbar flow resistance. These findings suggest a close association between ocular blood flow dysfunction and glaucoma pathogenesis [33, 36].

Based on the previous findings, subsequent studies have focused on the retinal vascular changes before and after decreasing CSFP. We collected the fundus photographs at day 1, day 4, and day 7 after CSFP reduction modeling in rats, and it was observed that the mean diameters of the retinal artery and vein gradually narrowed, and the vessel diameter changes were more apparent in the retinal artery than in the vein [37]. Apart from retinal blood vessels, a significant decrease in the subfoveal choroidal thickness has also been observed 15 min after diagnostic lumbar puncture in human subjects in another study [38]. Similarly, some clinical studies reported a narrower retinal diameter in glaucoma patients when compared with a healthy population, and the sites of retinal vascular stenosis are usually accompanied by a thinner RNFL. We hypothesized that dysfunction of retinal microcirculation cannot meet the oxygen

requirement of the retina, thus potentially accelerating the glaucomatous progression [39, 40].

Glia-mediated mechanical stress signal transduction in elevated TLCPD condition

Recent literature identified that optic nerve degeneration of glaucoma may share a similar neuroinflammatory response with other central nervous system diseases such as Alzheimer's disease and Parkinson's disease [41]. On the one hand, although the eye and the cranial cavity are two separate anatomical chambers, these two cavities are connected by the optic nerve, and IOP and ICP interact via CSF-containing subarachnoid space around the optic nerve. On the other hand, both of the organs are similar in microenvironment, including immune features, neurotrophic factors, vascular regulation, and biological barrier [42].

Our previous finite element analysis investigated the accumulative biomechanical sites and strain-induced biological effects on the ONH. Increasing TLCPD significantly enhanced the strain in the optic nerve head, with the largest strains occurring in the pre-laminar neural tissue and lamina cribrosa [43]. Comparatively, CSFP reduction showed a smaller increase in strain than in IOP elevation at the site of the ONH even at the same level of TLCPD change, indicating a different potential role of low ICP in the pathogenesis of glaucoma [43].

It is known that the mechanical strain derived from high IOP contributes to the activation of retinal glial cells, such as microglia and astrocytes. Transcriptomic evidence identified the upregulated immune/inflammatory-related genes at an early stage in the large animal glaucoma model, before morphologically detectable RGC loss [44]. We have detected that the anterograde axonal flow from the retina to both the lateral geniculate nucleus and the superior colliculus was obstructed in experimental low CSFP and high IOP eyes of rats, accompanied by the selective early glial reactivity induced by TLCPD elevation [45]. Similar retinal glial cell activation has been also observed in the retina and ONH sites of Tg-MYOC^{P370L} mice, a transgenic mouse model for POAG research and developed via the CRISPR/Cas9 system [46]. Cheng et al. [47] further identified the characteristics of glia-mediated inflammation, that occurred in rats with TLCPD elevation induced by low ICP, and involving excessive activation of retinal microglia and astrocytes, blood-retinal barrier compromise, and secondary T cell-mediated adaptive immunity, altogether leading to the RGC dysfunction in low ICP rat eyes. Of note, the glial activation level is more dramatic in high IOP rats than in the low ICP rat retinas. The unique patterns of T-lymphocyte imbalance were also detected in low ICP, high IOP, and normal rats, and these patterns may be utilized as diagnostic indicators to distinguish NTG, POAG, and healthy populations.

Astrocytes account for over 60% of the total number of cells within the ONH, providing structural, nutritional, and metabolic support to RGC axons in developmental, physiological, and pathological progression [48]. To date, a cluster of mechanosensitive channels such

as integrin family, transient receptor potential (TRP) family, and Piezo family have been identified as being distributed on the cell membrane. These channels help to convert mechanical stress into an electrochemical signal, thus regulating a series of biological processes, including cell proliferation, cell deformation, cell migration, cytokine secretion, and extracellular matrix remodeling, etc. [49, 50]. For instance, the classic integrin-FAK signaling pathway regulates the cytoskeletal rearrangement of astrocytes in the ONH [51]. The TRPV ion channel family functions in mechanical stimuli-driven intracellular calcium regulation, leading to inflammatory response and cell apoptosis. It has been observed that the TRPV family is upregulated in retinal tissues of the high IOP mouse model [52]. Previous study performed in lung tissues has indicated that TRPV4, on alveolar epithelial and pulmonary capillary endothelial cells, is activated by mechanical stress in ventilator-associated lung injury, resulting in an increased cellular calcium flow, and in secondary damage to the integrity of the alveolar epithelial barrier and release of inflammatory factors [53]. Up to now, the specific regulative role of the TRPV family in ONH astrocytes and its association with typical pathological alternation-ONH cupping of glaucoma are not fully understood.

As mentioned above, astrocytes are the main cell types of the ONH. Thus, we confirmed that the mechanosensitive ion channel Piezo is distributed on astrocytes *in vivo*. Piezo1 mRNA is expressed in all parts of the eye, especially overexpressed in the site of the ONH, while Piezo2 is only expressed in the cornea, iris, and sclera. In addition, we identified that Piezo1 is necessary but insufficient for ONH astrocyte proliferation through yes-associated protein (YAP) nuclear localization and YAP-target cell cycle-associated factors,

including cyclin D1 and c-Myc. These results showed that Piezo1 is an essential regulator in cell cycle progression in ONH astrocytes [54]. Other studies verified that chemical inhibition or genetic ablation of these mechanosensitive channels significantly ameliorates pathological phenotypes of optic nerve degeneration caused by IOP elevation, indicating the potential therapeutic roles of targeting mechanosensitive channels in glaucoma [52, 54, 55].

MEASUREMENT TECHNIQUES OF TLCPD

TLCDP refers to the difference between the values of IOP and ICP. IOP measurement methods such as Goldmann applanation tonometry, rebound tonometry, and noncontact tonometry are mature and widely utilized in clinics. Traditionally, lumbar puncture is the direct approach to measure ICP, which is usually applied to patients with neurological diseases. However, in POAG patients, lumbar puncture is controversial when used to monitor the ICP because of its invasiveness.

The orbital subarachnoid space surrounding the optic nerve is continuous with the CSF and can be visualized by using MRI. The Beijing iCOP study utilized a T2-weighted fat-suppressed fast recovery fast spin echo sequence, and three oblique coronal slices perpendicular to the optic nerve at 3, 9, and 15 mm behind the globe were captured to obtain the orbital subarachnoid space width (OSASW) (Figure 2). After adjusting for the body mass index (BMI) and mean arterial blood pressure (MABP), algorithms for the relationship between CSFP and OSASW were calculated as follows:

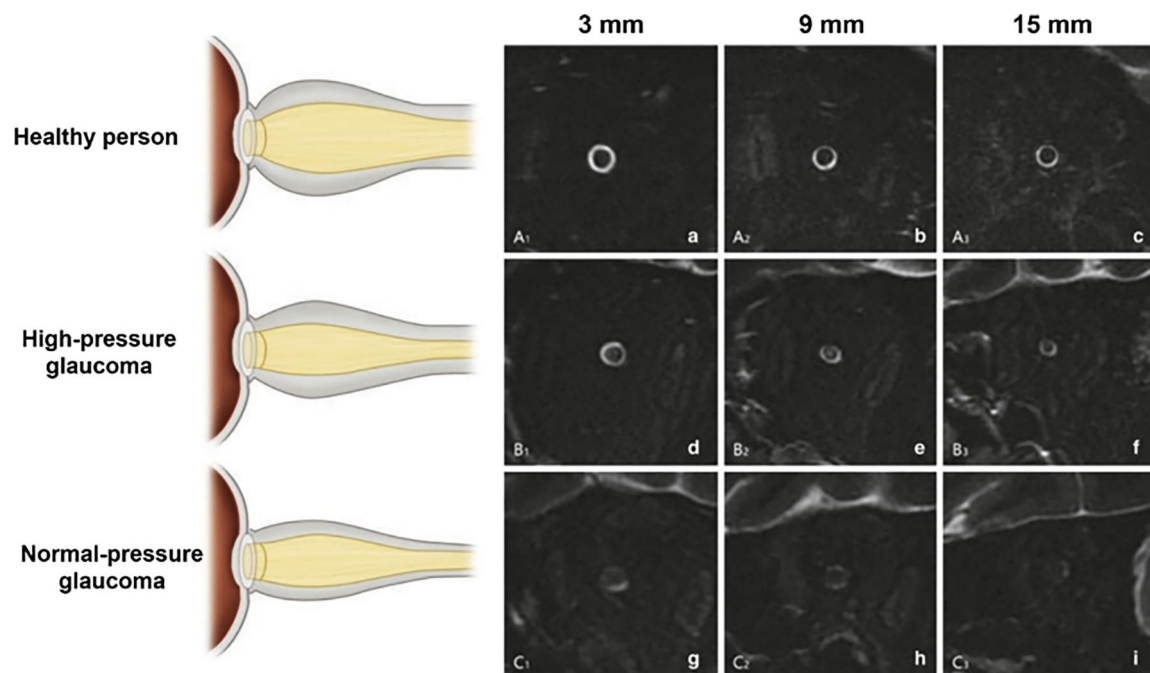


FIGURE 2 Oblique magnetic resonance coronal T2WI-FRFSE slices perpendicular to the optic nerve at 3, 9, and 15 mm behind the globe with fat suppression were captured to visualize the optic nerve sheath complex, shown as a faint white circular ring in the center of the image. Reprinted with permission from [78].

- (a) CSFP [mmHg] = $9.31 \times \text{OSASW [mm}^2\text{]} \text{ (at 3 mm)} + 0.48 \times \text{BMI [kg/m}^2\text{]} + 0.14 \times \text{MABP [mmHg]} - 19.94$;
- (b) CSFP [mmHg] = $16.95 \times \text{OSASW [mm}^2\text{]} \text{ (at 9 mm)} + 0.39 \times \text{BMI [kg/m}^2\text{]} + 0.14 \times \text{MABP [mmHg]} - 20.90$;
- (c) CSFP [mmHg] = $17.54 \times \text{OSASW [mm}^2\text{]} \text{ (at 15 mm)} + 0.47 \times \text{BMI [kg/m}^2\text{]} + 0.13 \times \text{MABP [mmHg]} - 21.52$.

The intraclass correlation coefficients between lumbar CSFP and MRI-calculated CSFP of these three formulas are 0.8, 0.87, and 0.87, respectively [56]. MRI-assisted OSASW measurement can be regarded as one of the promising indicators for noninvasive evaluation of ICP, and has been utilized in several subsequent studies. However, the cost of MRI-based ICP measurement is relatively high and is difficult to promote in primary hospitals.

The Beijing iCOP study has revealed that low BMI relates to low ICP; thus, low BMI could be considered as a risk factor for NTG occurrence [57–59]. According to this important finding, the formula for noninvasive ICP calculation has been established:

$$\text{ICP [mmHg]} = 0.44 \times \text{BMI [kg/m}^2\text{]} + 0.16 \times \text{Diastolic Blood Pressure [mmHg]} - 0.18 \times \text{Age [Years]} - 1.91 \text{ [17].}$$

The formula has been verified and used in several large-scale natural population studies including the Beijing Eye Study [17], Handan Eye Study [60], and Central Indian Eye Disease Study [18]. The technique has been evaluated as “a simple and elegant solution to the challenge of clinically non-invasive ICP measurement [61]”.

Recently, Zhang et al. [62] tried to utilize transorbital ultrasonography to measure ICP; the results showed the size of the area of the ONSAS (ONSASA) has a high correlation with ICP compared with the optic nerve sheath diameter (ONSD) and ONSASW at 3 mm behind the globe, and the weighting function for prediction of the ICP was established based on ONSASA:

$$\text{Noninvasive ICP [mmHg]} = 2.050 \times \text{ONSASA [mm}^2\text{]} - 0.051 \times \text{BMI [kg/m}^2\text{]} + 0.036 \times \text{MABP [mmHg]} - 5.837.$$

The sensitivity and specificity of ONSASA value for ICP prediction could reach 1.00 and 0.92, respectively, when a 20 mmHg cutoff point for ICP grading was set. To update, this measuring method has been applied for early monitoring of spaceflight-associated neuro-ocular syndrome (SANS). SANS is featured as fluid redistribution in the optic nerve sheath and the cerebrospinal fluid cavity due to long-term exposure to the unique microgravity environment during extended spaceflight [55, 63]. This novel and noninvasive method could help rapidly obtain a relatively accurate ICP through a mathematical formula based on ultrasonography; its future application in the detection and assessment of NTG is promising.

LATEST UPDATES OF THE “DUAL-PRESSURE THEORY” STUDY

Establishment of TLCPD reference values

The “Dual-Pressure Theory” has been widely accepted, not only for consideration in glaucoma but also for approaches to multiple ophthalmic and neurological diseases including idiopathic intracranial

hypertension [64], SANS [55], and high-altitude retinopathy [65]. However, no standard reference value of TLCPD has been set up; the direct subtraction of IOP and ICP values from different studies may bring statistical bias caused by complicated influencing factors such as measurement approaches, inclusion criteria of subjects, races, measuring position, and so on. To solve this problem, we conducted a cross-sectional study containing 526 quasi-healthy subjects with 776 eyes that required lumbar puncture for medical reasons. The ICP value was acquired by lumbar puncture in the left lateral decubitus position, and IOP was obtained using a handheld iCare tonometer in a seated position of patient. After careful analysis, we reported the reference values for TLCPD in the Chinese population: TLCPD was 4.4 ± 3.6 mmHg, and the 95% reference interval of TLCPD was from -2.27 to 11.94 mmHg [66]. The establishment of the TLCPD reference interval provides the primary and essential basis for the diagnosis and treatment of glaucoma and various TLCPD-imbalance ocular or neurological diseases.

Association between body mass index and TLCPD

It has been shown that TLCPD was significantly negatively correlated with BMI [66]. Another clinical interventional study containing 71 subjects also exhibited a significantly positive correlation between CSFP and BMI [57]. Similarly, Berdahl et al. [67] conducted a retrospective study with 4235 Caucasian subjects, and the results confirmed the positive and linear relationship between CSFP and BMI, while IOP was not influenced by BMI, suggesting that lower BMI may be a risk factor for POAG, especially for NTG. Pasquale et al. [68] performed a prospective large-scale cohort study, and they found that each unit increase in the BMI was associated with a 6% reduced risk of POAG in women with IOP of 22 mmHg or less at diagnosis.

Previous clinical trials reported that females younger than 43 years old who underwent bilateral oophorectomy have a higher risk of POAG [69], and hormone replacement therapy could reduce the risk of POAG in postmenopausal women [70]. These studies confirmed the protective role of estrogen in relation to the optic nerve. In addition, it is reported that a higher BMI is related to higher circulating estrogen levels in postmenopausal women. For postmenopausal females, estrogen is converted from adipose tissue [71]; therefore, NTG patients who possess double-risk factors including “low BMI” and “low estrogen level” may exhibit a more rapid progression of visual field damage. For these patients, it may be beneficial to support corresponding therapy to help increase their BMI appropriately. In addition, an appropriate estrogen supplement should be given under professional guidance.

Preliminary exploration of the association between Vitamin A and TLCPD

Vitamin A (VA) is a generic term for a group of organic compounds that include retinol, retinal, retinoic acid, and provitamin A carotenoids. Vitamin A deficiency, primarily caused by insufficient VA intake, is a

common public health issue worldwide [72]. Previous studies revealed that a low dietary intake of retinol equivalents is associated with an increased risk of glaucoma in Europeans [73], Africans [74], and Japanese Americans [75]. Our prospective cross-sectional study included 101 NTG patients, 106 patients with high-pressure POAG, and 138 healthy control subjects, and assessed the relationship between serum retinol concentration and NTG. We noticed that the serum retinol concentrations were significantly lower in NTG patients compared with POAG or control subjects, and the serum retinol concentration in 37.62% of patients with NTG met the diagnostic criteria of marginal vitamin A deficiency [76]. Intriguingly, serum retinol was verified to positively correlate with ONSD [7], a reliable imaging marker for ICP. Further multivariate logistic regression revealed that lower serum retinol may be associated with the incidence of NTG [76]. Recently, our unpublished data have implied that retinoic acid has a protective role in RGCs of mice with optic nerve crush, suggesting the possibility that the oral supplement of retinoic acid could partly alleviate the RGC loss.

SUMMARY AND PROSPECT

This article systematically reviews the “Dual-Pressure Theory” relating to glaucoma, mainly based on The Beijing iCOP Study. There is emphasis on the importance of an abnormally high TLCPD in the pathophysiology of glaucoma. Moreover, the novel therapeutic insight into conciliating the abnormally elevated TLCPD including lowering IOP and increasing ICP has been underscored, which might help slow glaucoma worsening. Based on present studies, we speculate that NTG patients with a rapid progression of optic nerve damage should be treated with ocular hypotensive agents to reduce the IOP by 30% from baseline. If there is insufficient IOP lowering, surgery should be considered to decrease IOP to 8–12 mmHg. Measures aiming to increase ICP may also be beneficial. Potential methods for this purpose identified in our studies include moderately increasing BMI, supplementing VA, antioxidants, and medicines to increase optic nerve blood perfusion, etc. [9]. Overall, the proposal of “Dual-Pressure Theory” enhances the understanding and provides the original insights for the clinical diagnosis and management of glaucoma.

AUTHOR CONTRIBUTIONS

Ying Cheng: Conceptualization (equal); visualization (lead); writing – original draft (lead); writing – review & editing (lead). **Mayinuer Yusufu:** Writing – original draft (supporting). **Robert N. Weinreb:** Writing – review & editing (supporting). **Ningli Wang:** Conceptualization (lead); data curation (lead); funding acquisition (lead); investigation (lead); methodology (lead); supervision (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known conflict of interest. The authors are responsible for the content and writing of the paper.

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