Road Map for the Pathogenesis of Glaucomatous Optic Neuropathy

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Glaucoma has been recognized for several hundred years. Initially, it was defined as an eye disease of characteristic structural change of optic nerves and specific visual field change caused by increased intraocular pressure (IOP). However, when we comprehended the development and progress of glaucoma only limiting to the perspective of the eye itself, we could hardly interpret some problems we encountered clinically. For example, some glaucoma patients' IOP is in the normal range (normal-tension glaucoma); some people have long-term IOP higher than the normal range, and there is no pathological change of their optic nerves though; some glaucoma patients have IOP controlled in normal range by drugs or surgeries, while impairment of their optic nerves and vision is still gradually worsening; and some patients with disease of the nervous system have glaucoma at the same time. Are those phenomena occasional, or are there some correlations not yet discovered? In order to answer above questions, the ophthalmologist have started to explore the structures beyond the eyeball per se, and proposed an innovative theory of "trans-lamina cribrosa pressure gradient", a concept that defines glaucoma as "a disease of central visual pathway" by considering both ocular pathological changes and body fluid circulation, which shall open a new chapter in glaucoma study.

In this article, we reviewed some milestone studies of "trans-lamina cribrosa pressure gradient in glaucoma" to retrospect the road map for the pathogenesis of glaucomatous optic neuropathy (Fig. 1.1).

In 1976, Volkov VV first discussed about the effect of low CSF pressure on glaucoma [1]. In 1979, Yablonski ME, Ritch R, and Pokorny KS found chronic lowering of intracranial pressure led to glaucoma damage of the optic nerve and that simultaneous lowering of IOP prevented damage [2]. At this time, the hypothesis that low cerebrospinal fluid pressure (CSFp) might be involved in glaucoma was proposed.

Thirty years later, two clinical studies, a prospective study from Tongren Hospital [3] and a retrospective study from Duke [4], both found that cerebrospinal fluid pressure was low in NTG patients. These are pioneer clinical studies focusing on the role of CSFp in the pathogenesis of glaucoma. The same study groups did some further studies based on the concept of trans-lamina cribrosa pressure difference (TLPD). The results suggested that the TLPD as compared to the IOP was significantly better correlated with cup to disc ratio, rim width, and visual field loss [5]. This may provide some indirect evidence that the CSFp might play some role in the pathogenesis of glaucomatous optic neuropathy.

Followed by this lead, the same study groups found that body mass index (BMI) had a positive linear relationship with CSFp, whereas IOP was unaffected by BMI and CSFp [6, 7]. This finding indicated that the higher BMI may be a protective factor for glaucoma.

In 2011, Mader et al. [8] first reported that after long-duration space flight, optic disc edema, globe flattening, choroidal folds, and hyperopic shifts were observed in astronauts. This finding proved that zero-gravity environment may cause CSFp elevation and a reversal TLPD. As the optic change of the astronauts was opposite of the glaucomatous neuropathy, we may speculate that the TLPD-related conditions existed and breaking the balance of difference between IOP and CSFp may cause either side of the optic neuropathy.

In practice, lumbar puncture is often used to measure the CSFp. However, the CSFp at the lumbar area cannot represent the CSFp around the optic nerve. In addition, there's no indication for POAG patients to perform the lumber puncture. Therefore, our team proposed a noninvasive method to measure the orbital CSFp with MRI [9]. According to the image, we found that CSFp around the optic nerve was decreased in NTG patients, which further approved our former findings (Fig. 1.2).

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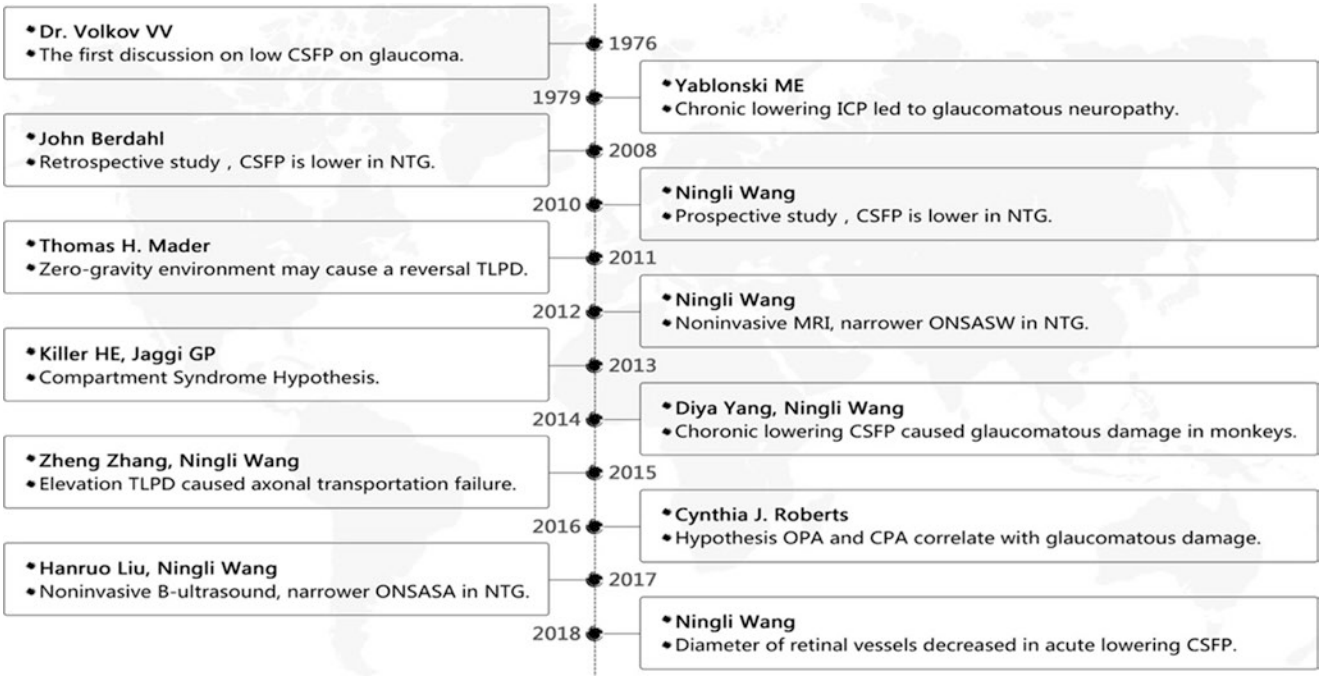

Fig. 1.1 Milestone studies of trans-lamina cribrosa pressure difference

At the same time, Dr. Killer et al. [10] described a compartment syndrome of subarachnoid space of the nerve in glaucoma first. In the study, they found that the circulation of CSF in the subarachnoid space of the nerve and the brain cannot communicate with the CSF around the ventricle, so the CSF there just keep static around the optic nerve. This is the new hypothesis that CSF circulation may be disrupted and a chemical toxic effect may damage the optic nerve.

Recently, our team analyzed the correlation between ICP and IOP in normal dog models and found three different stages of the ICP-IOP relationship [11]. There is an ICP-IOP dependent zone where ICP and IOP change in parallel, so the TLPD is unchanged. Right below the breakpoint, which is the second stage, there is also an ICP-IOP independent zone, where IOP changes no longer parallel ICP changes and lead to an increasing TLPD. We proposed that the imbalanced relationship between ICP and IOP may play a role in the glaucomatous optic neuropathy in patients with lower ICP.

Beijing iCOP study group made the monkey model by lowering of CSFp by placing the lumbar peritoneal shunt [12]. After 1 year, we found five out of eight eyes show optic neuropathy changes similar to glaucoma (Fig. 1.3). Then, we did the comparative study between high IOP and low ICP monkey model and found that nearly all the glaucomatous optic neuropathy-related parameters showed similar changes; however, the deformation and thinning of lamina cribrosa only existed in the high IOP model. Moreover, after another year of observation, there were no any further changes or damages in the optic nerve and nerve fiber layers in monkeys. Why does optic damage ceased?

The same study group used the infinite analysis method to answer the question. In the infinite model, at the same level of TLPD, elevated IOP caused more severe deformation than that in reduced CSFp condition. Moreover, lower CSFp group exhibited less cup to disc ratio change than that in the higher IOP group.

Zhang et al. [13] used the lower CSFp rats to observe the optic changes without the deformation of lamina cribrosa. They found that both short-term lowering CSFp and acute rising in IOP were all associated with a disturbance of both the orthograde and retrograde axonal transport (Fig. 1.4). Furthermore, the results showed an accumulation of dynein IC (intermediate chain) at the optic nerve head and retina when the TLPD dramatically increased. Meanwhile, the kinesin HC (heavy chain) immunoreactivity in the optic nerve fiber axons reduced. From this study, we note that the low CSFp or mild IOP elevation can cause the failure of axonal transport, while high IOP cannot just cause the failure of axonal transport but also the direct stress on laminar RGC loss. Therefore, a new hypothesis was proposed that lower CSFp may only affect axonal transport but have no effect on lamina cribrosa structure, although TLPD increased with higher IOP or lower CSFp.

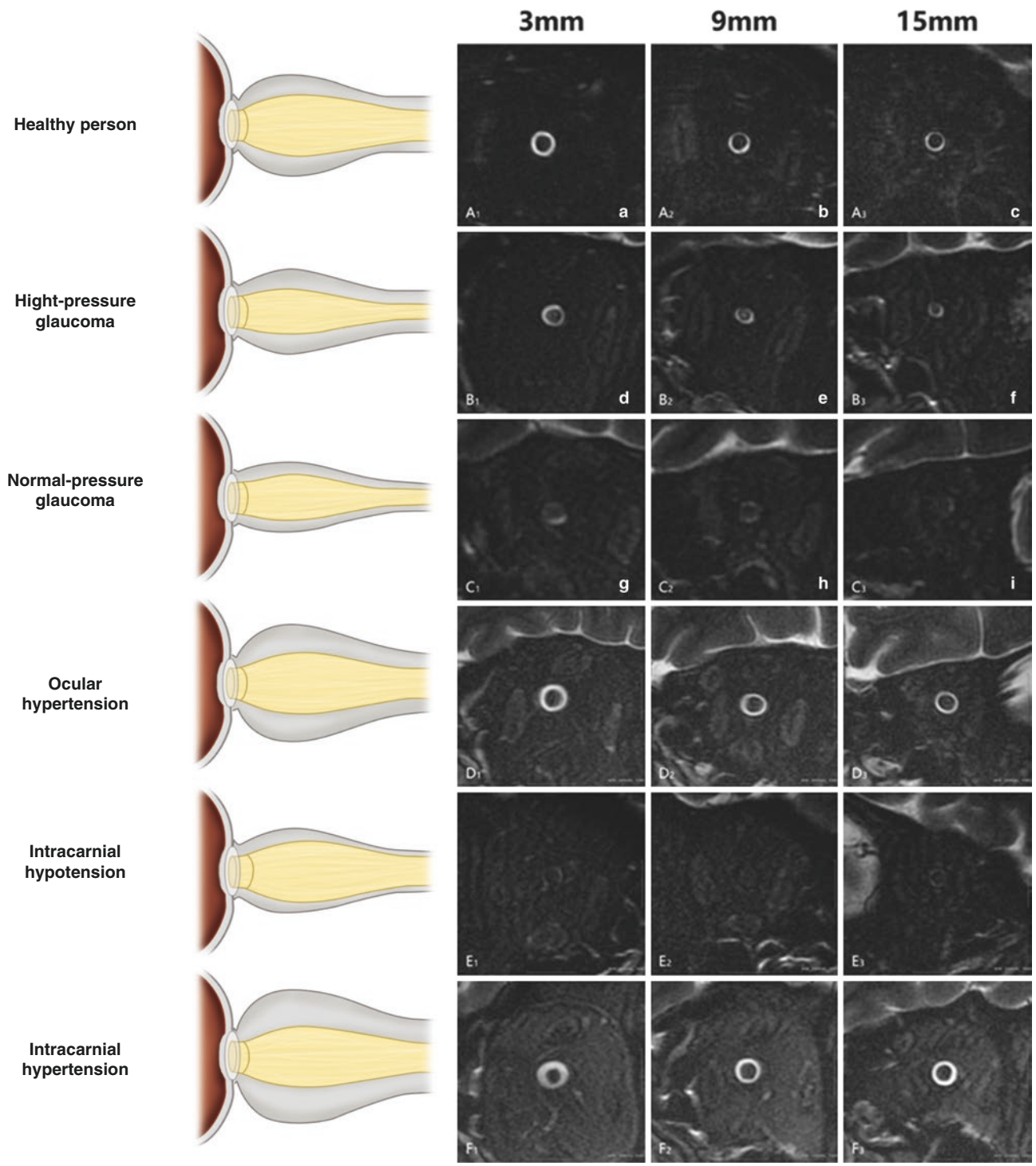

Fig. 1.2 Oblique magnetic resonance coronal T2WI-FRFSE image with fat suppression for demonstrating the optic nerve sheath complex (digital field of view 4, window width 2000, window level 1000), taken at 3 mm (**a**, **d**, **g**), 9 mm (**b**, **e**, **h**), and 15 mm (**c**, **f**, **i**) behind the globe. (**a**–**c**) A 57-year-old healthy man. Note the decreasing optic nerve diameter and ONSASW with increasing distance to the globe. (**d**–**f**) A 45-year-old man with high-pressure glaucoma. Note the optic nerve diameter is smaller than in (**a**–**c**). The ONSASW relatively wide and bright. (**g**–**i**) A 40-year-old man with normal-pressure glaucoma. Note the faint optic nerve subarachnoid space (Reprinted with permission from Wang N, Xie X, Yang D, Xian J, Li Y, Ren R, Peng X, Jonas JB, Weinreb RN. Orbital cerebrospinal fluid space in glaucoma: the Beijing intracranial and intraocular pressure (iCOP) study. Ophthalmology, 2012, 119: 2065-2073 e2061)

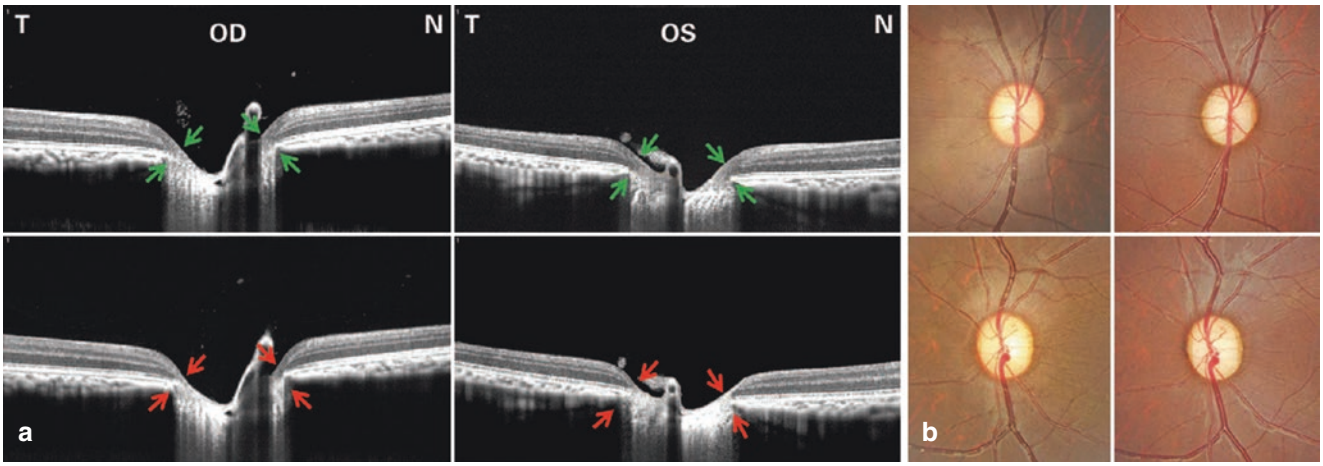

Fig. 1.3 (**a**) Optical coherence tomograms of the optic nerve head in monkey 1 (OD) and monkey 3 (OS) after lumbar-peritoneal shunting and reduction of cerebrospinal fluid pressure, taken at baseline (upper row) and at 12 months of follow-up (lower row). Note reduction in neuroretinal rim tissue. (**b**) Fundus photograph at baseline (left column) and at 12 months after lowering of cerebrospinal fluid pressure (right column) of monkey 1. Note decreased visibility of the retinal nerve fiber layer (Reprinted with permission from Yang D, Fu J, Hou R, et al. Optic neuropathy induced by experimentally reduced cerebrospinal fluid pressure in monkeys.[J]. Invest Ophthalmol Vis Sci, 2014, 55(5):3067–3073)

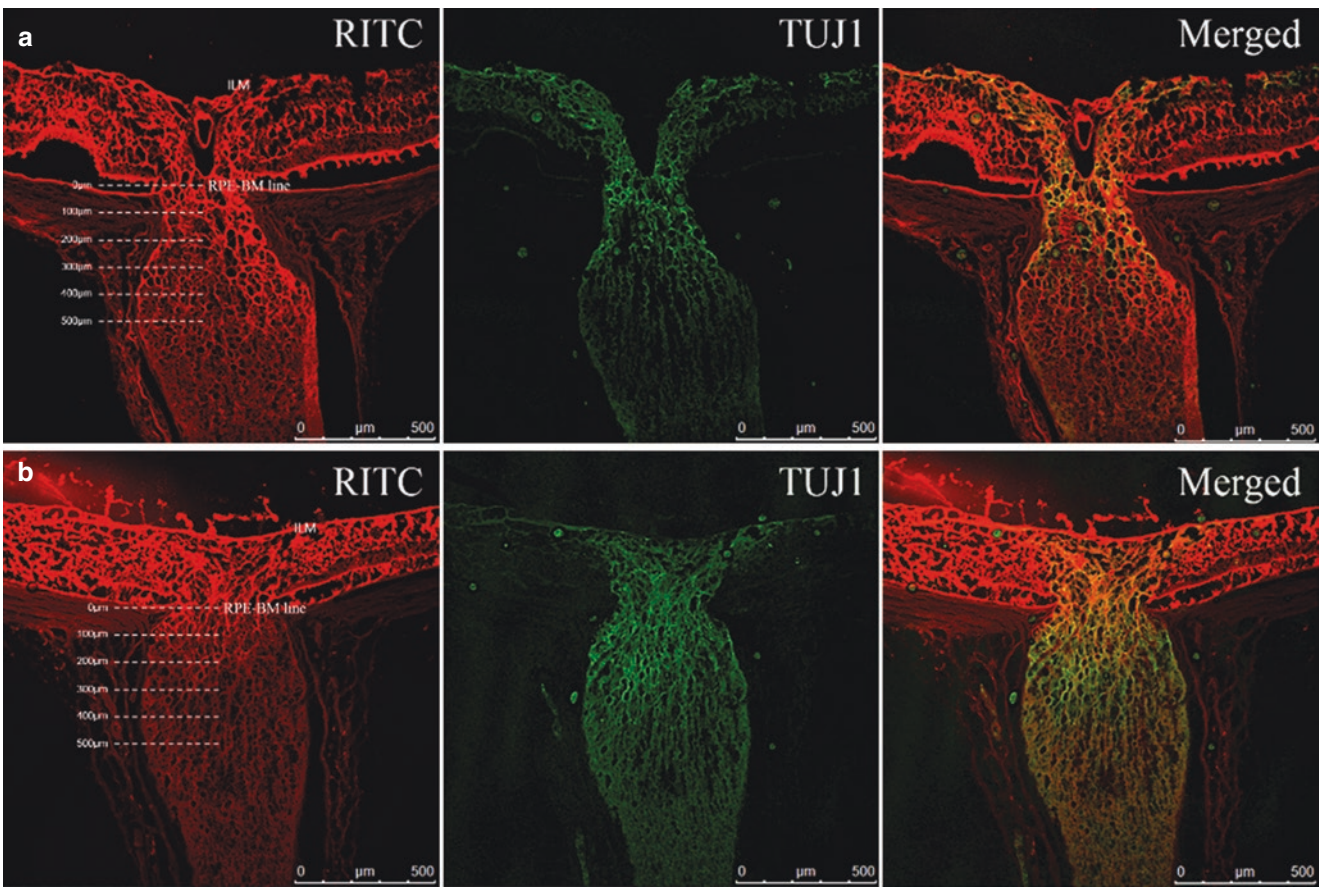

Fig. 1.4 Orthograde axonal transport of rhodamine isothiocyanate (RITC) in the optic nerve of rats of the control group (**a**) and in the optic nerve of rats with an experimental short-term (6 h) reduction in cerebrospinal fluid pressure (**b**), imaged at 1 day after baseline (Reprinted with permission from Zhang Z, Liu D, Jonas J B, et al. Axonal Transport in the Rat Optic Nerve Following Short-Term Reduction in Cerebrospinal Fluid Pressure or Elevation in Intraocular Pressure.[J]. Investigative Ophthalmology & Visual Science, 2015, 56(8):4257–66)

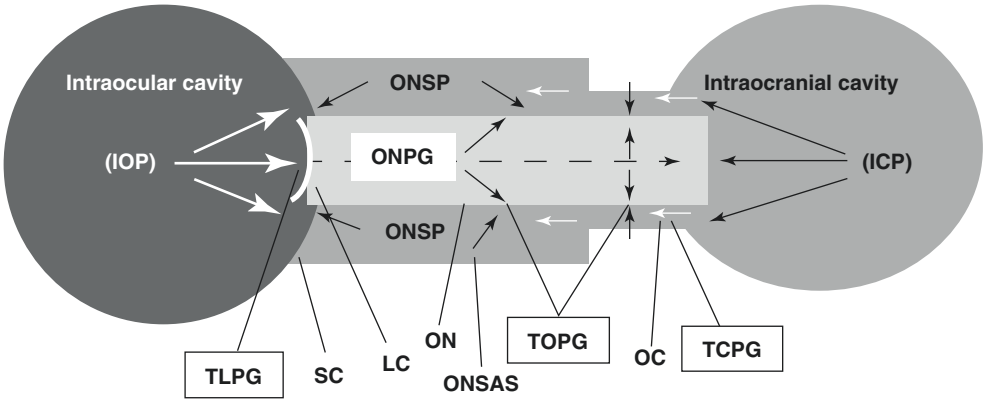

Fig. 1.5 The scheme of the pressures around the optic nerve (Reprinted with permission from Hou R, Zheng Z, Yang D, et al. Pressure balance and imbalance in the optic nerve chamber: The Beijing Intracranial and Intraocular Pressure (iCOP) Study[J]. Science China, 2016, 59(5):495–503)

So far, the pressure difference we study now is static. As we know, IOP and ICP change with the heartbeats and respiratory rhythm. Professor Cynthia Roberts et al. (unpublished) proposed another hypothesis that ocular pulse amplitude (OPA) that interacts with cerebral pulse amplitude (CPA) would cause nerve damage. Of these, the sclera stiffness plays an important risk factor. So we get the new ideas about the TLPD; we should not only think it in static but also in dynamics. What's more, the optic nerve damage has not only happened in the site of the laminar cribrosa but all along the optic nerve, where pressure gradients exist. So the concept of "trans-lamina cribrosa pressure difference" may be changed into "optic nerve pressure gradient (ONPG)" to be more precise (Fig. 1.5).

In review of the literatures, either in the prospective study or retrospective study, we found that not every normal-tension glaucoma patient had lower CSFp [3, 14–17]. Besides the different ICP measurements, some other possible factors should be considered, such as the different definitions of NTG and racial differences as BMI is related to the CSFp which was mentioned before. Since all the related studies have small sample sizes, we suggested that a further international cooperative study among different ethnic groups based on standard protocol is in need.

In conclusion, POAG is an entity of diseases that is caused by various reasons but with characterized optic neuropathy. The future directions include noninvasive measurement of CSFp and IOP dynamics and the change of optic blood flow; therefore, we may have the new classification or the formula to calculate the risk factors and the technique to rebalance the IOP and ICP.

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